Solano County

675 Texas Street
Fairfield, California 94533
www.solanocounty.com

Agenda - Final

Thursday, March 16, 2017

7:00 PM

Board of Supervisors Chambers

Planning Commission

Any person wishing to address any item listed on the Agenda may do so by submitting a Speaker Card to the Clerk before the Commission considers the specific item. Cards are available at the entrance to the meeting chambers. Please limit your comments to five (5) minutes. For items not listed on the Agenda, please see “Items From the Public”.

All actions of the Solano County Planning Commission can be appealed to the Board of Supervisors in writing within 10 days of the decision to be appealed. The fee for appeal is $150.

Any person wishing to review the application(s) and accompanying information may do so at the Solano County Department of Resource Management, Planning Division, 675 Texas Street, Suite 5500, Fairfield, CA. Non-confidential materials related to an item on this Agenda submitted to the Commission after distribution of the agenda packet are available for public inspection during normal business hours and on our website at www.solanocounty.com under Departments, Resource Management, Boards and Commissions.

The County of Solano does not discriminate against persons with disabilities and is an accessible facility. If you wish to attend this meeting and you will require assistance in order to participate, please contact Kristine Sowards, Department of Resource Management at (707) 784-6765 at least 24 hours in advance of the event to make reasonable arrangements to ensure accessibility to this meeting.

AGENDA

CALL TO ORDER

SALUTE TO THE FLAG

ROLL CALL

APPROVAL OF AGENDA

APPROVAL OF THE MINUTES

PC 17-009 Minutes of the meeting of January 5, 2017

Attachments: minutes

PC 17-010 Minutes of the meeting of January 19, 2017

Attachments: minutes

PC 17-011 Minutes of the meeting of February 16, 2017

Attachments: minutes

ITEMS FROM THE PUBLIC:

This is your opportunity to address the Commission on a matter not heard on the Agenda, but it must be within the subject matter jurisdiction of the Commission. Please submit a Speaker Card before the first speaker is called and limit your comments to five minutes. Items from the public will be taken under consideration without discussion by the Commission and may be referred to staff.

REGULAR CALENDAR

1 **PC 17-012** Public hearing to consider a proposed ordinance to amend Chapter 28 (Zoning Regulations) to regulate non-commercial cultivation of marijuana and cannabis for personal and caregiver use in all zones that allow a residence as a primary use and determine whether to recommend that the Board of Supervisors adopt such an ordinance; and Consider whether to recommend the Board of Supervisors find the project exempt from further environmental review under the General Rule Exemption. (Project Planner: Karen Avery)

Attachments: A - Draft Personal Cannabis Ordinance
A - Exhibit A (Zoning Tables)
B - Draft Resolution Personal Cannabis Cultivation
C - Cannabis Effects Highlights.pd
C - Monitoring_Health_Concerns_Report_FINAL
C - National Academics Press

ANNOUNCEMENTS AND REPORTS

ADJOURN

To the Planning Commission meeting of April 6, 2017 at 7:00 P.M., Board Chambers, 675 Texas Street, Fairfield, CA

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Agenda Submittal

Agenda #:		**Status:**	PC Minutes
Type:	PC-Document	**Department:**	Planning Commission
File #:	PC 17-009	**Contact:**	
Agenda date:	3/16/2017	**Final action:**	
Title:	Minutes of the meeting of January 5, 2017		

Governing body:

District:

Attachments: minutes

Date	Ver.	Action By	Action	Result

MINUTES OF THE SOLANO COUNTY PLANNING COMMISSION

Meeting of January 5, 2017

The regular meeting of the Solano County Planning Commission was held in the Solano County Administration Center, Board of Supervisors' Chambers (1st floor), 675 Texas Street, Fairfield, California.

PRESENT: Commissioners Rhoads-Poston, Walker, Hollingsworth, and Chairperson Cayler

EXCUSED: Commissioner Castellblanch

STAFF PRESENT: Bill Emlen, Director, Mike Yankovich, Planning Program Manager; Jim Laughlin, Deputy County Counsel; and Kristine Sowards, Planning Commission Clerk

Chairperson Cayler called the meeting to order at 7:00 p.m. with a salute to the flag. Roll call was taken and a quorum was present.

Approval of the Agenda
The Agenda was approved with no additions or deletions.

Approval of the Minutes
The minutes of the regular meeting of November 17, 2016 were approved as prepared.

Items from the Public
There was no one from the public wishing to speak.

Regular Calendar

Item No. 1.

STUDY SESSION to obtain public testimony on the draft Noise Ordinance for the unincorporated area of Solano County.

Mike Yankovich introduced the item by stating that the Solano County General Plan was updated in 2008 and included in the Public Health and Safety Chapter is a section devoted to noise. The section identifies the County's strategy for dealing with unwanted noise as "reducing excessive noise exposure through cost-effective measures and appropriate zoning that avoids placing incompatible land uses in proximity of each other." The section includes Land Use Noise Compatibility Guidelines (Table HS-2) for various land use categories as well as Noise Standards for New Uses (Tables HS-3 and HS-4). As part of the Implementation Program for the Public Health and Safety Chapter measure, HS.I-60 states that a county noise ordinance should be developed, adopted, and implemented.

Jeff Henderson with the Michael Baker Consulting firm led a team of project consultants who gave an overview of the process that led to the ordinance creation. The presentation included noise fundamentals which covered decibel level comparisons; types of noise measurements and how noise increases are perceived; content of the draft noise ordinance; other noise sources regulated; and exemptions and enforcement. One member of the team also provided a noise demonstration of typical background noise levels.

Mike Yankovich mentioned that county staff is currently working with the Sheriff's Department with regard to noise complaints. He said complaints usually take place at night or over the weekend and Sheriff's deputies would most likely be responding to the complaints. Mr. Yankovich cited loud parties as the top complaint received. He said staff will incorporate in the proposed ordinance a request for funds for the purchase of noise meters, as well as training for staff both in the Sheriff and Resource Management Departments.

Mr. Henderson provided some clarity with regard to Tables 28.1-40 and HS-2 that Commissioner Walker inquired about relating to agricultural noise. Mr. Henderson commented that agricultural uses creating noise are exempt from the limitations in the tables.

Commissioner Walker inquired as to how the hours of 10am to 3pm Monday through Friday were derived for the limitation on construction noise. He said that it appears somewhat restrictive. He felt 9am to 4pm or 8am to 5pm to be more of a standard workday.

Mr. Yankovich stated that staff was looking at the most active part of the day. He said the majority of people are up and around and able to deal with noise during that time period. Mr. Henderson made a clarification that there is a difference between the time limitations for construction which is Monday through Friday from 7am to 6pm and the time within which the peak noise can occur which is 10am to 3pm.

Commissioner Walker said that he personally felt 9am to 4pm to be acceptable.

Deanna Garcia, 9401 Fruitridge Road, Sacramento, appeared before the commission. She stated that in her experience in living close to two construction companies she has had to put up with a lot of dirt and dust. She suggested adding in the ordinance the requirement for water trucks to control dust when construction is taking place.

Commissioner Walker suggested, and the commission agreed, to change the peak construction hours from 10am to 3pm to 9am to 4 pm.

There were no further questions or comments from the commissioners or the public at large.

Item No. 2.

STUDY SESSION to obtain public testimony on possible Tourist Home and Tourist House regulations for the unincorporated area of Solano County.

Mike Yankovich provided a brief summary of staff's written report. The report indicated that there are an increasing number of complaints regarding the short-term rental of rooms and whole houses for periods of less than 30 days. In some cases, these rentals have included the conduct of special events. The use of a dwelling unit as a tourist home or tourist house rather

than as a residence is a land use that is not currently authorized by Chapter 28 (Zoning Regulations) of the Solano County Code.

Staff is suggesting that a tourist home/house be considered a compatible use in the A-20 zone district since this land is primarily grazing and located adjacent or close to urbanized areas with future potential for development beyond the time frame of the General Plan. The A-40, A-80 and A-160 zone districts are not included because virtually all agriculture takes place in these three zone districts. The A-SV-20 and ATC zone districts are located exclusively in the Suisun Valley which has a tourist emphasis and the Rural Residential (RR 2½, RR5 & RR10) zone districts are residential in character and have the lot area that is sufficient to enable the operation of a tourist home/house.

Commissioner Walker stated that he agreed with the list of recommended zoning districts as identified in staff's report. He said if there was interest in amending the Uniform Rules and Procedures Governing Agricultural Preserves and Land Conservation Contracts to allow properties under a Williamson Act to be considered, he would be in favor of that as long as the ag remains where it is. Mr. Walker spoke to the limitations on a tourist home of the 90-days within a calendar year, the limit of only 6 persons, and the turnover limited to once every 7 days. He commented that with such restrictions it would appear to him to not be a viable business venture.

Mr. Yankovich stated that the county is being cautious with regard to the use itself. Possibly in the future if there is a need, an amendment to the ordinance could be made for an increase. He stated that staff looked at different vacation rental restrictions from other counties and jurisdictions and used those as a guideline, although those jurisdictions may have a higher need than in Solano County.

In response to Commissioner Rhoads-Poston's inquiry, Jim Laughlin provided an explanation with regard to number of dwelling units and their definitions. He stated that a tourist home is a house where someone already resides and are renting out a portion of the home to guests. He said the 90-day limit is somewhat arbitrary and the commission can extend that or eliminate it entirely. He noted that because someone is already living in the home the idea is that they should be able to afford to live there without needing the extra income, and therefore not having extra guests on a fulltime basis. The seven day required stay does not mean people have to stay for a full seven days, but many other jurisdictions that have dealt with this wanted to cut down on the amount of turnover so new people are not constantly coming and going. Mr. Laughlin stated that if there is a second home on the property and guests are not being allowed into the primary home, then that is being referred to as a Tourist House which has a different category of restrictions.

Commissioner Hollingsworth asked if the intensity of the use were to increase if there would be another level of requirements such as health and safety concerns. Mr. Laughlin stated that there are no other outside state imposed standards. He said this is a local creation and the commission is free to change the standards in any way they feel appropriate for the county.

Commissioner Rhoads-Poston said that she would suggest an increase to the 90 days. In viewing this from an agricultural standpoint, she said if a farmer was in need of help in making ends meet due to a bad crop year this would be a helpful way in doing that. She said in

looking at the Suisun Valley tourist plan she can see this as a budding industry. She also noted that she was in agreement with the turnover limit to once every seven days.

Mr. Laughlin commented that the concern about agricultural areas and farmers' need for extra income raises an important point. He said staff has not yet delved into all of the areas related to this matter. He said before the commission tonight for review are the two definitions: Tourist House (a house where the entire structure is rented out) and Tourist Home (where someone is taken into an existing home where people already reside).

Mr. Laughlin stated that the tourist house definition is staff's primary concern at this time because it appears to be the problem and there is some confusion in the existing ordinance. He explained that until 2011 there were two definitions in the zoning code: rooming and boarding house and hotel. A rooming and boarding house is anyplace where three or more guests are taken in. It is considered a rooming house if it is for rooming purposes only, once meals are provided then it becomes a boarding house. Under the pre 2011 zoning code, three guests and under were considered a residential use of the property and allowed by right; more than three became a rooming or boarding house; six or more guest rooms then became a hotel, and so there were clear cut distinctions and whatever was being done fell into one of those three categories.

Mr. Laughlin explained that in 2011 the county adopted amendments for the Suisun Valley area and two new land use definitions were introduced; Bed and Breakfast Inn and Agricultural Homestay. Those new definitions overlap with the existing ones so the problem with the existing code is that the use is not clear. With regard to agricultural properties, Mr. Laughlin stated that there are agricultural homestays which is essentially a bed and breakfast on a working ranch with the idea that people come to observe the working ranch operations. The commission's concern about farmers needing to make extra income might be a situation that could be allowed today as an agricultural homestay. Mr. Laughlin said the county can start regulating whole house rentals but the partial home rental which is taking guests into an occupied dwelling will need some work in order to straighten out the definition.

Chairperson Cayler asked how the agricultural homestay and tourist house will be differentiated within the code.

Mr. Laughlin explained that tourist house as proposed is defined as a whole house rental where no one is living in the home. Guests are allowed to take over the entire home for a period of time up to 30 days. An agricultural homestay is a working ranch occupied by the farming family who are taking guests into their home.

Commissioner Walker said he did not see the need for the 90-day limit under the provisions of Tourist Home and suggested the restriction be removed. He agreed with the seven day period turnover and agreed with the provision for preventing events. With respect to occupancy, Mr. Walker felt the standard listed under Tourist House as 2.g. should also be used under Tourist Home replacing the existing standard 1.h. so that the same language is used under both instances.

Commissioner Walker inquired if the county has a mechanism to collect for Transient Occupancy Tax. Jim Laughlin stated that there is an ordinance in place but the county has not

used the ordinance since the Ranchotel located outside of Vacaville was annexed into the City of Vacaville. He said that was the county's last transient structure. Mr. Laughlin stated that now with these types of uses popping up there is already an ordinance on the books. He noted that staff is working with the county Tax Collector on making some procedural amendments to make tax collection easier. Mr. Laughlin commented that the county's current transient tax is 5% which was customary back when the ordinance was adopted, but most jurisdictions are up to 10 or 12 percent. He said a tax increase would be something for the county to consider in the future but would require voter approval.

Commissioner Hollingsworth asked if the 90-day restriction were to be eliminated if this would cause a problem with other definitions for similar activities. Mr. Laughlin stated that the only time limit that is important is the 30 days or less. If it is more than 30 days the county cannot collect the transient occupancy tax because at that point the person becomes a residential tenant, and so staff is crafting these to apply to land uses where people stay 30 days or less.

With regard to amending the county's rules and procedures governing the Williamson Act, Commissioner Hollingsworth inquired if additional action would be needed. Mr. Laughlin replied in the affirmative noting that the regulations already need updating due to the additional Suisun Valley zoning.

There were no further questions of staff from the commission or testimony from the public at large. There was consensus among the commission to eliminate the 90-day limitation and recommend raising the transient occupancy tax. Chairperson Cayler said another recommendation the commission may want to consider is to change the requirement of the Williamson Act so that it would permit some rental residential within the "A-20" and "A-SV-20" zone districts.

Mr. Yankovich stated that staff will take the commission's input and bring this back before them at a future date for further review.

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Deanna Garcia, 9401 Fruitridge Road, Sacramento; Dr. Marion Fry, 8698 Winding Way, Fair Oaks; and Kimberly Kargile *(spelling not verified)* spoke briefly on the topic of cannabis which was not on the commission's agenda, but Chairperson Cayler opened the floor for public comment due to the late arrival of the aforementioned speakers.

The commission received an invitation from Ms. Kargile to visit the holistic health center and medical cannabis dispensary in the City of Sacramento.

It was noted by staff that the issue with regard to cannabis will be discussed at the next regular Planning Commission meeting on January 19, 2017.

ANNOUNCEMENTS and REPORTS

There were no announcements and reports.

Since there was no further business, the meeting was **adjourned**.

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Agenda Submittal

Agenda #:		**Status:**	PC Minutes
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File #:	PC 17-010	**Contact:**	
Agenda date:	3/16/2017	**Final action:**	
Title:	Minutes of the meeting of January 19, 2017		

Governing body:

District:

Attachments: minutes

Date	Ver.	Action By	Action	Result

MINUTES OF THE SOLANO COUNTY PLANNING COMMISSION

Meeting of January 19, 2017

The regular meeting of the Solano County Planning Commission was held in the Solano County Administration Center, Board of Supervisors' Chambers (1st floor), 675 Texas Street, Fairfield, California.

PRESENT: Commissioners Rhoads-Poston, Walker, Hollingsworth, Castellblanch, and Chairperson Cayler

EXCUSED: None

STAFF PRESENT: Mike Yankovich, Planning Program Manager; Karen Avery, Senior Planner; Davina Smith, Deputy County Counsel; and Kristine Sowards, Planning Commission Clerk

Chairperson Cayler called the meeting to order at 7:00 p.m. with a salute to the flag. Roll call was taken and a quorum was present.

Approval of the Agenda
The Agenda was approved with no additions or deletions.

Approval of the Minutes
There were no minutes available for approval.

Items from the Public
There was no one from the public wishing to speak.

Regular Calendar

Item No. 1 -

CONTINUED PUBLIC HEARING, no action or formal recommendation is anticipated, to collect public input on how the County should regulate indoor and outdoor personal and caregiver cultivation of medical cannabis and non-medical marijuana in all zones that allow a residence; and to collect public input on whether the County should consider allowing three types of commercial marijuana activity in the manufacturing and industrial zones: 1) cultivation indoors up to 10,000 sq. ft., 2) non-volatile-solvent marijuana manufacturing, and 3) marijuana testing laboratories; and prohibiting all other commercial marijuana activities in the unincorporated county. Receive presentations from the Solano County's Department of Agriculture and Department of Public Health; and Consider designating one or two representatives of the Planning Commission to assist staff in collecting cannabis/marijuana data and report back to the full Commission. (Project Planner: Karen Avery)

Karen Avery gave a brief introduction to staff's written report. The report noted Solano County is considering adopting regulations for personal cultivation of medical cannabis and nonmedical

marijuana. The draft regulations are to reflect both the Medical Cannabis Regulation and Safety Act (MCRSA) and the Adult Use of Marijuana Act (AUMA) both of which allow local jurisdictions to further regulate cannabis/marijuana. Currently, the focus is on personal cultivation as indoor personal cultivation cannot be prohibited by local jurisdictions per AUMA.

The staff report explained that the Board of Supervisors considered this issue and directed staff to develop an ordinance on personal cultivation. Staff prepared and presented a draft ordinance to the Planning Commission on November 17, 2016. After listening to input from the public and after discussion amongst the Commissioners, the Planning Commission meeting was continued to January 19, 2017. The Planning Commission wanted additional time to evaluate personal cultivation regulatory options and in particular additional options in regards to outdoor cultivation.

Ms. Avery noted that Robin Cox and Felicia Flores-Workman will be speaking on behalf of the Solano County Public Health Department about how the new laws may affect Health and Social Service programs, and Agricultural Commissioner, Jim Allan will be speaking on behalf of the Solano County Agriculture Department giving an agricultural perspective of the new laws and how they may affect the Agriculture Department's operations.

Robin Cox's presentation included an overview of public health impacts of marijuana use, public health and mental health responsibilities and what the impact of Prop 64 is likely to be on the need for services and increased services in county health and social services, specifically around public health and mental health. Ms. Cox's presentation also touched on regulation considerations. She said the Department's mission is to protect public health and to look at the community as a whole.

Commissioner Castellblanch noted that Prop 64 just passed in the State of California with Solano County voting 58% in favor. He commented that he did not want to sit here and debate the public health consequences. He said the commission is here to decide on matters of cultivation in the unincorporated areas of this county and what the appropriate practices are. Mr. Castellblanch said he did not feel the public health presentation to be germane to the question of cultivation and whether or not people can grow marijuana in their backyard or in their homes.

Davina Smith, deputy county counsel, explained that what is happening tonight is a process. She said that because this is a process the idea is to get a variety of perspectives. Additional information on a variety of topics relating to marijuana is being sought and staff is hoping to get input from the public tonight as well as from public health and the ag commissioner about various topics relating to both commercial marijuana, cultivation, commercial marijuana businesses, if they are right for the county, if they are not right, if we should have them, and if we do, what kind of regulations would be appropriate.

Commissioner Hollingsworth asked if the smoking rules in California are the same for marijuana as for tobacco. Felicia Flores-Workman stated that related to where someone cannot smoke, it would be the same. She said for example the City of Fairfield does not have an ordinance that says a person cannot smoke in the downtown area, so someone could walk by the businesses and smoke, but a person is not allowed by state law to go outside and smoke marijuana. Ms. Flores-Workman said in terms of prohibitions, places the state has barred someone from smoking like smoke free parks and tot lots, neither would be allowed. She commented that it is

a hard question to answer outright because smoking tobacco and cigarettes can be done unless a jurisdiction has specific policies around it.

Commissioner Rhoads-Poston said she would like to see some comparisons and contrasts between marijuana and alcohol. She mentioned that a statement was made that 17% of persons who use marijuana are more likely to become addicted. She questioned if those persons would have become addicted to anything, or would have become addicted to alcohol at some point as well. She said she would also like to see the difference between the benefits and the downside of marijuana and alcohol use. Ms. Rhoads-Poston noted that alcohol is legal but there have been many documentaries and studies about how people drive under the influence of marijuana vs alcohol. She said she would also like to see any studies on how marijuana helps medicinally.

Robin Cox stated that there is not a tremendous amount of youth and teen studies because the substance was illicit. She said the Food and Drug Administration(FDA) and Environmental Protection Agency(EPA) did not grant many researchers the ability to experiment with an illicit substance on humans, so most of the data available is from people who were already using. Ms. Cox commented that she attended a health conference recently and met a father of a child with a rare form of epilepsy and his son has found benefit through cannabis. Ms. Cox reiterated that her presentation tonight is about the community at large and not about trying to interfere in the medical space between a patent and their doctor.

Commissioner Walker commented that it would be interesting to see the updated 2016 Colorado Department of Public Health report as edification. He said the commission's role tonight pertains to land use authority and jurisdiction recommendations to the Board of Supervisors. He commented that social policy and what works and does not work in the county is in the hands of the Board to decide.

Davina Smith clarified for the commission and for the audience that the current legal status of the county with regard to medical marijuana dispensaries is that they are not allowed by ordinance. Given the fact that Prop 64 came into effect and then MCRSA, it is uncertain if that is something the Board will want to revisit. Ms. Smith said at this point staff is trying to gather information and obtain public comment. The interest expressed by the Board is to deal with the personal cultivation aspect first, then commercial second, and third, dispensaries.

Commissioner Walker asked about the impact of the passing of Measure C. Ms. Smith stated that Measure C is the taxation measure that would be applied if the county were to adopt any commercial marijuana businesses in the unincorporated county; the Board would be able to set a tax limit on the gross profits. She said the impact is that it is in place in the event the Board decides to allow those commercial opportunities in the county.

Chairperson Cayler thanked Ms. Cox and Ms. Flores-Workman for sharing their information because when it comes time to decide where the county is going to allow these plants to grow, the effect on the population is an important piece of the consideration.

Jim Allan, county agricultural commissioner provided a White Paper from his professional association that largely speaks to the regulatory impacts to ag commissioners once the cannabis industry is fully realized, the areas that currently have regulatory authority, and how

those would be impacted as cannabis is rolled out in different jurisdictions. The paper also talks about the rolls of the department. Mr. Allan's main purpose in being here tonight is to be a subject matter expert for the commission on the horticultural and botanical aspects of cannabis, and if so desired, the agricultural aspects of industrial hemp. Mr. Allan provided an overview of the items he described. He noted that when he approached the Farm Bureau and the Ag Advisory Committee their main concern centered around security and environmental issues not agricultural or horticultural issues.

Mike Yankovich said that in the forthcoming months staff will be bringing other speakers from other areas of interest to also give the commission a baseline from which to work from when deliberating on this matter.

Ms. Avery finished up staff's presentation by reminding the commission about the personal cultivation comparisons with regard to MCRSA and AUMA and she briefly reviewed the list of regulatory goals which included theft and trespassing, preventing access to underage and unauthorized people, health risks, neighborhood impacts, electrical improvements, water usage, compliance with building, electrical and fire codes, and organic marijuana.

Since there were no further questions of staff, Chairperson Cayler opened the public hearing.

Dante De La Cerna, 185 Hastings Avenue, Vallejo, stated that he works at Fighting Back Partnership in Vallejo and coordinates the Vallejo Community Change Coalition which strives to create a heathy environment for Vallejo kids and families where the negative impact of alcohol, tobacco and other harmful products are minimized. He said he is also a member of the Solano County Alcohol, Tabaco and Other Drugs (ATOD) prevention collaborative. He said the collaborative is a countywide group of stakeholders working to reduce ATOD use among youth in Solano County. Mr. De La Cerna urged the commission to encourage responsible and thoughtful regulation of medical and recreational marijuana activities to honor the health and safety of the entire community. He spoke of the increase of marijuana use coinciding with the proliferation of marijuana dispensaries. The ATOD prevention collaborative urged the planning commission to recommend to the Board to prohibit the delivery of marijuana, prohibit outdoor cultivation of marijuana, prohibit commercial cultivation of marijuana, prohibit commercial or retail sales of marijuana, and regulate personal indoor cultivation of marijuana.

Toni Tucker, 742 Laurel Way, Rio Vista, said that she is an ATOD prevention coordinator for the Rio Vista Alliance. She said their mission is to work on limiting access of marijuana to their youth. The ATOD collaborative recommends prohibiting personal outdoor cultivation as well as commercial cultivation due to safety impacts, quality of life, and environmental impacts. Cultivation is a challenging activity for communities to consider and Ms. Tucker said it will be difficult to regulate and monitor yet can easily impact surrounding properties. Given that the new laws allow for prohibition of outdoor cultivation and commercial cultivation the ATOD collaborative strongly urges the county to err towards the side of caution and safety in protecting its citizens from those harms that these activities shall bring, particularly in lieu of successful examples within the state.

Cathy Dacanay-Rader, 523 El Camino Drive, Fairfield, stated that she works for the Suisun Recreation Department. She is also the coordinator for the Suisun ATOD prevention coalition and a member of the Solano ATOD collaborative. Ms. Dacanay-Rader said she is very

concerned about public safety and quality of life in the neighborhoods. Given that the personal indoor cultivation of non-medical marijuana cannot be prohibited under the AUMA, the ATOD prevention collaborative urges the county to adequately regulate indoor cultivation of marijuana. She provided a document to the commission entitled Position Statements on Marijuana and in that document it provided a list of 14 policy recommendations based on research from jurisdictions both within California and from other states to better protect residents, youth, and the environment from the harm brought about by indoor marijuana cultivation.

Darrell Ogden, 960 Rolling Green Drive, Rio Vista, voiced concern with the effects on the children living in the home where there is an indoor cultivation of marijuana. He believed that indoor grows should comply with building, fire, and electrical codes and there should be inspections that would allow the county to confirm the grower has safely complied. This would keep any youths living in the home safe and also the health and safety of fire and police that may need to go inside. Mr. Ogden said sometimes houses and other buildings used to grow marijuana contain high levels of mold which could pose a health threat to residents living there and to law enforcement agents investigating them. To help prevent this he encouraged the commission to require ventilation and filtration systems. These systems would also keep the odor from getting outside and becoming a public nuisance. Mr. Ogden said these permits and inspections are not meant to control what the grower is doing, but to help make sure that our community youth are safe.

Thomas Lamothe, Rio Vista, stated as a former recreation commissioner and chairman of the recreation commission in Rio Vista, he totally agreed with the ATOD collaborative that marijuana should not be readily attainable to the youth. He explained that the endocannabinoid system is something that was never mentioned by public health even though it is the most revolutionary discovery in biological science. He stated that the research that was presented was not conducted by a scientific community; it was mostly by government. He commented that the use is here to stay regardless of what the county implements.

Zach Ortiz, 5317 11th Avenue, Sacramento, is the recreation supervisor for Suisun City and also a member of the Suisun City ATOD. His stated that his main concern is for the youth of Solano County. Mr. Ortriz spoke to several facts focusing on the dangers of the decreased and perceived harm of marijuana and its increased access to youth.

Patrick Byron, Rio Vista, spoke with regard to the presentation made by public health staff and the remarks about product packaging of marketed edibles. He stated that there are sections in Prop 64 that specifically prohibit advertising on products that are marketed toward children, as well as advertising that looks like other existing products. He said it is no secret that the majority of people in attendance tonight and the majority of people in this state support safe access to medicine. He said although there are known risks, we also need to understand how those risks are related to a regulated and unregulated market. Mr. Byron said that in reading Prop 64, MCRSA and the Compassionate Use Act it is very clear what the intent and purpose of those acts are. He said the intent is for regulation of the activity. Many people who have this need cannot grow. He said it is not as easy as one may think to grow medical grade products, so by limiting safe access you are forcing patients into an unregulated market and that market is supplied by unregulated growers who are not following the rules. These are criminal organizations that do not care if they damage the environment. He asked the commission to please consider personal use outdoor cultivation; personal use indoor cultivation with

reasonable restrictions; permitting of micro-business, permitting of cultivation, and permitting of the retail sale of cannabis products either from a delivery or dispensary. Mr. Byron said that the county needs to look at what they are doing and reconsider this prohibition because they are inviting criminals to take over this billion dollar market.

Frank Grouziano, 755 Sequoia Drive, Fairfield, commented that over the thousands of years of known marijuana use there has not ever been one known death attributed to marijuana. He asked that the commission not trample on the rights of medical marijuana users. He said those rights were voted upon and passed and people are here still fighting for those rights to be upheld. Mr. Grouziano commented that others can brew alcohol in their own homes but he cannot grow his own medicine. He noted that most dispensaries are well run they follow the law and provide high quality medication. Mr. Grouziano said that it is important to have a safe place to get medicine.

Crystal Roe, 1208 Mayfield Circle, Suisun, stated that for her and her husband marijuana is medication. She said that some of the regulations the county is proposing are over the top. She said they do not want to have to dedicate a special room for growing their marijuana or pay for additional electricity or worry about possible fire hazards. She said they just want to be able to have their medication and develop the strain that helps them which they can grow outdoors. There should be safe access for everyone. Ms. Roe commented that folks are already growing their medicine and no one is going to follow these regulations except for commercial institutions who are trying to turn a profit. Ms. Roe stated that she hoped the commission will take a less crazy approach and realize that they are parents and know how to talk to and protect their kids.

James Hinton appeared before the commission. He said that he is speaking on behalf of the Vallejo Patients Coalition. Mr. Hinton noted that two years ago Vallejo had the first successful referendum in the history of Vallejo and for the last year the City of Vallejo has been successfully taxing and regulating the medicine which has been an economic blessing to the city. Mr. Hinton said that he had the opportunity to tour a large licensed hydroponic farm in Washington State and it was an amazing and clean operation. He said that by having commercial grows in the county there is an opportunity to create jobs. He said the Vallejo Holistic Health Center is a union dispensary with over 30 employees. If there were a commercial cultivation site somewhere in Solano County there could be more union jobs and tax revenue. Mr. Hinton said that the county is going to see a lot of people try to grow indoors to make up for their economic short comings and there will be more risk associated with that.

Since there were no further speakers, Chairperson Cayler closed the public hearing.

Commissioner Castellblanch stated that this has come down to some serious issues, particularly within Prop 64. He said there is the age limit that has to be dealt with if the county is going to be regulating cultivation and commercial and personal use. He said the consideration of keeping it away from people under 21 is a germane issue for the commission to discuss and seems to fit within the law and the commission's jurisdiction. Mr. Castellblanch said if there is some definite harm such as it makes it easier for people under 21, or turns out that odor is an issue to the extent that there are substantive issues of nuisance or violations of state law that fall within the jurisdiction of the commission then he believed they should deal with it. But generally, Commissioner Castellblanch said he did not believe the commission should be making up laws to deal with problems that are not apparent and in front of the commission and

demonstrated. He did believe that Solano County should observe what the people in California and Solano County have voted in favor of.

Commissioner Walker referred to Attachment B of the staff report which listed the possible regulations of personal grows. He wanted to know the intent of item S where it states the authorized grower shall not participate in other cultivation sites in any other locations within the county. Davina Smith responded by saying that the idea is to not have the cultivation occur in multiple places. Mr. Walker also inquired about item A which proposes a requirement for a water catchment system and he did not understand why this system would be necessary.

Mike Yankovich stated the proposed regulations are only suggestions for the commission to consider and are not necessarily being encouraged. He said the idea behind item A is that the county has a no net increase rule in terms of water leaving one property and impacting another. In this instance the requirement is to make sure there is a catchment system so that the water remains on the property and does not cause problems downstream.

Chairperson Cayler speculated that the issues that can occur around organic farming where a farmer is concerned with neighboring properties who use pesticides that can contaminate irrigation water may have played a part in the consideration of item A.

Commissioner Walker said that would make sense when talking about a large scale operation, but for six to twelve plants he could not imagine on the parcel sizes that are being considered that it would be an impact. Commissioner Castellblanch agreed that he did not see the point of requirement A.

The commission at this point decided to consider and discuss each regulation separately.

Item B) If lights are used to cultivate marijuana, the lights must be CFLs or LEDs, or the cultivator must have alternative energy system (such as solar or wind) to alleviate electrical loads.

Commissioner Hollingsworth stated that he did not see the reasoning in this requirement. Mr. Yankovich stated that it is to recognize the reduction in energy usage.

Commissioner Castellblanch commented that he felt it to be an overreach. Commissioner Walker said that he felt the commission could certainly suggest it as part of the climate action goals for both the county and the state, but it should not be a requirement.

Item C) Total lights must be kept under a maximum wattage.

Mike Yankovich said this is a safety related requirement. Once a total load is achieved it is important that it is on an adequate electrical system. Commissioner Rhoads-Poston commented that she sees this as the same as monitoring what someone is plugging into their outlets.

Item D) No maximum size on reflectors; Item E) No burning of any substance in the grow room.

There were no negative comments made by the commission on these two items.

Item F) No use of CO2 generators in the grow room.

Commissioner Castellblanch said that he did not see the need for this requirement.

Item G) Outdoor grows must be inside an opaque, locking fence.

Commissioner Walker said he felt this meets the suggestion that was discussed in the past that if it were going to be contemplated to allow people to grow outside then it needed to be screened from public view and protected from minors.

Item H) No marijuana may be visible from outside the room or fenced enclosure it is grown in.

Commissioner Walker commented that this goes along with the spirit of the previous condition. Commissioner Castellblanch said an opaque locking fence is an added cost that could become a problem, but if the idea is to keep it away from the kids in the neighborhood then it could make sense.

Item I) Indoor cultivation room must be secured with a lock.

The commission all seemed to agree with this suggestion.

Item J) No other activities may take place in the indoor cultivation room beyond cultivation and processing of marijuana.

Commissioner Rhoads-Poston said that she sees this as an extreme and did not think it should be regulated or required. If someone is going to have a grow room and it has a lock then that would be safe.

Chairperson Cayler said that she could see this as one of those things where a room may not be used very often such as a media room and a grow room all in one and it becomes a special room that is seldom used. She felt this is probably some of the things the regulation is geared toward and believed it should be something the commission should pay attention to.

Commissioner Rhoads-Poston said she sees this on the same lines of having to have alcohol confined to a separate room or maybe poisonous plants, etc. so that children are not around these things. She said this would be something that would start to interfere with basic parenting responsibilities.

Item K) - No use of any fertilizers/pesticides/rodenticides/fungicides/herbicides that are not approved for use on marijuana.

Commissioner Hollingsworth said he understood that the EPA does not have a list of products that can or cannot be used. He questioned if a product that is safe to use on tobacco would also be safe to use on marijuana.

Jim Allan, county ag commissioner, reappeared before the commission He said the Federal Insecticide, Fungicide, and Rodenticide Act governs all the pesticide laws in the country and it basically says that the label is the law for pesticides. He said the EPA has only pesticides for

certain commodities. Currently because the label is the law and there are no products labeled specifically for cannabis the products allowed to be used are the substances like rosemary or cedar oil, the very generic things that have broad use across all plants.

Commissioner Hollingsworth questioned how the county can require folks not to use something if there is nothing that can be used. Mr. Allan agreed saying that is probably unnecessary since it is already against existing law to use something in conflict with its label.

Item L) Any alterations to the structure or electrical system or the means of ingress and egress of a grow room must be done pursuant to current adopted code and have a finaled permit.

The commission agreed with this regulation.

Item M) Indoor cultivation room must have a working air filtration system sized to insure that odors are not detectable from the exterior of the structure the grow room is located in.

To clarify this regulation, Mr. Yankovich stated that the intent is for the room itself and not the entire home. Ms. Smith further clarified that the system would have to be sized to the room, it would have filters that would need to be changed regularly, and it would necessitate putting a hole in either an exterior wall or through the roof.

Commissioner Castellblanch stated that he remains to be convinced that odor is an issue. He commented that there are other odors that exist and that are a nuisance, but there are no laws prohibiting them. He said this regulation strikes him as being a potential barrier just in the expense, and it is not clear to him that it is even necessary.

Commissioners Walker and Rhoads-Poston agreed that such a system would not be necessary for only six plants.

Chairperson Cayler said that she would be in favor of the condition because odor could permeate the entire house.

Commissioner Hollingsworth said if this condition is to remain then it needs to be made more specific. He said every home that has a central heating and air system has an air filter system and so it needs to be defined better. He commented if it is going to be restricted to just that room, then a central air conditioning system is going to pull the air and comingle it with the rest of the house.

Item N) Outdoor cultivation may not occur within 50 feet of any property line or easement for road traffic or pedestrian access.

Commissioner Castellblanch commented that he lives in Solar Village in Benicia and he did not believe there is any part of his lot that is 50 feet from the fence line. He said there are a lot of lots in the county that are small and he thought the 50 foot rule is arbitrary and would be unfair to folks that have less lot to utilize.

Commissioner Rhoads-Poston said that this requirement almost seems redundant if the grow is already required to not be visible from any point.

Commissioner Walker mentioned that this condition might have been to address some of the comments from the last meeting where there were concerns about odor.

Chairperson Cayler stated that there are setback rules that apply when a landowner builds a structure on their property and so this concept is not a new one. She said that maybe 50 feet is extensive but some type of rule should be required.

Item O) Outdoor cultivation may not occur on any parcel under 2.5 acres.

Commissioner Walker noted that the conversation the commission had at the last meeting about acreage prompted staff to generate the maps that were contained in the staff report. He said the commission talked a lot in general about the large size of parcels in the county and that most are 2½ acres or larger, which in his mind mitigates issues people had with respect to outdoor cultivation so long as it is screened. Mr. Walker commented that there are some neighborhoods such as Homeacres and old Glen Cove in unincorporated Vallejo where numerous parcels are under the 2½ size and would directly be impacted by the limitation of acreage size.

Commissioner Castellblanch said that he believed this should go back to the basic idea of keeping the product out of the hands of children and doing what is necessary. He commented that 2½ acres is a big lot and the limitation should be based around the purposes of preventing people under 21 of getting ahold of the product.

Commissioner Walker noted if the minimum acreage requirement is eliminated then the discussion of setbacks would need to be revisited.

Chairperson Cayler said she would be in favor of a setback similar to that required of a swimming pool which is probably 10 feet. She said the commission may want to stick with acreage of some variety, or if it is a smaller lot a conditional use permit might be the way to approach it.

Davina Smith noted that currently there is no permit requirement to grow six plants recreationally or for 100 square feet for personal use as a medical patient or up to 500 square feet for a caregiver. She said if you are a person who is a medical marijuana patient or caregiver then a recommendation is required from a physician or possession of a medical card from Public Health.

Chairperson Cayler reiterated that she still felt some restrictions are needed. Commissioners Walker and Rhoads-Poston both felt that the issue has been addressed with a requirement of setbacks and screening.

Item P) Require all cultivation sites within the unincorporated county to register with Resource Management or Public Health and declare under penalty of perjury that they comply with all local and state regulations.

Commissioner Walker stated that he would absolutely not support anything that includes a registration. He said there may be an entirely different ideology starting soon with the incoming administration and it is not known if the Department of Justice is going to start coming at counties and cities in the state and require them to provide their lists of registrants.

Commissioner Castellblanch also commented that it is not known what the new administration is going to be doing and if the county is setting up registries to facilitate that then a bad mistake would have been made.

Chairperson Cayler spoke about code enforcement as it relates to electrical and safety codes and that there is no way to get totally around that. She said she would like to support a registration concept, but being uncertain about the upcoming administration she thought the commission probably should not require it.

Item Q) Require all grow sites registered with the County provide proof of property ownership or approval for cultivation from property owner.

Chairperson Cayler looked to Commissioner Walker for his opinion due to his experience in the real estate business. Mr. Walker stated that this could become a civil issue between the property owner and the tenant. He said that his real estate association's leases specifically state no smoking which means no smoking of any substance. Mr. Walker commented that the members of his association are currently discussing this topic and have been for several months. He said their generic lease template will be modified so that the owner has the right to opt in or out.

Item R) The authorized grower shall reside full-time in the residence where the cultivation occurs.

The commission had no negative comments with regard to this item.

Item S) The authorized grower shall not participate in other cultivation sites in any other location within the county.

Commissioner Rhoads-Poston made a suggestion that this may need to be made clearer. Ms. Smith explained if someone is cultivating for themselves the idea is to cultivate at their residence and to keep it in one spot. For example, if someone were to have 100 square feet it would not be in a bunch of different locations. The idea is to keep track of it and to keep it in one place. Ms. Smith said it is up to the commission's discretion if they would like the idea of allowing for multiple sites and dividing up part of the caregiver portion.

Chairperson Cayler asked if that regulation could be more refined.

Item T) If cultivation occurs within residence, the residence shall primarily be maintained as a residence.

There was agreement among the commission.

Mr. Yankovich stated that staff will now go through and take stock of the comments made by the commission, repackage it, making sure everything is compliant with the new law and bring this back to the commission sometime in March.

Commissioner Hollingsworth inquired about staff's request in their report that the Commission designate one or two representatives to assist staff in collecting cannabis/marijuana data.

Ms. Avery said staff was just wondering if there was interest among the commission to help draft the ordinance and possibly attend several tours that have been set up.

Each planning commissioner voiced their desire to attend any field trips or help out as time would allow.

ANNOUNCEMENTS and REPORTS
There were no announcements or reports.

Since there was no further business, the meeting was **adjourned**.

Solano County

675 Texas Street
Fairfield, California 94533
www.solanocounty.com

Agenda Submittal

Agenda #:		**Status:**	PC Minutes
Type:	PC-Document	**Department:**	Planning Commission
File #:	PC 17-011	**Contact:**	
Agenda date:	3/16/2017	**Final action:**	
Title:	Minutes of the meeting of February 16, 2017		

Governing body:

District:

Attachments: minutes

Date	Ver.	Action By	Action	Result

MINUTES OF THE SOLANO COUNTY PLANNING COMMISSION

Meeting of February 16, 2017

The regular meeting of the Solano County Planning Commission was held in the Solano County Administration Center, Board of Supervisors' Chambers (1st floor), 675 Texas Street, Fairfield, California.

PRESENT: Commissioners Rhoads-Poston, Hollingsworth, and Chairperson Cayler

EXCUSED: Commissioners Walker and Castellblanch

STAFF PRESENT: Mike Yankovich, Planning Program Manager; Eric Wilberg, Planner Associate; Jim Laughlin, Deputy County Counsel; and Kristine Sowards, Planning Commission Clerk

Chairperson Cayler called the meeting to order at 7:00 p.m. with a salute to the flag. Roll call was taken and a quorum was present.

Approval of the Agenda
The Agenda was approved with no additions or deletions.

Approval of the Minutes
There were no minutes available for approval.

Items from the Public
There was no one from the public wishing to speak.

Regular Calendar

Item No. 1 -

NOMINATION and ELECTION of Chair and Vice-Chair for the ensuing year.

It was motioned and seconded to nominate Commissioners Cayler and Hollingsworth as Chair and Vice-Chair, respectively. The motion passed unanimously.

Item No. 2 -

PUBLIC HEARING to consider Public hearing to consider Lot Line Adjustment Application No. LLA-16-03 of Cordelia Winery LLC and Ryan German & Michael and Janis German to reconfigure the common parcel boundary between two adjacent lots located at 4991 Suisun Valley Road, 2 miles northwest of the City of Fairfield within the Suisun Valley Agriculture "A-SV-20" Zoning District; APNs 0149-060-030, 05, 06, 08, and 09. The two properties are entered into Williamson Act Contract No. 671. (Project Planner: Eric Wilberg)

Eric Wilberg briefly reviewed staff's written report. The proposal involves adjusting the common property line between the German lot and the Cordelia Winery lot. The resulting configuration will transfer 5.16 acres of land under vines from Lot A to Lot B. In addition, 0.10 acres of interior access road will transfer from Lot B to Lot A. The table in the staff report showed the detailed lot information, parcel ownership, and acreages. Staff recommended approval of the project.

Since there were no questions of staff, Chairperson Cayler opened the public hearing.

Mike Carlson, vice-president of general counsel for Cordelia Winery stated that he wanted to introduce himself to the commission and to make himself available for questions if needed. He commented that this is the first step toward the project they have envisioned for this property which is a winery and have submitted an application to the county.

The applicant, Chuck Wagner appeared before the commission. He stated that they are farmers first and wine makers second. He commented that they own a winery in Napa County and also grow grapes in Solano County. He said that this is a family run operation and they have been in the business for many years. Mr. Wagner noted that they also farm property in four other counties of California as well. He said they are happy about doing business in Solano County.

Since there were no further speakers, Chairperson Cayler closed the public hearing.

A motion was made by Commissioner Hollingsworth and seconded by Commissioner Rhoads-Poston to approve Lot Line Adjustment Application No. LLA-16-03 subject to the recommended conditions of approval. The motion passed unanimously. (Resolution No. 4642)

ANNOUNCEMENTS and REPORTS
There were no announcements or reports.

Since there was no further business, the meeting was **adjourned**.

Solano County

675 Texas Street
Fairfield, California 94533
www.solanocounty.com

Agenda Submittal

Agenda #:	1	**Status:**	PC-Regular
Type:	PC-Document	**Department:**	Planning Commission
File #:	PC 17-012	**Contact:**	
Agenda date:	3/16/2017	**Final action:**	
Title:	Public hearing to consider a proposed ordinance to amend Chapter 28 (Zoning Regulations) to regulate non-commercial cultivation of marijuana and cannabis for personal and caregiver use in all zones that allow a residence as a primary use and determine whether to recommend that the Board of Supervisors adopt such an ordinance; and Consider whether to recommend the Board of Supervisors find the project exempt from further environmental review under the General Rule Exemption. (Project Planner: Karen Avery)		
Governing body:			
District:			
Attachments:	A - Draft Personal Cannabis Ordinance A - Exhibit A (Zoning Tables) B - Draft Resolution Personal Cannabis Cultivation C - Cannabis Effects Highlights.pd C - Monitoring_Health_Concerns_Report_FINAL C - National Academics Press		

Date	Ver.	Action By	Action	Result

Public Hearing Required? Yes _X___ No __ _

RECOMMENDATION:

The Department of Resource Management recommends that the Planning Commission:

1. Conduct a public hearing to consider a proposed ordinance to amend Chapter 28 (Zoning Regulations) to regulate non-commercial cultivation of marijuana and cannabis for personal and caregiver use in all zones that allow a residence as a primary use and determine whether to recommend that the Board of Supervisors adopt such an ordinance;

2. Consider whether to recommend to the Board of Supervisors that the project (zoning ordinance) is exempt from further environmental review under the General Rule Exemption of Section 15061(b)(3) of Title 14 of the California Code of Regulations;

3. Receive an update from staff on the status of Commercial Cannabis Regulations.

SUMMARY:

Solano County is considering adopting regulations for personal cultivation of medical cannabis and nonmedical marijuana. The draft regulations are to reflect both the Medical Cannabis Regulation and Safety Act (MCRSA) and the Adult Use of Marijuana Act (AUMA) both of which allow local jurisdictions to further regulate cannabis/marijuana. Currently, the focus is on personal cultivation as indoor personal cultivation cannot be prohibited by local jurisdictions per AUMA.

The Board of Supervisors considered this issue and directed staff to develop an ordinance on personal cultivation. Staff prepared and presented a draft ordinance to the Planning Commission on November 17, 2016. After listening to input from the public and after discussion amongst the Commissioners, the Planning Commission meeting was continued to January 19, 2017. The Planning Commission wanted additional time to evaluate personal cultivation regulatory options and in particular additional options in regards to outdoor cultivation.

At the January 19, 2017 Planning Commission meeting, the Commission received more input from the public as to how the County should regulate medical cannabis and non-medical marijuana including discussion in regards to indoor and outdoor personal and caregiver cultivation. Staff presented a list of possible regulations for both indoor and outdoor personal cultivation for discussion by the Commission. The Commission also received presentations from the Solano County Agricultural Commissioner on the horticultural and agricultural impacts to cultivating cannabis and Solano County Public Health representatives on possible public health impacts of marijuana regulation.
Staff has prepared an updated draft ordinance addressing personal cultivation based on comments received from the Planning Commission on January 19th and the draft ordinance is now ready for further consideration by the Commission.

ENVIRONMENTAL ANALYSIS:
The project (zoning ordinance) is exempt from further environmental review under the General Rule Exemption of Section 15060(c)(2) of Title 14 of the California Code of Regulations because the project will not result in a direct or reasonably foreseeable indirect physical change in the environment.

DISCUSSION:
Based on input from the public and discussion by the Planning Commission during the hearings held November 17, 2016, January 19, 2017, and a Community meeting held February 8, 2017, staff has prepared a draft ordinance addressing indoor and outdoor cultivation of cannabis for personal and caregiver cultivation.

The purpose of regulating personal cultivation and medical cannabis cultivation is to alleviate or minimize possible negative impacts that arise from this activity. Staff presented a list of possible regulatory options to the Commission on January 19th for consideration. These options were discussed one-by-one by the Commission and the proposed draft regulation reflect that discussion.

The draft regulations separate personal cannabis cultivation standards from caregiver cultivation standards due to the size of the grow sites. The Medical Cannabis Regulation and Safety Act (MCRSA) allows 100 square feet for personal medical cultivation and 500 square feet of cultivation for a primary caregiver supplying up to five patients. The Adult Use of Marijuana Act allows personal recreational cultivation of up to six plants. The six plants can be grown within a private residence or in a secured structure on the grounds of a private residence by law. Local jurisdictions can reasonably regulate indoor and outdoor cultivation of the six plants. Below are some of the key areas addressed in the updated draft ordinance based on Commission and public input received.

Personal Outdoor Cultivation - Medical and Recreational
In regards to personal outdoor cultivation, the Commission expressed concerns about keeping outdoor grow sites secure from the general public and minors. The proposed draft regulations

address those concerns by requiring minimum setbacks, screening, and security of outdoor personal cultivation sites.

Personal Indoor Cultivation - Medical and Recreational
In regards to personal indoor cultivation, the draft regulations reflect the Commission's concerns with government overreach and eliminated wattage limits, security requirements, and instead left the location, set-up and grow methods within the purview of the resident or qualified patient.

Primary Caregiver Cultivation - Medical
As stated earlier, under MCRSA, primary caregivers may grow up to 500 square feet of cannabis for up to five qualified patients. The impacts of 500 square feet of cannabis grow may be more intense than 100 square feet of cannabis grow or the growing of six recreational plants. Odor and potential nuisances of outdoor grows on smaller parcels were mentioned as concerns due to the larger grow site. This has been taken into consideration in the draft regulations. General standards for Primary Caregiver cultivation includes obtaining an annual Administrative Permit from the Department of Resource Management, submitting a plot plan of the grow site, documentation for each patient, permission from the landlord and a site visit with County personnel to review compliance with the primary cultivation standards:

a. Standards for Outdoor Primary Caregiver Cultivation includes cultivating on properties larger than one acre in size that has a residence inhabited by the primary caregiver or patient. Locating the grow site so that it is in the rear half of the property, 20' from the property boundaries and screened from public view.

b. Standards for Indoor Primary Caregiver Cultivation includes indoor cultivation in a private residence inhabited by the caregiver or patient or in a permanent residential accessory structure on the grounds. Artificial light used in the grow room must not be visible from the outside, no gas products, ozone generators or open flames allowed in the cultivation room and no power generator use except for an emergency back-up generator.

Status of Commercial Cannabis Business Regulations
Staff has toured a commercial indoor cannabis cultivation facility, a cannabis lab testing facility and a cannabis manufacturing facility which uses CO2 to process cannabis trimmings into oil. Staff will be touring a nursery facility and edible manufacturer later this month.

In addition to the Community Outreach meeting held on February 8th, staff conducted an Industry Stakeholder meeting on March 8th to gain insight from current operators as to what types of regulations they believe should be considered in unincorporated Solano County.

Project Schedule
Solano County Agricultural Commissioner Jim Allan will be speaking to the Board of Supervisors on Tuesday, March 14th. He will be giving a horticultural and agricultural aspect of cannabis cultivation and an update on the status of regulations from the California Department of Food and Agriculture.

At the Board meeting of April 11, 2107, Alex Spelman from SICPA will be speaking about the "track and trace" aspect of commercial cannabis. Mr. Spelman is the Vice President of Business Development for Meyercord Revenue, a SICPA Company. SICPA has been working on a trial "track and trace" system with Humboldt County and has just started a similar program with Yolo County's Department of Agriculture. Yolo County currently allows outdoor medical cultivation.

On May 23, 2017, Nick Caston of CannaCraft, will be speaking as an Industry Stakeholder. Mr. Caston is the Vice-President of Public Affairs and Policy for the CannaCraft family of companies. CannaCraft operates one of the largest cannabis manufacturing plants in California. He has worked in public policy for a number of years and served as the Vice-Chair of the Planning Commission in Santa Rosa.

Staff anticipates that the State Bureau of Medical Cannabis will be releasing a copy of their draft regulations in late spring or early summer.

STAFF RECOMMENDATION

The current interim urgency ordinance does address personal cultivation as defined by MCRSA and AUMA; however, staff believes separating personal cultivation from the possibly of regulating commercial cannabis businesses as the most appropriate way for the County to consider regulating cannabis under the new state laws. Staff is continuing to conduct research in regards to drafting commercial cannabis regulations for the review of the Planning Commission.

Staff is asking the Planning Commission to review and recommend adoption to the Board of the Personal Cannabis Cultivation Ordinance (Attachment A/Exhibit A) addressing personal cultivation specific to MCRSA and AUMA.

ATTACHMENTS:

A. Draft Ordinance for Recommendation to Board
B. Draft Resolution for Adoption of Recommendation
C. Follow-Up Materials to January Planning Commission Meeting re: Public Health Impacts of Recreational Marijuana Use

ORDINANCE NO. 2017-_____

AN ORDINANCE AMENDING SECTIONS 28.21, 28.22, 28.23, 28.31, 28.32, 28.41, 28.42, 28.43, 28.51, 28.52, 28.61 AND ADDING SECTION 28.82 TO REGULATE CANNABIS CULTIVATION FOR PERSONAL USE IN UNINCORPORATED SOLANO COUNTY

The Board of Supervisors of Solano County do hereby ordain as follows:

SECTION I. Findings

A. The Federal Controlled Substances Act, 21 U.S.C. §§ 801 et seq., classifies cannabis as a Schedule I Drug; as such, it is unlawful, under federal law, for any person to cultivate, manufacture, distribute, dispense, or possess cannabis, whether for medical or recreational purposes.

B. In 1996, the voters of the State of California approved Proposition 215, the Compassionate Use Act (Health and Safety Code Section 11362.5), which was intended to provide a defense to criminal charges for the cultivation and possession of medical cannabis by a seriously ill patient, or the patient's primary caregiver, for the patient's personal use. The Compassionate Use Act further provided that nothing in it shall be construed to supersede legislation prohibiting persons from engaging in conduct that endangers others, or to condone the diversion of cannabis for non-medical purposes.

C. SB 420, the Medical Marijuana Program Act (Health and Safety Code Section 11362.7 *et seq*.), was enacted in 2004 to expand and clarify the scope of Proposition 215 by creating the Medical Marijuana Identification Card program, creating reasonable regulations for cultivating, processing, transporting and administering medical cannabis, as well as limiting the amount of medical cannabis a qualified individual may possess.

D. SB 420 defines a "primary caregiver" as an individual who is designated by a qualified patient or by a person with an identification card, and who has consistently assumed responsibility for the housing, health, or safety of that patient or person.

E. The State enacted the Medical Marijuana Regulation and Safety Act (MMRSA) on September 11, 2015 (SB 643, AB 266, and AB 243), instituting a comprehensive state-level licensure and regulatory scheme for cultivation, manufacturing, distribution, transportation, laboratory testing, and dispensing of medical cannabis. Although MMRSA provides that patients may cultivate up to 100 square feet of cannabis for their personal use, and caregivers may cultivate up to 500 square feet of cannabis for the personal use of up to five patients, cities and counties retain local regulatory authority over medical cannabis, including personal cultivation.

F. The Governor signed SB 837 on June 27, 2016, changing references to the term "marijuana" in MMRSA to "cannabis" and renaming MMRSA the "Medical Cannabis Regulation and Safety Act" (MCRSA).

G. On November 8, 2016, Proposition 64, the Control, Regulate and Tax Adult Use of Marijuana Act (AUMA) was enacted by the voters to decriminalize and regulate commercial and non-commercial recreational cannabis. AUMA provides that cities and counties retain local regulatory control over commercial recreational cannabis, but personal cultivation of up to six plants must be allowed inside a private residence or in a secured structure on the grounds of a private residence.

H. In response to MCRSA and AUMA, the Board of Supervisors, at an open public meeting, directed staff to bring forward a zoning ordinance allowing but regulating medical and recreational cannabis cultivation for personal use within the jurisdictional boundaries of Solano County.

I. The unregulated personal cultivation of cannabis in the unincorporated area of Solano County can adversely affect the health, safety, and well-being of the County, its residents and environment. Comprehensive civil regulation of premises used for personal cannabis cultivation, including zoning regulation, is proper and necessary to reduce the risks of criminal activity, degradation of the natural environment, malodorous smells, and indoor electrical fire hazards that may result from unregulated indoor cannabis cultivation.

J. Children are particularly vulnerable to the effects of cannabis use and the presence of cannabis plants or products is an attractive nuisance for children, creating an unreasonable hazard in areas frequented by children, such as schools, parks, and other similar locations.

K. Outdoor cannabis cultivation, especially within the remote areas, is creating significant impacts to California's surface and groundwater resources. The State Water Resources Control Board, the San Francisco Regional Water Quality Control Board, the Central Valley Regional Water Quality Control Board and the Department of Fish and Wildlife have seen a dramatic increase in the number of cannabis cultivation operations, and corresponding increases in impacts to water supply and water quality, including the discharges into water of sediments, pesticides, fertilizers, petroleum hydrocarbons, trash and human waste.

L. The ability to cultivate cannabis plants for medical or recreational purposes conferred by MCRSA and AUMA does not confer the right to create or maintain a public nuisance. By adopting the regulations contained in this Chapter in coordination with MCRSA and AUMA, the County intends to minimize the risks and complaints regarding fire, odor, crime and pollution caused or threatened by the unregulated cultivation of cannabis in the unincorporated area of Solano County.

M. Nothing herein shall be construed to allow the cultivation or use or allow any activity relating to the cultivation or use of cannabis that is otherwise illegal under State law.

N. The Board finds and declares that the adoption of this Ordinance is necessary and desirable to ensure that environmental, public health, safety and nuisance factors related to the cultivation of cannabis for personal use are adequately addressed.

SECTION II.

The Residential Allowed Uses in the Tables of Allowed Uses in sections 28.21, 28.22, 28.23, 28.31, 28.32, 28.41, 28.42, 28.43, 28.51, 28.52, 28.61 of Article II, Chapter 28 are hereby amended as depicted in Attachment A to allow by right personal cultivation of medical and recreational cannabis in a residence or on the grounds of a residence, subject to the land use regulations at section 28.82, in all zones where a residence is a use allowed by right. Primary caregiver cultivation of up to 500 square feet is allowed with an administrative permit in in all zones where a residence is a use allowed by right, subject to the land use regulations at section 28.82.

SECTION III.

Section 28.82 is added to Article III, Chapter 28 of the Solano County Code to read as follows:

28.82 Personal Cannabis Cultivation and Primary Caregiver Cultivation Uses

A. General Requirements.

1. Personal and primary caregiver cannabis cultivation indoors in a residence or inside a permanent residential accessory structure on the grounds of a residence shall be allowed if it meets the applicable standards in this Chapter and complies with all state and county laws.

2. Personal and primary caregiver cannabis cultivation outdoors on the grounds of a residence is allowed if it meets the applicable standards in this Chapter and complies with all state and county laws.

B. Definitions

1. Cannabis: all parts of the plant Cannabis sativa Linnaeus, Cannabis indica, or Cannabis ruderalis, or any other strain or varietal of the genus Cannabis that may exist or hereafter be discovered or developed that has psychoactive or medicinal properties, whether growing or not, including the seeds thereof. “Cannabis” also means marijuana as defined by Section 11018 of the Health and Safety Code as enacted by Chapter 1407 of the Statutes of 1972. For the purpose of this section, “cannabis” does not mean “industrial hemp” as defined by Section 81000 of the Food and Agricultural Code or Section 11018.5 of the Health and Safety Code. Cannabis is classified as an agricultural product separately from other agricultural crops.

2. Canopy (plant): the square footage dedicated to live plant production, such as maintaining mother plants, propagating plants from seed, clones, including plants in vegetative or flowering states. The canopy shall be measured by the aggregate area of vegetative growth of live cannabis plants on the premises.

3. Cultivation Room: the premises or structure where cannabis is planted, grown, and harvested.

4. Indoor Cannabis Cultivation: cultivation of cannabis using artificial lighting inside a structure with permanent floor, walls, and roof that can be secured with a lock.

5. Marijuana: see “Cannabis”, above.

6. Medical Marijuana Identification Card: document issued by the State Department of Health Services that identifies a person authorized to engage in the medical use of marijuana and the person's designated primary caregiver, if any.

7. Outdoor Cannabis Cultivation: outdoor cultivation of cannabis exclusively outdoors, using natural light and not within a structure. Cultivation inside a hoop house, greenhouse or similar shall be deemed outdoor cultivation.

8. Personal Cannabis Cultivation: any activity involving the planting, growing, harvesting, drying, curing, grading, or trimming of cannabis in compliance with state and county law for medical or recreational use that is intended for use by a) medical cannabis patients in accordance with Health and Safety Code section 11362.777(g), as may be amended, pursuant to the Compassionate Use Act of 1996 (Proposition 215); or b) recreational cannabis users in accordance with Health & Safety Code section 11362.1(a)(3), as may be amended.

9. Primary Caregiver Cultivation or Caregiver Cultivation: any activity involving the planting, growing, harvesting, drying, curing, grading, or trimming of up to 500 square feet of medical cannabis canopy by a designated primary caregiver for up to five qualified patients or holders of Medical Marijuana Identification cards in compliance with county and state laws, including Health and Safety Code section 11362.777(g), as may be amended.

10. Primary Caregiver Administrative Permit: a permit that must be obtained by a primary caregiver prior to cultivating for qualified patients or holders of Medical Marijuana Identification Cards. This permit shall be issued pursuant to the requirements of section 28.101(Administrative Permit) and this section.

11. Primary Caregiver or Caregiver: an individual who is designated by a qualified patient or by a person with a Medical Marijuana Identification Card, and who has consistently assumed responsibility for the housing, health, or safety of that patient or person, as defined in Health & Safety Code section 11362.7(d), as may be amended.

12. Qualified Patient: a person who is entitled to the protections of Health and Safety Code section 11362.5, but who does not have a Medical Marijuana Identification Card, as defined in Health and Safety Code section 11362.7(f), as may be amended.

13. Recreational Cannabis: cannabis used by and intended for an individual over 21, who is neither a qualified patient nor a holder of a Medical Marijuana Identification Card, in accordance with Health & Safety Code section 11362.1(a)(3), as may be amended.

C. Personal and Caregiver Cultivation Amounts

The following amounts of personal and caregiver cannabis may be cultivated so long as the cultivation is in compliance with county and state law and regulations and the Cultivation Standards provided herein:

1. Qualified patients or individuals with a Medical Marijuana Identification Card who are over 18 may cultivate up to 100 square feet of medical cannabis canopy for their own use outside, inside a private residence, or in a permanent residential accessory structure located on the grounds of a private residence in compliance with the personal cannabis cultivation standards.

2. Individuals over 18 designated as the primary caregiver of qualified patients or individual(s) with a Medical Marijuana Identification Card may cultivate up to 500 square feet of medical cannabis outside, inside a private residence, or in a permanent residential accessory structure on the grounds of a private residence for up to five patients or card-holders in compliance with the caregiver cultivation standards and upon obtaining a Primary Caregiver Administrative Permit from the County.

3. Individuals over 21 may cultivate up to 6 cannabis plants for their own recreational use outside, inside a private residence, or in a permanent residential accessory structure located on the grounds of a private residence in compliance with the personal cannabis cultivation standards.

D. Personal Cannabis Cultivation Standards

1. Outdoor Cannabis Cultivation

    a. The outdoor cultivation must occur on a parcel with an inhabited residence. The residence must be occupied by the person for whom the personal use cannabis is intended.

    b. Outdoor personal cannabis cultivation must occur in the rear 50% of the parcel and any cannabis canopy area must be at least 10 feet from any property line or easement and must be screened from public view and or right-of way.

    c. The location of cannabis cultivation, drying, curing, and trimming activities must be in a fenced and secured area not accessible to household visitors or underage individuals

2. Indoor Cannabis Cultivation

    a. The indoor cultivation of personal use cannabis must occur within either an inhabited residence or in a permanent residential accessory structure on the grounds of an inhabited residence. The residence must be occupied by the person for whom the personal use cannabis is intended.

b. The location of cannabis cultivation, drying, curing, and trimming activities must be in a secured room not accessible to visitors or underage individuals.

c. Gas products (including, but not limited to CO2, butane, propane, and natural gas) or ozone generators shall not be used in any cultivation room.

d. No open flame or burning of any substance may occur in the cultivation room.

E. Primary Caregiver Cultivation

1. Primary Caregiver Administrative Permit

a. All individuals who intend to cultivate cannabis as a primary caregiver must obtain a yearly administrative permit from the Department of Resource Management in compliance with the requirements of this section and section 28.101. The following shall be provided, along with any other information required in section 28.101, in order to process a caregiver cultivation administrative permit:

i. Proof of legal ownership of the parcel or written documentation from a landlord that the applicant has permission to cultivate cannabis as a caregiver at the subject location.

ii. A copy of the Medical Marijuana Identification Card number for each individual the primary caregiver is cultivating for, which will be verified on the California Department of Public Health website. If the qualified patient does not have a Medical Marijuana Identification Card, then a copy of the patient's physician recommendation for medical cannabis, along with a signed statement from the qualified patient naming the applicant as his/her primary caregiver.

iii. Plot plan of where the cultivation will occur on the parcel, in the permanent residential accessory structure on the parcel, or in the residence on the parcel.

iv. Acknowledgement that County personnel will schedule a site visit with the applicant to review compliance with the primary caregiver cultivation standards, as well as any applicable requirements of the County Code.

v. Acknowledgement that a permit automatically expires after one year, at which time a new permit application must be made, and that no caregiver cultivation may occur prior to issuance of a permit or if the permit has expired.

vi. Acknowledgement that a caregiver cultivation administrative permit may be denied or revoked in the event the cultivation does not occur in compliance with the requirements of this Chapter and state law.

vii. Payment of a fee, as established by the Board of Supervisors to recover the reasonable costs of administering this administrative permit program.

2. Primary Caregiver Cultivation Standards

a. Outdoor Caregiver Cultivation

i. Upon obtaining a yearly administrative permit, caregiver cultivation may occur outdoors on a parcel one acre or larger that has a residence inhabited by the primary caregiver or the patient for whom the medical cannabis is intended.

ii. Caregiver cultivation must occur in the rear 50% of the parcel and any cannabis canopy area must be at least 20 feet from any property line or easement and must be screened from public view and or public right-of-way.

iii. Drying, curing, trimming, and any other cannabis processing activities must be in a secured area not accessible to visitors or underage individuals.

iv. Electrical lights shall not be used for outdoor cannabis cultivation.

v. In the absence of regulations from the State of California providing guidance on which substances may be safely used on cannabis, only substances that are exempt from residue tolerance requirements as established by the U.S. EPA and either exempt from registration requirements (40 CFR § 152.25 and 3 CCR § 6147, as they may be amended) or registered for a use that is broad enough to include use on cannabis may be used on medical cannabis cultivated by primary caregivers.

b. Indoor Caregiver Cultivation

i. Upon obtaining a yearly administrative permit, a primary caregiver may cultivate medical cannabis in an inhabited residence or in a permanent residential accessory structure on the grounds of an inhabited residence. The caregiver or the patient for whom the medical cannabis is intended must inhabit the residence.

ii. Artificial light used for the indoor cultivation must not be visible from outside the cultivation room.

iii. Gas products (including, but not limited to CO2, butane, propane, and natural gas) or ozone generators shall not be used in any cultivation room.

iv. No open flame or burning of any substance may occur in the cultivation room.

v. The use of generators to power any cultivation equipment is prohibited, except as an emergency back-up system. The use of extension cords in the cultivation room are likewise prohibited.

vi. In the absence of regulations from the State of California providing guidance on which substances may be safely used on cannabis, only substances that are exempt from residue tolerance requirements as established by the U.S. EPA and either exempt from registration requirements (40 CFR § 152.25 and 3 CCR § 6147, as they may be amended) or registered for a use that is broad enough to include use on cannabis may be used on medical cannabis cultivated by primary caregivers.

F. Confidentiality

To the extent permitted by law, any personal or medical information submitted with a primary caregiver administrative permit application shall be kept confidential and shall only be used for purposes of administering this section.

G. Enforcement

It is hereby declared unlawful and a public nuisance for any person to cultivate cannabis for personal or primary caregiver use except as provided for in this Chapter. The County may elect to pursue any and all available administrative remedies and civil causes of action to enforce this Section.

SECTION IV. Environmental Determination.

In accordance with the California Environmental Quality Act (CEQA), it has been determined that this project is exempt from further environmental review under Section 15061(b)(3) of Title 14 of the California Code of Regulations because because there is no possibility that the project may have a significant effect on the environment. The Director of Resource Management is directed to file a Notice of Exemption in accordance with CEQA.

SECTION V. Severability.

If any section, subsection, sentence, clause or phrase of this Ordinance is for any reason held to be unconstitutional and invalid, such decision shall not affect the validity of the remaining portion(s) of this Ordinance. The Board of Supervisors hereby declares that it would have passed this Ordinance and every section, subsection, sentence, clause or phrase thereof, irrespective of the fact that any one or more sections, subsections, sentences, clauses or phrases be declared unconstitutional or invalid.

SECTION VI. Effective Date.

This Ordinance and all amendments to the Solano County Code as set forth within shall be and the same is hereby declared to be in full force and effect from and after thirty (30) days after the date of Board adoption. This Ordinance shall be published once before the expiration of fifteen (15) days after adoption, with the names of the Supervisors voting for or against the same, in a newspaper of general circulation published in Solano County, California.

****

Passed and adopted by the Solano County Board of Supervisors at its regular meeting on _____by the following vote:

AYES: Supervisors _____

_____

NOES: Supervisors _____

EXCUSED: Supervisors _____

_____
JOHN M. VASQUEZ, Chair
Solano County Board of Supervisors

ATTEST:
Birgitta E. Corsello, Clerk
Board of Supervisors

By: _____
Jeanette Neiger, Chief Deputy Clerk

ARTICLE II

DISTRICTS AND ALLOWABLE USES

Sections

28.10 Zoning Districts Established

(Reserved)

28.11 Zoning Maps

The zoning maps shall consist of a series of maps which show the zoning plan being part of this Chapter under the provisions of Section 28-13, and are hereby designated as follows:

1-N	7-N	13-N	19-N
1-S	7-S	13-S	19-S
2-N	8-N	14-N	20-N
2-S	8-S	14-S	20-S
3-N	9-N	15-N	21-N
3-S	9-S	15-S	21-S
4-N	----	16-N	22-N
4-S	10-S	16-S	22-S
---	11-N	17-N	23-N
5-S	11-S	17-S	23-S
6-N	12-N	18-N	
6-S	12-S	18-S	

28.12 Uncertainty of Boundaries

Where uncertainty exists as to the boundaries of any of the districts described in this Chapter or as shown on the zoning maps, the Planning Commission, upon written application or upon its own motion, shall determine the location of such boundaries.

28.13 Districts Designated and Established

A. The several districts established by this Chapter and into which the County is divided are designated as follows:

Agricultural Districts

A District	EXCLUSIVE AGRICULTURAL DISTRICTS
A-SM District	SUISUN MARSH AGRICULTURAL DISTRICTS
A-SV District	SUISUN VALLEY AGRICULTURAL DISTRICT
ATC District	AGRICULTURAL TOURIST CENTER DISTRICTS

Residential Districts

R-R District	RURAL RESIDENTIAL DISTRICTS
R-TC Districts	RESIDENTIAL-TRADITIONAL COMMUNITY DISTRICTS
R-TC-1AC	Residential Traditional Community 1 Acre
R-TC-20	Residential Traditional Community ½ Acre
R-TC-15	Residential Traditional Community 1/3 Acre
R-TC-10	Residential Traditional Community ¼ Acre
R-TC-6	Residential Traditional Community 6,000 Square Feet
R-TC-5	Residential Traditional Community 5,000 Square Feet
R-TC-4	Residential Traditional Community 4,000 Square Feet
R-TC-D-4	Residential Traditional Community Duplex 4,000 Square Feet
R-TC-D-6	Residential Traditional Community Duplex 6,000 Square Feet
R-TC-MF	Residential Traditional Community Multi-Family
R-TC-MU	Residential Traditional Community Mixed Use

Commercial and Industrial Districts

Commercial Districts

C-H District	HIGHWAY COMMERCIAL DISTRICT
C-N District	NEIGHBORHOOD COMMERCIAL DISTRICT
C-R District	COMMERCIAL RECREATION DISTRICT
C-S District	COMMERCIAL SERVICE DISTRICT
C-O District	BUSINESS AND PROFESSIONAL OFFICE DISTRICT

Manufacturing and Industrial Districts

M-L District LIMITED MANUFACTURING DISTRICT

M-G Districts GENERAL MANUFACTURING DISTRICTS

I-WD District WATER DEPENDENT INDUSTRIAL DISTRICT

I-AS District AGRICULTURAL SERVICE DISTRICT

Resource Conservation Districts

W Districts WATERSHED AND CONSERVATION DISTRICT

MP Districts MARSH PRESERVATION DISTRICT

Specialty and Overlay Districts

P Districts PARK DISTRICT

PP Overlay POLICY PLAN OVERLAY

MIDDLE GREEN VALLEY ZONING DISTRICTS [1]

[1]See Middle Green Valley Specific Plan for Zoning Regulations within the Middle Green Valley.

B. The aforesaid districts are hereby established insofar as the designations, locations, and boundaries thereof are set forth and indicated in this Section and in other Sections of this Chapter, which describe certain of such districts. Section 28.11 consists of a series of maps, each entitled "Solano County Zoning Map," identified by a number and a letter. Such maps and all notations, references, data, and other information shown thereon are hereby adopted and made part of this Chapter.

28.20 Agricultural Districts

Subsections:

28.21 Exclusive Agricultural (A) Districts

Subsections:

28-21.10 Exclusive Agricultural (A) Districts

This Section includes regulations for the A-20, A-40, A-80 and A-160 zoning districts.

28.21.11 Purpose of Agricultural Districts

This Section lists the uses of land that may be allowed within the agricultural zoning districts. It also determines the type of land use approval required for each use, and provides general standards for site development.

Agriculture is the major industry in the County generating the majority of the tax revenue in the unincorporated county. Also, agriculture is the largest single zone district classification on the County zoning map. Therefore, the Board of Supervisors has determined that the promotion and preservation of agriculture is of vital interest to the county. The standards stated in this section preserve agriculture in a number of ways, including allowing agricultural-related support uses, excluding incompatible uses, and protecting the viability of the family farm. These regulations support the family farm by allowing a secondary dwelling for family members that acts as a form of affordable housing and, for farms with larger acreage, permits a reasonable number of farm labor housing on or near the farming activity.

28.21.20 Agriculture Districts Uses and Permit Requirements

A. Allowed Uses and Permit Requirements:

Table 28-21A identifies the land uses allowed by this Zoning Ordinance in each agricultural district and the land use permit required to establish each use. In addition to the land use permit required by Table 28-21A, special requirements may apply to certain uses.

B. Architectural Review:

Architectural Approval may be required for certain uses in compliance with Section 28.102 (Architectural Approval).

C. Land Use Regulations

Where the last column in the Table 28.21A (Land Use Regulations") includes a section number, e.g. 28.71.20(A), the zoning regulations in the referenced section apply to the use. Where the last column includes a chapter number, e.g. Chapter 13.6, the regulations in the referenced Solano County Code apply to the use. Provisions in other sections of this Zoning Ordinance may also apply.

D. Site Development and Other Standards

All uses shall comply with the provisions of Article IV, Section 28-90 Site Development and Other Standards which includes standards for parking, signs and other project elements.

TABLE 28.21A TABLE OF ALLOWED USES

A= Allowed by right, AP= Administrative Permit, MUP= Minor Use Permit, UP= Use Permit, E=Exempt,

- - - = Prohibited

ALLOWED USES* *See Definitions Section 28-01	**Permit Requirements**				**Land Use Regulations**** **See Section 28-70.10
	A-40	**A-80**	**A-20**	**A-160**	
AGRICULTURAL USES					
A. CROP PRODUCTION AND GRAZING					
Agricultural accessory structures	A	A	A	A	28.71.10(B)(1)
Cultivated and irrigated farming	A	A	A	A	28.71.10
Non-irrigated and non-cultivated farming, Grazing	A	A	A	A	28.71.10
Grazing or pastured livestock	A	A	A	A	28.71.10
Pastured Poultry					
Not adjacent to a R District	A	A	A	A	28.71.30(A) & (B)(4)
Adjacent to a R District	MUP	MUP	MUP	MUP	
With an agricultural commercial kitchen	MUP	MUP	MUP	MUP	
With sales	MUP	MUP	MUP	MUP	
With special events	MUP	MUP	MUP	MUP	28.71.30(A) & (B)(4); 28.73.30(A) & (B)(6)
With more than 4 crowing fowl	UP	UP	UP	UP	28.71.30(A) & (B)(4)
B. AGRICULTURAL PROCESSING USES					
Agricultural processing facility					
Small Agricultural Processing Facility	AP	AP	AP	AP	28.71.20(A) & (B)(1)
Medium Agricultural Processing Facility	MUP	MUP	MUP	MUP	
Large Agricultural Processing Facility	UP	UP	UP	UP	
With Special Events (existing facility)					
6 per year max, and 150 persons or less	A	A	A	A	28.71.20(A) & (B)(1); 28.73.30(A) & (B)(6)
12 per year max, and 150 persons or less	AP	AP	AP	AP	
More than 12 per year, or more than 150 persons	MUP	MUP	MUP	MUP	
Aquaculture					
Small Aquaculture Facility	AP	AP	AP	AP	28.71.20(A)
Medium Aquaculture Facility	MUP	MUP	MUP	MUP	28.71.20(A)

A= Allowed by right, AP= Administrative Permit, MUP= Minor Use Permit, UP= Use Permit, E=Exempt,

- - - = Prohibited

ALLOWED USES* *See Definitions Section 28-01	**Permit Requirements**				**Land Use Regulations**** **See Section 28-70.10
	A-40	**A-80**	**A-20**	**A-160**	
AGRICULTURAL USES					
Large Aquaculture Facility	UP	UP	UP	UP	
Nursery with public sales [6]	A	A	A	A	28.71.20(A) & (B)(2)
Winery - *25% or greater on-site grapes*					
Winery, small	A	A	A	A	28.71.20(A) & (B)(3)
Winery, medium	AP	AP	AP	AP	
Winery, large	UP	UP	UP	UP	
Winery with less than *25% on-site grapes*	UP	UP	UP	UP	28.71.20(A) & (B)(3)
Winery *with Special Events*					
6 per year max, and 150 persons or less	A	A	A	A	28.71.20(A) & (B)(3); 28.73.30(A) & (B)(6)
12 per year max, and 150 persons or less	AP	AP	AP	AP	
More than 12 per year, or more than 150 persons	MUP	MUP	MUP	MUP	
C. ANIMAL FACILITIES AND OPERATIONS					
Confined animal facility, including dairy					
Small	MUP	MUP	MUP	MUP	28.71.30(A) & (B)(1)
Medium and Large	UP	UP	UP	UP	
Fowl and Poultry Ranch					
Small (100 - 1,000 birds)	MUP	MUP	MUP	MUP	28.71.30(A) & (B)(2)
Large (1,001 birds or more)	UP	UP	UP	UP	
Hog Ranch					
Small (20 - 100 hogs)	AP	AP	AP	AP	28.71.30(A) & (B)(3)
Medium (101 - 750 hogs)	MUP	MUP	MUP	MUP	
Large (751 hogs or more)	UP	UP	UP	UP	
Slaughterhouse					
Small Slaughterhouse (1,000 head per year or less)	MUP	MUP	MUP	MUP	28.71.30(A) & (B)(5)
Large Slaughterhouse (More than 1,000 head per year)	UP	UP	UP	UP	28.71.30(A) & (B)(5)

A= Allowed by right, AP= Administrative Permit, MUP= Minor Use Permit, UP= Use Permit, E=Exempt,

- - - = Prohibited

ALLOWED USES* *See Definitions Section 28-01	**Permit Requirements**				**Land Use Regulations**** **See Section 28-70.10
	A-40	**A-80**	**A-20**	**A-160**	
AGRICULTURAL USES					
D. OTHER AGRICULTURAL OPERATIONS					
Agricultural employee housing	AP	AP	AP	AP	28.71.40(A) & (B)(1)
Commercial auction and agricultural equipment sales, temporary	MUP	MUP	MUP	MUP	28.71.40(A) & (B)(2)
HCD Agricultural employee housing	A	A	A	A	28.71.40(A) & (B)(3)
Labor Camp	A	A	A	A	28.71.40(A) & (B)(4)
Temporary Commercial Coach	AP	AP	AP	AP	28.71.40(A) & (B)(5)

TABLE 28.21A TABLE OF ALLOWED USES

A= Allowed by right, AP= Administrative Permit, MUP= Minor Use Permit, UP= Use Permit, E=Exempt,

- - - = Prohibited

ALLOWED USES* *See Definitions Section 28-01	**Permit Requirements**				**Land Use Regulations**** **See Section 28-70.10**
	A-40	**A-80**	**A-20**	**A-160**	
RESIDENTIAL USES					
A. DWELLINGS					
Primary dwelling	A	A	A	A	28.72.10(A)
Secondary dwelling	A	A	A	A	28.72.10(A) & (B)(6)
Second Kitchen	AP	AP	AP	AP	28.72.10(A) & (B)(7)
Cannabis Cultivation					
Caregiver	AP	AP	AP	AP	28.82
Personal					
Medical	A	A	A	A	28.82
Recreational	A	A	A	A	28.82
B. TEMPORARY RESIDENTIAL USES					
Security quarters for a construction site (commercial coach, manufactured home or recreational vehicle)	AP	AP	AP	AP	28.72.20(A) & (B)(1)
Temporary Manufactured Home Storage	AP	AP	AP	AP	28.72.20(A) & (B)(4)
Temporary single family home	AP	AP	AP	AP	28.72.20(A) & (B)(6)
C. AGRICULTURAL AND ANIMAL FACILITIES INCIDENTAL TO A RESIDENCE					
Small Kennel or Cattery	AP	AP	AP	AP	28.72.30(A) & (B)(3)
Stable, private	A	A	A	A	28.72.30(A) & (B)(5)
D. OTHER RESIDENTIAL USES					
Cottage Industry					
Type I	MUP	MUP	MUP	MUP	28.72.40(A) & (B)(1)
Type II	UP	UP	UP	UP	
Home occupation					
Type I	A	A	A	A	28.72.40(A) & (B)(2)
Type II	AP	AP	AP	AP	

TABLE 28.21A TABLE OF ALLOWED USES

A= Allowed by right, AP= Administrative Permit, MUP= Minor Use Permit, UP= Use Permit, E=Exempt,

- - - = Prohibited

ALLOWED USES* *See Definitions Section 28-01	**Permit Requirements**				**Land Use Regulations**** **See Section 28-70.10
	A-40	**A-80**	**A-20**	**A-160**	
RECREATION, EDUCATION AND PUBLIC ASSEMBLY USES					
A. RECREATION USES					
Boating or swimming facility on existing waterway	UP	UP	UP	UP	28.73.10(A)
Hunting or fishing club	UP	UP	UP	UP	28.73.10(A) & (B)(1)
Public open space area	- - -	- - -	A	A	28.73.10(A)
Stable, public without horse shows	UP	UP	UP	UP	28.73.10(A) & (B)(3)
B. EDUCATION USES					
Agricultural education					
Minor Facility	AP	AP	AP	AP	28.73.20(A) & (B)(1)
Major Facility	MUP	MUP	MUP	MUP	
C. PUBLIC ASSEMBLY USES					
Limited special event	- - -	- - -	UP	- - -	28.73.30(A) & (B)(3)
Public Stable with Horse shows	UP	UP	UP	UP	28.73.30(A) & (B)(5)
Special Events Facility (other than Winery or Agricultural Processing Facility)					
6 per year max, and 150 persons or less	AP	AP	AP	AP	28.73.30(A) & (B)(6)
12 per year max, and 150 persons or less	MUP	MUP	MUP	MUP	
More than 12 per year, or more than 150 persons	UP	UP	UP	UP	
With Off-Site Parking	MUP	MUP	MUP	MUP	

TABLE 28.21A TABLE OF ALLOWED USES

A= Allowed by right, AP= Administrative Permit, MUP= Minor Use Permit, UP= Use Permit, E=Exempt,

- - - = Prohibited

ALLOWED USES* *See Definitions Section 28-01	**Permit Requirements**				**Land Use Regulations**** **See Section 28-70.10
	A-40	**A-80**	**A-20**	**A-160**	
RETAIL AND OFFICE USES					
A. RETAIL USES					
Farm/Ranch Supply Store	MUP	MUP	MUP	MUP	28.74.10(A) & (B)(5)
Roadside Stand					
1,000 square feet or less in size	A	A	A	A	28.74.10(A) & (B)(8)
Between 1,000 and 2,500 square feet	AP	AP	AP	AP	
Greater than 2,500 square feet in size	MUP	MUP	MUP	MUP	
Non-agricultural product sales, less than 10%.	A	A	A	A	
Non-agricultural product sales, between 10% and 25%	MUP	MUP	MUP	MUP	
Non-agricultural product sales, greater than 25%	UP	UP	UP	UP	
Any of the above with a Certified Farmers Market					
Small Certified Farmers Market	AP	AP	AP	AP	28.74.10(A) & (B)(8); 28.75.20(A) & (B)(2)
Medium Certified Farmers Market	MUP	MUP	MUP	MUP	
Large Certified Farmers Market	- - -	- - -	- - -	- - -	
B. OFFICE USES					
Agricultural Research Facility					
Small (less than 20,000 sq. ft.)	AP	AP	AP	AP	28.74.20(A) & (B)(1)
Medium (between 20,000 and 40,000 sq. ft.)	MUP	MUP	MUP	MUP	
Large (more than 40,000 sq. ft.)	UP	UP	UP	UP	

TABLE 28.21A TABLE OF ALLOWED USES

A= Allowed by right, AP= Administrative Permit, MUP= Minor Use Permit, UP= Use Permit, E=Exempt,

- - - = Prohibited

ALLOWED USES* *See Definitions Section 28-01	**Permit Requirements**				**Land Use Regulations**** **See Section 28-70.10
	A-40	**A-80**	**A-20**	**A-160**	
TOURIST USES					
A. AGRITOURISM					
Agricultural homestay	A	A	A	A	28.75.10(A) & (B)(1)
B. TEMPORARY AGRITOURISM					
Amusement and entertainment uses	MUP	MUP	MUP	MUP	28.75.20(A) & (B)(1)
Certified Farmers Market					
Small Certified Farmers Market	AP	AP	AP	AP	28.75.20(A) & (B)(2)
Medium Certified Farmers Market	MUP	MUP	MUP	MUP	
Large Certified Farmers Market	- - -	- - -	- - -	- - -	
Seasonal sales lot	MUP	MUP	MUP	MUP	28.75.20(A) & (B)(3)

TABLE 28.21A TABLE OF ALLOWED USES for THE EXCLUSIVE AGRICULTURAL DISTRICT

A= Allowed by right, AP= Administrative Permit, MUP= Minor Use Permit, UP= Use Permit, E=Exempt,

- - - = Prohibited

ALLOWED USES* *See Definitions Section 28-01	**Permit Requirements**				**Land Use Regulations**** **See Section 28-70.10
	A-40	**A-80**	**A-20**	**A-160**	
COMMERCIAL SERVICE USES					
A. AGRICULTURAL SERVICES					
Agricultural Commercial Kitchen	MUP	MUP	MUP	MUP	28.76.10(A) & (B)(1)
Agricultural trucking services and facility					
Small (1 to 5 trucks)	AP	AP	AP	AP	28.76.10(A) & (B)(2)
Medium (between 6 and 10 trucks)	MUP	MUP	MUP	MUP	
Large (11 or more trucks)	UP	UP	UP	UP	
Airfield or heliport, Agricultural	MUP	MUP	MUP	MUP	28.76.10(A)
Commercial farm equipment fabrication and repair	MUP	MUP	MUP	MUP	
Custom farm services, e.g. hay baling	MUP	MUP	MUP	MUP	
Storage and sale of agricultural service products(fertilizer/fuel)	UP	UP	UP	UP	
B. COMMERCIAL SERVICES					
Large Animal Hospital or Veterinary Clinic	MUP	MUP	MUP	MUP	28.76.20(A) & (B)(1)
Kennel or Cattery, Large	MUP	MUP	MUP	MUP	28.76.20(A) & (B)(2)
Transitional Commercial	MUP	- - -	- - -	- - -	28.76.20(A) & (B)(3)

TABLE 28.21A TABLE OF ALLOWED USES for the EXCLUSIVE AGRICULTURAL DISTRICT

A= Allowed by right, AP= Administrative Permit, MUP= Minor Use Permit, UP= Use Permit, E=Exempt,

- - - = Prohibited

ALLOWED USES* *See Definitions Section 28-01	**Permit Requirements**				**Land Use Regulations**** **See Section 28-70.10
	A-40	**A-80**	**A-20**	**A-160**	
INDUSTRIAL, MANUFACTURING, PROCESSING AND WHOLESALE USES					
A. Industrial, Manufacturing and Processing Uses	- - -	- - -	- - -	- - -	
Transitional Industrial	MUP	- - -	- - -	- - -	28.77.10(A) & (B) (4)
B. Wholesale Uses	- - -	- - -	- - -	- - -	

TABLE 28.21A TABLE OF ALLOWED USES for the EXCLUSIVE AGRICULTURAL DISTRICT

A= Allowed by right, AP= Administrative Permit, MUP= Minor Use Permit, UP= Use Permit, E=Exempt,

- - - = Prohibited

ALLOWED USES* *See Definitions Section 28-01	**Permit Requirements**				**Land Use Regulations**** **See Section 28-70.10
	A-40	**A-80**	**A-20**	**A-160**	
COMMUNICATION AND INFRASTUCTURE USES					
A. COMMUNICATION USES					
Wireless communication facilities					
Co-locations	MUP	MUP	MUP	MUP	28.78.10(A) & 28.81
New towers	UP	UP	UP	UP	
B. INFRASTRUCTURE USES					
Commercial wind turbine generator	UP	UP	UP	UP	28.80
Injection well	UP	UP	UP	UP	28.78.20(A) & (B)(4)
Non-commercial wind turbine					
100 feet or less in height	A	A	A	A	28.80
Over 100 feet in height	MUP	MUP	MUP	MUP	
Oil or gas well	AP	AP	AP	AP	28.78.20(A) & (B)(7)
Pipeline, transmission or distribution line, in R.O.W.	A	A	A	A	28.78.20(A) & (B)(8)
Refuse, disposal, incineration, recycling or composting (10)	UP	UP	UP	UP	28.78.20(B)(3)
Surface mining operation	UP	UP	UP	UP	28.78.20(A)
Utility facility or infrastructure, outside of R.O.W.	UP	UP	UP	UP	28.78.20(A) & (B)(9)
C. PUBLIC SERVICE USES					
Public service facility	UP	UP	UP	UP	28.78.30(A) & (B)(4)

A= Allowed by right, AP= Administrative Permit, MUP= Minor Use Permit, UP= Use Permit, E=Exempt,

- - - = Prohibited

ALLOWED USES* *See Definitions Section 28-01	**Permit Requirements**				**Land Use Regulations**** **See Section 28-70.10
	A-40	**A-80**	**A-20**	**A-160**	
COMMUNICATION AND INFRASTUCTURE USES					
D. TEMPORARY CONSTRUCTION AND INFRASTRUCTURE					
Concrete/asphaltic concrete mixing plant	MUP	MUP	MUP	MUP	28.78.40(A) & (B)(2)
Construction storage yard	MUP	MUP	MUP	MUP	28.78.40(A) & (B)(2)
Construction office, storage, stockpiling, or construction yard for public infrastructure project	MUP	MUP	MUP	MUP	28.78.40(A) & (B)(3)
Meteorological Tower, 100 feet or less in height	AP	AP	AP	AP	28.78.20(A) & (B)(6)
Meteorological Tower, greater than 100 feet in height	MUP	MUP	MUP	MUP	

Table 28.21A TABLE OF ALLOWED USES for the EXCLUSIVE AGRICULTURAL DISTRICT

A= Allowed by right, AP= Administrative Permit, MUP= Minor Use Permit, UP= Use Permit, E=Exempt,

- - - = Prohibited

ALLOWED USES* *See Definitions Section 28-01	**Permit Requirements**				**Land Use Regulations**** **See Section 28-70.10
	A-40	**A-80**	**A-20**	**A-160**	
RESOURCE PROTECTION USES					
A. RESOURCE PROTECTION USES					
Conservation and Mitigation Bank	UP	UP	UP	UP	28.79.10(A)

28.21.30 Agricultural Districts General Development Standards

A. **General site and building standards**. Subdivisions, new land uses**,** main buildings including primary and secondary dwellings, and alterations to existing land uses and buildings, shall be designed, constructed, and/or established in compliance with the applicable development standards delineated or referenced in Table 28-21B.

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Table 28.21B

Development Standards for Main Building or Primary and Secondary Dwelling		
	A-20, A-40	**A-80, A-160**
MAIN BUILDING or PRIMARY DWELLING		
Dwelling Size	*Minimum of 1,000 Square Feet*	
Setbacks [1]		
Front	*30 feet, but at least 50 feet from the street centerline and unless otherwise indicated by building lines on the Zoning Maps.*	
Sides (each)	*20 feet*	
Rear	*25 feet*	
Between structures	*10 feet*	
Height limit	*35 feet, and as allowed by 28-93 Special regulations*	
Height limit for agricultural processing uses	*50 feet, and as allowed by 28-93 Special regulations*	
SECONDARY DWELLING		
	A-20, A-40	**A-80, A-160**
Dwelling Size	*Maximum of 1,800 Square Feet*	
Setbacks [2]		
Front	*30 feet, but at least 50 feet from the street centerline and unless otherwise indicated by building lines on the Zoning Maps*	
Sides (each)	*20 feet*	
Rear	*25 feet*	
Between structures[3]	*10 feet*	
Height limit	*35 feet, and as allowed by 28-93 Special regulations*	

Notes:

(1) Other setbacks may be required for specific uses listed in Table 28-21A, as provided elsewhere in this Chapter.

(2) The side or rear yard requirements may be waived for an accessory building other than an animal shelter, except that such building shall not be located closer to any side street line than the main building. Waiver of said requirements shall be subject to notice as set forth in Section 04(f) of this Chapter.

(3) Other separation between structures may be required by County Building Code.

B. Accessory Buildings and Structures

New accessory buildings and other structures, including alterations to existing accessory buildings and other structures, shall be designed, constructed, and/or established in compliance with the applicable development standards in Section 28.71.10(B)(1) and in Table 28.21C below. Only one residential accessory building is allowed per lot.

Table 28.21C
DEVELOPMENT STANDARDS FOR ACCESSORY BUILDINGS

	A-20, A-40	**A-80, A-160**
AGRICULTURAL ACCESSORY BUILDINGS (1)		
Setbacks (2)(3)		
Attached	*An accessory building attached to the main building shall comply with the setback requirements for the main building*	
Detached		
Front	*60 feet or on the rear 50% of the lot*	
Sides (each)	*20 feet*	
Rear	*20 feet*	
Between structures (4)	*10 feet from any dwelling or other main building on the same lot* *Stables: 20 feet from any dwelling or other main building on the same lot*	
Height limit	*35 feet, and as allowed by 28-93 General Building regulations*	
Height limit for agricultural processing uses	*50 feet, and as allowed by 28-93 Special regulations*	
Parking	*As required by 28-94, Parking Requirements*	
Signs	*See Section 28.96 Signs*	
RESIDENTIAL ACCESSORY BUILDINGS (1)		
	A-20, A-40	**A-80, A-160**
Setbacks (2)(3)		
Attached	*An accessory building attached to the main building shall comply with the setback requirements for the main building*	
Detached		
Front	*60 feet or on the rear 50% of the lot*	
Sides (each)	*20 feet*	
Rear	*20 feet*	
Between structures (4)	*10 feet from any dwelling or other main building on the same lot* *Stables: 20 feet from any dwelling or other main building on the same lot*	
Height limit	*35 feet, and as allowed by 28-93 Special regulations*	
Parking	*As required by 28-94, Parking Requirements*	
Signs	*See Section 28.96 Signs*	

Notes: (1) Does not include a secondary dwelling as defined in Section 28-01.

(2) Other setbacks may be required for specific uses listed in Table 28-21A, as referenced.

(3) The side or rear yard requirements may be waived for an accessory building other than an animal shelter, except that such building shall not be located closer to any side street line than the main building. Waiver of said requirements shall be subject to notice as set forth in Section 04(f) of this Chapter.

(4) Other separation between structures may be required by County Building Code.

28.22 Suisun Marsh Agricultural (A-SM) Districts

Subsections:

28-22.10 – Suisun Marsh Agriculture Districts

This section includes regulations for the A-SM-80 and A-SM-160 zoning districts.

28.22.11 – Purpose of Suisun Marsh Agriculture Districts

This Section lists the uses of land that may be allowed within the Suisun Marsh Agricultural zoning districts, established by Section 28.13 (Districts Designated and Established). It also determines the type of land use approval required for each type of use and provides general standards for site development.

Agriculture is the major industry in Solano County, generating the majority of the tax revenue in the unincorporated County. In addition, certain agricultural lands serve an important function in buffering contiguous environmentally sensitive lands of the Suisun Marsh from the effects of urbanization. Therefore, the Board of Supervisors has determined that it is in the interest of the County to prevent further encroachment upon such agricultural lands by incompatible uses of property.

The purpose and intent of the A-SM districts is to preserve lands best suited for permanent agricultural use while limiting certain intensive agricultural practices which may conflict with adjoining sensitive lands. A primary intent of the A-SM districts is to assure the retention of upland and lowland grasslands adjacent to the Suisun Marsh in uses compatible with its protection.

28.22.20 – Suisun Marsh Agricultural District Land Uses and Permit Requirements

A. Allowed Uses and Permit Requirements

Table 28-22A identifies the land uses allowed by this Zoning Ordinance in each Suisun Marsh Agricultural district and the land use permit required to establish each use. In addition to the land use permit required by Table 28-22A, special requirements may apply to certain uses.

B. Marsh Development Permit Requirements

Any development within the Suisun Marsh, as defined by Section 29114 of the Public Resources Code, shall be subject to obtaining a Marsh Development Permit pursuant to the Suisun Marsh Preservation Act of 1977, and as provided for in Section 28.104 of this Code. When a land use subject to a marsh development permit is proposed in both the Primary Management Area and Secondary Management Area, as defined in the Suisun Marsh Preservation Act of 1977, the land use shall be subject to a use permit covering the whole of the project.

C. Architectural Review

Architectural Approval may be required for certain uses, in compliance with Section 28.102 (Architectural Approval).

D. Building Permits

A Building Permit shall be required prior to any construction.

E. Land Use Regulations

Where the last column in Table 28.22A (Land Use Regulations) includes a section number, e.g. 28.70.10, the zoning regulations in the referenced section apply to the use. Where the last column includes a chapter number, e.g. Chapter 13.6, the regulations in the referenced Solano County Code apply to the use. Provisions in other sections of this Zoning Ordinance may also apply.

F. Non-Conforming Uses

Within the Suisun Marsh, as defined by Section 29101of the Public Resources Code, uses established prior to 1977 that do not conform to the uses set forth in Table 28-22A shall be considered nonconforming uses under Section 28.114, except that non-substantial changes, alterations, and additions to nonconforming uses may be allowed within the existing established project footprint area subject to a marsh development permit, pursuant to the Suisun Marsh Preservation Act of 1977 and as provided for in Section 28.104 of this code. The overall existing development area may not be expanded under these provisions. Development within the existing development area should minimize additional impervious surfaces. An adequate buffer should be established or maintained between the development areas and any water, wetlands, or other Marsh habitat to protect the habitat from adverse environmental impacts. An erosion, sediment, and runoff control plan shall be prepared in accordance with Section 31.26(b) of the Solano County Grading, Drainage, Land Leveling and Erosion Control Ordinance. When the non-conforming use is located in both the Primary and Secondary Management Areas, as defined by the Suisun Marsh Preservation Act of 1977, non-substantial changes, alterations, and additions to the nonconforming use shall be subject to a use permit covering the whole of the project.

G. Site Development and Other Standards

All uses shall comply with the provisions of Article IV, Section 28-90 Site Development and Other Standards, which includes standards for parking, signs, and other project elements.

Table 28.22A TABLE OF ALLOWED USES

A = Allowed by right, AP = Administrative Permit, MUP = Minor Use Permit, UP = Use Permit, - - - = Prohibited

ALLOWED USES See Definitions Section 28.10	Permit Requirements A-SM-80 & A-SM-160 Zoning Districts	Land Use Regulations See Section 28.70.10
28.71 AGRICULTURAL USES		
A. CROP PRODUCTION AND GRAZING		
Agricultural accessory buildings	A	28.71(A) & (B)(1)
Cultivated and irrigated farming	A[(2)]	
Non-irrigated and non-cultivated farming	A[(2)]	
Grazing	A[(2)]	
Pastured Poultry		
Not adjacent to a R District	A	28.71.10(A) & (B)(4)
Adjacent to a R District	MUP	28.71.10(A) & (B)(4)
With an agricultural commercial kitchen	- - -	
With sales	- - -	
With Special events	- - -	
With more than 4 crowing fowl	UP	28.71.10(A) & (B)(4)
B. AGRICULTURAL PROCESSING USES		
None allowed		
C. ANIMAL FACILITIES AND OPERATIONS		
None allowed		
D. OTHER AGRICULTURAL OPERATIONS		
Agricultural employee housing	AP	28.71.40(A) & (B)(1)
HCD Agricultural employee housing	A	28.71.40(A) & (B)(3)
Temporary commercial coach	AP	28.71.40(A) & (B)(5)
28.72 RESIDENTIAL USES		
A. DWELLINGS		
Primary Dwelling[(3)]	A	28.72.10(A)
Secondary Dwelling	A	28.72.10(A) & (B)(6)
Second Kitchen	AP	28.72.10(A) & (B)(7)
Cannabis Cultivation		
Caregiver	AP	28.82
Personal		
Medical	A	28.82
Recreational	A	28.82
B. TEMPORARY RESIDENTIAL USES		
Temporary single family dwelling	AP	28.72.20(A) & (B)(6)
C. AGRICULTURAL AND ANIMAL FACILITIES INCIDENTAL TO A RESIDENCE		
Small kennels and catteries	AP	28.72.30(A) & (B)(3)

Table 28.22A TABLE OF ALLOWED USES

A = Allowed by right, AP = Administrative Permit, MUP = Minor Use Permit, UP = Use Permit, - - - = Prohibited

ALLOWED USES See Definitions Section 28.10	Permit Requirements A-SM-80 & A-SM-160 Zoning Districts	Land Use Regulations See Section 28.70.10
D. OTHER RESIDENTIAL USES		
Home occupation, Type I	A	28.72.40(A) & (B)(2)
28.73 RECREATION, EDUCATION, AND PUBLIC ASSEMBLY USES		
A. RECREATION USES		
Marsh oriented recreation	UP	28.73.10(A) & (B)(1)
Public open space area	A	28.73.10(A)
Stable, public without Horse Shows	UP	28.73.10(A) & (B)(3)
B. EDUCATION USES		

Marsh Education	UP	28.73.20(A)
C. PUBLIC ASSEMBLY USES		
Special Events Facility (other than Winery or Agricultural Processing Facility)		
6 per year max, and 150 persons or less	AP	28.73.30(A) & (B)(6)
12 per year max, and 150 persons or less	MUP	28.73.30(A) & (B)(6)
More than 12 per year, or more than 150 persons	UP	28.73.30(A) & (B)(6)
28.74 RETAIL AND OFFICE USES		
A. RETAIL USES		
None Allowed		
B. OFFICE USES		
Agricultural research facility, Small	UP	28.74.20(A) & (B)(1)
Marsh research facility	UP	28.74.20(A)
28.75 TOURIST USES		
A. AGRITOURISM		
None Allowed		
B. TEMPORARY AGRITOURISM		
None Allowed		
28.76 COMMERCIAL SERVICE USES		
A. AGRICULTURAL SERVICES		
None Allowed		
B. COMMERCIAL SERVICES		
None Allowed		

Table 28.22A TABLE OF ALLOWED USES

A = Allowed by right, AP = Administrative Permit, MUP = Minor Use Permit, UP = Use Permit, - - - = Prohibited

ALLOWED USES See Definitions Section 28.10	Permit Requirements A-SM-80 & A-SM-160 Zoning Districts	Land Use Regulations See Section 28.70.10
28.77 INDUSTRIAL, MANUFACTURING, PROCESSING AND WHOLESALE USES		
A. INDUSTRIAL, MANUFACTURING AND PROCESSING USES		
None Allowed		
B. WHOLESALE USES		
None Allowed		
28.78 COMMUNICATION, INFRASTRUCTURE AND SERVICE USES		
A. COMMUNICATION USES		
Wireless communication facility		
Co-location	MUP	28.81
New tower	UP	28.81
B. INFRASTRUCTURE USES		
Commercial wind turbine generator	UP	28.80
Extraction and Removal of Minerals or Natural Materials from Quarries and Borrow Areas existing as of January 1, 1982	UP	28.78.20(A)
Non-commercial wind turbine		
100 feet or less in height	A	28.80
Over 100 feet in height	- - -	28.80
Oil or Gas Well(4)	AP	28.78.20(A) & (B)(7)
Pipeline, transmission, or distribution line, in R.O.W.	A	28.78.20(A) & (B)(8)
Utility facilities or infrastructure, outside of R.O.W.	UP	28.78.20(A) & (B)(9)
Waste disposal, processing, and composting	UP(5)	28.78.20(A) & (B)(3)
C. PUBLIC SERVICE USES		
Public Service Facility	UP	28.78.30(A) & (B)(4)
D. TEMPORARY CONSTRUCTION AND INFRASTRUCTURE		
Meteorological Tower, 100 feet or less in height	AP	28.78.20(A) & (B)(6)
Meteorological Tower, greater than 100 feet in height	MUP	28.78.20(A) & (B)(6)
28.79 RESOURCE CONSERVATION USES		
Conservation and Mitigation Bank	UP	28.79.10(A)

Notes:

1. Any development within the Suisun Marsh, as defined by Section 29114 of the Public Resources Code, shall be subject to obtaining a Marsh Development Permit pursuant to the Suisun Marsh Preservation Act of 1977, and as provided for in Section 28.104 of this Code.
2. Management of wetlands and agricultural operations, with emphasis on grain and hay crop production, pasture, grazing, and the growing of plants and natural feed important to wildlife habitat.
3. Buildings and uses clearly accessory or incidental to any permitted use located on the premises, including a one-family dwelling or a manufactured dwelling, barns, private stables, sheds, and other associated buildings.
4. Oil wells not permitted in the Suisun Marsh Primary and Secondary Management Areas.
5. During or subsequent to final closure of any waste disposal site, the Planning Commission may approve any beneficial reuse of the waste disposal site that (i) is compatible with the approved closure and/or post-closure plans for the site, (ii) would not be detrimental to existing or anticipated agricultural land uses in the vicinity, and (iii) would not subject occupants of the site, neighbors, or the environment, to risks associated with the wastes which have been disposed of at the site.

28.22.30 – Suisun Marsh Agricultural District Development Standards

Subdivision, new land uses, main buildings including primary and secondary dwellings, and alterations to existing land uses and buildings, shall be designed, constructed, and/or established in compliance with the applicable development standards delineated or referenced in Table 28-22B.

TABLE 28.22B

DEVELOPMENT STANDARDS FOR MAIN BUILDING, ACCESSORY STRUCTURES, AND USES

MAIN BUILDING, ACCESSORY STRUCTURES, AND USES	
Minimum Lot Area	ASM-80 = 80 acres
	ASM-160 = 160 acres
Setbacks	
Front	Thirty feet; except that buildings shall not be less than fifty feet from the centerline of the street, and unless otherwise indicated by building lines on the zoning maps.
Sides (each)	20 feet
Rear	25 feet
Between structures	10 feet
Height limit	Thirty-five feet; and as allowed by 28-93 Special regulations

OTHER STANDARDS	
Parking Requirements	Parking shall be provided in conformance with the parking standards in Section 28.94
Signs	All signs shall comply with the sign requirements in Section 28.96

28.23 Suisun Valley Agricultural Districts

Subsections

28.23.10 - Purpose of Section

The purpose of this Section is to preserve and enhance the environment and economy of the Suisun Valley as a rural agricultural community by maintaining the agricultural character, improving agricultural production and income, promoting agricultural products grown in Solano, and providing for agricultural tourist centers.

This Section lists the uses of land allowed within the Agriculture-Suisun Valley and the Agriculture Tourist Center zoning districts (ATC and ATC-NC) zoning districts as established by Section 28.13 (Districts Designated and Established). It also determines the type of land use approval required for each use, and provides general standards for site development.

28.23.11 - Purposes of Agriculture - Suisun Valley District

The majority of land within Suisun Valley is in agricultural use, producing grapes for wine, small grains, or other fruit crops. This farmland is essential to the Valley's agricultural economy and quality of life. The standards in this section maximize the viability of the family farm by allowing uses that support agriculture and excluding incompatible uses.

28.23.12 - Purposes of Agricultural Tourist Center Districts

Development of agricultural tourism is critical to the future viability of agriculture in Solano County. The standards in this section allow a variety of uses that will help foster small tourist-oriented centers within the Valley, help attract tourists, and provide additional opportunities to market local products

28.23.20 - Definitions Applicable only to the A-SV-20, ATC and ATC-NC DISTRICTS

Hotel.

Any building, portion of a building, or group of buildings containing six or more guest rooms designed, or intended to be used, let or hired out for transient accommodations. A hotel may include accessory uses, including commercial kitchens and dining facilities open to the public.

Retail Stores and Services:

Retail stores and services, businesses and professional offices providing convenience goods and services to serve a residential neighborhood or rural community, conducted entirely within a building or buildings on a single ownership where such building(s) or uses does not exceed one thousand five hundred square feet of floor area, unless referred to the Planning Commission by the Director of Resource Management for determination of consistency with the intent of the Agricultural Tourist Center (A-T-C and A-T-C-NC) districts.

Seasonal Sales Lots:

Seasonal sales lots, including pumpkin patches, Christmas tree lots and other similar sales events, where the sale of agriculturally related products is seasonal and/or tied to an annual holiday event.

Winery: An agricultural processing facility used for the commercial purpose of processing grapes, berries, or other fruit products, to produce wine or similar wine products. Processing includes wholesale sales, crushing, fermentation and refermentation, blending, bottling, packaging, storage, aging, handling, shipping, and receiving of such products. Includes related accessory uses such as: office, laboratory, wine tasting facilities, retail sales of wine and other agricultural products produced on the premises or off-site by the winery operator, retail sales of wine and agricultural related promotional and/or educational items, and winery tours.

Winery-Small: A winery with annual production less than 20,000 gallons per year, in bulk and bottles combined.

Winery-Medium: A winery with annual production between 20,000 and 100,000 gallons per year, in bulk and bottles combined.

Winery-Large: A winery with annual production greater than 100,000 gallons per year, in bulk and bottles combined.

28.23.30 Agriculture - Suisun Valley District Uses and Permit Requirements

A. Allowable uses: Table 28-23A identifies the land uses allowed by these Zoning Regulations in the Agriculture – Suisun Valley (A-SV) District, the Agriculture Tourist Center (ATC) District and the Agriculture Tourist Center – North Connector (ATC-NC) District, as well as, the land use permit required to establish each use. In addition to the land use permit required by Table 28-23A, special requirements may apply to certain uses (See Section 28.23.50). Where the last column of Table 28.23A (Land Use regulations) includes a section number, e.g. 28.70, the zoning regulations referenced apply to the use. Where the last column includes a chapter number, e.g. Chapter 13.6, the regulations in the referenced Solano County Code section apply to the use. Provisions contained in other sections of the Zoning Regulations may also apply.

B. **Building and Other Permits:** A building permit, as required under Chapter 6.3 of the County Code, and any other permits required by the County Code, shall also be required prior to any construction, demolition, or change of occupancy type.

C. **Design Review:** Design review, as described in Section 28-23.103 of the Solano County Zoning Regulations, shall be required for all new construction requiring a building permit within the Agriculture – Suisun Valley District and the Agriculture Tourist Center (ATC and ATC-NC) Districts. In carrying out the purposes of this Section, the Zoning Administrator or Planning Commission shall consider the Suisun Valley Design Guidelines as a manual for determining Architectural Approval.

TABLE 28-23A Table of Allowed Uses and Permit Requirements

A= Allowed by right, AP= Administrative Permit, MUP= Minor Use Permit, UP= Use Permit, E=Exempt, - - - = Prohibited

ALLOWED USES* *See Definitions Section 28-10	**A-SV-20**	**ATC**	**ATC-NC**	**Land Use Regulations**** **See Section 28-70.10
AGRICULTURAL USES				
Crop production, including orchards and vineyards	A	A	A	
Agricultural accessory structures	A	A	A	
Agricultural processing facility				
On-site products(1)	A	A	A	28.71.20(A) & (B)(1)
Off-Site product(2)	UP	UP	UP	28.71.20(A) & (B)(1)
With Special Events	UP			28.71.20(A) & (B)(1) & 28-23.50(A)(B)(C4)
Wineries				
Winery, small	A/UP[3,4]	A	A	*28.23.50.10*
Winery, medium	A/UP[3,4]	AP	AP	*28.23.50.10*
Winery. large	UP[5]	UP	UP	*28.23.50.10*
Animal facilities and operations				
Confined animal facility, including dairy	- - -	- - -	- - -	- - -
Fowl and Poultry Ranch	- - -	- - -	- - -	- - -
Pastured poultry and livestock	A/MUP	- - -	- - -	*28.23.50.10*
Grazing	A	- - -	- - -	
Slaughterhouse	- - -	- - -	- - -	- - -
Aquaculture	UP	- - -	- - -	28.71.20(A)
Auctions, agricultural equipment sales, temporary	AP/MUP	AP/MUP	AP/MUP	28.23.50.10
Conservation Bank	UP	- - -	- - -	28.79.10(A)
Nursery with public sales(6)	A	- - -	- - -	28.71.20(B)(3)
Temporary Agricultural office	AP	AP	AP	28.23.50.10
Wind turbine, non-commercial under 100 feet	A	A	A	*28.80*
Wind turbine, non-commercial over 100 feet	MUP	MUP	MUP	*28.80*

Notes:

1) Products originating on-site or off-site on land owned or leased by the operator within Solano County.

2) Products originating on land not owned or leased by the operator within Solano County.

3) At least twenty-five percent (25%) of the grapes or other fruit used in production, averaged over 5 consecutive years, must be grown on-site or off-site on land owned or leased by the operator within Solano County. If less than twenty-five percent (25%) of the grapes are sourced in this way, then a conditional use permit is required.

4) Six or fewer special events per year are allowed by right, with 150 or fewer guests per event. Otherwise, a Use Permit is required.

5) Special events as permitted with a large winery use permit.

6) No more than 1,500 square feet of non-plant inventory, indoor and outdoor combined, for display and sales to the general public shall be allowed.

7) Does not include a guest house.

TABLE 28-23A Table of Allowed Uses and Permit Requirements (continued)

A= Allowed by right, AP= Administrative Permit, MUP= Minor Use Permit, UP= Use Permit, E=Exempt, - - - = Prohibited

ALLOWED USES* *See Definitions Section 28-10				
	A-SV-20	**ATC**	**ATC-NC**	**Land Use Regulations**** **See Section 28-70.10
RESIDENTIAL USES				
Accessory buildings and uses(7)	A	A	A	28.72.10(A) & (B)(1)
Agricultural employee housing	AP	- - -	- - -	28.23.50.20
HCD Agricultural employee housing	AP	- - -	- - -	
Cottage Industry	UP	UP	- - -	28.72.40(A) & (B)(1)
Home occupation	A/AP	A/AP	- - -	28.72.40(A) & (B)(2)
Primary dwelling	A	AP	AP	28.72.10(A)
Secondary dwelling	A	- - -	- - -	28.23.50.20
Small Kennel or Cattery	AP	- - -	- - -	28.72.30(A) & (B)(3)
Stable, private (9 horses or less)	A	A	- - -	28.72.30(A) & (B)(5)
Storage, manufactured home (one per parcel)	A	A	- - -	28.23.70.40
Temporary Accommodations				
Security quarters for a business operation (commercial coach, manufactured home or recreational vehicle)	AP	AP	AP	28.23.50.20
Temporary single family home	UP	UP	- - -	28.23.70.30
Temporary storage of a mobile home	AP	AP	AP	28.23.50.20
Cannabis Cultivation				
Caregiver	AP	AP	AP	28.82
Personal				
Medical	A	A	A	28.82
Recreational	A	A	A	28.82

RECREATION, EDUCATION AND PUBLIC ASSEMBLY USES				
Agricultural education	A	A	A	28.73.20(A) & (B)(1)
Boating and swimming facility on existing waterways	- - -	UP	UP	28.73.10(A)
Hunting or fishing club	- - -	- - -	- - -	28.73.10(A) & (B)(1)
Limited Public Events	UP	UP	UP	28.23.50.30
Special Events	See Specific Use Regulations			28-23.50.50(A)(B)(C4)
Stable, public and horse show	- - -	- - -	- - -	---

TABLE 28-23A Table of Allowed Uses and Permit Requirements (continued)

A= Allowed by right, AP= Administrative Permit, MUP= Minor Use Permit, UP= Use Permit, E=Exempt, - - - = Prohibited

ALLOWED USES* *See Definitions Section 28-10				
	A-SV-20	**ATC**	**ATC-NC**	**Land Use Regulations**** **See Section 28-70.10
RETAIL TRADE USES				
Farm/Ranch Supply Store	- - -	A	A	*28.23.50.40*
Farm supplies and farm equipment sales	- - -	- - -	A	*28.23.50.40*
Neighborhood Commercial Use				*28.23.50.40*
1,500 square feet or less	- - -	A	A	*28.23.50.40*
Greater than 1,500 square feet	- - -	MUP	MUP	*28.23.50.40*
Roadside stand				
1,000 square feet or less in size	A	A	A	*28.23.50.40*
Between 1,000 and 2,500 square feet	AP	A	A	*28.23.50.40*
Greater than 2,500 square feet in size	UP	A	A	*28.23.50.40*
Non-agricultural product sales, less than 10%	A	A	A	*28.23.50.40*
Non-agricultural product sales, greater than 10%	UP	A	A	*28.23.50.40*
TOURIST USES				
Agricultural homestay	A	- - -	- - -	*28.23.50.50*
Agricultural homestay with special events	UP	- - -	- - -	*28.23.50.50*
Agritourism	A	A	A	*28.23.50.50*
Bakery/Cafe/Restaurant				
1,000 square feet or less in size	A	A	A	*28.23.50.50*
1,001 to 5,000 square feet	AP	A	A	*28.23.50.50*
5,001 or more square feet in size	UP	MUP	MUP	*28.23.50.50*
Bed and Breakfast Inn	AP	A	A	*28.23.50.50*
Gallery	AP	A	A	*28.23.50.50*
Hotel	- - -	A	A	*28.23.50.50*
Local products store	- - -	A	A	*28.23.50.50*
Resort Hotel	UP	UP	UP	*28.23.50.50*
Tasting Facility	AP	A	A	*28.23.50.50*
Temporary Agritourism				
Amusement and entertainment use	AP/MUP	AP/MUP	AP/MUP	28.23.50.50
Farmer's Market	AP/MUP	AP/MUP	AP/MUP	28.23.50.50
Seasonal sales lot	AP/MUP	AP/MUP	AP/MUP	28.23.50.50

TABLE 28-23A Table of Allowed Uses and Permit Requirements (continued)

A= Allowed by right, AP= Administrative Permit, MUP= Minor Use Permit, UP= Use Permit, E=Exempt, - - - = Prohibited

ALLOWED USES* *See Definitions Section 28-10				
	A-SV-20	**ATC**	**ATC-NC**	**Land Use Regulations**** **See Section 28-70.10
COMMERCIAL SERVICE USES				
Airfield or heliport, Agricultural	- - -	- - -	- - -	- - -
Commercial agricultural trucking service and facility	- - -	- - -	UP	28.76.10(A) & (B)(2)
Commercial custom farm services, e.g. hay bailing	UP	- - -	UP	28.76.10(A)
Commercial farm equipment fabrication and repair	UP	- - -	A	28.76.10(A)
Commercial storage and sale of agricultural service products(fertilizer/fuel)	UP	UP	A	28.76.10(A)
Large Kennel or Cattery	MUP	- - -	- - -	28.76.20(A) & (B)(2)
Veterinary facility	UP	UP	UP	28.76.10(A) & (B)(1)
COMMUNICATION AND INFRASTUCTURE USES				
Pipeline, transmission or distribution line in R.O.W.	A	A	A	28.78.20(A) & (B)(8)
Public service facility	UP	UP	UP	28.28.78.30(A) & (B)(4)
Refuse dumping, disposal, processing, composting(10)	UP	- - -	- - -	28.78.20(A) & (B)(3)
Surface mining operation	UP	UP	UP	28.78.20(A)
Wind turbine generator, commercial	- - -	- - -	- - -	
Temporary Construction and Infrastructure				
Construction office, storage and construction yard	AP	AP	AP	28.23.50.70
Utility facilities or infrastructure, outside of R.O.W.	UP	UP	UP	28.78.20(A) & (B)(9)
Wireless communication facility	UP	UP	UP	28.81
OTHER USES				

28.23.40 - General Development Standards

TABLE 28-23B Table of General Development Standards

Development Standards for Main Building, Primary and Secondary Dwelling			
	A-SV	**ATC**	**ATC-NC**
MAIN BUILDING, PRIMARY or SECONDARY DWELLING			
Dwelling Size	Minimum of 1,000 Square Feet		
Minimum Lot Area	Minimum area required for new parcels		
w/ water and sewer	20 acres	2,000 square feet	5,000 square feet
w/ water or sewer	20 acres	2.5 acres	2.5 acres
w/o water or sewer	20 acres	*5 acres*	5 acres
Floor Area Ratio	Maximum gross floor area for new dwellings		
w/ water and sewer	- - -	*0.5*	0.5
w/o water or sewer	- - -	*0.3*	0.3
Setbacks	Minimum Setbacks required. See Section 28-97 for setback measurement, allowed projections into setback and exceptions to setbacks.		
Front	30 feet, but at least 50 feet from the street centerline and unless otherwise indicated by building lines on the Zoning Maps.	None to 25 feet	10 to 25 feet maximum
Sides (each)	20 feet	None	15 feet on corner lot, none on interior lots
Rear	25 feet	None	15
Between structures	10 feet	None, except per building code	
Height limit	35 feet, and as allowed by 28-93 Special regulations and 28-93		
SECONDARY DWELLING			
Dwelling Size	Maximum of 1,800 Square Feet	None	N/A
Setbacks			
Front	30 feet, but at least 50 feet from the street centerline and unless otherwise indicated by building lines on the Zoning Maps	N/A	
Sides (each)	20 feet	N/A	
Rear	25 feet	N/A	
Between structures	10 feet		
Height limit	35 feet, and as allowed by 28-93 Special regulations		
Parking	As required by 28-94, Parking Requirements and the Suisun Valley Design Guidelines. Off-street parking requirements may be met through participation in a parking district that apportions off-site parking.		
Signs	See Section 28-96 Signs		

TABLE 28-23C Table of General Development Standards

Development Standards for Accessory Buildings[2]	A-SV	ATC	ATC-NC
ACCESSORY BUILDINGS			
Minimum Lot Area[1]	Minimum area required for new parcels		
w/ water and sewer	20 acres	2,000 square feet	5,000 square feet
w/ water or sewer	20 acres	2.5 acres	2.5 acres
w/o water or sewer	20 acres	5 acres	5 acres
Floor Area Ratio	Maximum gross floor area for new dwellings		
w/ water and sewer	- - -	0.5	0.5
w/o water or sewer	- - -	0.3	0.3
Setbacks[3]	Minimum Setbacks required. See Section 28-50(e) for setback measurement, allowed projections into setback and exceptions to setbacks.		
Attached	An accessory building attached to the main building shall comply with the setback requirements for the main building		
Detached			
Front	60 feet or on the rear 50% of the lot	None to 25 feet	10 to 25 feet
Sides (each)[4]	20 feet	None	15 feet on corner lots, none for interior lots
Rear[4]	20 feet	None	15 feet
Between structures[5]	10 feet from any dwelling or other main building on the same lot Stables: 20 feet from any dwelling or other main building on the same lot		
Height limit	35 feet, and as allowed by 28-93 Special regulations		
Parking	As required by 28-94, Parking Requirements		
Signs	See Section 28.96 Signs		

Notes:

(1) The actual number of parcels allowed is determined through the applicable subdivision process, based on specific site characteristics and potential environmental impacts, and there is no guarantee that the maximum possible number may be achieved.

(2) Does not include a secondary dwelling as defined in Section 28-01.

(3) Other setbacks may be required for specific uses listed in Table 28-23A, as referenced.

(4) The side or rear yard requirements may be waived for an accessory building other than an animal shelter, except that such building shall not be located closer to any side street line than the main building. Waiver of said requirements shall be subject to notice as set forth in Section 28.04(F) of this Chapter.

(5) Other separation between structures may be required by County Building Code.

28.23.50 - Special Uses Regulations:

28.23.50.10 - Agricultural Uses

A. Permit Required. Agricultural uses are permitted uses, subject to the permit requirements in 28-23A.

B. Standards Agricultural uses must meet the applicable development standards delineated in Tables 28-23B and 28-23C and comply with the following:

1. Auctions, Agricultural Equipment Sales

a. Permit Required. An administrative permit is required for auctions and agricultural equipment sales uses, provided any such use shall meet the standards delineated in Table 28-23B. Permits issued under this shall be for a fixed term not to exceed one year, unless otherwise specified in this section. In the event that an agritourism use cannot meet the standards in this section, then a minor use permit shall be required to alter any of the standards in (b) below.

b. Standards. Auctions and agricultural equipment sales in the A-SV-20 and A-T-C districts zoning district shall comply with the following standards:

1. Duration. Auctions and agricultural equipment sales shall be limited to one event, not to exceed seven days per event.

2. Access. Shall provide ingress and egress designed so as to avoid traffic congestion;

3. Roads. Shall be located on a public road or a private road if there is a recorded maintenance agreement executed by all lot owners served by the private road. All connections to County roads shall meet the encroachment permit requirements of the Director of Resource Management, which generally include, but shall not be limited to, paving of the connection within the County road right-of-way.

4. Hours of Operation. Shall be limited to 8:00am until 6:00 pm Mondays through Sunday

5. Prevent Offensive Noise, Dust, Glare, Vibration or Odor. Shall provide adequate controls or measures to prevent noise, dust, glare, vibration or odor.

2. Pastured Livestock

a. Permit Required. Pastured livestock operations are a permitted use, subject to the provisions below:

1. When a Permit Is Not Required. A pastured livestock operation is a permitted use when the parcel is located is located more than 1,320 feet from any lot in an (R) District, and meets the standards in (b) below are met.

2. **When a Minor Use Permit Is Required.** A pastured livestock operation is a permitted use upon approval of a minor use permit, if the parcel is located within 1,320 feet on any lot in an (R) District, and/or any of the standards in (b) below cannot be met.

b. Standards. Pastured livestock operations shall comply with the following general standards:

1. Manage storm water to prevent feed and manure from entering any natural or constructed storm water facility or creek, stream or river,

2. Maintain a setback of 200 feet from any (R) district parcel,

3. Manage supplemental feeds, manure, bedding and nesting materials to lessen any potential adverse impacts that the pastured livestock operation might have on neighbors or the larger community. Pastured livestock operators are required to submit to the Agricultural Commissioner, on an annual basis, a plan for the management of the operation which will provide policies and procedures for insuring that the pastured livestock operation is not likely to become a nuisance to surrounding property owners or the community and that no health and safety problems will arise due to its operation. The Plan should describe policies and procedures that:

(a) Regulate, control or prohibit the accumulation of manure.

(b) Prevent any accumulation of animal or vegetable matter in which fly larvae exist or any accumulation of filth or source of foulness hazardous to health or comfort of people

(c) Protect pollutants from entering in creeks, streams, drainage ditches or groundwater supplies.

(d) Prohibit any nuisance, offensive matter, foul or noxious odors.

(e) Provide adequate parking and circulation for the operation.

3. Pastured Poultry

a. Permit Required. Pastured poultry is a permitted use, subject to the provisions below:

1. **When a Permit Is Not Required.** A pastured poultry operation is a permitted use if the parcel is located more than 1,320 feet from any lot in an (R) District, and meets the standards in (b) below are met.

2. **When a Minor Use Permit Is Required.** A pastured poultry operation is a permitted use upon approval of a minor use permit, if the parcel is located

within 1,320 feet on any lot in an (R) District, and/or any of the standards in (b) below cannot be met.

3. **Exemptions.** Any minor raising fowl or a 4H or similar type of agricultural education program is exempt from these requirements.

b. Standards. Pastured poultry operations shall comply with the following general standards:

1. Manage storm water to prevent feed and manure from entering any natural or constructed storm water facility or creek, stream or river,

2. Maintain a setback of 200 feet from any (R) district parcel,

3. Employee best practices to ensure that stray birds do not trespass onto adjacent public rights-of-way or private lands.

4. Be limited to 3,000 birds or less,

5. Contain no more than 5 crowing fowl, and

6. Manage supplemental feeds, manure, bedding and nesting materials to lessen any potential adverse impacts that the pastured poultry operation might have on neighbors or the larger community. Pastured poultry operators are required to submit to the Agricultural Commissioner, on an annual basis, a plan for the management of the operation which will provide policies and procedures for insuring that the pastured poultry operation is not likely to become a nuisance to surrounding property owners or the community and that no health and safety problems will arise due to its operation. The Plan should describe policies and procedures that

   i. Regulate, control or prohibit the accumulation of manure.

   ii. Prevent any accumulation of animal or vegetable matter in which fly larvae exist or any accumulation of filth or source of foulness hazardous to health or comfort of people

   iii. Protect pollutants from entering in creeks, streams, drainage ditches or groundwater supplies.

   iv. Prohibit any nuisance, offensive matter, foul or noxious odors.

4. Temporary Agricultural Office

a. Permit Required. A commercial coach may be used as temporary agricultural offices, incidental to the commercial agricultural operation on the property, as permitted in Table 28-23A, subject to the standards below:

b. Standards.

1. Building permit required. No commercial coach shall be used as temporary agricultural offices without first securing a building permit from the County of Solano.

2. Only one commercial coach or vehicle shall be allowed on the site,

3. The commercial coach shall be either made permanent or removed upon the expiration of 24 months.

4. The commercial coach may not be used as a residence and shall meet all building setbacks applicable to permanent development on the parcel.

5. Wineries

a. Small winery. A small winery, as defined in Section 28-10, is allowed by right subject to compliance with the applicable development standards delineated in Tables 28-23B and 28-23C and as follows:

1. At least twenty-five percent (25%) of the grapes or other fruit used in production, averaged over 5 consecutive years, must be grown on-site or off-site on land owned or leased by the operator within Solano County.

2. The winery operator shall report at the end of each calendar year to the Department of Resource Management the total gallons of wine produced, in bulk and bottles combined, during the calendar year. Such reporting may alternatively include proof of payment of the annual license renewal fee to the Department of Alcoholic Beverage Control (ABC), including the dollar amount of the fee paid.

3. A conditional use permit is required for a small winery if less than 25% of the grapes or other fruit used in production are grown on-site or off-site on land owned or leased by the operator within Solano County.

4. Shall obtain Environmental Health Services Division, Department of Resource Management, and Fire Department approval, if required, prior to hosting special events.

5. Subject to (4) above, six or fewer special events, with 150 or fewer guests each, are permitted each calendar year at a small winery by right. A conditional use permit is required if more than six special events are offered at the facility in a calendar year or if any single event exceeds 150 guests.

6. A tasting facility is allowed by right, ancillary to the processing facility, and must be no larger than 1,000 square feet or 30 percent of the size of the processing facility, whichever is greater.

b. **Medium winery.** A medium winery, as defined in Section 28-10, is allowed by administrative permit, subject to compliance with the applicable development standards delineated in Tables 28-23B and 28-23C and as follows:

1. Shall obtain Environmental Health Services Division, Department of Resource Management, and Fire Department approval, if required, prior to hosting special events.

2. Subject to (1) above, six or fewer special events, with 150 guests or fewer each, are permitted each calendar year at a medium winery by right. A use permit is required if more than six special events are offered at the facility during a calendar year or if any single event exceeds 150 guests.

3. The winery operator shall report at the end of each calendar year to the Department of Resource Management the total gallons of wine produced, in bulk and bottles combined, during the calendar year. Such reporting may alternatively include proof of payment of the annual license renewal fee to the Department of Alcoholic Beverage Control (ABC), including the dollar amount of the fee paid.

4. A tasting facility is allowed by right, ancillary to the processing facility, and must be no larger than 2,000 square feet or 30 percent of the size of the processing facility, whichever is greater.

5. At least twenty-five percent (25%) of the grapes or other fruit used in production, averaged over 5 consecutive years, must be grown on-site or off-site on land owned or leased by the operator within Solano County. A use permit is required for a medium winery if less than 25% of the grapes or other fruit used in production are grown on-site or off-site on land owned or leased by the operator within Solano County.

c. **Large winery.** A use permit, subject to compliance with the applicable development standards delineated in Tables 28-23B and 28-23C. large winery, as defined in Section 28-10, is allowed with

1. A tasting facility is allowed by right, ancillary to the processing facility, and must be no larger than 2,000 square feet or 30 percent of the size of the processing facility, whichever is greater. Size shall be determined by measuring the total roof covered area.

2. The winery operator shall report at the end of each calendar year to the Department of Resource Management the total gallons of wine produced, in bulk and bottles combined, during the calendar year. Such reporting may alternatively include proof of payment of the annual license renewal fee to the Department of Alcoholic Beverage Control (ABC), including the dollar amount of the fee paid.

3. Shall obtain Environmental Health Services Division, Department of Resource Management, and Fire Department approval, if required, prior to hosting special events.

4. Subject to (3) above special events at large wineries are subject to the terms of the conditional use permit.

28.23.50.20 Residential Uses

A. Permit Required. Residential uses are permitted uses, subject to the permit requirements in Table 28-23A.

B. Standards. Residential uses must meet the applicable development standards delineated in Tables 28-23B and 28-23C and comply with the following:

1. Agricultural Employee Housing.

a. Permit Required. Agricultural employee housing is a permitted use upon approval of an administrative permit, provided it meets the standards in (b) below, otherwise a minor use permit is required.

b. Standards. A temporary manufactured dwelling unit for an employee on parcels of twenty (20) acres or more is permitted for a maximum five (5) year period upon approval of a conditional use permit and subject to the following conditions as well as the applicable development standards delineated in Tables 28-23B and 28-23C.

(1) One or more occupants of the dwelling are employed by the owner or the lessee of the parcel;

(2) Non-employee occupants of the dwelling are members of the employee's family;

(3) The employee occupant(s) of the dwelling has rent deducted from his or her wages; and

(4) The employee occupant is required to live in the dwelling as a condition of his or her employment.

2. Secondary Dwelling

a. Standards. A secondary dwelling, as permitted in Table 28-23A, must meet the following specific development standards as well as the development standards delineated in Table 28-23B.

(1) The maximum size of the secondary dwelling shall not exceed 1,800 square feet of gross floor area.

(2) A secondary dwelling may be a detached structure or may be attached to another building on the same lot. If attached to another building, a separate exterior entrance shall be provided, independent from the entrance for the building to which it is attached.

(3) A secondary dwelling shall not be allowed on a parcel that has a companion living unit or other similar accessory housing unit. It shall be allowed under the following conditions:

(a) Use of an existing dwelling while the replacement dwelling is under construction, in accordance with Section 28-72.20B6;

(b) Use of temporary dwelling while the primary dwelling is under construction, with a use permit;

(c) Agricultural employee housing or HCD agricultural employee housing, as permitted in Table 28-23A.

b. **Existing secondary dwellings, companion living units or guest houses.** Secondary dwellings, companion living units or guest house, existing:

(1) A secondary living unit legally existing on the lot prior to February 1, 2011, which does not comply with the size or setback requirements of this Section shall be considered legal non-conforming and subject to the provisions of Section 28-114 ("Nonconforming Uses"). Such use may continue, provided that it is not enlarged, increased or otherwise modified and fully complies with any conditions of approval that may have been adopted.

(2) A guest house legally existing on the lot prior to February 1, 2011, shall be considered legal non-conforming and subject to the provisions of Section 28-60 ("Nonconforming Uses"). Such a guest house may be converted to a secondary dwelling provided all of the following are met: (1) no other secondary dwelling is on the lot; (2) all facilities necessary to convert the structure to a dwelling, including cooking, sanitation, and parking facilities shall be installed in compliance with County building and zoning standards as applicable; (3) either the primary residence or the secondary dwelling is owner-occupied; and (4) if the structure does not meet the size or setback requirements of this Section for a secondary dwelling, it shall be considered legal non-conforming and subject to the provisions of Section 28-114 ("Nonconforming Uses").

(3) A companion living unit legally existing on the lot prior to February 1, 2011, pursuant to an approved conditional use permit, may be converted to a secondary dwelling provided all of the following are met: (1) no other secondary dwelling is on the lot; (2) the unit is installed on a foundation system as a fixture or improvement to the real property, in accordance with section 18551(a) of the Health and Safety Code and implementing regulations; (3) either the primary residence or the secondary dwelling is owner-occupied; and (4) if the unit does

not meet the size or setback requirements of this Section, it shall be considered legal non-conforming and subject to the provisions of Section 28-114 ("Nonconforming Uses"). If an existing companion living unit is converted to a secondary dwelling, the conditions of the use permit shall no longer be applicable. If an existing companion living unit is not converted to a secondary dwelling, it shall remain subject to the conditions of the use permit, and shall be promptly removed from the lot upon expiration or revocation of the permit.

(4) If both a secondary living unit and a companion living unit legally exist on the lot prior to June 13, 2008, the secondary living unit shall be considered the secondary dwelling on the lot and the companion living unit may continue on the lot as a temporary dwelling for the remaining term of the conditional use permit.

(5) **Additional Extensions.** A companion living unit legally existing on the lot prior to February 1, 2011, pursuant to an approved conditional use permit which expires, may be extended for a temporary period, not to exceed two years, upon securing a minor use permit, provided:

(a) All of the findings made in the original use permit still apply.

(b) The property owner and the occupant of the companion living unit have not changed since the original issuance of a use permit.

3. Temporary Dwellings and Accommodations

a. **General Development Standards.** All temporary accommodations shall comply with the standards in Tables 28.23B and Table 28.23C, as well as the standards in (b) and (c) below.

b. **Security Quarters for a Business Operation**

(1) **Permit Required.** Security quarters for a business operation may be established as permitted in Table 28-23A, subject to the standards below:

(2) **Standards.** Commercial coaches, manufactured homes or recreational vehicles may be maintained on a building site for use as a security guard or watchman's quarters during periods of construction of structures on the site, provided:

(a) Building permits have been issued for the construction of the structures,

(b) Only one security coach or vehicle shall be allowed on the site,

(c) The security coach or vehicle shall be removed upon completion of construction of the structures.

(d) The manufactured home or recreational vehicle may not be used as a residence and shall meet all building setbacks applicable to permanent development on the parcel.

(e) A recreational vehicle shall be connected to permanent power and utilities provided by the installation of an RV pad. The RV pad shall be removed at the completion of construction of the structures.

c. Temporary Dwellings

(1) Permit Required. Temporary dwellings may be temporarily allowed during the construction of a permanent dwelling as permitted in Table 28-23A, subject to the standards below:

(2) Standards. Temporary dwellings may be permitted subject to the standards below:

(a) Building permits have been issued for the construction of the permanent dwelling,

(b) The manufactured home shall meet all building setbacks applicable to permanent development on the parcel.

(c) The manufactured home shall be removed 60 days after final inspection of the permanent dwelling

d. Temporary Mobilehome Storage

(1) Permit Required. Storage of mobilehomes shall be allowed in the A-SV-20, A-T-C or A-T-C-NC districts upon issuance of an administrative permit by the Zoning Administrator; provided, the Zoning Administrator finds the conditions of this Section have been or will be met. A permit shall be issued upon submission of an application and payment of such fees as may be set by the Board of Supervisors pursuant to Section 11-111 of this code. The Zoning Administrator may require the submission of such information deemed necessary to make this determination, and may require the posting of security satisfactory to the Zoning Administrator to guarantee performance of any conditions.

(2) Standards. Storage of mobilehomes shall meet the standards below:

(a) The number of units stored shall be limited to one (1) per ownership.

(b) The term of a permit shall not exceed one (1) year. In no case shall more than two (2) six month time extensions be granted or a successive permit is issued.

(c) All utilities must be disconnected and remain disconnected from a stored mobilehome.

(d) All appurtenances shall be removed including skirting, decking, and awnings.

(e) A stored mobilehome shall not be occupied or otherwise utilized.

28.23.50.30 - Recreation, Education and Public Assembly Uses

A. Permit Required. Recreation, education and public assembly uses are permitted uses, subject to the permit requirements in Table 28-23A.

B. Standards. Recreation, education and public assembly uses must meet the applicable development standards delineated in Tables 28-23B and 28-23C and comply with the following:

1. Limited Public Events

a. Standards. Limited Public Events in the A-SV-20 and A-T-C districts zoning district shall comply with the following standards:

(1) Shall be limited to once per year,

(2) Shall not be open to the public for more than 10 weeks,

(3) Shall not cause significant adverse impacts to adjacent agricultural operations,

(4) Shall not operate on land which has been utilized for crop production within the past five years (operation on grazing land is acceptable), shall be limited to outdoor events (no fully enclosed structures or tents open to the public),

(5) Shall not utilize electric sound amplification systems, and shall require only minimal site alterations or permanent physical improvements.

(6) Upon termination, expiration, or revocation of the use permit, the site shall be fully restored to its original condition.

28.23.50.40 - Retail Trade Uses

A. Permit Required. Retail trade uses are permitted uses, subject to the permit requirements in Table 28-23A.

B. Standards. Retail Trade uses must meet the applicable development standards delineated in Tables 28-23B and 28-23C and comply with the following:

1. Retail stores and services,

a. Permit Required. Retail stores and services are permitted uses, subject to the provisions below:

(1) When a Permit Is Not Required. A permit is not required when the building area is 1,500 square feet or less.

(2) When a Minor Use Permit Is Required. A minor use permit is required when the building area exceeds 1,500 square feet.

b. Standards. Retail stores and services, as permitted in Table 28-23A, must meet the applicable development standards delineated in Tables 28-23B and 28-23C and comply with the following:

(1) Shall be conducted entirely within a building or buildings on a single ownership where such building(s) or uses does not exceed one thousand five hundred square feet of floor area, unless referred to the planning commission by the director of Resource Management for determination of consistency with the intent of ATC or ATC-NC districts.

(2) Shall provide adequate utilities, access roads, drainage and other necessary facilities.

c. Conditional Uses. Conditional uses, provided the conditions for a use permit and requirements set forth in Section 28-106 are fulfilled:

(1) Retail stores and services, businesses and professional offices providing convenience goods and services to serve a residential neighborhood or rural community conducted entirely within a building or buildings on a single ownership where such building(s) or use exceeds one thousand five hundred square feet of floor area, or where any yard area is utilized for the provision of goods and services regardless of the size of the building(s).

(2) Automobile service station and repair garage.

2. Roadside stand.

a. Standards. A roadside stand, as permitted in Table 28-23A, must meet the applicable development standards delineated in Tables 28-23B and 28-23C and comply with the following:

(1) Shall be operated by the property owner or occupant.

(2) Size, as regulated in Table 28-23A, shall be determined by measuring the total roof-covered area. Where a roadside stand is operated within a portion of a larger building, the roadside stand shall be functionally separated from the remainder of the building by either temporary or permanent walls and size shall be determined by measuring the gross floor area of the enclosed space plus any outdoor display area.

(3) At least twenty-five percent (25%) of the crops sold shall be grown on-site or off-site on land owned or leased by the operator within Solano County. The balance of the stand shall be used for the sale and inventory of crops or other agricultural products, including nonagricultural products as regulated by this Chapter, grown or produced on-site or off-site.

(4) An area not exceeding 50 square feet may be used for the sale and inventory of prepackaged food, provided that such food sales and inventory complies with the

requirements of the Department of Resource Management, Environmental Health Services Division, and is from an "approved source" and is not a "potentially hazardous food" as defined by the California Health and Safety Code.

(5) Nonagricultural product sales shall mean the on-site sales of nonagricultural products produced on and off the property, where the total inventory and sales area for such products is limited to a maximum percentage of the size of the stand, as specified in Table 28-23A, except that sales and inventory of prepackaged food shall be further subject to the requirements of subsection E.4.

(6) Minimum setback from an adjacent street shall be the same as required for the main building.

(7) Shall have ingress and egress designed so as to avoid traffic congestion and hazards. All connections to County roads shall meet the encroachment permit requirements of the Director of Resource Management, which generally include, but shall not be limited to, paving of the connection within the County road right-of-way.

(8) Shall provide adequate controls or measures to prevent dust, odor or light.

(9) Shall provide off-street parking in accordance with Section 28-55 in addition to paved parking spaces, aisles and pathways for the disabled in accordance with Building Code.

(10) Shall obtain Department of Resource Management, Environmental Health Services Division approval, if required, prior to operation.

28.23.50.50 - Tourist Uses

A. Permit Required. Tourist uses are permitted uses, subject to the permit requirements in Table 28-23A.

B. General Standards. Tourist uses must meet the applicable development standards delineated in Tables 28-23B and 28-23C and comply with the following:

1. Within the A-SV-20 District, tourist uses shall be operated by the property owner or occupant, subject to possession of a valid Solano County business license.

2. Minimum setback from an adjacent street shall be the same as required for the main building.

3. Shall have ingress and egress designed so as to avoid traffic congestion and hazards. All connections to County roads shall meet the encroachment permit requirements of the Director of Resource Management, which generally include, but shall not be limited to, paving of the connection within the County road right-of-way.

4. Shall provide off-street parking in accordance with Section 28-94 in addition to paved parking spaces, aisles and pathways for the disabled in accordance with the Building Code.

5. Shall obtain necessary approvals for sale of prepared food, including Department of Resource Management (if required) and Environmental Health Services Division approval prior to operation.

6. Shall obtain all necessary approvals with other County departments, if required, prior to operation.

7. Shall provide off-street parking in accordance with Section 28-94 in addition to paved parking spaces, aisles and pathways for the disabled in accordance with Building Code.

C. Standards for Specific Agritourism Uses.

1. **Bakeries, Cafés and Restaurants.** A bakery, café, or restaurant as permitted in Table-28-23A. Such uses must meet the applicable development standards contained in Tables 28-23 B and 28-23 C, conditions of Section 28.76.20B2, and comply with the following specific requirements:

   a. Shall be incidental to the principal agricultural use on the property in the Agriculture-Suisun Valley (A-SV) District.

2. **Galleries.** Such use must meet the applicable development standards delineated in Tables 28-23B and 28-23C and comply with the following specific requirements:

   a. Shall be incidental to the principal agricultural use on the property in the Agriculture-Suisun Valley (A-SV) District.

3. **Resort Hotel.** Resort Hotels may be permitted by conditional use permit. Such uses must meet the applicable development standards delineated in Tables 28-23B and 28-23C and all standards specified in the use permit.

4. **Special Events.** Special events may be permitted by conditional use permit, incidental to the principal agricultural use on the property, except as specified for small and medium wineries above. Such use must meet the applicable development standards delineated in Tables 28-23B and 28-23C.

5. **Marketing Events.** Marketing events are allowed by right, incidental to the principal agricultural use on the property. Such use must meet the applicable development standards delineated in Tables 28-23B and 28-23C.

6. **Bed and Breakfast Inn.** Bed and Breakfast Inns are allowed by right, incidental to the principal agricultural use on the property. Such use must meet the applicable development standards delineated in Tables 28-23B and 28-23C and comply with the following:

a. Signage shall be limited to one (1) non-illuminated wall-mounted sign not to exceed four (4) square feet in area.

b. Shall have no more than 10 guest rooms.

7. Tasting Facilities. Tasting facilities are allowed by right, incidental to a principal agricultural processing use or winery on the property. Such use must meet the applicable development standards delineated in Tables 28-23B and 28-23C and comply with the following:

a. Tasting facilities must be no larger than 2,000 square feet or 30 percent of the size of the processing facility, whichever is greater. Size shall be determined by measuring the total roof covered area.

b. Products tasted and sold must by produced on-site or off-site on land owned or leased by the operator within Solano County.

8. Local Products Store. Local Products Stores are provided by right, subject to compliance with the applicable development standards delineated in Table 28-23B.

9. Hotels. Hotels are permitted by right. Such use must meet the applicable development standards delineated in Table 28-23B and all standards specified in the use permit.

a. Shall have no more than 30 guest rooms.

10. Agricultural homestay. An agricultural homestay is subject to compliance with the applicable development standards delineated in Table 28-23B and the standards specified in this section (b) above and listed below:

a. Shall be restricted to one single family dwelling. No accessory structure shall be allowed for use as transient occupancy.

b. Shall be operated, maintained, and occupied by the property owner.

D. Standards for Temporary Agritourism

1. Permit Required. An administrative permit is required for agritourism uses, provided any such use shall meet the standards delineated in Table 28-23B. Permits issued under this shall be for a fixed term not to exceed one year, unless otherwise specified in this section. In the event that an agritourism use cannot meet the standards in this section, then a minor use permit shall be required to alter any of the standards in (2) below.

2. Standards.

a Amusement and Entertainment Uses

(1) Amusement activities may be conducted as permitted in Table 28-23A, subject to the standards below:

(a) Shall provide a minimum six foot solid board fence or masonry wall separating parking areas from abutting residential property; and,

(b) No amusement event where liquor is served shall be established on a lot closer than two hundred feet to any boundary of any residential district unless a use permit is first secured in each case.

b. Farmer's Market

(1) A Farmer's Market may be conducted as permitted in Table 28-23A, subject to the standards below:

(a) The Farmers Market shall be operated by the property owner or occupant.

(b) Only the producer or the producers' parents, children, grandparents and grandchildren or a relative regularly residing in the producer's household or an employee of the producer may sell the producer's products at the market. An employee is any person employed by the producer at a regular salary or wage, on either a full or part time basis. It does not include a person who is reselling or for whom show compensation is primarily based on a commission on sales. Proof of status of an employee is an authorized agreement proving that the person selling is an employee of the Qualified Seller. An employee may not sell for more than one Qualified Seller at a time.

(c) The sale and inventory of prepackaged food, provided that such food sales and inventory complies with the requirements of the Department of Resource Management, Environmental Health Services Division, and is from an "approved source" and is not a "potentially hazardous food" as defined by the California Health and Safety Code is permitted.

(d) Nonagricultural product sales shall mean the on-site sales of nonagricultural products produced on and off the property, where the total inventory and sales area for such products is limited to 10% of the total sales area.

(e) Minimum setback from an adjacent street shall be the same as required for the main building.

(f) Shall have ingress and egress designed so as to avoid traffic congestion and hazards. All connections to County roads shall meet the encroachment permit requirements of the Director of Resource Management, which generally include, but shall not be limited to, paving of the connection within the County road right-of-way.

(g) Shall provide adequate controls or measures to prevent dust, odor or light.

(h) Shall provide off-street parking in accordance with Section 28-94 in addition to paved parking spaces, aisles and pathways for the disabled in accordance with Building Code.

(i) Shall obtain Department of Resource Management, Environmental Health Services Division approval, if required, prior to operation.

c. Seasonal Sales Lots

(1) Seasonal sales events shall be operated such that:

(a) Adequate measures and controls shall be taken to prevent offensive noise, odors and dust, and,

(b) Shall have a minimum six-foot high, solid board fence or masonry wall separating the lot from abutting residential uses.

(c) Seasonal sales events are limited to one 60 day period annually, per seasonal event.

28.23.50.60 - Commercial Service Uses

A. Permit Required. Commercial service uses are permitted uses, subject to the permit requirements in Table 28-23A.

B. Standards. Commercial service uses must meet the applicable development standards delineated in Tables 28-23B and 28-23C and comply with the following:

1. Access. Commercial service uses shall provide ingress and egress designed so as to avoid traffic congestion;

2. Roads. Commercial service uses shall be located on a public road or a private road if there is a recorded maintenance agreement executed by all lot owners served by the private road. All connections to County roads shall meet the encroachment permit requirements of the Director of Resource Management, which generally include, but shall not be limited to, paving of the connection within the County road right-of-way.

3. Prevent Offensive Noise, Dust, Glare, Vibration or Odor. Commercial service uses shall provide adequate controls or measures to prevent noise, dust, glare, vibration or odor.

28.23.50.70 - Communication and Infrastructure Uses

A. Specific Requirements for Temporary Construction and Infrastructure projects

1. On-site Construction Office, Storage and Construction Yard

a. Standards. On-site construction offices, storage and construction yards while construction is being actively conducted pursuant to a valid building permit shall comply with the standards in Tables 28.23B and Table 28.23C, as well as the standards below.

(1) No Removal of Agricultural Uses. Facilities, temporary commercial coaches, construction yards for the storage of materials and/or construction vehicles shall not require the removal of productive agricultural uses of the land.

(2) Time Limits. On-site construction offices, storage and construction yards may be permitted for up to 24 months.

(3) Temporary Commercial Coach. A temporary commercial coach may be utilized on any construction site as an office. The commercial coach may not be used as a residence and shall meet all building setbacks applicable to permanent development on the parcel.

2. Off-Site Construction Office, Storage and Construction Yard

a. Standards. Off-site construction offices, storage and construction yards shall comply with the standards in Tables 28.23B and Table 28.23C, as well as the standards below.

(1) No Removal of Agricultural Uses. Facilities, temporary commercial coaches, construction yards for the storage of materials and/or construction vehicles shall not require the removal of productive agricultural uses of the land.

(2) Time Limits. Temporary construction and public infrastructure uses shall be permitted for up to 24 months, provided a public infrastructure project which is actively under construction in the vicinity.

(3) Temporary Commercial Coach. A temporary commercial coach may be utilized on any lot as a construction office for a public infrastructure project.

28.23.60 - Design Guidelines and Design Review

A. Purpose. The purpose of design review is to promote a quality rural character in new development for Suisun Valley and to unify the design and construction of individual neighborhood agricultural tourist centers into the existing agriculturally-focused context.

B. Design Review Process. Design review is required for any new construction in the A-SV-20, A-T-C and A-T-C-NC Districts and shall follow the process described below:

1. **Preliminary Plan Review.** Applicants should contact the Resource Management Department to schedule a preliminary application meeting to clarify the County approval process for their particular project and discuss the Design Guidelines as adopted by resolution of the Board of Supervisors.

2. **Final Design Review.** Based upon the type of permitting required for the project, design review permits will be issued according the provisions of either (a) or (b), as described below:

   a. **Discretionary Permits.** When a project requires a discretionary permit, including any rezoning, use permit, sign permit or variance, Design Review will be approved by the hearing authority as a part of the discretionary permit. The hearing authority shall consider recommendations from staff in its decision. The adopted Design Guidelines and any other established standards shall provide the basis for final approvals.

   b. **Non-discretionary permits.** When a project requires a non-discretionary permit, such as an administrative permit or building permit, then the Director of Resource Management, or his or her designee, shall take action administratively on the design review within 10 days of filing of the non-discretionary permit. The Director shall consider recommendations from staff along with the adopted Design Guidelines and any other established standards shall provide the basis for final approvals.

C. Design Guidelines. The Suisun Valley design Guidelines (Chapter 4 of the Suisun Valley Strategic Plan) shall serve as the guidelines for the design review of all new construction in the A-SV-20, A-T-C and A-T-C-NC Districts.

D. Action by the Hearing Authority. The hearing authority shall take action to approve, conditionally approve or deny the design review within 10 days of the filing of a complete application for design review. If the hearing authority denies a Design Review Permit, then the hearing authority shall provide the applicant with written descriptions of any development proposal design features in a form that constitutes recommended modifications to the project in order to clearly provide the applicant an understanding of the desired changes that would obtain an approval from the hearing authority.

E. Findings. The hearing authority shall make the following findings prior to taking action to approve, or conditionally approve design review. The hearing authority finds that:

1. the project conforms to the Suisun Valley Design Guidelines,

2. the project will maintain and enhance the Valley's agricultural character.

3. the project will maintain, enhance, or restore natural features.

4. the project will preserve the indigenous landscape and rural character.

5. the project will enhance quality of life and economic vitality.

6. the project will enhance the community brand and destination marketing the Valley.

7. the project will ensure the highest quality new construction.

8. the project will minimize site disturbance.

9. the project will preserve views of natural and cultural features.

10. the project will ensure compatibility of new projects with natural and rural landscapes.

F. **Approval.** Design Review approval shall remain valid for a period of one year after which the approval shall lapse and become null and void. The issuance of a building permit shall constitute an extension of the Design Review approval which shall remain valid during the time period the building permit is considered active.

G. **Occupancy.** No structure which has received Design Review approval shall be occupied or used in any manner or receive a certificate of occupancy until the Resource Management Department has inspected and determined that the structure(s) and site development comply with the Development Review approval.

H. **Appeals.** Appeal from any finding or action by the Director of Resource Management or the Planning Commission, unless otherwise provided for in this Division, shall be made pursuant to Section 28-112.

I. **Amendments.** Amendments or changes to existing plans: It shall be at the discretion of the Director of Resource Management to make a determination whether the proposed change or amendment constitutes a significant change requiring additional Design Review. In cases where such changes are determined to be minor in nature, the proposed changes shall be subject to administrative review and approval by the Director of Resource Management for compliance with the adopted Design Guidelines.

J. **Submittal Requirements.** All applications for Design Review shall be submitted to the Resource Management Department on forms approved by the Director of Resource Management and the Director shall establish written application instructions describing the type and size of drawings and other materials required for submittal.

K. **Fees.** Fees for design review shall be established by the Board of supervisors pursuant to Section 11-110.4 of the County Code.

28.24 (Reserved)

28.30 Residential Districts

Subsections:

28.31. Rural Residential (R-R) Districts

Subsections:

28.31.10 Rural Residential Districts

This Section includes regulations for the RR-2.5, RR-5 and RR-10 zoning districts.

28.31.11 Purpose of Rural Residential Districts

This Section lists the uses of land that may be allowed within rural residential areas of the County represented by the Rural Residential (R-R) zoning districts. It also determines the type of land use approval required for each use within each district, and provides general standards for site development.

Rural Residential zoning is applied to areas appropriate for rural, low density, single-family homes, where agriculture is not the sole land use and commercial agricultural production capability is low, where self-sufficiency and privacy are desirable and only minimal essential public services and facilities are available. Homesites are to be self-sufficient, with individual wells and individual septic systems. Water may be supplied by a public water system, operated by a public agency, in areas where water from individual wells may be of marginal quantity or quality.

Rural Residential is to be applied in a manner that preserves rural character and scenic qualities and protects sensitive resources including agricultural lands, creeks, native trees, open spaces and views. Rural Residential zoning shall not be applied to agricultural lands, or to areas with a high risk of wild fires, landslides, or flooding. Rural Residential zoning is consistent with and implements the Rural Residential land use designation of the General Plan. The three Rural Residential zoning districts are differentiated primarily by density classifications that correspond to potential agricultural productivity and the types of public services required for each district, as follows:

District	Minimum Parcel Size	Land Features	Services Required
R-R 2½	2.5 acres	Non-productive	Public water supply and individual private sewage disposal systems
R-R 5	5 acres	Non-productive	Private water wells and individual private sewage disposal systems
R-R 10	10 acres	Low capability for agricultural production	Private water wells and individual private sewage disposal systems

28.31.20 – Rural Residential District Land Uses and Permit Requirements

A. Allowed Uses and Permit Requirements:

Table 28-31A identifies the land uses allowed by this Zoning Ordinance in each rural residential district and the land use permit required to establish each use. In addition to the land use permit required by Table 28-31A, special requirements may apply to certain uses.

B. Architectural Review:

Architectural Approval may be required for certain uses in compliance with Section 28.102 (Architectural Approval).

C. Building Permits:

A Building Permit shall be required prior to any construction.

D. Special Use Regulations:

Where the last column in Table 28.31A ("Land Use Regulations") includes a section number, e.g. 28.70.10, the zoning regulations in the referenced section apply to the use. Where the last column includes a chapter number, e.g. Chapter 13.6, the regulations in the referenced Solano County Code apply to the use. Provisions in other sections of this Zoning Ordinance may also apply.

TABLE 28.31A TABLE OF ALLOWED USES

A= Allowed by right, AP= Administrative Permit, MUP= Minor Use Permit, UP= Use Permit, E=Exempt,

- - - = Prohibited

ALLOWED USES* *See Definitions Section 28-10	**Permitted Uses**			**Land Use Regulations**** **See Section 28-70.10
	RR-2.5	**RR-5**	**RR-10**	
28.71 AGRICULTURAL USES				
A. CROP PRODUCTION AND GRAZING				
Cultivated and irrigated farming	A	A	A	28.71.10(B)(1)
Non-irrigated and non-cultivated farming	A	A	A	28.71.10(B)(1)
B. AGRICULTURAL PROCESSING USES				
None Allowed	- - -	- - -	- - -	
C. ANIMAL FACILITIES AND OPERATIONS				
None Allowed	- - -	- - -	- - -	
D. OTHER AGRICULTURAL OPERATIONS				
None Allowed	- - -	- - -	- - -	

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ALLOWED USES* *See Definitions Section 28-10	**Permitted Uses**			**Land Use Regulations**** **See Section 28-70.10**
	RR-2.5	**RR-5**	**RR-10**	
28.72 RESIDENTIAL USES				
A. DWELLINGS				
Accessory buildings and uses (1)				
Accessory building greater than 2,500 square feet in size(4)	MUP	MUP	MUP	28.72.10(A) & (B)(1)
Accessory buildings, in aggregate: 1) greater than 2,500 square feet in size combined on a lot 4 acres or less; or, 2) greater than 5,000 square feet in size combined on a lot greater than 4 acres (2)	MUP	MUP	MUP	28.72.10(A) & (B)(1)
Guest house	- - -	- - -	- - -	
Primary dwelling	A	A	A	28.72.10 (A)
Rooming and boarding of not more than 3 persons per dwelling unit	A	A	A	28.72.10(A)
Secondary dwelling	A	A	A	28.72.10(A) & (B)(6)
Transitional Housing/Supportive Housing (4)	A	A	A	
Cannabis Cultivation				
Caregiver	AP	AP	AP	28.82
Personal				
Medical	A	A	A	28.82
Recreational	A	A	A	28.82
B. TEMPORARY RESIDENTIAL USES				
Temporary manufactured home storage	AP	AP	AP	28.72.20(A) & (B)(4)
Temporary occupancy of existing dwelling while replacement dwelling is under construction	A	A	A	28.70.20(B)(5)
Temporary single-family dwelling (3)	MUP	MUP	MUP	28.72.20(B)(6)
C. AGRICULTURAL AND ANIMAL FACILITIES INCIDENTAL TO A RESIDENCE				
Grazing or keeping of animals other than hogs, not	A	A	A	28.72.30(A) & (B)(1)

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ALLOWED USES* *See Definitions Section 28-10	**Permitted Uses**			**Land Use Regulations**** **See Section 28-70.10
	RR-2.5	**RR-5**	**RR-10**	
28.72 RESIDENTIAL USES				
exceeding two animal units per net acre of ownership				
Hog raising	A	A	A	28.72.30(A) & (B)(2)
Small animal husbandry	A	A	A	28.72.30(A) & (B)(4)
Kennel or cattery, small	MUP	MUP	MUP	28.72.30(A) & (B)(3)
Stable, private	A	A	A	28.72.30(A) & (B)(5)
D. OTHER RESIDENTIAL USES				
Cottage Industry				
Type I	MUP	MUP	MUP	28.72.40(A).& (B)(1)
Type II	UP	UP	UP	28.72.40(A) & (B)(1)
Home occupation				
Type I	A	A	A	28.72.40(A) & (B)(2)
Type II	AP	AP	AP	28.72.40(A) & (B)(2)
Temporary subdivision sales office	MUP	MUP	MUP	28.72.40(A) & (B)(4)

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ALLOWED USES* *See Definitions Section 28-10	**Permitted Uses**			**Land Use Regulations**** **See Section 28-70.10
	RR-2.5	**RR-5**	**RR-10**	
28.73 RECREATION, EDUCATION AND PUBLIC ASSEMBLY USES				
A. RECREATION USES				
None Allowed	- - -	- - -	- - -	
B. EDUCATION USES				
None Allowed	- - -	- - -	- - -	
C. PUBLIC ASSEMBLY USES				
Church	MUP	MUP	MUP	28.73.30(A) & (B)(1)
Nursery school	MUP	MUP	MUP	28.73.30(A)
Nursing home, rest home	MUP	MUP	MUP	28.73.30(A)
Public Stable with horse show	MUP	MUP	MUP	28.73.30(A) & (B)(5)
28.74 RETAIL AND OFFICE USES				
A. RETAIL USES				
Bulk storage and sales of hay crops other than those produced on the premises	MUP	MUP	MUP	28.74.10(A)
Roadside stand for sales of agricultural crop products grown or produced on the premises	A	A	A	28.74.10(A) & (B)(8)
B. OFFICE USES				
None Allowed	- - -	- - -	- - -	
28.75 TOURIST USES				
C. AGRITOURISM				
None Allowed	- - -	- - -	- - -	
D. TEMPORARY AGRITOURISM				
None Allowed	- - -	- - -	- - -	

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ALLOWED USES* *See Definitions Section 28-10	**Permitted Uses**			**Land Use Regulations**** **See Section 28-70.10
	RR-2.5	**RR-5**	**RR-10**	
28.76 COMMERCIAL SERVICE USES				
A. AGRICULTURAL SERVICES				
None Allowed	- - -	- - -	- - -	
B. COMMERCIAL SERVICES				
Kennel or Cattery, Large	MUP	MUP	MUP	28.76.20(A) & (B)(2)
28.77 INDUSTRIAL, MANUFACTURING, PROCESSING AND WHOLESALE USES				
A. INDUSTRIAL, MANUFACTURING AND PROCESSING USES				
None Allowed	- - -	- - -	- - -	
B. WHOLESALE USES				
None Allowed	- - -	- - -	- - -	

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ALLOWED USES* *See Definitions Section 28-10	**Permitted Uses**			**Land Use Regulations**** **See Section 28-70.10
	RR-2.5	**RR-5**	**RR-10**	
28.78 COMMUNICATION, INFRASTUCTURE AND PUBLIC SERVICE USES				
A. COMMUNICATION USES				
Wireless communication facility				
Co-location	MUP	MUP	MUP	
New tower	UP	UP	UP	
B. INFRASTRUCTURE USES				
Commercial wind turbine generator	- - -	- - -	- - -	
Non-commercial wind turbine				28.80
100 feet or less in height	A	A	A	28.80
Over 100 feet in height	MUP	MUP	MUP	28.80
Oil or Gas Well	UP	UP	UP	28.78.20(A) & (B)(7)
Pipeline, transmission or distribution line in R.O.W.	A	A	A	28.78.20(A) & (B)(8)
Utility facilities or infrastructure, outside of R.O.W.	UP	UP	UP	28.78.20(A) & (B)(9)
C. TEMPORARY CONSTRUCTION AND INFRASTRUCTURE				
Meteorological Tower, 100 feet or less in height	AP	AP	AP	28.78.20(A) & (B)(6)
Meteorological Tower, greater than 100 feet in height	MUP	MUP	MUP	28.78.20(A) & (B)(6)
D. PUBLIC SERVICE USES				
Cemetery	UP	UP	UP	28.78.30(A) & (B)(1)
Community care facility	UP	UP	UP	28.78.30(A) & (B)(2)
Hospital or sanitarium	UP	UP	UP	28.78.30(A) & (B)(3)
Public Service Facility	UP	UP	UP	28.78.30(A) & (B)(4)
28.79 RESOURCE CONSERVATION USES				
None Allowed	- - -	- - -	- - -	

A= Allowed by right, AP= Administrative Permit, MUP= Minor Use Permit, UP= Use Permit, E=Exempt,

- - - = Prohibited

ALLOWED USES* *See Definitions Section 28-10	**Permitted Uses**			**Land Use Regulations**** **See Section 28-70.10
	RR-2.5	**RR-5**	**RR-10**	
28.78 COMMUNICATION, INFRASTUCTURE AND PUBLIC SERVICE USES				

Notes:

(1) Accessory building:

a) Does not include a guest house.

b) May be established prior to construction or installation of a dwelling on the same property.

(2) Use permit approval is required by the Zoning Administrator only, unless otherwise referred to the Planning Commission by the Zoning Administrator. Aggregate square footage shall include all accessory buildings, except as follows:

a) Any structure used for the keeping of animals, such as a stable or corral, or for crop storage, which is unenclosed with an open side and no flooring, shall not require a use permit and shall not be counted as part of the aggregate total for accessory buildings.

b) Any structure 120 square feet in size or less and exempt from the permit requirements of County Building Code shall not be counted as part of the aggregate total for accessory buildings.

(3) Allowed only when the primary dwelling is under construction, and the temporary dwelling is installed on a temporary foundation.

(4) These land uses are subject to the same restrictions on residential uses contained in the same type of structure.

28.31.030 Rural Residential Districts General Development Standards

A. General site and building standards. Subdivision, new land uses, main buildings inclusive of primary dwellings, secondary dwellings, and alterations to existing land uses and buildings, shall be designed, constructed, and/or established in compliance with the applicable development standards delineated or referenced in Table 28-31B.

TABLE 28-31B

Development Standards for Main Building[(1)] and Secondary Dwelling

Development Feature	Requirement by Zoning District		
	R-R 2-1/2	R-R 5	R-R 10
Minimum Lot Area[(2)]	*Minimum area required for new lots*		
	2-1/2 acres	5 acres	10 acres
Minimum Lot Frontage	*Minimum frontage required for new lots*		
Lot (typical)	40 feet	40 feet	40 feet
Flag lot or cul-de-sac[(3)]	30 feet	30 feet	30 feet
Dwelling Size	*Minimum or maximum gross floor area for new dwellings*		
Primary dwelling	1,000 square feet minimum		
Secondary dwelling	See Section 28.72.10 B.8		
Setbacks[(4)]	*Minimum setbacks required. See Section 28-97 for setback measurement, allowed projections into setbacks, and exceptions.*		
Front	30 feet, and 50 feet from the street centerline, unless otherwise indicated by building lines on the Zoning Map.		
Sides (each)	10 feet		
Rear	25 feet		
Between structures[(5)]	10 feet		

TABLE 28-31B - Continued **Development Standards for Main Building[(1)] and Secondary Dwelling**			
Development Feature	Requirement by Zoning District		
	R-R 2-1/2	R-R 5	R-R 10
Height limit	*Maximum allowed height of structures. See also: Sect. 28-80 (wind turbine generators), Sect. 28-93 (height exceptions), and Sect. 28-99 (Airport Flight Obstruction Areas)*		
	35 feet		
Parking	As required by Section 28-94 ("Parking Requirements") and Section 28-102 ("Architectural Approval")		
Signs	See Section 28.96 ("Signs")		

Notes:

(1) In any R district, the primary dwelling shall be deemed the main building on the building site.

(2) The following may be used to determine acceptable lot area:

a) The actual number of lots allowed is determined through the applicable subdivision process, based on specific site characteristics and potential environmental impacts, and there is no guarantee that the maximum possible number may be achieved.

b) The area bounded by the centerline of the right-of-way on which the lot fronts, and the lot sidelines extended to such right-of-way centerline may be included in the computation of the minimum lot area requirement.

c) Reduced lot area may be allowed for specific uses with a use permit, see Section 28-97.

(3) For flag lot requirements, see Subdivision Ordinance Section 26-72.2. The required minimum lot frontage for a flag lot shall be measured along the access strip frontage, and no flag lot shall have an access strip less than 30 feet or more than 40 feet in width at any point.

(4) Other setbacks may be required for specific uses listed in Table 28-31A, as referenced.

(5) Other separation between structures may be required by County Building Code.

B. Accessory buildings and structures. New accessory buildings and other structures, including alterations to existing accessory buildings and other structures, shall be designed, constructed, and/or established in compliance with the applicable development standards in Table 28-31C.

TABLE 28-31C

Development Standards for Accessory Buildings[(1)]

Development Feature	Requirement by Zoning District		
	R-R 2-1/2	R-R 5	R-R 10
Setbacks[(2)]	*Minimum setbacks required. See Section 28-93 for setback measurement, allowed projections into setbacks, and exceptions. See also: Section 28-72.10B1 (Regulations for accessory buildings)*		
Attached	An accessory building attached to the main building shall comply with the setback requirements for the main building.		
Detached			
Front	60 feet or on the rear 50% of the lot, 60 feet for private stables		
Side (each)[(3)]	10 feet, 20 feet for private stables		
Rear	10 feet, 20 feet for private stables		
Between structures[(4)]	10 feet from any dwelling or other main building on the same lot Stables: 20 feet from any dwelling or other main building on the same lot		
Height limit	*Maximum allowed height of structures. See also: Sect. 28-93 (height exceptions), and Sect. 28.99 (Airport Flight Obstruction Areas)*		
	35 feet, and as allowed by 28-93 Special regulations		
Parking	As required by Section 28-94 ("Parking Requirements") and Section 28-102 ("Architectural Approval")		
Signs	See Section 28.96 ("Signs")		

Notes:

(1) Does not include a secondary dwelling as defined in Section 28-01.

(2) Other setbacks may be required for specific uses listed in Table 28-31A, as referenced.

(3) The side or rear yard requirements may be waived for an accessory building other than an animal shelter, except that such building shall not be located closer to any side street line than the main building. Waiver of said requirements shall be subject to notice as set forth in Section 28-04(F) of this Chapter.

(4) Other separation between structures may be required by County Building Code.

28.32 Residential--Traditional Community Districts

Subsections:

28.32.10 – Residential–Traditional Community Districts

This Section includes regulations for the following zoning districts
A. Residential – Traditional Community (R-TC) Districts
B. Residential – Traditional Community Mixed Use (R-TC-MU) Districts

28.32.11 – Purpose of Residential–Traditional Community Districts

This Section lists the uses of land that may be allowed within the traditional community residential areas of the County represented by the Residential–Traditional Community (R-TC) zoning districts. It also determines the type of land use approval required for each use within each district, and provides general standards for site development.

Residential–Traditional Community districts recognize current residential and mixed-use communities located outside agricultural or municipal service areas where previous development has occurred at higher densities or intensities than currently allowed under County policy. It is the intent to preserve and enhance the character and quality of these communities and promote future infill residential and mixed use development but not to expand the area of these communities.

The R-TC Districts replace the following previous districts:

R-TC-1AC replaces RE-1;
R-TC-20 replaces RE-1/2
R-TC-15 replaces RE-1/3
R-TC-10 replaces RE-1/4
R-TC-6 replaces R-S-6
R-TC-5 replaces R-S-5
R-TC-D-4 replaces R-D (Starr Subdivision)
R-TC-D-6 replaces R-D (Homeacres)
R-TC-MF replaces R-M

The purpose of the different residential – traditional community zoning districts and the manner in which they are applied are as follows:

A. Residential–Traditional Community (R-TC) Districts

The R-TC zoning districts are intended for areas that have previously been subdivided for single family residential development and provide the community services appurtenant thereto. The regulations for these districts are designed to stabilize and protect the residential characteristics of the districts, to promote and encourage a suitable environment for family life. Nine R-TC zoning districts are denoted with a suffix to indicate the minimum parcel size (e.g. R-TC-4 requires a minimum parcel size of 4,000 square feet), minimum building setbacks, and other requirements. The R-TC zoning districts are consistent with and implement the Traditional Community - Residential land use designation of the General Plan as follows:

Birds Landing	R-TC-1AC
Collinsville Township	R-TC-4
Cordelia area	R-TC-15
Elmira area	R-TC-1AC and R-TC-20
Fairfield Unincorporated area	R-TC-1AC, R-TC-20, R-TC-10 and R-TC-D
Green Valley area	R-TC-1AC, R-TC-20, and R-TC-15
Rockville Corners	R-TC-1AC
Snug Harbor area	R-TC-10
Vallejo Unincorporated area	R-TC-20, R-TC-10, R-TC-6, R-TC-5, R-TC-D & R-TC-MF
Willotta Oaks area	R-TC-15, R-TC-10

B. Residential–Traditional Community Mixed Use (R-TC-MU) Districts

The Residential -Traditional Community Mixed Use (R-TC-MU) zoning district is intended for certain medium-density residential and retail commercial and business areas that are appropriate for residential and commercial uses, and that can be served by community services. The regulations for this district are designed to stabilize and protect the essential residential characteristics of the district, to promote and encourage a suitable environment for family life and to provide for the integration of retail shops and businesses into the neighborhood. The R-TC-MU zoning district is consistent with and implements the Traditional Community-Mixed Use land use designation of the General Plan as follows:

Vallejo Unincorporated Area	R-TC-MU
Birds Landing Area	R-TC-MU
Cordelia area	R-TC-MU
Elmira area	R-TC-MU

28.32.20 Residential--Traditional Community District Land Uses and Permit Requirements

A. Allowed Uses and Permit Requirements

Tables 28-32A and 28-32A1 identifies the land uses allowed by this Zoning Ordinance in each residential-traditional community district and the land use permit required to establish

each use. In addition to the land use permit required by Tables 28-32A and 28-32B, special requirements may apply to certain uses.

B. Marsh Development Permit Requirements

Any development within the Suisun Marsh, as defined by Section 29114 of the Public Resources Code, shall be subject to obtaining a Marsh Development Permit, pursuant to the Suisun Marsh Preservation Act of 1977 and as provided for in Section 28.104 of this Code. When a land use subject to a marsh development permit is proposed in both the Primary Management Area and Secondary Management Area as defined in the Suisun Marsh Preservation Act of 1977, the land use shall be subject to a use permit covering the whole of the project.

C. Architectural Review

Architectural Approval may be required for certain uses, in compliance with Section 28.102 (Architectural Approval).

D. Building Permits

A Building Permit shall be required prior to any construction.

E. Land Use Regulations

Where the last column in Table 28.32A or 28.32B (Land Use Regulations) includes a section number, e.g. 28.70.10, the zoning regulations in the referenced section apply to the use. Where the last column includes a chapter number, e.g. Chapter 13.6, the regulations in the referenced Solano County Code apply to the use. Provisions in other sections of this Zoning Ordinance may also apply.

F. Non-Conforming Uses.

Within the Suisun Marsh, as defined by Section 29101 of the Public Resources Code, uses established prior to 1977 that do not conform to the uses set forth in Table 28.32B shall be considered nonconforming uses under Section 28.114, except that non-substantial changes, alterations, and additions to nonconforming uses may be allowed within the existing established project footprint area subject to a marsh development permit, pursuant to the Suisun Marsh Preservation Act of 1977 and as provided for in Section 28.104 of this Code. The overall existing development area may not be expanded under these provisions. Development within the existing development area should minimize additional impervious surfaces. An adequate buffer should be established or maintained between the development areas and any water, wetlands, or other Marsh habitat to protect the habitat from adverse environmental impacts. An erosion, sediment, and runoff control plan shall be prepared in accordance with Section 31.26(b) of the Solano County Grading, Drainage, Land Leveling and Erosion Control Ordinance. When the non-conforming uses is located in both the Primary Management Area and Secondary Management Area, as defined by the Suisun

Marsh Preservation Act of 1977, non-substantial changes, alterations, and additions to the nonconforming use shall be subject to a use permit covering the whole of the project.

G. Site Development and Other Standards

All uses shall comply with the provisions of Article IV, Section 28-90 Site Development and Other Standards which includes standards for parking, signs and other project elements.

TABLE 28.32A ALLOWED USES: R-TC-1AC, R-TC-20, R-TC-15, R-TC-10, R-TC-6 DISTRICTS

A= Allowed by right, AP= Administrative Permit, MUP= Minor Use Permit, UP= Use Permit, E=Exempt,

- - - = Prohibited

ALLOWED USES* *See Definitions Section 28-10	**Permitted Uses**					**Land Use Regulations**** **See Section 28-70.10**
	R-TC-1AC	**R-TC-20**	**R-TC-15**	**R-TC-10**	**R-TC-6**	
AGRICULTURAL USES						
A. CROP PRODUCTION						
Cultivated and irrigated farming	A	A	A	A	- - -	
Non-irrigated and non-cultivated farming	A	A	A	A	- - -	
RESIDENTIAL USES						
A. DWELLINGS						
Accessory buildings and uses[1]						28.72.10 (A) & (B)(1)
Accessory building greater than 2,500 square feet in size[2]	A	A	A	A	A	28.72.10 (A) & (B)(1)
Accessory buildings, aggregate: 1) greater than 2,500 square feet in size combined on a lot 4 acres or less; or, 2) greater than 5,000 square feet in size combined on a lot greater than 4 acres[2]	MUP	MUP	MUP	MUP	MUP	28.72.10 (A) & (B)(1)
Duplex	- - -	- - -	- - -	- - -	- - -	28.72.10(A)
Dwelling group	- - -	- - -	- - -	- - -	- - -	28.72.10 (A) & (B)(2)
Guest house	- - -	- - -	- - -	- - -	- - -	28.72.10 (A) & (B)(6)
Multifamily Dwelling	- - -	- - -	- - -	- - -	- - -	28.72.10(A)
Primary dwelling	A	A	A	A	A	28.72.10(A)
Rooming and boarding house	- - -	- - -	- - -	- - -	- - -	
Secondary dwelling	A	A	A	A	A	28.72.10 (A) & (B)(6).
Second kitchen	AP	AP	AP	AP	AP	28.72.10 (A) & (B)(7)
Transitional Housing/Supportive Housing [5]	A	A	A	A	A	
Cannabis Cultivation						
Caregiver	AP	AP	AP	AP	AP	28.82
Personal						
Medical	A	A	A	A	A	28.82
Recreational	A	A	A	A	A	28.82

A= Allowed by right, AP= Administrative Permit, MUP= Minor Use Permit, UP= Use Permit, E=Exempt,

- - - = Prohibited

ALLOWED USES* *See Definitions Section 28-10	**Permitted Uses**					**Land Use Regulations**** **See Section 28-70.10
	R-TC-1AC	**R-TC-20**	**R-TC-15**	**R-TC-10**	**R-TC-6**	
B. TEMPORARY RESIDENTIAL USES						
Temporary emergency dwelling	AP	AP	AP	AP	AP	28.72.20 (A) & (B)(3)
Temporary manufactured home storage	AP	AP	AP	AP	AP	28.72.20 (A) & (B)(4)
Temporary occupancy of existing dwelling while replacement dwelling is under construction	AP	AP	AP	AP	AP	28.72.20 (A) & (B)(5)
Temporary single-family dwelling [3]	AP	AP	AP	AP	AP	28.72.20 (A) & (B)(6)
C. AGRICULTURAL AND ANIMAL FACILITIES INCIDENTAL TO A RESIDENCE						
Grazing or keeping of animals, not exceeding two animal units per net acre of ownership, excepting an animal feed yard, which shall not be allowed	A	A	A	A	- - -	28.72.30 (A) & (B)(1)
Small animal husbandry	A	A	A	A	- - -	28.72.30 (A) & (B)(4)
Stable, private	A	A	A	A	- - -	28.72.30 (A) & (B)(5)
D. OTHER RESIDENTIAL USES						
Home occupation						
Type I	A	A	A	A	A	28.72.40 (A) & (B)(2)
Type II	AP	AP	AP	AP	AP	28.72.40 (A) & (B)(2)
Temporary subdivision sales office	MUP	MUP	MUP	MUP	MUP	28.72.40 (A) & (B)(3)

A= Allowed by right, AP= Administrative Permit, MUP= Minor Use Permit, UP= Use Permit, E=Exempt,

- - - = Prohibited

ALLOWED USES* *See Definitions Section 28-10	**Permitted Uses**					**Land Use Regulations**** **See Section 28-70.10**
	R-TC-1AC	**R-TC-20**	**R-TC-15**	**R-TC-10**	**R-TC-6**	
RECREATION, EDUCATION AND PUBLIC ASSEMBLY USES [2]						
A. RECREATION USES						
None Allowed						
B. EDUCATION USES						
None Allowed						
C. PUBLIC ASSEMBLY USES						
Church	- - -	UP	UP	UP	UP	28.73.30 (A) & (B)(1)
Club, lodge, or fraternal organization	- - -	- - -	- - -	- - -	- - -	28.73.30 (A) & (B)(2)
Nursery school	- - -	MUP	MUP	MUP	MUP	
Nursing home, rest home	- - -	MUP	MUP	MUP	MUP	
RETAIL AND OFFICE USES						
A. RETAIL USES						
Automobile parking lot [(4)]	UP	UP	UP	UP	UP	28.78.10 (A) & (B)(2)
B. OFFICE USES						
None Allowed						

A= Allowed by right, AP= Administrative Permit, MUP= Minor Use Permit, UP= Use Permit, E=Exempt,

- - - = Prohibited

ALLOWED USES* *See Definitions Section 28-10	**Permitted Uses**					**Land Use Regulations**** **See Section 28-70.10
	R-TC-1AC	**R-TC-20**	**R-TC-15**	**R-TC-10**	**R-TC-6**	
TOURIST USES						
None Allowed						
COMMERCIAL SERVICE USES						
None Allowed						
INDUSTRIAL, MANUFACTURING, PROCESSING AND WHOLESALE USES						
None Allowed						

A= Allowed by right, AP= Administrative Permit, MUP= Minor Use Permit, UP= Use Permit, E=Exempt,

- - - = Prohibited

ALLOWED USES* *See Definitions Section 28-10	**Permitted Uses**					**Land Use Regulations**** **See Section 28-70.10**
	R-TC-1AC	**R-TC-20**	**R-TC-15**	**R-TC-10**	**R-TC-6**	
COMMUNICATION, INFRASTRUCTURE AND SERVICE USES						
A. COMMUNICATION USES						
Wireless communication facility						
Co-location	MUP	MUP	MUP	MUP	MUP	See Section 28.81
New tower	UP	UP	UP	UP	UP	See Section 28.81
B. INFRASTRUCTURE USES						
Pipeline, transmission, or distribution line, in R.O.W.	A	A	A	A	A	28.78.20 (A) &(B)(8)
Utility facilities or infrastructure, outside of R.O.W.	MUP	MUP	MUP	MUP	MUP	28.78.20 (A)& (B)(9)
C. SERVICE USES						
Community care facility	UP	UP	UP	UP	UP	28.78.30 (A) & (B)(2)
Public Service Facility	UP	UP	UP	UP	UP	28.78.30 (A) & (B)(4)
D. TEMPORARY CONSTRUCTION AND INFRASTRUCTURE USES						
None Allowed	- - -	- - -	- - -	- - -	- - -	
RESOURCE CONSERVATION USES						
None Allowed	- - -	- - -	- - -	- - -	- - -	

Notes:

(1) Accessory building:
a) Does not include a guest house
b) May be established prior to construction or installation of a dwelling on the same property.

(2) Use permit approval is required by the Zoning Administrator only, unless otherwise referred to the Planning Commission by the Zoning Administrator. Aggregate square footage shall include all accessory buildings, except as follows:
a) Any structure used for the keeping of animals, such as a stable or corral, or for crop storage, which is unenclosed with an open side and no flooring, shall not required a use permit and shall not be counted as part of the aggregate total for accessory buildings
b) Any structure 120 square fee in size or less and exempt from the permit requirements of County Building Code shall not be counted as part of the aggregate total for accessory buildings.

(3) Allowed only when the primary dwelling is under construction, and the temporary dwelling is installed on a temporary foundation.

(4) An automobile parking lot must be adjacent to any C or M District.

(5) These land uses are subject to the same restrictions on residential uses contained in the same type of structure.

Table 28.32B ALLOWED USES: R-TC-5, R-TC-4 R-TC-D, R-TC-MF, R-TC-MU DISTRICTS

A= Allowed by right, AP= Administrative Permit, MUP= Minor Use Permit, UP= Use Permit, E=Exempt,

- - - = Prohibited

ALLOWED USES* *See Definitions Section 28-10	**Permitted Uses**						**Land Use Regulations**** **See Section 28-70.10
	R-TC-5	**R-TC-4[(1)]**	**R-TC-D-4**	**R-TC-D-6**	**R-TC-MF**	**R-TC-MU**	
AGRICULTURAL USES							
A. CROP PRODUCTION							
Cultivated and irrigated farming	- - -	- - -	- - -	- - -	- - -	- - -	
Non-irrigated and non-cultivated farming	- - -	- - -	- - -	- - -	- - -	- - -	
RESIDENTIAL USES							
A. DWELLINGS							
Accessory buildings and uses[(2)]							28.72.10 (A) & (B)(1)
Accessory building greater than 2,500 square feet in size[(3)]	A	A	A	A	A	A	28.72.10 (A) & (B)(1)
Accessory buildings, aggregate: 1) greater than 2,500 square feet in size combined on a lot 4 acres or less; or, 2) greater than 5,000 square feet in size combined on a lot greater than 4 acres[(3)]	MUP	MUP	MUP	MUP	MUP	MUP	28.72.10 (A) & (B)(1)
Duplex	- - -	- - -	A	A	A	- - -	28.72.10(A)
Dwelling group	- - -	- - -	- - -	- - -	A	- - -	28.72.10(A) & (B)(1)
Guest house	- - -	- - -	- - -	- - -	- - -	- - -	
Multifamily Dwelling	- - -	- - -	- - -	- - -	A	A	28.72.10(A)
Primary dwelling	A	A	A	A	A	A	28.72.10(A)
Rooming and boarding house	- - -	- - -	- - -	- - -	A		28.72.10(A)
Secondary dwelling	A	A	- - -	- - -	- - -	- - -	28.72.10(A) & (B)(6)
Second kitchen	AP	AP	- - -	- - -	- - -	- - -	28.72.10(A) & (B)(7)
Single Room Occupancy Hotel	---	---	---	---	A	---	
Cannabis Cultivation							
Caregiver	AP	AP	AP	AP	AP	AP	28.82
Personal							
Medical	A	A	A	A	A	A	28.82
Recreational	A	A	A	A	A	A	28.82

A= Allowed by right, AP= Administrative Permit, MUP= Minor Use Permit, UP= Use Permit, E=Exempt,

- - - = Prohibited

ALLOWED USES* *See Definitions Section 28-10	**Permitted Uses**						**Land Use Regulations**** **See Section 28-70.10
	R-TC-5	**R-TC-4(1)**	**R-TC-D-4**	**R-TC-D-6**	**R-TC-MF**	**R-TC-MU**	
B. TEMPORARY RESIDENTIAL USES							
Temporary emergency dwelling	AP	AP	AP	AP	AP	AP	28.72.20(A) & (B)(3)
Temporary manufactured home storage	AP	AP	AP	AP	- - -	- - -	28.72.20(A) & (B)(4)
Temporary occupancy of existing dwelling while replacement dwelling is under construction	AP	AP	AP	AP	AP	A	28.72.20(A) & (B)(5)
Temporary single-family dwelling (4)	AP	AP	AP	AP	- - -	AP	28.72.20(A) & (B)(6)
C. AGRICULTURAL AND ANIMAL FACILITIES INCIDENTAL TO A RESIDENCE							
Grazing or keeping of animals, not exceeding two animal units per net acre of ownership, excepting an animal feed yard, which shall not be allowed	- - -	- - -	- - -	- - -	- - -	- - -	28.72.30(A) & (B)(1)
Small animal husbandry	- - -	- - -	- - -	- - -	- - -	- - -	28.72.30(A) & (B)(4)
Stable, private	- - -	- - -	- - -	- - -	- - -	- - -	28.72.30(A) & (B)(5)
D. OTHER RESIDENTIAL USES							
Home occupation							
Type I	A	A	A	A	A	A	28.72.40(A) & (B)(2)
Type II	AP	AP	AP	AP	AP	AP	28.72.40(A) & (B)(2)
Temporary subdivision sales office	MUP	MUP	MUP	MUP	MUP	- - -	28.72.40(A) & (B)(3)

A= Allowed by right, AP= Administrative Permit, MUP= Minor Use Permit, UP= Use Permit, E=Exempt,

- - - = Prohibited

ALLOWED USES* *See Definitions Section 28-10	**Permitted Uses**						**Land Use Regulations**** **See Section 28-70.10
	R-TC-5	**R-TC-4(1)**	**R-TC-D-4**	**R-TC-D-6**	**R-TC-MF**	**R-TC-MU**	
RECREATION, EDUCATION AND PUBLIC ASSEMBLY USES [2]							
A. RECREATION USES							
None Allowed							
B. EDUCATION USES							
None Allowed							
C. PUBLIC ASSEMBLY USES							
Church	UP	- - -	UP	UP	UP	UP	28.73.30 (A) & (B)(1)
Club, lodge, or fraternal organization	- - -	- - -	- - -	- - -	UP	UP	28.73.30 (A) & (B)(2)
Nursery school	MUP	- - -	MUP	MUP	MUP	MUP	28.73.30 (A)
Nursing home, rest home	MUP	- - -	MUP	MUP	MUP	MUP	28.73.30 (A)
School						MUP	28.73.30 (A)
RETAIL AND OFFICE USES							
A. RETAIL USES							
Automobile parking lot [5]	MUP	- - -	MUP	MUP	MUP	A	28.74.10 (A) & (B)(2)
Automobile Repair Garage	- - -	- - -	- - -	- - -	- - -	MUP	28.74.10 (A) & (B)(3)
Automobile Service Station	- - -	- - -	- - -	- - -	- - -	MUP	28.74.10 (A)
Indoor merchandise showroom	- - -	- - -	- - -	- - -	- - -	MUP	28.74.10 (A)
Mortuary, funeral home	- - -	- - -	- - -	- - -	- - -	MUP	28.74.10 (A)
Neighborhood Commercial Use							
Less than 1,500 square feet	- - -	- - -	- - -	- - -	- - -	MUP	28.74.10 (A)
More than 1,500 square feet	- - -	- - -	- - -	- - -	- - -	MUP	28.74.10 (A)
Outdoor sales and service	- - -	- - -	- - -	- - -	- - -	MUP	28.74.10 (A)
Serving Liquor within 200 feet of an R-District	- - -	- - -	- - -	- - -	- - -	MUP	28.74.10 (A)
B. OFFICE USES							
Bank	- - -	- - -	- - -	- - -	- - -	MUP	28.74.20 (A)
Business and Professional Office	- - -	- - -	- - -	- - -	- - -	MUP	28.74.20 (A)
Medical and dental clinic or laboratory	- - -	- - -	- - -	- - -	- - -	MUP	28.74.20 (A)

A= Allowed by right, AP= Administrative Permit, MUP= Minor Use Permit, UP= Use Permit, E=Exempt,

- - - = Prohibited

ALLOWED USES* *See Definitions Section 28-10	**Permitted Uses**						**Land Use Regulations**** **See Section 28-70.10
	R-TC-5	**R-TC-4(1)**	**R-TC-D-4**	**R-TC-D-6**	**R-TC-MF**	**R-TC-MU**	
TOURIST USES							
None Allowed							
COMMERCIAL SERVICE USES							
None Allowed							
INDUSTRIAL, MANUFACTURING, PROCESSING AND WHOLESALE USES							
None Allowed							

A= Allowed by right, AP= Administrative Permit, MUP= Minor Use Permit, UP= Use Permit, E=Exempt,

- - - = Prohibited

ALLOWED USES* *See Definitions Section 28-10	**Permitted Uses**						**Land Use Regulations**** **See Section 28-70.10
	R-TC-5	**R-TC-4(1)**	**R-TC-D-4**	**R-TC-D-6**	**R-TC-MF**	**R-TC-MU**	
COMMUNICATION, INFRASTRUCTURE AND SERVICE USES							
A. COMMUNICATION USES							
Wireless communication facility							
Co-location	MUP	MUP	MUP	MUP	MUP	MUP	See Section 28.81
New tower	UP	UP	UP	UP	UP	UP	See Section 28.81
B. INFRASTRUCTURE USES							
Pipeline, transmission, or distribution line, in R.O.W.	A	A	A	A	A	A	28.78.20 (A) & (B)(8)
Utility facilities or infrastructure, outside of R.O.W.	UP	UP	UP	UP	UP	UP	28.78.20 (A) & (B)(9)
C. SERVICE USES							
Community care facility	UP	- - -	UP	UP	UP	UP	28.78.30 (A) & (B)(2)
Public Service Facility	UP	- - -	UP	UP	UP	UP	28.78.30 (A) & (B)(4)
D. TEMPORARY CONSTRUCTION AND INFRASTRUCTURE USES							
None Allowed							
RESOURCE CONSERVATION USES							
None Allowed							

Notes:

(1) Any development within the Suisun Marsh, as defined by Section 29114 of the Public Resources Code, shall be subject to obtaining a Marsh Development Permit, pursuant to the Suisun Marsh Preservation Act of 1977 and as provided for in Section 28.104 of this Code.

(2) Accessory building:
a) Does not include a guest house
b) May be established prior to construction or installation of a dwelling on the same property.

(3) Use permit approval is required by the Zoning Administrator only, unless otherwise referred to the Planning Commission by the Zoning Administrator. Aggregate square footage shall include all accessory buildings, except as follows:

a) Any structure used for the keeping of animals, such as a stable or corral, or for crop storage, which is unenclosed with an open side and no flooring, shall not required a use permit and shall not be counted as part of the aggregate total for accessory buildings
b) Any structure 120 square fee in size or less and exempt from the permit requirements of County Building Code shall not be counted as part of the aggregate total for accessory buildings.

(4) Allowed only when the primary dwelling is under construction, and the temporary dwelling is installed on a temporary foundation.

(5) An automobile parking lot must be adjacent to any C or M District.

(6) These land uses are subject to the same restrictions on residential uses contained in the same type of structure.

28.32.40 Residential - Traditional Community District General Development Standards

A. General site and building standards.

Subdivision, new land uses, main buildings inclusive of primary dwellings, secondary dwellings, and alterations to existing land uses and buildings, shall be designed, constructed, and/or established in compliance with the applicable development standards delineated or referenced in Tables 28-32C.

TABLE 28-32C
Development Standards for Main Building [(1)] and Secondary Dwelling

Development Feature	Requirement by Zoning District									
	R-TC-1AC	R-TC-20	R-TC-15	R-TC-10	R-TC-6	R-TC-5	R-TC-D-4	R-TC-D-6	R-TC-MF	R-TC-MU
Minimum Lot Area [(2)]	*Minimum area required for new lots*									
	1 acre	20,000 s.f.	15,000 s.f.	10,000 s.f.	6,000 s.f.	5,000 s.f.	4,000 s.f.[(3)]	6,000 s.f.[(3)]	5,000 s.f.	4.000 s.f.
Dwelling Size	*Minimum or maximum gross floor area for new dwellings*									
Primary dwelling	1,000 square feet minimum									
Secondary dwelling	850 square feet maximum. See Section 28.72.10.A.1. & B.10.						NA			
Setbacks [(4)]	*Minimum setbacks required. See Section 28-50(e) for setback measurement, allowed projections into setbacks, and exceptions.*									
Front	20 feet [(5)]				20 feet [(6)]	0 feet[(6)]	20 feet[(6)]		30 feet[(6)]	0 feet[(6)]
Sides (each)	10 feet					5 feet			10 feet	5 feet
Sides (combined)	N/A				15 feet	10 feet			20 feet	10 feet
Rear	25 feet				20% of lot depth, not exceeding 25 feet, and no less than 15 feet	0 feet	20% of lot depth, not exceeding 25 feet, and no less than 15 feet		15 feet	0 feet
Between structures[(7)]	10 feet						10 feet between single family dwelling on the same lot when placed side-by-side and 20 feet between such buildings placed in any other manner		10 feet	10 feet between single family dwelling on the same lot when placed side-by-side and 20 feet between such buildings placed in any other manner

Height limit	*Maximum allowed height of structures.* *See Section 28.93 (height exceptions) and Section 28-99 (Airport Flight Obstruction Areas)*		
	35 feet	50 feet	35 feet
Parking	As required by Section 28-94 (Parking Requirements) and Section 28-102 (Architectural Approval)		

Notes:

(1) In any R district, the primary dwelling shall be deemed the main building on the building site on which the same is situated.

(2) The following may be used to determine acceptable lot area:

a) The actual number of lots allowed is determined through the applicable subdivision process, based on specific site characteristics and potential environmental impacts, and there is no guarantee that the maximum possible number may be achieved.

b) Reduced lot area may be allowed with a use permit for specific uses permitted by zoning district, see Section 28-97.

(3) A duplex or up to two single family dwellings in any arrangement is allowed on a lot in the R-TC-D -4 District when a minimum of 2,000 sq. ft. of land area is provided for each one family dwelling or a minimum of 2,000 sq. ft. of land area is provided for each duplex unit.

A duplex or up to two single family dwellings in any arrangement is allowed on a lot in the R-TC-D -6 District when a minimum of 3,000 sq. ft. of land area is provided for each one family dwelling or a minimum of 3,000 sq. ft. of land area is provided for each duplex unit. An allowed second single family dwelling shall be deemed to be a second main building and not a secondary dwelling or accessory building.

(4) Other setbacks may be required for specific uses listed in Table 28-32A and 28-32B, as referenced.

(5) Exception: buildings shall be not less than 50 feet from the centerline of the street, and unless otherwise indicated by building lines on the zoning maps.

(6) Exception: unless otherwise indicated by building lines shown on the zoning maps.

(7) Other separation between structures may be required by County Building Code.

B. Accessory Buildings and Structures Development Standards.

New accessory buildings and other structures including alternations to existing accessory buildings and other structures, shall be designed, constructed, and/or established in compliance with the applicable development standards in Tables 28-32D.

TABLE 28-32D

Development Standards for Accessory Buildings and Structures [(1)]

Development Feature	Requirement by Zoning District									
	R-TC-1AC	R-TC-20	R-TC-15	R-TC-10	R-TC-6	R-TC-5		R-TC-D	R-TC-MF	R-TC-MU
Setbacks [(2)]	*Minimum setbacks required. See Section 28.90 for setback measurement, allowed projections into setbacks, and exceptions. See also: Section 28.72.10 A.1. & B.1. (Accessory buildings and uses, residential)*									
Attached	An accessory building attached to the main building shall comply with the setback requirements for the main building.									
Detached	60 feet or on the rear 50% of the lot									
Front				60 feet for private stables						
Sides (each) [(3)]	10 feet			10 feet, 20 feet for private stables	5 feet				10 feet	5 feet
Sides (combined)	N/A				15 feet	10 feet			20 feet	10 feet
Rear [(3)]	10 feet			10 feet, 20 feet for private stables	10 feet	0 feet	10 feet			0 feet
Between structures [(4)]	10 feet from any dwelling or other main building on the same lot									
				Stables 20 feet from any dwelling or other main building on the same lot						
Site coverage (maximum)	In a required rear setback for the main building: the aggregate total of all accessory buildings shall not occupy more than 30% of the required rear setback area for the main building.									
Height limit	*Maximum allowed height of structures. See Section 28.93 (height exceptions) and Section 28-99 (Airport Flight Obstruction Areas)*									
	15 feet									
Parking	As required by Section 28-94 (Parking Requirements) and Section 28.72.10.A.1.									

SIGNS	See Section 28.96 (Signs)

Notes:

(1) Does not include a secondary dwelling as defined in Section 28.01.

(2) Other setbacks may be required for specific uses listed in Table 28-32A and 28-32B, as referenced.

(3) The side or rear yard requirements may be waived for an accessory building other than an animal shelter, except that: (a) such building shall not be located closer to any side street line than the main building; and, (b) such buildings in the aggregate shall not exceed the maximum site coverage in the rear yard for the main building. Waiver of said requirements shall be subject to provisions set forth in Section 28.102 and notice as set forth in Section 28.04(F) of this Chapter.

(4) Other separation between structures may be required by County Building Code.

28.40 Commercial and Industrial Districts

Sections:

28.41. Commercial (C) Districts

Subsections:
28.32.10 - Purpose of Section
28.32.11 – Purpose of Commercial Districts
28.32.20 – Commercial Districts Land Uses and Permit requirements
28.32.30 – Commercial District Development Standards

28.41.10 Commercial District(s)

This Section includes regulations for the following zoning districts

A. Highway Commercial (C-H) District

B. Neighborhood Commercial (C-N) District

C. Commercial Recreation (C-R) District

D. Commercial Recreation – Limited (C-R-L)

E. Commercial-Service (C-S) District

F. Commercial-Office (C-O) District

28.41.11 Purpose of Commercial Districts

This Section lists the uses of land that may be allowed within the areas of the County designated for commercial land uses. It also determines the type of land use approval required for each use within each district, and provides general standards for site development.

The purposes of the different commercial zoning districts are as follows:

A. Highway Commercial (C-H) District

The C-H districts are intended for commercial uses to serve the highway traveler. The bulk of highway frontage throughout the County is not appropriate for commercial uses but is reserved for exclusive agricultural uses, and is so zoned. C-H districts are to be established in areas of four acres or larger, and shall be located only where need is clearly indicated.

B. Neighborhood Commercial (C-N) District

The C-N district is designed to provide an area for a limited number of small retail and service establishments to provide for businesses serving the daily needs of nearby residential neighborhoods or rural community. The intent of this district is to promote convenience shopping goods and services for nearby residents and not for patrons outside the community to be served. Uses established shall be found compatible and developed with standards that prevent significant adverse impacts on land uses adjoining the C-N districts.

C. Commercial Recreation (C-R) District

The C-R zoning district is intended to provide appropriate commercial recreation uses that support recreational activities and resource based recreational uses within the County in a manner compatible with surrounding land uses. The C-R zoning district is consistent with the commercial recreation designations of the General Plan outside the Suisun Marsh management area.

D. Commercial Recreation- Limited (C-R-L) District

The C-R-L zoning district is intended to provide for limited commercial recreational uses adjacent to the Suisun Marsh compatible with its protection. The C-R-L zoning district is consistent with the Commercial Recreation land use designation of the General Plan within the Secondary Management Area of the Suisun Marsh.

E. Commercial Service (C-S) District

The C-S district is designed to provide an area for commercial services of an extensive or heavy nature in support of industrial, construction, or other business activities.

F. Business and Professional Office (C-O) District

The C-O district is designated primarily to provide an area for business and professional offices.

28.41.20 Commercial District(s) Land Uses and Permit Requirements

A. Allowed Uses and Permit Requirements

Table 28.41A identifies the land uses allowed by this Zoning Ordinance in each commercial zoning district and the land use permit required to establish each use. In addition to the land use permit required by Table 28.41A, special requirements may apply to certain uses.

B. Marsh Development Permit Requirements

Any development within the Suisun Marsh, as defined by Section 29114 of the Public Resources Code, shall be subject to obtaining a Marsh Development Permit pursuant to the Suisun Marsh Preservation Act of 1977 and as provided for in Section 28.104 of this Code. When a land use subject to a marsh development permit is proposed in both the Primary Management Area and Secondary Management Area, as defined in the Suisun Marsh Preservation Act of 1977, the land use shall be subject to a use permit covering the whole of the project.

C. Architectural Review

Architectural Approval may be required for certain uses, in compliance with Section 28.102 (Architectural Approval).

D. Building Permits

A Building Permit shall be required prior to any construction.

E. Land Use Regulations

Where the last column in Table 28-41A (Land Use Regulations) includes a section number, e.g. 28.70.10, the zoning regulations in the referenced section apply to the use. Where the last column includes a chapter number, e.g. Chapter 13.6, the regulations in the referenced Solano County Code apply to the use. Provisions in other sections of this Zoning Ordinance may also apply.

F. Non-Conforming Uses

Within the Suisun Marsh, as defined by Section 29114 of the Public Resources Code, uses established prior to August 4, 1981 that do not conform to the uses set forth in Table 28-41A shall be considered nonconforming uses under Section 28.114, except that non-substantial changes, alterations, and additions to nonconforming uses may be allowed within the existing established project footprint area subject to a marsh development permit, pursuant to the Suisun Marsh Preservation Act of 1977 and as provided for in Section 28.104 of this Code. The overall existing development area may not be expanded under these provisions. Development within the existing development area should minimize additional impervious surfaces. An adequate buffer should be established or maintained between the development areas and any water, wetlands, or other Marsh habitat to protect the habitat from adverse environmental impacts. An erosion, sediment, and runoff control plan shall be prepared in accordance with Section 31.26(b) of the Solano County Grading, Drainage, Land Leveling and Erosion Control Ordinance. When the non-conforming uses is located in both the Primary Management Area and Secondary Management Area, as defined by the Suisun Marsh Preservation Act of 1977, non-substantial changes, alterations, and additions to the nonconforming use shall be subject to a use permit covering the whole of the project.

G. Site Development and Other Standards

All uses shall comply with the provisions of Section 28-90, Site Development and Other Standards, which includes standards for parking, signs, and other project elements

TABLE 28.41A ALLOWED USES: (C-H), (C-N), (C-R), (C-R-L), (C-S), (C-O) DISTRICTS

A= Allowed by right, AP= Administrative Permit, MUP= Minor use permit, PD = Planned Unit Development, UP= Use permit, E=Exempt, - - -= Prohibited

ALLOWED USES* *See Definition Section 28-10	**Permitted Uses**						**Land Use Regulations**** **See Section 28.70.10**
	C-H	**C-N**	**C-R**	**C-R-L[6]**	**C-S**	**C-O**	
28.71 AGRICULTURAL USES [2]							
A. CROP PRODUCTION							
Accessory uses and structures	---	---	A	A	---	---	28.71.10(A) & (B)(1)
Crop Production	---	---	A	---	---	---	28.71.10(A)
Non-irrigated and non-cultivated farming	---	---	---	A	---		28.71.10(A)
Grazing	---	---	A	A	---	---	28.71.10(A)
B. AGRICULTURAL PROCESSING USES							
On-site Agricultural Processing	---	---	A	---	---	---	28.71.20(A) & (B)(1)
28.72 RESIDENTIAL USES							
A. DWELLINGS							
Primary Dwelling	---	---	A	A	---	---	28.72.10
Emergency Shelter	---	---	---	---	A	---	
Cannabis Cultivation							
Caregiver	---	---	AP	AP	---	---	28.82
Personal							
Medical	---	---	A	A	---	---	28.82
Recreational	---	---	A	A	---	---	28.82
B. TEMPORARY RESIDENTIAL USES							
None Allowed							
C. AGRICULTURAL AND ANIMAL FACILITIES INCIDENTAL TO A RESIDENCE							
None Allowed							
D. OTHER RESIDENTIAL USES							
None Allowed							

TABLE 28.412A ALLOWED USES: (C-H), (C-N), (C-R), (C-R-L), (C-S), (C-O) DISTRICTS

A= Allowed by right, AP= Administrative Permit, MUP= Minor use permit, PD = Planned Unit Development, UP= Use permit, E=Exempt, - - -= Prohibited

ALLOWED USES* *See Definition Section 28-10	Permitted Uses						Land Use Regulations** **See Section 28.70.10
	C-H	C-N	C-R	C-R-L(6)	C-S	C-O	
28.73 RECREATION, EDUCATION AND PUBLIC ASSEMBLY USES [2]							
A. RECREATION USES							
Amusement Facilities	MUP	---	---	---	---	---	
Commercial Outdoor Recreation							28.73.10(A)
Not including enclosed structures	---	---	A	A	---	---	28.73.10(A)
Including enclosed structures	---	---	UP	UP	---	---	28.73.10(A)
Complementary commercial facilities	---	---	---	UP	---	---	
Marina							
Boat launching facilities	---	---	UP	UP	---	---	
Boat and boat trailer storage	---	---	UP	UP	---	---	
Boat construction, servicing, sales and repair	---	---	UP	UP	---	---	
Floating home	---	---	UP	---	---	---	
Marsh oriented recreation	---	---	---	UP	---	---	
Recreational Vehicle Park and/or Campground	---	---	UP[1]	UP[1]	---	---	28.73.10(A)
B. EDUCATION USES							
Ecological and agricultural education	---	---	UP	UP	---	---	
Business school; art, modeling, music, or dance studio	---	---	---	---	---	---	
C. PUBLIC ASSEMBLY USES							
Auditorium, exhibition hall, sports arena, drive-in theater	---	---	---	---	UP[4]	---	28.73.30(A)
Church	MUP	MUP	---	---	MUP[4]	MUP	28.73.30(A) & (B)(1)
Circus, Carnival, Fair, or Revival	MUP	---	---	---	MUP[4]	---	28.73.30(A)
Nursery School	---	---	---	---	MUP[4]	MUP	28.73.30(A)
28.74 RETAIL AND OFFICE USES							
A. RETAIL USES							
Automobile parking lot	---	A	---	---	A[4]	A	28.74.10(A) & (B)(2)

A= Allowed by right, AP= Administrative Permit, MUP= Minor use permit, PD = Planned Unit Development, UP= Use permit, E=Exempt, - - -= Prohibited

ALLOWED USES* *See Definition Section 28-10	**Permitted Uses**						**Land Use Regulations**** **See Section 28.70.10**
	C-H	**C-N**	**C-R**	**C-R-L[6]**	**C-S**	**C-O**	
Automobile Repair Garage	MUP	MUP	---	---	MUP[4]	---	28.74.10(A) & (B)(3)
Automobile Service Station	A	MUP	---	---	A[4]	---	28.74.10(A)
Food Establishments open to the outside air	MUP	---	---	---	---	---	28.74.10(A)
Bank	---	---	---	---	---	A	28.74.10(A)
Florist Shop (Indoor)	---	---	---	---	---	A	28.74.10(A)
Hotel, Motel	A	---			---	---	28.74.10(A)
Massage establishments, slenderizing establishments, and similar personal services	---	---	UP	---	---	---	28.74.10(A)
Merchandise Showroom	---	---	---	---	---	A	28.74.10(A)
Neighborhood Commercial Uses							28.74.10(A)
Less than 1,500 square feet	---	A	---	---	MUP[4]	---	28.74.10(A)
More than 1,500 square feet	---	UP	---	---	UP[4]	---	28.74.10(A)
Outdoor sales and service	---	MUP	---	---	MUP[4]	---	28.74.10(A)
Serving Liquor within 200 feet of an R-District	---	MUP	---	---	MUP[4]	---	28.74.10(A)
Pharmacy	---	---	---	---	---	A	28.74.10(A)
Refreshment Stand	A	---	---	---	---	---	28.74.10(A)
Restaurant	A	---	---	---	---	MUP	28.74.10(A)
Serving Liquor within 200 feet of an R-District	UP	---	---	---	---	MUP	28.74.10(A)
Retail Dairies	MUP	---	---	---	---	---	28.74.10(A)
Roadside Stand	MUP	---	---	---	---	---	28.74.10(A) & (B)(8)
Roadside stand for the sale of agricultural products grown on-site							28.74.10(A) & (B)(8)
More than 80 feet from the centerline of the street	---	---	A	---	---	---	28.74.10(A) & (B)(8)
Less than 80 feet from the centerline of the street	---	---	MUP	---	---	---	28.74.10(A) & (B)(8)
Shop, store and service for retail sales (indoor)	---	---	A	---	---	---	28.74.10(A)
Serving Liquor within 200 feet of an R-District	---	---	MUP	---	---	---	28.74.10(A)

A= Allowed by right, AP= Administrative Permit, MUP= Minor use permit, PD = Planned Unit Development, UP= Use permit, E=Exempt, - - -= Prohibited

ALLOWED USES* *See Definition Section 28-10	**Permitted Uses**						**Land Use Regulations**** **See Section 28.70.10**
	C-H	**C-N**	**C-R**	**C-R-L(6)**	**C-S**	**C-O**	
B. OFFICE USES							
Business and Professional Office	---	---	A	---	---	A	28.74.20(A)
Component Assembly of Pre-manufactured items	---	---	---	---	---	A[1,2]	28.74.20(A)
Indoor General Storage	---	---	---	---	---	A[1,2,3]	28.74.20(A)
Medical and Dental Clinic	---	---	---	---	---	A	28.74.20(A)
Research and Development	---	---	---	---	---	A[1,2]	28.74.20(A)

TABLE 28.41A ALLOWED USES: (C-H), (C-N), (C-R), (C-R-L), (C-S), (C-O) DISTRICTS

A= Allowed by right, AP= Administrative Permit, MUP= Minor use permit, PD = Planned Unit Development, UP= Use permit, E=Exempt, - - -= Prohibited

ALLOWED USES* *See Definition Section 28-10	**Permitted Uses**						**Land Use Regulations**** **See Section 28.70.10**
	C-H	**C-N**	**C-R**	**C-R-L[6]**	**C-S**	**C-O**	
28.75 TOURIST USES							
None Allowed							
28.76 COMMERCIAL SERVICE USES							
Animal Hospital					MUP[4]	---	28.76.20(A) & (B)(1)
Automobile, mobilehome, recreational vehicle or boat sales garage	---	---	---	---	A[4]	---	28.76.20(A)
Automobile, mobilehome, recreational vehicle or boat sales lot	---	---	---	---	A[4]	---	28.76.20(A)
Bakery, dairy creamery, laundry and dry cleaning establishment	---	---	---	---	A[4]	---	28.76.20(A)
Corporation Yard	---	---	---	---	A[4,5]	---	28.76.20(A)
Equipment Rental Lot	---	---	---	---	MUP[4]	---	28.76.20(A)
General Service Uses	---	---	---	---	A[4]	---	28.76.20(A)
Lumber yard	---	---	---	---	MUP[4]	---	28.76.20(A)
Medical laboratory	---	---	---	---	A[4]	MUP	28.76.20(A)
Mortuary, Funeral Home	---	---	---	---	---	MUP	28.76.20(A)
Newspaper and commercial printing shop, blueprint shop	---	---	---	---	A[4]	---	28.76.20(A)
Nursery and Landscaping Materials and Supplies	UP	---	---	---	A[4]	---	28.76.20(A)
Outdoor Storage	---	---	---	---	MUP[4]	---	28.76.20(A)
Sales of Construction and Landscaping Supplies and Materials	---	---	---	---	MUP[4]	---	28.76.20(A)

A= Allowed by right, AP= Administrative Permit, MUP= Minor use permit, PD = Planned Unit Development, UP= Use permit, E=Exempt, - - -= Prohibited							
ALLOWED USES* *See Definition Section 28-10	**Permitted Uses**						**Land Use Regulations**** **See Section 28.70.10**
	C-H	**C-N**	**C-R**	**C-R-L[6]**	**C-S**	**C-O**	
28.77 INDUSTRIAL, MANUFACTURING, PROCESSING AND WHOLESALE USES							
A. Industrial, Manufacturing and Processing Uses							
None Allowed							
B. Wholesale Uses							
Wholesale uses, warehouse	---	---	---	---	A[4]	---	28.77.20(A)

TABLE 28.41A ALLOWED USES: (C-H), (C-N), (C-G), (C-S), (C-O) DISTRICTS

A= Allowed by right, AP= Administrative Permit, MUP= Minor use permit, PD = Planned Unit Development, UP= Use permit, E=Exempt, - - -= Prohibited

ALLOWED USES* ***See Definition Section 28-10**	**Permitted Uses**						**Land Use Regulations**** ****See Section 28.70.10**
	C-H	**C-N**	**C-R**	**C-R-L[(6)]**	**C-S**	**C-O**	
28.78 COMMUNICATION, INFRASTRUCTURE AND SERVICE USES							
A. COMMUNICATION USES							
Wireless communication facility							
Co-location	MUP	MUP	MUP	- - -	MUP	MUP	28.78.10 & 28.81
New tower	UP	UP	UP	- - -	UP	UP	28.78.10 & 28.81
B. INFRASTRUCTURE USES							
Commercial wind turbine generator	UP	UP	---	---	UP	UP	28.80
Non-commercial wind turbine							28.80
Under 100 feet	A	A	A	A	A	A	28.80
Over 100 feet	MUP	MUP	MUP	---	MUP	MUP	28.80
Pipeline, transmission, or distribution line, in R.O.W.	A	A	A	A	A	A	28.78.20(B)(8)
Utility facilities or infrastructure, outside of R.O.W.	UP	UP	UP	UP	UP	UP	28.78.20(B)(9)
C. TEMPORARY CONSTRUCTION AND INFRASTRUCTURE USES							
Meteorological Tower, 1000 feet or less in height	AP	AP	AP	AP	AP	AP	28.78.20(A) & (B)(6)
Meteorological Tower, greater than 100 feet in height	MUP	MUP	MUP	MUP	MUP	MUP	28.78.20(A) & (B)(6)
D. SERVICE USES							
Hospital	---	---	---	---	---	A	28.78.30(A) & (B)(3)
Club, lodge, fraternal organization	---	MUP	---	---	MUP		28.78.30(A)

A= Allowed by right, AP= Administrative Permit, MUP= Minor use permit, PD = Planned Unit Development, UP= Use permit, E=Exempt, - - -= Prohibited

ALLOWED USES* *See Definition Section 28-10	**Permitted Uses**						**Land Use Regulations**** **See Section 28.70.10**
	C-H	**C-N**	**C-R**	**C-R-L[(6)]**	**C-S**	**C-O**	
Public Service Facility	UP	UP	UP	---	UP	UP	28.78.30(A) & (B)(4)
28.79 RESOURCE CONSERVATION USES							
None Allowed							

Notes:

1. Where uses are conducted entirely within a building and do not produce any dangerous, injurious, noxious or otherwise objectionable fire, explosive or other hazard; noise or vibration; smoke, dust, odor, or other form of air pollution; radioactivity, electrical or other disturbances; glare; liquid or solid refuse or wastes; in such amount as to adversely affect the surrounding area or adjoining premises and shall not exceed 50% of the net usable floor area per tenant.

2. Total square footage devoted to uses allowed shall not exceed 80% of the net usable floor area per tenant space and shall not generate more than one commercial delivery per day per tenant.

3. Shall not exceed 50% of the net usable floor area per tenant space and shall not generate more than one commercial delivery per day per tenant.

4 Incidental accessory uses, including processing and repair operations and services; provided, that such uses shall be clearly incidental to the sale or storage of products on the premises, and shall be so placed and constructed as not to be offensive or objectionable because of odor, dust, smoke, noise or vibration.

5 When enclosed by a minimum eight foot fence, wall or vegetative screening.

6 Any development within the Suisun Marsh, as defined by Section 29114 of the Public Resources Code, shall be subject to obtaining a Marsh Development Permit pursuant to the Suisun Marsh Preservation Act of 1977, and as provided for in Section 28.104 of this Code.

28.41.30 Commercial District Development Standards

Subdivision, new land uses, main buildings including primary and secondary dwellings, and alterations to existing land uses and buildings, shall be designed, constructed, and/or established in compliance with the applicable development standards delineated or referenced in Table 28-41B.

TABLE 28-41B

Development Standards for Main Building, ACCESSORY STRUCTURES and USES

PRIMARY BUILDING	
Minimum Lot Area	*None*
Setbacks	
Front	
C-H District	*Twenty feet; unless otherwise indicated by building lines on the zoning maps.*
C-N District **C-S District**	*None, except that where the frontage of a block is partially in an R or A district, in which case the front yard shall be the same as required in such R or A districts; and except that buildings shall not encroach upon the building lines established on the zoning maps.*
C-R-District **C-R-L District**	*Twenty feet; except that buildings shall not be less than fifty feet from the centerline of the street, and unless otherwise indicated by building lines on the zoning maps.*
C-O District	*15 feet*
Sides (each)	
C-H District	*None, except that where C-H districts abut upon any R or A district, side yards of not less than ten feet shall be required.*
C-N District **C-S District**	*None; except that where the side of a lot abuts upon the side of a lot in an R or A district, in which case the abutting side yard shall be not less than five feet; and except that, where the side yard of a corner lot abuts on a street where the frontage of the block is partially in an R or A district, in which case the side yard adjacent to the street shall be ten feet.*
C-R District **C-R-L District**	*None*
C-O District	*10 feet*
Rear	*None; except in the C-O District, 10 feet; except when adjacent to a residential zone, then the minimum yard shall be fifteen feet.*
Between structures	*10 feet*
Height limit	
C-H District **C-R District** **C-N District**	*Thirty-five feet; provided that additional height may be permitted if a use permit is first secured.*
C-R-L District	*Thirty-five feet; provided that additional height may be permitted if a use permit is first secured, but in no case more than 50 feet*
C-S District	*50 feet; provided, that the additional height may be allowed upon the obtaining of a use permit.*
C-O District	*35 feet; provided, that additional height may be permitted if the required yards are increased by one foot for each one foot of building height over the height limit.*

Accessory Structures	*Accessory buildings shall not be less than sixty feet from the front property line nor less than twenty feet from any side or rear property line, nor less than thirty feet from any dwelling unit on the property.*
OTHER STANDARDS	
Loading Requirements	*Adequate, private, off-street space for the loading and unloading of all materials.*
Parking Requirements	*Parking shall be provided in conformance with the parking standards in Section 28.94*
Signs	*All signs shall comply with the sign requirements in Section 28.96*
Fencing Requirements **Walls and Fences**	*In the C-S District, a minimum, six-foot high separating masonry wall or solid board shall be erected and maintained where any use abuts any R district.* *In the C-O District, a six foot high decorative masonry wall shall be constructed and maintained on all side and rear property lines abutting R Districts, excepting the Rural Residential (R-R) District. For property lines abutting R-R Districts, a screen consisting of walls, fences, landscaping, berms or any combination to form a six foot high opaque screen shall be provided.*
Lighting	*In the C-O District, parking areas shall have lighting capable of providing adequate illumination for security and safety. Any illumination shall be directed away from adjacent properties and public rights-of-way. Low level lighting shall be used where possible.*
Other Standards	***1.*** *Table 28.41A refers identifies allowable uses and permitting requirements. The last column of the table points to additional land use regulations for permitted uses, contained within Section 28-70. Please refer to this section for the additional requirements.*

28.42 Manufacturing and Industrial Districts

Subsections:

28.42.10 Manufacturing and Industrial Districts

This Section includes regulations for the following zoning districts

A. Manufacturing - Limited (M-L) District

B. Manufacturing - General (M-G) Districts

1. M-G-1/2 District
2. M-G-3 District

C. Industrial – Water Dependent (I-WD) District

28.42.11 Purpose of Manufacturing and Industrial District(s)

This Section lists the uses of land that may be allowed within the areas of the County designated for industrial and manufacturing land uses. It also determines the type of land use approval required for each use within each district, and provides general standards for site development.

The purpose of the different industrial and manufacturing zoning districts and the manner in which they are applied are as follows:

A. Manufacturing - Limited (M-L) District

The M-L district is designed to provide an environment conducive to the development and protection of modern, large scale administrative facilities, research institutions, warehousing, and specialized or light manufacturing organizations, all of a non-nuisance type, in accordance with the concept of an industrial park.

B. Manufacturing - General (M-G) District

The purpose of the M-G district is to permit the normal operations of almost all industries, subject only to those regulations needed to control congestion and to protect the surrounding area or adjoining premises. The two size designations are designed to provide a differentiation between an intensive and an extensive type of development.

C. Industrial – Water Dependent (I-WD) District

Certain waterfront lands within Solano County are of statewide and regional significance because they are among the few remaining deep-water sites suitable for water-dependent

industries. Furthermore, significant agricultural and marsh lands are nearby resources which the County is committed to preserve. For this reason, the I-WD district is established to reserve waterfront lands for large-scale, water-dependent industries to assure the efficient use of waterfront industrial sites, and to ensure that impact upon nearby environmentally sensitive lands are minimized.

The provisions of this Section shall be strictly interpreted to assure that only those industries which depend on a waterfront site are to locate within this district. It is expressly understood that prior to consideration of any industrial proposal within the district, the Planning Commission shall determine the industry's need for a waterfront site and assure its conformance with the provisions of the Solano County General Plan, this Chapter, and where applicable, the Suisun Marsh Preservation Act of 1977. Industries seeking to locate in the area designated Water Related Industrial Reserve on the Suisun Marsh Protection Plan Map are to be governed by the definition of water-related industry contained in the San Francisco Bay Plan. Those industries which are not considered to be water dependent may continue to locate within other industrial districts.

Some of the land in this district is lowland grassland or seasonal marsh which has existing value as wetland habitat or is suitable for restoration to wetland habitat. These areas have subsided and may be filled, using approved dredged sediments, and restored to tidal, managed, or seasonal wetlands, for the purpose of increasing their natural resource value and restoring some of the formerly natural tidal wetland area. Restored wetlands shall remain as wetlands and not be developed for industrial uses.

28.42.20 Manufacturing and Industrial (s) Land Uses and Permit Requirements

A. Allowed Uses and Permit Requirements

Tables 28-42A and 28-42B identifies the land uses allowed by this Zoning Ordinance in each manufacturing and industrial district and the land use permit required to establish each use. In addition to the land use permit required by Tables 28-42A and 28-42B, special requirements may apply to certain uses.

B. Marsh Development Permit Requirements

Any development within the Suisun Marsh, as defined by Section 29114 of the Public Resources Code, shall be subject to obtaining a Marsh Development Permit pursuant to the Suisun Marsh Preservation Act of 1977 and as provided for in Section 28.104 of this Code. When a land use subject to a marsh development permit is proposed in both the Primary Management Area and Secondary Management Area, as defined in the Suisun Marsh Preservation Act of 1977, the land use shall be subject to a use permit covering the whole of the project.

C. Architectural Review

Architectural Approval may be required for certain uses, in compliance with Section

28.102 (Architectural Approval).

D. Building Permits

A Building Permit shall be required prior to any construction. Prior to the issuance of a building permit, the Zoning Administrator or Planning Commission may require evidence that adequate controls, measures or devices will be provided to meet performance standards for this zone, as provided in Section 28.95, all to insure and protect the public interest, health, comfort, convenience, safety, and general welfare.

E. Land Use Regulations

Where the last column in Table 28.42A (Land Use Regulations) includes a section number, e.g. 28.70.10, the zoning regulations in the referenced section apply to the use. Where the last column includes a chapter number, e.g. Chapter 13.6, the regulations in the referenced Solano County Code apply to the use. Provisions in other sections of this Zoning Ordinance may also apply.

F. Non-Conforming Uses

Within the Suisun Marsh, as defined by Section 29114 of the Public Resources Code, uses established prior to August 4, 1981 that do not conform to the uses set forth in Table 28.41A shall be considered nonconforming uses under Section 28.114, except that non-substantial changes, alterations, and additions to nonconforming uses may be allowed within the existing established project footprint area subject to a marsh development permit, pursuant to the Suisun Marsh Preservation Act of 1977 and as provided for in Section 28.104 of this Code. The overall existing development area may not be expanded under these provisions. Development within the existing development area should minimize additional impervious surfaces. An adequate buffer should be established or maintained between the development areas and any water, wetlands, or other Marsh habitat to protect the habitat from adverse environmental impacts. An erosion, sediment, and runoff control plan shall be prepared in accordance with Section 31.26(b) of the Solano County Grading, Drainage, Land Leveling and Erosion Control Ordinance. When the non-conforming uses is located in both the Primary Management Area and Secondary Management Area, as defined by the Suisun Marsh Preservation Act of 1977, non-substantial changes, alterations, and additions to the nonconforming use shall be subject to a use permit covering the whole of the project.

G. Site Development and Other Standards

All uses shall comply with the provisions of Article IV, Section 28-90 Site Development and Other Standards which includes standards for parking, signs and other project elements.

TABLE 28.42A ALLOWED USES: (M-L), (M-G), (I-WD) DISTRICTS

A= Allowed by right, AP= Administrative Permit, MUP= Minor Use Permit, UP= Use Permit, E=Exempt,

- - - = Prohibited

ALLOWED USES* *See Definitions Section 28-10	**Permitted Uses**					**Land Use Regulations**** **See Section 28-70.10
	M-L	**M-G-1/2**	**M-G-3**	**I-WD[8]**		
28.71 AGRICULTURAL USES						
A. CROP PRODUCTION						
Crop Production and Grazing	A	- - -	- - -	- --		
Non-irrigated and non-cultivated farming, grazing	- - -	- - -	- - -	A[5]		
B. AGRICULTURAL PROCESSING USES						
None Allowed						
C. ANIMAL FACILITIES AND OPERATIONS						
Confined Animal Facility	- - -	- - -	- - -	UP[65]		28.73.30(A) & (B)(1)
Fowl and Poultry Ranch	- - -	- - -	- - -	UP[65]		28.73.30(A) & (B)(2)
28.72 RESIDENTIAL USES						
A. DWELLINGS						
Primary residence	A[1]	A[1,4]	A[1,4]	- - -		28.72.10(A)
Cannabis Cultivation						
Caregiver	AP	AP	AP	---		28.82
Personal						
Medical	A	A	A	---		28.82
Recreational	A	A	A	---		28.82
B. TEMPORARY RESIDENTIAL USES						
None Allowed						
A. AGRICULTURAL AND ANIMAL FACILITIES INCIDENTAL TO A RESIDENCE						
None Allowed						
C. OTHER RESIDENTIAL USES						

A= Allowed by right, AP= Administrative Permit, MUP= Minor Use Permit, UP= Use Permit, E=Exempt,

- - - = Prohibited

ALLOWED USES* *See Definitions Section 28-10	**Permitted Uses**					**Land Use Regulations**** **See Section 28-70.10**
	M-L	**M-G-1/2**	**M-G-3**	**I-WD[8]**		
None Allowed						

TABLE 28.42A ALLOWED USES: (M-L), (M-G), (I-WD) DISTRICTS

A= Allowed by right, AP= Administrative Permit, MUP= Minor Use Permit, UP= Use Permit, E=Exempt,

- - - = Prohibited

ALLOWED USES* *See Definitions Section 28-10	**Permitted Uses**					**Land Use Regulations**** **See Section 28-70.10
	M-L	**M-G-1/2**	**M-G-3**	**I-WD[8]**		
28.73 RECREATION, EDUCATION AND PUBLIC ASSEMBLY USES						
A. RECREATION USES						
None Allowed						
B. EDUCATION USES						
None Allowed	- - -	- - -	- - -	- - -		
C. PUBLIC ASSEMBLY USES						
Circus, Carnival, Fair, or Revival	MUP	MUP	MUP	- - -		28.73.30(A)
28.74 RETAIL AND OFFICE USES						
A. RETAIL USES						
Automobile parking lot [(7)]	A	A	A	- - -		28.74.10(A) & (B)(2)
B. OFFICE USES						
Administrative, Executive, and Financial Office	A	- - -	- - -	- - -		28.74.20(A)

TABLE 28.42A ALLOWED USES: (M-L), (M-G), (I-WD) DISTRICTS

A= Allowed by right, AP= Administrative Permit, MUP= Minor Use Permit, UP= Use Permit, E=Exempt,

- - - = Prohibited

ALLOWED USES* *See Definitions Section 28-10	**Permitted Uses**					**Land Use Regulations**** **See Section 28-70.10
	M-L	**M-G-1/2**	**M-G-3**	**I-WD[8]**		
28.75 TOURIST USES						
None Allowed						
28.76 COMMERCIAL SERVICE USES						
Research and Development Laboratory	A	- - -	- - -	- - -		28.76.20(A)
28.77 INDUSTRIAL, MANUFACTURING, PROCESSING AND WHOLESALE USES						
A. Industrial, Manufacturing and Processing Uses						28.77.10
Accessory buildings and uses	A	- - -	- - -	- - -		28.77.10(A)
General Manufacturing	- - -	A[4]	A[4]	- - -		28.77.10(A) & (B)(1)
Junk Yard, Wrecking Yard	- - -	MUP[4]	MUP[4]	- - -		28.77.10(A) & (B)(2)
Manufacturing, Assembly, Printing or Packaging from previously prepared materials.	A	- - -	- - -	- - -		28.77.10(A)
Manufacturing of electrical and electronic instruments	A	- - -	- - -	- - -		28.77.10(A))
Manufacturing of bakery goods, candy, cosmetics, pharmaceuticals	A	- - -	- - -	- - -		28.77.10(A)
Outdoor storage, incidental to an allowed use	A[3]	- - -	- - -	- - -		28.77.10(A)
Waterfront Facilities						
Waterfront Storage Facility	- - -	- - -	- - -	UP7		
Waterfront Manufacturing or Processing Facility	- - -	- - -	- - -	UP7		
Water-Using Facility	- - -	- - -	- - -	UP7		
Associated Manufacturing or Processing Uses	- - -	- - -	- - -	UP7		
Berthing Facility	- - -	- - -	- - -	UP7		
Support Facilities	- - -	- - -	- - -	UP7		
Accessory Structures and Uses	- - -	- - -	- - -	UP7		

A= Allowed by right, AP= Administrative Permit, MUP= Minor Use Permit, UP= Use Permit, E=Exempt,

- - - = Prohibited

ALLOWED USES* *See Definitions Section 28-10	**Permitted Uses**					**Land Use Regulations**** **See Section 28-70.10**
	M-L	**M-G-1/2**	**M-G-3**	**I-WD[8]**		
B. Wholesale Uses						
Wholesale uses, warehouse	A	- - -	- - -	- - -		28.77.20(A)

TABLE 28.42A ALLOWED USES: (M-L), (M-G), (I-WD) DISTRICTS

A= Allowed by right, AP= Administrative Permit, MUP= Minor Use Permit, UP= Use Permit, E=Exempt,

- - - = Prohibited

ALLOWED USES* *See Definitions Section 28-10	**Permitted Uses**					**Land Use Regulations**** **See Section 28-70.10
	M-L	**M-G-1/2**	**M-G-3**	**I-WD[8]**		
28.78 COMMUNICATION, INFRASTRUCTURE AND SERVICE USES						
A. COMMUNICATION USES						
Wireless communication facility						
Co-location	MUP	MUP	MUP	MUP		28.78.10(A) & (B)(1) and 28.81
New tower	UP	UP	UP	UP		28.78.10(A) & (B)(1) and 28.81
B. INFRASTRUCTURE USES						
Airport, heliport	A	- - -	- - -	- - -		28.78.20(A) & (B)(1)
Commercial wind turbine generator	UP	UP	UP	UP		28.78.20(A) & 28.80
Dredge Disposal Site	- - -	- - -	- - -	UP		28.78.20(A)
Waste disposal, processing, and composting	- - -	UP[4]	UP[4]	- - -		28.78.20(A) & (B)(3)
Non-commercial wind turbine						28.80
100 feet or less in height	A	A	A	A		28.80
Over 100 feet in height	MUP	MUP	MUP	~~MUP~~		28.80
Gas Well[(9)]	- - -	AP	AP	AP		28.78.20(A) & (B)(7)
Pipeline, transmission, or distribution line, in R.O.W.	A	A	A	A		28.78.20(A) & (B)(8)
Utility facilities or infrastructure, outside of R.O.W.	UP	UP	UP	UP		28.78.20(A) & (B)(9)
C. TEMPORARY CONSTRUCTION AND INFRASTRUCTURE USES						
Meteorological Tower, 100 feet or less in height	AP	AP	AP	AP	AP	28.78.20(A) & (B)(6)
Meteorological Tower, greater than 100 feet in height	MUP	MUP	MUP	MUP	MUP	28.78.20(A) & (B)(6)

A= Allowed by right, AP= Administrative Permit, MUP= Minor Use Permit, UP= Use Permit, E=Exempt,

- - - = Prohibited

ALLOWED USES* *See Definitions Section 28-10	**Permitted Uses**					**Land Use Regulations**** **See Section 28-70.10**
	M-L	**M-G-1/2**	**M-G-3**	**I-WD[8]**		
D. SERVICE USES						
Public Service Facility	UP	UP[5]	UP[5]	- - -		28.78.20(A) & (B)(4)
28.79 RESOURCE CONSERVATION USES						
Rehandling of dredged materials for on-site and off-site use.	- - -	- - -	- - -	UP[6]		28.79(A)
Restoration of Tidal, Managed and Seasonal Wetlands using dredge sediments	- - -	- - -	- - -	UP		28.79(A)

Notes:

1 On parcels of twenty acres or more

2 All uses located within the Fairfield Train Station Area, designated an Urban Project Area by the Solano County General Plan require a minor use permit.

3 Outdoor storage incidental to an allowed use on any portion of the lot, excepting any portion of the required front yard or any required parking area. Such outdoor storage shall not occupy a greater area than the buildings on the lot, and shall be screened by fencing or buildings from view or surrounding properties. Fencing shall be not less than six feet in height.

4 Except Public Utility Uses

5 As an interim use.

6 Where a use is granted pursuant to an approved and certified Specific Plan or Policy Plan the further requirement of a Use Permit may be waived

7 Water Front facilities are subject to adoption of a Specific Plan or Policy Plan by the Board of Supervisors and certification of the plan by the Bay Conservation and Development Commission prior to development.

8 Any development within the Suisun Marsh, as defined by Section 29114 of the Public Resources Code, shall be subject to obtaining a Marsh Development Permit pursuant to the Suisun Marsh Preservation Act of 1977 and as provided for in Section 28.104 of this Code.

9. Oil wells not permitted in the Suisun Marsh primary and secondary management areas

28.42.30 Manufacturing and Industrial District Development Standards

Subdivision, new land uses, main buildings including primary and secondary dwellings, and alterations to existing land uses and buildings, shall be designed, constructed, and/or established in compliance with the applicable development standards delineated or referenced in Table 28-42B.

TABLE 28.42B

Development Standards for Main Building, ACCESSORY STRUCTURES and USES

PRIMARY BUILDING	
Minimum Lot Area	
M-L District	*One acre; except that for parking lots and as may otherwise be as specified for any use for which a use permit is required by this Section.*
M-G-1/2 District	*One-half acre*
M-G-3 District	*Three acres*
I-WD District	*Determined by the conditions of the approved planned unit development permit. Parcels less than two hundred acres in area are permitted only if they accommodate uses which are directly auxiliary to approved industrial uses on larger sites.*
Front	
M-L District	*Thirty feet, unless otherwise indicated by building lines on the zoning maps.*
M-G-1/2 District	*Ten feet; except that buildings shall not be less than fifty feet from the centerline of the public road, or unless otherwise indicated by building lines on the zoning maps.*
M-G-3 District	
I-WD District	*Where parcel abuts an agricultural district, the minimum building setback shall be five hundred feet except where otherwise provided by specific guidelines set forth in a specific plan or policy plan for the Collinsville area. Other setbacks shall be established by the Planning Commission or Zoning Administrator in conformance with the specific setback requirements set forth in a specific plan or policy plan for the Collinsville area.*
Sides (each)	
M-L District	*Ten feet; except that twenty-five feet shall be required adjacent to any R-TC district; and except that the minimum of twenty-five feet shall be increased one foot for each foot over thirty-five feet of building height.*

TABLE 28.42B Development Standards for Main Building, ACCESSORY STRUCTURES and USES	
M-G-1/2 District	*Twenty feet; except that forty feet shall be required for any building over one story or twenty-five feet in height when adjacent to any R district.*
M-G-3 District	
I-WD District	*Where parcel abuts an agricultural district, the minimum building setback shall be five hundred feet except where otherwise provided by specific guidelines set forth in a specific plan or policy plan for the Collinsville area. Other setbacks shall be established by the Planning Commission or Zoning Administrator in conformance with the specific setback requirements set forth in a specific plan or policy plan for the Collinsville area.*
Rear	*Twenty feet; except that forty feet shall be required for any building over one story or twenty-five feet in height when adjacent to any R district.*
Between structures	*10 feet*
Height limit	
M-L District	*50 feet; provided, that additional height may be permitted if the required yards are increased by one foot for each one foot of building height over the height limit.*
M-G-1/2 District	*50 feet; provided that additional height may be allowed provided a use permit is first secured in each case and that no structure shall exceed the height limitations of Section 28-99, if located in an airport flight obstruction area.*
M-G-3 District	
I-WD District	*Height limits as established in a specific plan or policy plan for the Collinsville area; provided, that no structure shall exceed the height limitations of Section 28-99 if located in an airport flight obstruction area.*
Accessory Structures	*Accessory buildings shall not be less than sixty feet from the front property line nor less than twenty feet from any side or rear property line, nor less than thirty feet from any dwelling unit on the property.*
OTHER STANDARDS	
Loading Requirements	*Loading and unloading spaces shall be provided as required by the Zoning Administrator and Planning Commission. Loading space shall not be located in the required front yard.*
Parking Requirements	*Parking shall be provided in conformance with the parking standards in Section 28.94*
Signs **Fencing Requirements** **Walls and Fences** **Lighting**	*All signs shall comply with the sign requirements in Section 28.96*

TABLE 28.42B Development Standards for Main Building, ACCESSORY STRUCTURES and USES	
Other Requirements	*Table 28.42A refers identifies allowable uses and permitting requirements. The last column of the table points to additional land use regulations for permitted uses, contained within Article III. Please refer to this section for the additional requirements.* *In the M-L District, all uses shall be conducted wholly within a completely enclosed building except for agriculture, allowed outdoor storage, parking and loading facilities, and as otherwise specified in any use permit.* *Manufacturing processes shall use only gas or electricity as a source of power.*
	In the I-WD District, application for planned unit development permits shall be prepared in accordance with the provisions of Section 28-105, and shall follow the seven-step development review process for siting waterfront industries as set forth within the Solano County general plan and the following criteria: ***2.*** *1. Adequate provision is made, through the dedication of property or by other means, to provide for the protection of adjacent agricultural uses, easements for connections to berth facilities, and where feasible, open space, public access, and wetlands preservation.* **3.** *2. Adequate safeguards are provided for the safe transport, transfer, storage, and emission of substances potentially hazardous to health, life or property.*

28.43 Industrial - Agricultural Service (I-AS) District

Subsections

28.43 Industrial - Agricultural Service (I-AS) District

This Section lists the uses of land that may be allowed within the Industrial - Agricultural Service (I-AS) zoning district. It also determines the type of land use approval required for each use, and provides general standards for site development.

28.43.10 Purpose of the Industrial - Agricultural Service (I-AS) District

The purpose of the Industrial - Agricultural Service (I-AS) District is to provide for the development of agricultural related industry in the agricultural regions of the county.

28.43.020 Industrial - Agricultural Service District Uses and Permit Requirements

E. Allowed Uses and Permit Requirements:

Table 28-43A identifies the land uses allowed by this Zoning Ordinance in the Industrial - Agricultural Service (I-AS) district and the land use permit required to establish each use. In addition to the land use permit required by Table 28-43A, special requirements may apply to certain uses.

F. Architectural Approval:

Architectural Approval may be required for certain uses in compliance with Section 28.102 (Architectural Approval) and in conformance with the *Design Guidelines for the Northeast Dixon Agricultural Service District*.

G. Building Permits:

A Building Permit may be required prior to any construction.

H. Land Use Regulations:

All uses in the Industrial - Agricultural Service (I-AS) District are subject to the land use standards in Article III of this Chapter. Where the last column in the table 28-43A (Table of Allowable Uses) includes a section number, e.g. 28.71.10, the zoning regulations in the referenced section apply to the use. Where the last column includes a chapter number, e.g.

Chapter 13.6, the regulations in the referenced Solano County Code apply to the use.

I. Site Development and Other Standards

All uses shall comply with the provisions of Section 28.43.30 and Article IV, Section 28-90 Site Development and Other Standards, which includes standards for parking, signs, and other project elements.

J. TABLE 28.43A TABLE OF ALLOWED USES

A= Allowed by right, AP= Administrative Permit, MUP= Minor Use Permit, PUD = Planned Unit Development, UP= Use Permit, E=Exempt, - - - = Prohibited

ALLOWED USES* *See Definitions Section 28-10	Permitted Uses	Land Use Regulations
28.71 AGRICULTURAL USES		See Section 28.71
A. CROP PRODUCTION AND GRAZING		
Crop production	A	28.71.10A
Grazing	A	28.71.10A
B. AGRICULTURAL PROCESSING USES		
Agricultural processing	A	28.71.20(A) & (B)(1)
Aquaculture	A	28.71.20(A)
Nurseries	A	28.71.20(A) & (B)(2)
Winery	A	28.71.20(A) & (B)(3); 28.73.30(A)
C. ANIMAL FACILITIES AND OPERATIONS		
Confined animal facility	---	
Fowl and poultry ranch	---	
Pastured Poultry	---	
Hog Farm	---	
Slaughterhouse	A	28.71.30(A) & (B)(5)
Livestock Auction Yard	A	28.71.40(A) & (B)(6)
D. OTHER AGRICULTURAL OPERATIONS		28.71.40
Agricultural employee housing	---	
28.72 RESIDENTIAL USES		
A. DWELLINGS		
Primary Dwelling	---	
Secondary dwelling	---	
Second Kitchen	---	
Cannabis Cultivation		
Caregiver	---	
Personal		
Medical	---	
Recreational	---	
B. TEMPORARY RESIDENTIAL USES		28.72.20

A= Allowed by right, AP= Administrative Permit, MUP= Minor Use Permit, PUD = Planned Unit Development, UP= Use Permit, E=Exempt, - - - = Prohibited

ALLOWED USES* *See Definitions Section 28-10	**Permitted Uses**	**Land Use Regulations**
Security quarters for a construction site (commercial coach, manufactured home or recreational vehicle)	AP	28.72.20(A) & (B)(1)
Temporary Manufactured Home Storage	AP	28.72.20(A) & (B)(4)
C. AGRICULTURAL AND ANIMAL FACILITIES INCIDENTAL TO A RESIDENCE		28.72.30
None Allowed	- - -	
D. OTHER RESIDENTIAL USES		28.72.40
Cottage Industries		
Type I	---	
Type II	---	
Home occupations		
Type I	---	
Type II	---	

TABLE 28.43A TABLE OF ALLOWED USES

A= Allowed by right, AP= Administrative Permit, MUP= Minor Use Permit, PUD = Planned Unit Development, UP= Use Permit, E=Exempt, - - - = Prohibited

ALLOWED USES* *See Definitions Section 28-10	**Permitted Uses**	**Land Use Regulations**
28.73 RECREATION, EDUCATION AND PUBLIC ASSEMBLY USES		See Section 28.73
A. RECREATION USES		28.73.10
None Allowed	- - -	
B. EDUCATION USES		28.73.20
Agricultural education		
Minor Facility	A	28.73.20(A) & (B)(1)
Major Facility	AP	28.73.20(A) & (B)(1)
See exemption for 4-H activities		
C. PUBLIC ASSEMBLY USES		28.73.30
None Allowed	- -	
28.74 RETAIL AND OFFICE USES		See Section 28.74
A. RETAIL USES		28.74.10
Farm Equipment Sales	A	28.74.10(A) & (B)(4)
Farm/Ranch Supply Store	A	28.74.10(A) & (B)(5)
Agricultural Commercial Kitchen	A	28.76.10(A) & (B)(1)
Roadside Stand		
1,000 square feet or less in size	A	28.74.10(A) & (B)(8)
Between 1,000 and 2,500 square feet	AP	28.74.10(A) & (B)(8)
Greater than 2,500 square feet in size	MUP	28.74.10(A) & (B)(8)
Non-agricultural product sales, less than 10%.	A	28.74.10(A) & (B)(8)
Non-agricultural product sales, between 10% and 25%	AP	28.74.10(A) & (B)(8)
Non-agricultural product sales, greater than 25%	MUP	28.74.10(A) & (B)(8)
Any of the above with a Certified Farmers Market		
Small Certified Farmers Market	A	28.74.10(A) & (B)(8); 28.75.20(A) & (B)(2)
Medium Certified Farmers Market	AP	28.74.10(A) & (B)(8); 28.75.20(A) & (B)(2)
Large Certified Farmers Market	MUP	28.74.10(A) & (B)(8); 28.75.20(A) & (B)(2)
Commercial auctions and agricultural equipment sales	A	28.71.40(A)&(B)(2)
B. **OFFICE USES**		28.74.20
Agricultural Research Facilities		
Small (less than 20,000 sq. ft.)	A	28.74.20(A) & (B)(1)
Medium (between 20,000 and 40,000 sq. ft.)	A	28.74.20(A) & (B)(1)

A= Allowed by right, AP= Administrative Permit, MUP= Minor Use Permit, PUD = Planned Unit Development, UP= Use Permit, E=Exempt, - - - = Prohibited

ALLOWED USES* *See Definitions Section 28-10	**Permitted Uses**	**Land Use Regulations**
28.73 RECREATION, EDUCATION AND PUBLIC ASSEMBLY USES		See Section 28.73
Large (more than 40,000 sq. ft.)	MUP	28.74.20(A) & (B)(1)
28.75 TOURIST USES		See Section 28.75
A. AGRITOURISM		28.75.10
Agricultural homestay	---	28.75.10(A) & (B)(1)
Agritourism Facility	MUP	28.75.10(A) & (B)(4)
B. TEMPORARY AGRITOURISM		28.75.20
Amusement and entertainment uses	---	
Certified Farmers Market		
Small Certified Farmers Market	A	28.75.20(A) & (B)(2)
Medium Certified Farmers Market	MUP	28.75.20(A) & (B)(2)
Large Certified Farmers Market	UP	28.75.20(A) & (B)(2)
Seasonal sales lot	AP	28.75.20(A) & (B)(3)
Temporary Agritourism Event	AP	28.75.20(A) & (B)(4)

TABLE 28.43A TABLE OF ALLOWED USES

A= Allowed by right, AP= Administrative Permit, MUP= Minor Use Permit, PUD = Planned Unit Development, UP= Use Permit, E=Exempt, - - - = Prohibited

ALLOWED USES* *See Definitions Section 28-10	Permitted Uses	Land Use Regulations
28.76 COMMERCIAL SERVICE USES		See Section 28.76
A. AGRICULTURAL SERVICES		28.76.10
Commercial Farm Equipment fabrication and repair	A	28.76.10(A)
Agricultural Recycling and Composting	MUP	28.76.10(A) & (B)(3)
Agricultural Trucking Services and Facilities	A	28.76.10(A)&(B)(2)
Agricultural Warehousing and Storage	A	28.76.10(A)
Agricultural Equipment Storage Yard	UP	28.76.10(A)
Custom Farm Services	A	28.76.10(A)
B. COMMERCIAL SERVICES		28.76.20
Large Animal Hospital or Veterinary Clinic	A	28.76.20(A) & (B)(1)
28.77 INDUSTRIAL, MANUFACTURING, PROCESSING AND WHOLESALE USES [2]		See Section 28.77
A. INDUSTRIAL, MANUFACTURING AND PROCESSING USES		28.77.10
None Allowed	- - -	
B. WHOLESALE USES		28.77.20
None Allowed	- - -	

Table 28.43A TABLE OF Allowed Uses

A= Allowed by right, AP= Administrative Permit, MUP= Minor Use Permit, PUD = Planned Unit Development, UP= Use Permit, E=Exempt, - - - = Prohibited

ALLOWED USES* *See Definitions Section 28-10	**Permitted Uses**	**Land Use Regulations**
28.78 COMMUNICATION, INFRASTUCTURE AND SERVICE USES		See Section 28.78
A. COMMUNICATION USES		28.78.10
Wireless communication facilities		
Co-locations	MUP	28.81
New towers	UP	28.81
B. INFRASTRUCTURE USES		28.78.20
Commercial wind turbine generators	UP	28.80
Non-commercial wind turbines		
100 feet or less in height	A	28.80
Over 100 feet in height	MUP	28.80
Pipelines, transmission and distribution lines in R.O.W.	A	28.78.20A and B10
Utility facilities or infrastructure, outside of R.O.W.	UP	28.78.20A and B11
C. **SERVICE USES**		28.78.30
Public Service Facility	UP	28.78.30A and B4
D. **TEMPORARY CONSTRUCTION AND INFRASTRUCTURE**		28.78.40
Meteorological Towers, 100 feet or less in height	AP	28.78.20A and B6
Meteorological Towers, greater than 100 feet in height	MUP	28.78.20A and B6
28.79 RESOURCE CONSERVATION USES		See Section 28.79
Mitigation Banks	- - -	

28.43.30 Industrial - Agricultural Service District (I-AS) General Development Standards

B. General site and building standards. Subdivisions, new land uses**,** main buildings, and alterations to existing land uses and buildings, shall be designed, constructed, and/or established in compliance with the applicable development standards delineated or referenced in Table 28-43B.

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Table 28.43B

Development Standards for Main Building, Accessory Dwelling	
	I-AS District
PRIMARY BUILDING	
Minimum Lot Size	*5 acres*[4]
Setbacks	
Front	*30 feet, but at least 50 feet from the street centerline and unless otherwise indicated by building lines on the Zoning Maps.*
Sides (each)	*20 feet*
Rear	*25 feet*
Between structures	*10 feet*
Height limit	*35 feet, and as allowed by 28-93 Special regulations*
Height limit for agricultural processing uses	*50 feet, and as allowed by 28-93 Special regulations*

Notes:

(1) Other setbacks may be required for specific uses listed in Table 28-43A, as provided elsewhere in this Chapter.

(2) Other separation between structures may be required by County Building Code.

(3) The actual number of parcels allowed is determined through the applicable subdivision process, based on specific site characteristics and potential environmental impacts, and there is no guarantee that the maximum possible number may be achieved.

(4) The minimum parcel size may be reduced provided a community or public sewer system is established to serve the parcel.. Parcel larger than 5 acres maybe required, depending on service capacity of the parcel for water, drainage and sewers. A use permit is required to reduce the minimum parcel size to less than 5 acres, but a parcel may not be less than 1 acre.

B. Accessory buildings and structures. New accessory buildings and other structures, including alterations to existing accessory buildings and other structures, shall be designed, constructed, and/or established in compliance with the applicable development standards in Section 28.71.10(B)(1) and in Table 28.43C below.

Table 28.43C
DEVELOPMENT STANDARDS FOR ACCESSORY BUILDINGS

	AS District
AGRICULTURAL ACCESSORY BUILDINGS (1)	
Setbacks	
Attached	*An accessory building attached to the main building shall comply with the setback requirements for the main building*
Detached	
Front	*60 feet or on the rear 50% of the lot*
Sides (each)	*20 feet*
Rear	*20 feet*
Between structures	*10 feet from any main building on the same lot*
Height limit	*35 feet, and as allowed by 28-93 General Building regulations*
Parking	*As required by 28-94, Parking Requirements*
Signs	*See Section 28.96 Signs*

Notes:

(1) Other setbacks may be required for specific uses listed in Table 28-43A, as referenced.

(2) Other separation between structures may be required by County Building Code.

28.50 Resource Conservation Districts

Subsections

28.51 Watershed and Conservation (W) District

A. Purpose:

The Board of Supervisors finds that the watershed and conservation district areas of Solano County are very valuable natural resources, and in order to protect these areas from the constant threat of wildfire, subsidence, and landslide leading to the destruction and financial loss to private and public property; and in order to prevent increased threats of these hazards through overdevelopment of these areas; and in order to protect the general welfare of the County as a whole, there is hereby created a zone classification within which the establishment, perpetuation and protection of watershed and conservation district shall be encouraged.

The provisions of this Section shall be liberally interpreted insofar as they apply to the protection of watershed and conservation district areas. It is the intention of this Section to deter developer from considering lands in a "W" zone as potential urban subdivision property, as residential uses are not compatible with watershed and conservation district areas by the fact that such areas are characterized by slope instability, fire hazards, and the unavailability of water and public services.

Those areas to be designated under this zone are fire hazard areas and are subject to slope instability as determined by the Solano County general plan, and are characterized by the following conditions:

1. Steep topography (defined as slopes in excess of twenty-five percent grade).

2. Excessive vegetation coverage (defined as fifty percent or more of the area or parcel being covered with chaparral or woodland).

3. Inadequate roads (defined as roads below the County standards as to width, alignment, grade or improvement).

4. Lack of available water (defined as insufficient water to sustain a flow of two hundred gallons a minute for twenty minutes).

5. Land susceptible to subsidence or landsliding (defined as characterized by slopes greater than fifteen percent underlain by landslide-prone deposits, or by existing landslide deposits).

A range of agricultural uses are found to be compatible with watershed management. However, these uses are specifically defined and prescribed to prevent an increase in the fire or landslide hazards that now exit, and such uses would not require additional public services. These agricultural uses should not attract increased habitation or encourage activities that are not compatible with watershed management.

B. W District Land Uses and Permit Requirements. Table 28-51A identifies the land uses allowed by this Zoning Ordinance in the W district and the land use permit required to establish each use. In addition to the land use permit required by Table 28-51A, special requirements may apply to certain uses. Architectural Approval may also be required for

certain uses in compliance with Section 28.102 (Architectural Approval). A Building Permit shall also be required prior to any construction, alteration, remodeling or change in occupancy from a previous building permit.

Note: Where the last column in Table 28-51A ("Land Use Regulations") includes a section number, e.g. 28.74, the zoning regulations in the referenced section apply to the use. Where the last column includes a chapter number, e.g. Chapter 13.6, the regulations in the referenced Solano County Code apply to the use. Provisions in other sections of this Zoning Ordinance may also apply.

TABLE 28.51A TABLE OF ALLOWED USES

A= Allowed by right, AP= Administrative Permit, MUP= Minor Use Permit, UP= Use Permit, E=Exempt, - - - = Prohibited

ALLOWED USES* *See Definitions Section 28-10	**Permitted Uses**	**Land Use Regulations**** **See Section 28-70.10
	W District	
28.71 AGRICULTURAL USES		
E. CROP PRODUCTION AND GRAZING		
Crop Production	A	28.70.10
Grazing	A	28.70.10
F. AGRICULTURAL PROCESSING USES		
None Allowed	- - -	
G. ANIMAL FACILITIES AND OPERATIONS		
Fowl and Poultry Ranch	UP[1]	28.71.30(B)(2)
H. OTHER AGRICULTURAL OPERATIONS		
Additional One-Family Homes for persons employed in agriculture	UP	28.71.40(A)
28.72 RESIDENTIAL USES		
D. DWELLINGS		
Primary ~~residence~~ dwelling	A	28.72.10(A)
Cannabis Cultivation		
Caregiver	AP	28.82
Personal		
Medical	A	28.82
Recreational	A	28.82
E. TEMPORARY RESIDENTIAL USES		
None Allowed	- - -	
F. AGRICULTURAL AND ANIMAL FACILITIES INCIDENTAL TO A RESIDENCE		
Private stable	A	28.72.30(A) & (B)(5)
D. OTHER RESIDENTIAL USES		
None Allowed	- - -	

TABLE 28.51A TABLE OF ALLOWED USES

A= Allowed by right, AP= Administrative Permit, MUP= Minor Use Permit, UP= Use Permit, E=Exempt, - - - = Prohibited

ALLOWED USES* *See Definitions Section 28-10	**Permitted Uses**	**Land Use Regulations**** **See Section 28-70.10
	W District	
28.73 RECREATION, EDUCATION AND PUBLIC ASSEMBLY USES		
D. RECREATION USES		
Lodge, club, resort for swimming, boating, fishing, hunting or shooting	UP	28.73.10(A) & (B)(1)
Public Stable	UP	28.73.10(A) & (B)(3)
E. EDUCATION USES		
None Allowed	- - -	
F. PUBLIC ASSEMBLY USES		
None Allowed	- - -	
28.74 RETAIL AND OFFICE USES		
C. RETAIL USES		
None Allowed	- - -	
D. OFFICE USES		
None Allowed	- - -	
28.75 TOURIST USES		
C. AGRITOURISM		
None Allowed	- - -	
D. TEMPORARY AGRITOURISM		
None Allowed	- - -	

TABLE 28.51A TABLE OF ALLOWED USES

A= Allowed by right, AP= Administrative Permit, MUP= Minor Use Permit, UP= Use Permit, E=Exempt, - - - = Prohibited

ALLOWED USES* *See Definitions Section 28-10	**Permitted Uses**	**Land Use Regulations**** **See Section 28-70.10
	W District	
28.76 COMMERCIAL SERVICE USES		
C. AGRICULTURAL SERVICES		
None Allowed	- - -	
D. COMMERCIAL SERVICES		
None Allowed	- - -	
28.77 INDUSTRIAL, MANUFACTURING, PROCESSING AND WHOLESALE USES [2]		
C. INDUSTRIAL, MANUFACTURING AND PROCESSING USES		
None Allowed	- - -	
D. WHOLESALE USES		
None Allowed	- - -	

TABLE 28.51A TABLE OF ALLOWED USES

A= Allowed by right, AP= Administrative Permit, MUP= Minor Use Permit, UP= Use Permit, E=Exempt, - - - = Prohibited

ALLOWED USES* *See Definitions Section 28-10	**Permitted Uses**	**Land Use Regulations**** **See Section 28-70.10
	W District	
28.78 COMMUNICATION, INFRASTUCTURE AND SERVICE USES		See Section 28.78
E. COMMUNICATION USES		
Wireless communication facility		
Co-location	MUP	28.81
New tower	UP	28.81
F. INFRASTRUCTURE USES		
Commercial wind turbine generator	UP	28.80
Non-commercial wind turbine		
100 feet or less in height	A	28.80
Over 100 feet in height	MUP	28.80
Pipeline, transmission or distribution line in R.O.W.	A	28.78.20(A) & (B)(8)
Utility facilities or infrastructure, outside of R.O.W.	UP	28.78.20(A) & (B)(9)
G. **SERVICE USES**		
Cemetery	UP	28.78.30(A) & (B)(1)
Public Service Facility	UP	28.78.30(A) & (B)(4)
H. **TEMPORARY CONSTRUCTION AND INFRASTRUCTURE**		
Meteorological Tower, 100 feet or less in height	AP	28.78.20(A) & (B)(6)
Meteorological Tower, greater than 100 feet in height	MUP	28.78.20(A) & (B)(6)
28.79 RESOURCE CONSERVATION USES		
None Allowed	- - -	

C. General Development Standards:

Subdivision, new land uses, main buildings including primary and secondary dwellings, and alterations to existing land uses and buildings, shall be designed, constructed, and/or established in compliance with the applicable development standards delineated or referenced in Table 28-51B.

TABLE 28-51B

DEVELOPMENT STANDARDS FOR MAIN BUILDING, ACCESSORY STRUCTURES AND USES

	W District
PRIMARY BUILDING	
Minimum Lot Area	*160 acres*
Setbacks	
Front	Thirty feet; except that buildings shall not be less than fifty feet from the centerline of the street, and unless otherwise indicated by building lines on the zoning maps.
Sides (each)	*20 feet*
Rear	*20 feet*
Between structures	*10 feet*
Height limit	*Thirty-five feet; provided, that additional height may be permitted for non-dwelling structures, including windmills, silos, private water tanks, and provided further, that no such structure shall exceed the heights allowed in Section 28-99, if located in an airport flight obstruction area.*
Accessory Structures	*Accessory buildings shall not be less than sixty feet from the front property line nor less than twenty feet from any side or rear property line, nor less than thirty feet from any dwelling unit on the property.*
OTHER STANDARDS	
Parking Requirements	*Parking shall be provided in conformance with the parking standards in Section 28.94*
Signs	*All signs shall comply with the sign requirements in Section 28.96*

D. **Special yards and distances between buildings required:** Accessory buildings shall not be less than sixty feet from the front property line nor less than twenty feet from any side or rear property line, nor less than thirty feet from any dwelling unit on the property.

E. **Maximum building height:** Thirty-five feet; provided, that additional height may be permitted for non-dwelling structures, including windmills, silos, private water tanks, and provided further, that no such structure shall exceed the heights allowed in Section 28-99, if located in an airport flight obstruction area.

28.52 Marsh Preservation (MP) District

Subsections:

28.52.10 – Marsh Preservation District

This Section includes regulations for MP zoning district.

28.52.11 – Purpose of Marsh Preservation District

This Section lists the uses of land that may be allowed within the Marsh Preservation (MP) zoning district, established by Section 28.13 (Districts Designated and Established). It also determines the type of land use approval required for each type of use and provides general standards for site development.

Marshes, wetlands, and certain adjacent grasslands within the County represent an area of significant aquatic and wildlife habitat and are an irreplaceable and unique resource to the people of the County, State, and the Nation. Therefore, the Board of Supervisors has determined it is in the interest of the County to preserve and enhance the quality and diversity of marsh habitats, within which marsh-oriented uses shall be encouraged to the exclusion of such other uses of land as may be in conflict with the long-term preservation and protection of marsh areas. The provisions of this Section shall be strictly interpreted to provide maximum protection to marsh areas.

28.52.20 – Marsh Preservation District Land Uses and Permit Requirements

A. Allowed Uses and Permit Requirements

Table 28-52A identifies the land uses allowed by this Zoning Ordinance in the marsh preservation district and the land use permit required to establish each use. In addition to the land use permit required by Table 28-38A, special requirements may apply to certain uses.

B Marsh Development Permit Requirements

Any development within the Suisun Marsh, as defined by Section 29114 of the Public Resources Code, shall be subject to obtaining a Marsh Development Permit pursuant to the Suisun Marsh Preservation Act of 1977 and as provided for in Section 28.104 of this Code. When a land use

subject to a marsh development permit is proposed in both the Primary Management Area and Secondary Management Area, as defined in the Suisun Marsh Preservation Act of 1977, the land use shall be subject to a use permit covering the whole of the project.

C. Architectural Review

Architectural Approval may be required for certain uses, in compliance with Section 28.102 (Architectural Approval).

D. Building Permits

A Building Permit shall be required prior to any construction.

E. Land Use Regulations

Where the last column in Table 28.52A (Land Use Regulations) includes a section number, e.g. 28.70.10, the zoning regulations in the referenced section apply to the use. Where the last column includes a chapter number, e.g. Chapter 13.6, the regulations in the referenced Solano County Code apply to the use. Provisions in other sections of this Zoning Ordinance may also apply.

F. Non-Conforming Uses

Within the Suisun Marsh, as defined by Section 29101 of the Public Resources Code, uses established prior to 1977 that do not conform to the uses set forth in Table 28.38A shall be considered nonconforming uses under Section 28.114 and subject to Section 28.18, except that non-substantial changes, alterations, and additions to nonconforming uses may be allowed within the existing established project footprint area subject to a marsh development permit pursuant to the Suisun Marsh Preservation Act of 1977 and as provided for in Section 28.104 of this code. The overall existing development area may not be expanded under these provisions. Development within the existing development area should minimize additional impervious surfaces. An adequate buffer should be established or maintained between the development areas and any water, wetlands, or other Marsh habitat to protect the habitat from adverse environmental impacts. An erosion, sediment, and runoff control plan shall be prepared in accordance with Section 31.26(b) of the Solano County Grading, Drainage, Land Leveling and Erosion Control Ordinance. When the non-conforming uses is located in both the Primary Management Area and Secondary Management Area, as defined by the Suisun Marsh Preservation Act of 1977, non-substantial changes, alterations, and additions to the nonconforming use shall be subject to a use permit covering the whole of the project.

G. Site Development and Other Standards

All uses shall comply with the provisions of Article IV, Section 28-90 Site Development and Other Standards which includes standards for parking, signs and other project elements.

Table 28.52A TABLE OF ALLOWED USES

A = Allowed by right, AP = Administrative Permit, MUP = Minor Use Permit, UP = Use Permit, - - - = Prohibited

ALLOWED USES See Definitions Section 28.10	Permit Requirements MP[1] Zoning District	Land Use Regulations See Section 28.70.10
28.71 AGRICULTURAL USES		
A. CROP PRODUCTION AND GRAZING		
Non-irrigated and non-cultivated farming	A[2]	
Grazing	A[2]	
B. AGRICULTURAL PROCESSING USES		
None allowed		
C. ANIMAL FACILITIES AND OPERATIONS		
None allowed		
D. OTHER AGRICULTURAL OPERATIONS		
Agricultural employee housing	UP	28.71.40(A) & (B)(1)
28.72 RESIDENTIAL USES		
A. DWELLINGS		
Primary Dwelling[3]	A	28.72.10(A)
Cannabis Cultivation		
Caregiver	AP	28.82
Personal		
Medical	A	28.82
Recreational	A	28.82
B. TEMPORARY RESIDENTIAL USES		
None allowed		
C. AGRICULTURAL AND ANIMAL FACILITIES INCIDENTAL TO A RESIDENCE		
None allowed		
D. OTHER RESIDENTIAL USES		
None allowed		
28.73 RECREATION, EDUCATION, AND PUBLIC ASSEMBLY USES		
A. RECREATION USES		
Complementary Commercial Facility	UP	28.73.10(A)
Marsh oriented recreation	UP	28.73.10(A)
Public open space area	A	28.73.10(A)
B. EDUCATION USES		
Marsh Education	UP	28.73.20(A)
C. PUBLIC ASSEMBLY USES		
None allowed		
28.74 RETAIL AND OFFICE USES		
A. RETAIL USES		
None Allowed		
B. OFFICE USES		
Marsh research facility	UP	28.74.20(A)
28.75 TOURIST USES		
None Allowed		
28.76 COMMERCIAL SERVICE USES		
None Allowed		

28.77 INDUSTRIAL, MANUFACTURING, PROCESSING AND WHOLESALE USES		
None Allowed		
28.78 COMMUNICATION, INFRASTRUCTURE AND SERVICE USES		
A. COMMUNICATION USES		
None Allowed		
B. INFRASTRUCTURE USES		
Commercial wind turbine generator	- - -	
Dredging of minerals and natural resources	UP	28.78.20(A)
Non-commercial wind turbine		
100 feet or less in height	A	28.80
Over 100 feet in height	- - -	
Oil or Gas Well[4], Natural Gas Storage	UP	28.78.20(A) & (B)(7)
Pipeline, transmission or distribution line in R.O.W.	A	28.78.20(A) & (B)(8)
Utility facilities or infrastructure, outside of R.O.W.	UP	28.78.20(A) & (B)(9)
C. PUBLIC SERVICE USES		
Public Service Facility	UP	28.78.30(A) & (B)(4)
D. TEMPORARY CONSTRUCTION AND INFRASTRUCTURE		
Temporary facility for the transfer of material from shore to barge	UP	28.78.40(A)
28.79 RESOURCE CONSERVATION USES		
Conservation and Mitigation Bank	UP	28.79.10(A)
Growing of plants and natural feed important to wildlife habitat	A	28.79.10(A)
Restoration of tidal, managed, and seasonal wetlands	UP	28.79.10(A)

Notes:

1. Any development within the Suisun Marsh, as defined by Section 29114 of the Public Resources Code, shall be subject to obtaining a Marsh Development Permit pursuant to the Suisun Marsh Preservation Act of 1977, and as provided for in Section 28.104 of this Code.

2 Management of wetlands and agricultural operations, with emphasis on grain and hay crop production, pasture, grazing, and the growing of plants and natural feed important to wildlife habitat.

3 Buildings and uses clearly accessory or incidental to any permitted use located on the premises, including a one-family dwelling or a manufactured dwelling, barns, private stables, sheds, and other associated buildings.

4. Oil wells not permitted in the Suisun Marsh primary and secondary management areas.

28.52.30 – Marsh Preservation District Development Standards

Subdivision, new land uses, main buildings including primary and secondary dwellings, and alterations to existing land uses and buildings, shall be designed, constructed, and/or established in compliance with the applicable development standards delineated or referenced in Table 28-52B.

TABLE 28.52B

DEVELOPMENT STANDARDS FOR MAIN BUILDING, ACCESSORY STRUCTURES, AND USES

MAIN BUILDING	
Minimum Lot Area	250 acres
Setbacks	
Front	Ten feet; unless otherwise indicated by building lines on the zoning maps.
Sides (each)	Ten feet; unless otherwise indicated by building lines on the zoning maps.
Rear	Ten feet; unless otherwise indicated by building lines on the zoning maps.
Between structures	*10 feet*
Height limit	*Thirty-five feet; provided, that additional height may be permitted for non-dwelling structures, including windmills, silos, and private water tanks; and provided further, that no such structure shall exclude the heights allowed in Section 28-99 of this code, if located in an airport flight obstruction area.*
ACCESSORY STRUCTURES AND USES	
Setbacks	*Accessory buildings shall not be less than sixty feet from the front property line nor less than twenty feet from any side or rear property line, nor less than thirty feet from any dwelling unit on the property.*
OTHER STANDARDS	
Parking Requirements	*Parking shall be provided in conformance with the parking standards in Section 28.94*
Signs	*All signs shall comply with the sign requirements in Section 28.96*

28.60 Special and Overlay Districts

Subsections

28.61 Park (P) District

A. Purpose:

The P District is designated to preserve land well suited for outdoor recreational purposes and to provide for recreation, amusement, play or relaxation.

B. P District Land Uses and Permit Requirements.

Table 28-61A identifies the land uses allowed by this Zoning Ordinance in the P District and the land use permit required to establish each use. In addition to the land use permit required by Table 28-61A, special requirements may apply to certain uses. Architectural Approval may also be required for certain uses in compliance with Section 28.102 (Architectural Approval). A Building Permit shall also be required prior to any construction, alteration, remodeling or change in occupancy from a previous building permit.

Note: Where the last column in the table ("Land Use Regulations") includes a section number, e.g. 28.74, the zoning regulations in the referenced section apply to the use. Where the last column includes a chapter number, e.g. Chapter 13.6, the regulations in the referenced Solano County Code apply to the use. Provisions in other sections of this Zoning Ordinance may also apply.

TABLE 28.61A TABLE OF ALLOWED USES

A= Allowed by right, AP= Administrative Permit, MUP= Minor Use Permit, UP= Use Permit, E=Exempt, - - - = Prohibited

ALLOWED USES* *See Definitions Section 28-10	**Permitted Uses**	**Land Use Regulations**** **See Section 28-70.10
	P District	
28.71 AGRICULTURAL USES		
A. CROP PRODUCTION AND GRAZING		28.71.10
Agricultural Accessory structures	A	28.71.10(A) & (B)(1)
Crop Production	A	28.71.10(A)
Grazing	A	28.71.10(A)
B. AGRICULTURAL PROCESSING USES		
On-site Agricultural Processing	- - -	28.71.20(A) & (B)(1)
C. ANIMAL FACILITIES AND OPERATIONS		
None Allowed	- - -	
D. OTHER AGRICULTURAL OPERATIONS		
None Allowed	- - -	
28.72 RESIDENTIAL USES		
A. DWELLINGS		28.72.10
Primary Dwelling	A[1]	28.72.10(A)
Cannabis Cultivation		
Caregiver	AP	28.82
Personal		
Medical	A	28.82
Recreational	A	28.82
B. TEMPORARY RESIDENTIAL USES		
None Allowed	- - -	
C. AGRICULTURAL AND ANIMAL FACILITIES INCIDENTAL TO A RESIDENCE		
None Allowed	- - -	
D. OTHER RESIDENTIAL USES		
None Allowed	- - -	

(1) TABLE 28.61A TABLE OF ALLOWED USES

A= Allowed by right, AP= Administrative Permit, MUP= Minor Use Permit, UP= Use Permit, E=Exempt, - - - = Prohibited

ALLOWED USES* *See Definitions Section 28-10	**Permitted Uses**	**Land Use Regulations**** **See Section 28-70.10
	P District	
28.73 RECREATION, EDUCATION AND PUBLIC ASSEMBLY USES		
A. RECREATION USES		
Commercial Outdoor Recreation		
Not including enclosed structures	A	28.73.10(A)
Including enclosed structures	UP	28.73.10(A)
Public Outdoor recreation	A	28.73.10(A)
B. EDUCATION USES		
Ecological and agricultural education	A	28.73.20(A)
C. PUBLIC ASSEMBLY USES		
Circus, Carnival, Fair, or Revival	MUP	28.70.10; 28.73.30(A)
Special Events incidental to Commercial Agriculture		
6 per year max, and 150 persons or less	AP	28.73.30(A) & (B)(6)
12 per year max, and 150 persons or less	MUP	28.73.30(A) & (B)(6)
More than 12 per year, or more than 150 persons	UP	28.73.30(A) & (B)(6)
28.74 RETAIL AND OFFICE USES		
A. RETAIL USES		
Roadside stand for the sale of agricultural products grown on-site		
More than 80 feet from the centerline of the street	A	28.74.10(A) & (B)(8)
Less than 80 feet from the centerline of the street	UP	28.74.10(A) & (B)(8)
B. OFFICE USES		
None Allowed	- - -	
28.75 TOURIST USES		
A. AGRITOURISM		
None Allowed	- - -	
B. TEMPORARY AGRITOURISM		
None Allowed	- - -	

1 Length of stay limited to twelve months

TABLE 28.61A TABLE OF ALLOWED USES

A= Allowed by right, AP= Administrative Permit, MUP= Minor Use Permit, UP= Use Permit, E=Exempt, - - - = Prohibited

ALLOWED USES* *See Definitions Section 28-10	**Permitted Uses**	**Land Use Regulations**** **See Section 28-70.10
	P District	
28.76 COMMERCIAL SERVICE USES		
A. AGRICULTURAL SERVICES		
None Allowed	- - -	
B. COMMERCIAL SERVICES		
None Allowed	- - -	
28.77 INDUSTRIAL, MANUFACTURING, PROCESSING AND WHOLESALE USES		
A. INDUSTRIAL, MANUFACTURING AND PROCESSING USES		
None Allowed	- - -	
B. WHOLESALE USES		
None Allowed	- - -	

TABLE 28.61A TABLE OF ALLOWED USES

A= Allowed by right, AP= Administrative Permit, MUP= Minor Use Permit, UP= Use Permit, E=Exempt, - - - = Prohibited

ALLOWED USES* *See Definitions Section 28-10	**Permitted Uses**	**Land Use Regulations**** **See Section 28-70.10
	P District	
28.78 COMMUNICATION, INFRASTUCTURE AND SERVICE USES		
A. COMMUNICATION USES		
Wireless communication facility		
Co-location	MUP	28.78.10; 28.81
New tower	UP	28.78.10; 28.81
B. INFRASTRUCTURE USES		
Commercial wind turbine generator	UP	28.80
Non-commercial wind turbine		
100 feet or less in height	A	28.80
Over 100 feet in height	MUP	28.80
Pipeline, transmission or distribution line in R.O.W.	A	28.78.20(A) & (B)(8)
Utility facilities or infrastructure, outside of R.O.W.	UP	28.78.20(A) & (B)(9)
C. **SERVICE USES**		
Public Service Facility	UP	28.78.30(A) & (B)(4)
D. **TEMPORARY CONSTRUCTION AND INFRASTRUCTURE**		
Meteorological Tower, 100 feet or less in height	AP	28.78.20(A) & (B)(6)
Meteorological Tower, greater than 100 feet in height	MUP	28.78.20(A) & (B)(6)
28.79 RESOURCE CONSERVATION USES		
None Allowed	- - -	

Notes:

(1) On parcels with 20 acres or more.

C. General Development Standards:

Subdivision, new land uses, main buildings including primary and secondary dwellings, and alterations to existing land uses and buildings, shall be designed, constructed, and/or established in compliance with the applicable development standards delineated or referenced in Table 28-61B.

TABLE 28-61B

DEVELOPMENT STANDARDS FOR MAIN BUILDING, ACCESSORY STRUCTURES AND USES

	P District
PRIMARY BUILDING	
Minimum Lot Area	*None*
Setbacks	
Front	Twenty feet; except that buildings shall not be less than fifty feet from the centerline of the street, and unless otherwise indicated by building lines on the zoning maps.
Sides (each)	*None*
Rear	*None*
Between structures	*Ten feet*
Height limit	*Thirty-five feet; provided, that additional height may be permitted if a use permit is first secured*
OTHER STANDARDS	
Parking Requirements	*Parking shall be provided in conformance with the parking standards in Section 28.94*
Signs	*All signs shall comply with the sign requirements in Section 28.96*

28.68. Policy Plan Overlay (PP) Districts

(a) **Purpose.** The policy plan overlay district is intended to encourage comprehensive planning on focused, large-scale or mixed land use developments. Policy plan overlay districts can provide zoning flexibility by establishing development standards and land use allocations which may vary with the type, density or intensity of use of the underlying district regulations for specific parcels or areas that will ensure balanced and integrated growth guided by creativity and innovation in architecture, planning and environmental design. These standards and uses should accommodate the special needs of the physical site and the community while being consistent with the Solano County General Plan. Development standards are intended to meet or exceed those of the underlying districts described in the other chapters of the Zoning Ordinance while promoting the public health, safety and general welfare without unduly inhibiting the advantages of modern planning and building techniques. The policy plan overlay district requires a detailed development plan that combines the functions of zoning, master, and precise plans, design review, and capital improvement plans in one coordinated process.

(b) **Applicability.** The policy plan overlay district may be combined with all or part of any general plan area or zoning district designated for this purpose by the general plan. Each policy plan overlay district shall be shown on the official Solano County zoning map by adding the symbol "-PP" as a designator to a base district along with a clear delineation of the boundaries of the overlay district and an identifying serial number. The serial number shall refer to the Department of Resource Management's rezoning petition file for the particular policy plan overlay zone application.

(c) **Initiation of Zone Change.** A petition for a policy plan overlay district may be initiated pursuant to Section 28-111 of this Chapter. Application shall be in the form prescribed by the Director of Resource management. The application shall consist of a written plan and graphics for policy guidance, and a detailed statement of standards and uses to determine consistency with the Solano County general plan. The application shall, at a minimum, include the items and information described in this Section.

1. Fee or fees as set by the Board of Supervisors pursuant to Section 11-111 of this code. No part of such fee shall be refundable.

2. A complete legal description of the subject property.

3. A narrative description of existing uses of the subject property and adjacent properties.

4. Enumeration of existing and proposed ordinance standards along with a detailed explanation of the differences between them.

5. Findings of fact demonstrating the proposed policy plan overlay district in its entirety is consistent with the Solano County general plan and findings set forth in subsection (d) of this Section.

6. A set of standards which will define the purpose, intended uses, development density, dimensional constraints and performance standards for the subject property and, in general, shall take the following form:

a. Statement of purpose

b. Permitted uses

c. Accessory uses

d. Conditional uses

e. Prohibited uses

f. Architectural and sign standards

g. Height, building coverage, and yard setbacks

h. Landscaping

i. Parking and loading requirements

j. Additional development standards

k. Performance standards (e.g., hazardous materials and waste management)

l. Site specific policies to ensure adequate protection of the public health and safety and consistency with the surrounding uses

m. Exceptions and general provisions

7. A development plan at a scale no smaller than one inch equals a hundred feet shall depict use areas and proposed circulation based on traffic density information provided in subsection (c)(6). The development plan shall include a schematic representation of subdivision, grading, landscaping and proposed systems of drainage, water supply, sewage disposal and utility service.

8. Representative design and improvement details shall accompany the development plan and be presented in detail to establish that development and construction will be consistent with the proposed policy plan overlay district. Minimum specific design and improvement details shall include typical building elevations, streetscape, and explanation of all relevant features required pursuant to this subsection.

9. A development schedule describing the sequence and timing of subdivision and capital improvements, along with estimated capital costs and proposed funding mechanism.

10. Such other information as may be required by the Board of Supervisors, Planning Commission, or Director of Resource Management concerning the proposed development and use of such property, or which the applicant may deem appropriate for a full consideration of the proposal by the Board of Supervisors, Planning Commission, and Director of Resource Management.

11. All information required by this Section shall be stated in a manner to describe the character and style of the proposed development and use in sufficient detail to constitute definite criteria under which subsequent development can be judged for compliance.

B. **Adoption of Policy Plan Overlay District.** Adoption of a policy plan overlay district shall be by action of the Planning Commission and Board of Supervisors, including adoption of an ordinance, pursuant to Section 28-111 of this code.

The Board of Supervisors shall not approve a policy plan overlay district unless it makes the following findings:

(1) The proposed development is in conformity with the general plan and any applicable specific plan.

(2) The proposed development is designed to produce an environment of stable and desirable character consistent with all applicable goals, objectives, policies, proposals, criteria, standards and procedures of the general plan, and any applicable specific plan for the area in which the proposed development is a part.

(3) The proposed development meets applicable development requirements and where possible, exhibits creativity and innovation in architectural, engineering, planning, and environmental design.

(4) Adequate mitigation is provided for any use, process, equipment, or materials which are found to be objectionable or to be injurious to property located in the vicinity by reason of odor, fumes, dust, smoke, cinders, glare, unsightliness, hazardous materials, traffic congestion, or to involve any hazard of fire or explosion.

Upon approval of the policy plan overlay district by the Planning Commission and adoption by the Board of Supervisors of an ordinance amending the underlying zoning district, no further review by the Board of Supervisors or Planning Commission shall be required under this Chapter except pursuant to Section 28-112 of this Chapter.

(e) **Interim Applicable Zoning.** During review of an application for a policy plan overlay district, no uses of the property subject to such application shall be allowed except those which would have been permitted under the zoning that existed at the time of the policy plan overlay district application.

(f) **Administration and Modification.** The Director of Resource Management is authorized to issue approvals for building construction, site development plans, and for all minor design,

site, sign, and building alterations that are deemed substantially in accord with the approved policy plan overlay district. All requests for minor alterations shall be submitted to the Director of Resource Management in writing, and shall include an explanation of the circumstances necessitating such alteration and the substantial conformity of the proposed modification with the approved policy plan overlay district.

(g) **Conflict and severability.** All uses and development in the policy plan overlay district shall also be subject to all other provisions of this code, except that where conflict in regulations occurs, the regulations specified in this Chapter shall prevail. All uses and development in the policy plan overlay district shall also be subject to all applicable provisions of state law, including the California Environmental Quality Act. Wherever possible, the requirements of that act shall be integrated into the approval process for a policy plan overlay district to ensure comprehensive and coordinated review in a timely manner.

SEE ATTACHED APPENDICES FOR THE FOLLOWING POLICY PLAN OVERLAY DISTRICTS:

A. Policy Plan Overlay No. PP-01-03 - (Dove Creek Trail) - Ordinance No. 2005-1669

B. Policy Plan Overlay No. PP-02-04 - (Karaouni) - Ordinance No. 2007-1688

C. Policy Plan Overlay No. PP-11-01 - (Woodcreek66) - Ordinance No. 2016-1769

SOLANO COUNTY PLANNING COMMISSION
RESOLUTION NO. ____

RECOMMENDING ADOPTION OF AN ORDINANCE AMENDING SECTIONS 28.21, 28.22, 28.23, 28.31, 28.32, 28.41, 28.42, 28.43, 28.51, 28.52, 28.61 AND ADDING SECTION 28.82 TO REGULATE CANNABIS CULTIVATION FOR PERSONAL USE IN UNINCORPORATED SOLANO COUNTY

WHEREAS, Proposition 64 decriminalizing the use, possession, and cultivation of recreational cannabis in the State of California was passed by voters on November 8, 2016; and

WHEREAS, Proposition 64 mandates that, at a minimum, an individual be allowed to cultivate up to 6 cannabis plants for recreational use in a residence or in a locked, secured structure on the grounds of a residence; and

WHEREAS, Proposition 64 permits a city or county to enact reasonable regulations on personal cannabis cultivation, although the city or county may not ban indoor personal cultivation; and

WHEREAS the Medical Marijuana Regulation and Safety Act (MMRSA) was enacted on September 11, 2015 (the Act was renamed the "Medical Cannabis Regulation and Safety Act" (MCRSA) on June 27, 2016) to provide a comprehensive state-wide licensure and regulatory scheme for medical cannabis; and

WHEREAS, MCRSA allows a medical cannabis patient to cultivate up to 100 square feet of cannabis for personal use and a designated primary caregiver to cultivate up to 500 square feet of cannabis for up to 5 patients' use; and

WHEREAS, MCRSA permits a city or county to regulate or ban such personal or caregiver cultivation of medical cannabis; and

WHEREAS, there are currently no provisions regulating or explicitly allowing for cultivation of personal or caregiver cannabis in the Solano County Zoning Regulations; and

WHEREAS, the Board of Supervisors enacted a moratorium on commercial marijuana activities and personal and caregiver outdoor cultivation on December 6, 2016 and extended it on January 10, 2017 to allow the County time to gather public input and consider how best to regulate cannabis locally under MCRSA and AUMA and to consider the regulations that the State of California are drafting; and

WHEREAS, the Board of Supervisors, at public meetings on November 1, 2016 and January 24, 2017 expressed a desire to apply reasonable regulations to personal cultivation and caregiver cultivation in order to mitigate potential nuisance impacts of cannabis cultivation; and

WHEREAS, the Solano County Planning Commission held public meetings on November 17, 2016 and January 19, 2017 to invite public comment and discuss potential reasonable regulations for personal and caregiver cultivation of cannabis; and

WHEREAS, on February 8, 2017, County staff held a community meeting to hear from the public regarding reasonable regulations for personal cultivation and caregiver cultivation; and

WHEREAS, the Solano County Planning Commission during the course of a duly noticed public hearing as required by Government Code section 65854, considered the

proposed amendments to the Chapter 28 Zoning Regulations (Exhibit A) on March 16, 2017; and

WHEREAS, at this hearing the Planning Commission received a report and materials from the Department of Resource Management and the proposed code amendments were explained and discussed and comments were invited from persons in attendance; and

WHEREAS, the Planning Commission has considered the determination made by staff that the proposed amendments top Chapter 28 are exempt from the California Environmental Quality Act (CEQA) under Section 15061(b)(3) of Title 14 of the California Code of Regulations because because there is no possibility that the project may have a significant effect on the environment; and

WHEREAS, after due consideration, the Planning Commission has made the following findings:

1. The proposed amendments to the Zoning Regulations are consistent with the General Plan; and

2. The proposed amendments to the Zoning Regulations will promote the general welfare of the County by clarifying particular uses and the appropriate standards for those uses within the various zoning districts in order to serve the needs of the public without detriment to the surrounding areas.

NOW THEREFORE, IT IS HEREBY RESOLVED as follows:

1. The above Recitations are true and correct; and

2. The Planning Commission does hereby recommend that the Board of Supervisors adopt the proposed amendments to the zoning code and enact the revisions to Chapter 28 (Exhibit A).

3. The Planning Commission further recommends that the Board find this project is exempt from further environmental review under Section 15061(b)(3) of Title 14 of the California Code of Regulations because because there is no possibility that the project may have a significant effect on the environment.

*** ***

I hereby certify that the foregoing resolution was adopted at the regular meeting of the Solano County Planning Commission on March 16, 2017 by the following vote:

AYES: Commissioners _____

_____

NOES: Commissioners _____

EXCUSED: Commissioners _____

By: _____

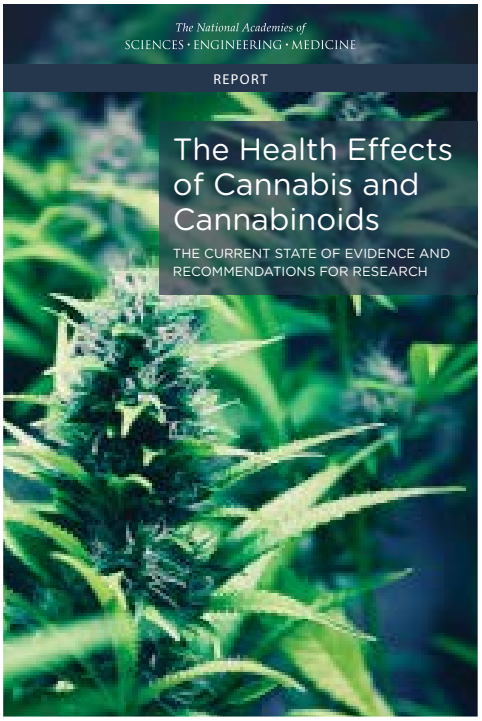
Bill Emlen, Secretary

THE HEALTH EFFECTS OF CANNABIS AND CANNABINOIDS

CHAPTER HIGHLIGHTS

January 2017

In the report *The Health Effects of Cannabis and Cannabinoids: The Current State of Evidence and Recommendations for Research,* an expert, ad hoc committee of the National Academies of Sciences, Engineering, and Medicine presents nearly 100 conclusions related to the health effects of cannabis and cannabinoid use and makes recommendations for an agenda to help expand and improve cannabis research efforts and better inform future public health decisions.



The Chapter Highlights below provide broad overview statements of the report's chapters regarding certain prioritized health conditions. To read the committee's conclusions in detail, as well as the definitions of weights of evidence, please see the "Committee's Conclusions" document at nationalacademies.org/CannabisHealthEffects.

Each blue header below links to the corresponding chapter in the report, providing much more detail. To read the full report, please visit **nationalacademies.org/CannabisHealthEffects.**

THERAPEUTIC EFFECTS

In adults with chemotherapy-induced nausea and vomiting, oral cannabinoids are effective antiemetics.

In adults with chronic pain, patients who were treated with cannabis or cannabinoids are more likely to experience a clinically significant reduction in pain symptoms.

In adults with multiple sclerosis (MS)-related spasticity, short-term use of oral cannabinoids improves patient-reported spasticity symptoms.

For these conditions, the effects of cannabinoids are modest; for all other conditions evaluated, there is inadequate information to assess their effects.

CANCER

The evidence suggests that smoking cannabis does not increase the risk for certain cancers (i.e., lung, head, and neck) in adults.

There is modest evidence that cannabis use is associated with one subtype of testicular cancer.

There is minimal evidence that parental cannabis use during pregnancy is associated with greater cancer risk in offspring.

CARDIOMETABOLIC RISK

The evidence is unclear as to whether and how cannabis use is associated with heart attack, stroke, and diabetes.

RESPIRATORY DISEASE

Smoking cannabis on a regular basis is associated with chronic cough and phlegm production.

Quitting cannabis smoking is likely to reduce chronic cough and phlegm production.

It is unclear whether cannabis use is associated with COPD, asthma, or worsened lung function.

IMMUNITY

There exists a paucity of data on the effects of cannabis or cannabinoid-based therapeutics on the human immune system.

There is insufficient data to draw overarching conclusions concerning the effects of cannabis smoke or cannabinoids on immune competence.

There is limited evidence to suggest that regular exposure to cannabis smoke may have anti-inflammatory activity.

There is insufficient evidence to support or refute a statistical association between cannabis or cannabinoid use and adverse effects on immune status in individuals with HIV.

PRENATAL, PERINATAL, AND NEONATAL EXPOSURE

Smoking cannabis during pregnancy is linked to lower birth weight in the offspring.

The relationship between smoking cannabis during pregnancy and other pregnancy and childhood outcomes is unclear.

PROBLEM CANNABIS USE

Greater frequency of cannabis use increases the likelihood of developing problem cannabis use.

Initiating cannabis use at a younger age increases the likelihood of developing problem cannabis use.

CANNABIS USE AND ABUSE OF OTHER SUBSTANCES

Cannabis use is likely to increase the risk for developing substance dependence (other than cannabis use disorder).

TO READ THE FULL REPORT AND VIEW RELATED RESOURCES, PLEASE VISIT

NATIONALACADEMIES.ORG/CANNABISHEALTHEFFECTS

INJURY AND DEATH

Cannabis use prior to driving increases the risk of being involved in a motor vehicle accident.

In states where cannabis use is legal, there is increased risk of unintentional cannabis overdose injuries among children.

It is unclear whether and how cannabis use is associated with all-cause mortality or with occupational injury.

PSYCHOSOCIAL

Recent cannabis use impairs the performance in cognitive domains of learning, memory, and attention. Recent use may be defined as cannabis use within 24 hours of evaluation.

A limited number of studies suggest that there are impairments in cognitive domains of learning, memory, and attention in individuals who have stopped smoking cannabis.

Cannabis use during adolescence is related to impairments in subsequent academic achievement and education, employment and income, and social relationships and social roles.

MENTAL HEALTH

Cannabis use is likely to increase the risk of developing schizophrenia and other psychoses; the higher the use the greater the risk.

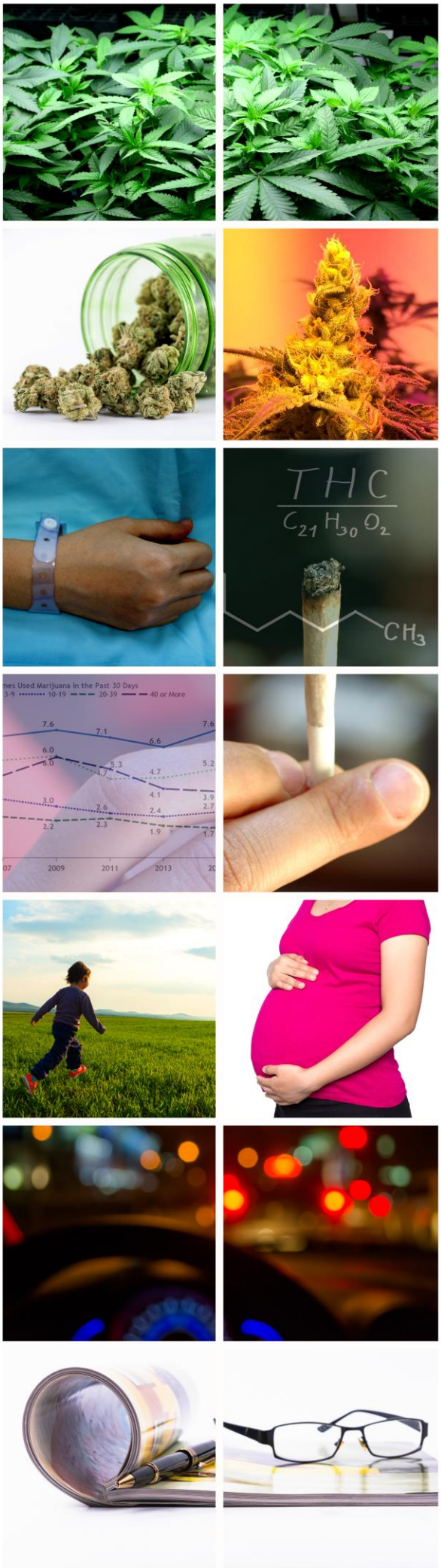
In individuals with schizophrenia and other psychoses, a history of cannabis use may be linked to better performance on learning and memory tasks.

Cannabis use does not appear to increase the likelihood of developing depression, anxiety, and posttraumatic stress disorder.

For individuals diagnosed with bipolar disorders, near daily cannabis use may be linked to greater symptoms of bipolar disorder than non-users.

Heavy cannabis users are more likely to report thoughts of suicide than non-users.

Regular cannabis use is likely to increase the risk for developing social anxiety disorder.



Monitoring Health Concerns Related to Marijuana in Colorado: 2016

Changes in Marijuana Use Patterns, Systematic Literature Review, and Possible Marijuana-Related Health Effects

COLORADO
Department of Public Health & Environment

colorado.gov/cdphe/marijuana-health-report

Presented to the Colorado State Board of Health, the Colorado Department of Revenue, and the Colorado General Assembly on Monday, January 30, 2017 by the Retail Marijuana Public Health Advisory Committee pursuant to 25-1.5-110, C.R.S.

This report has been reviewed by Larry Wolk, MD, MSPH, Executive Director and Chief Medical Officer, Colorado Department of Public Health and Environment

Retail Marijuana Public Health Advisory Committee

The Retail Marijuana Public Health Advisory Committee was established per Senate Bill 13-283 and 25-1.5-110, C.R.S. Duties of the Committee are to review the currently available scientific literature and data on health effects of marijuana use and data on patterns of marijuana use, on an ongoing basis. This document summarizes health topics and data reviewed beginning in 2014 with updates conducted through 2016. As a committee, we agree that reported findings reflect current science. Public health messages were developed by the committee to accurately communicate scientific findings. Recommendations reported were developed by the committee with the goal of protecting consumers of marijuana and the general public.

25-1.5-110, C.R.S. Monitor health effects of marijuana

"The department shall monitor changes in drug use patterns, broken down by county and race and ethnicity, and the emerging science and medical information relevant to the health effects associated with marijuana use. The department shall appoint a panel of health care professionals with expertise in cannabinoid physiology to monitor the relevant information. The panel shall provide a report by January 31, 2015, and every two years thereafter to the state Board of Health, the Department of Revenue, and the General Assembly. The department shall make the report available on its web site. The panel shall establish criteria for studies to be reviewed, reviewing studies and other data, and making recommendations, as appropriate, for policies intended to protect consumers of marijuana or marijuana products and the general public. The department may collect Colorado-specific data that reports adverse health events involving marijuana use from the all-payer claims database, hospital discharge data, and behavioral risk factors."

HISTORY: Source: L. 2013: Entire section added, (SB 13-283), ch. 332, p. 1894, § 10, effective May 28.L. 2016: Entire section amended, (SB 16-090), ch. 45, p. 107, § 1, effective August 10.

Retail Marijuana Public Health Advisory Committee members

Chairman: Mike Van Dyke, PhD, CIH, Chief, Environmental Epidemiology, Occupational Health and Toxicology Branch

Shireen Banerji, PharmD, DABAT, Clinical Manager, Rocky Mountain Poison Center

Laura Borgelt, PharmD, Associate Dean and Professor, Departments of Clinical Pharmacy and Family Medicine, University of Colorado Anschutz Medical Campus

Russell Bowler, MD, PhD, Professor of Medicine, National Jewish Health and University of Colorado

Ashley Brooks-Russell, PhD, MPH, Assistant Professor, Colorado School of Public Health; Member, Injury Prevention, Education and Research Program

Ken Gershman, MD, MPH, Manager, Medical Marijuana Research Grants Program Colorado Department of Public Health and Environment

Heath Harmon, MPH, Director of Health Divisions, Boulder County Public Health

Rebecca Helfand, PhD, Director of Data and Evaluation, Office of Behavioral Health, Colorado Department of Human Services

Sharon Langendoerfer, MD, Retired Pediatrician and Neonatologist, Denver Health Medical Center

Andrew Monte, MD, Emergency Medicine Physician, Medical Toxicologist, University of Colorado and Rocky Mountain Poison and Drug Center

Kristina T. Phillips, PhD, Clinical Psychologist, Professor, School of Psychological Sciences, University of Northern Colorado

Judith Shlay, MD, MSPH, Interim Director, Denver Public Health; Professor of Family Medicine, University of Colorado School of Medicine

Christian Thurstone, MD, Psychiatrist and Medical Director of Addiction Services, Denver Health; Associate Professor of Psychiatry, University of Colorado

George Sam Wang, MD, Assistant Professor of Pediatrics, Department of Pediatrics, Section of Emergency Medicine and Medical Toxicology, University of Colorado Anschutz Medical Campus and Children's Hospital Colorado; Volunteer Faculty, Rocky Mountain Poison and Drug Center

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Monitoring Health Concerns Related to Marijuana in Colorado: 2016

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Section 1

Monitoring Changes in Marijuana Use Patterns

Retail Marijuana Public Health Advisory Committee

COLORADO
Department of Public Health & Environment

Background

The Colorado Department of Public Health and Environment (CDPHE) was given statutory (In 25-1.5-110, C.R.S.) responsibility to:

- "… monitor changes in drug use patterns, broken down by county and race and ethnicity, and the emerging science and medical information relevant to the health effects associated with marijuana use."

Patterns of drug use are typically determined by using population-based surveys that ask specific questions about substance use. Colorado has created and manages several population-based surveys to assess the prevalence of a variety of health conditions and behaviors of specific populations. In addition, there are a few national surveys that collect state level data on marijuana use. The data from these surveys are compiled here to meet the reporting requirements set forth in 25-1.5-110, C.R.S. These data also have been presented to the Retail Marijuana Public Health Advisory Committee, which was charged with the duties outlined in 25-1.5-110, C.R.S. to "…establish criteria for studies to be reviewed, reviewing studies and other data, and making recommendations, as appropriate, for policies intended to protect consumers of marijuana or marijuana products and the general public." Reviewing marijuana use patterns in Colorado provides important insight to the committee members as they consider public health recommendations.

Data sources

Adult use: Behavioral Risk Factor Surveillance System (BRFSS)

The Behavioral Risk Factor Surveillance System (BRFSS) is a telephone survey of adults ages 18 years and older, sponsored by the U.S. Centers for Disease Control and Prevention (CDC). It is the nation's premier system of health-related telephone surveys that collect data from U.S. residents regarding their health-related risk behaviors, chronic health conditions and safety practices. CDPHE, in a cooperative agreement with CDC, manages and administers BRFSS in Colorado. In 2014 and 2015, Colorado added questions on marijuana use to the state-level BRFSS.

Marijuana in homes with children: Child Health Survey (CHS)

The Child Health Survey (CHS) is a telephone survey conducted among respondents to the BRFSS Survey who have children ages 1-14 in their home. Adult respondents answer questions about their children and the home environment. This annual survey provides data on a wide range of health issues and risk factors affecting children and youth in Colorado. Since 2014, questions about marijuana use and storage in the home have been included in the survey.

Adolescent and young adult use: Healthy Kids Colorado Survey (HKCS)

The Healthy Kids Colorado Survey (HKCS) collects health information from public high school and middle school students. It is a voluntary, anonymous survey, completed by students individually in their classrooms and parents are notified ahead of time. HKCS is a collaboration of CDPHE, Colorado Department of Education and Colorado Department of Human Services. This survey includes the questions on the national Youth Risk Behavioral Surveillance Survey (YRBSS). HKCS has included questions on marijuana since 1999.

Adolescent and adult use: National Survey on Drug Use and Health (NSDUH)

The Substance Abuse and Mental Health Services Administration (SAMHSA) tracks national and state level data on tobacco, alcohol, marijuana, and illicit drug use through the National Survey on Drug Use and Health (NSDUH). This survey is completed by in-person interview at the respondent's home, and includes one or two residents who are at least 12 years old. Although the survey design differs from BRFSS and HKCS, it can be used for comparisons of state and national marijuana use estimates. This report does not have a NSDUH-specific chapter, but NSDUH data are included for comparison in the BRFSS and HKCS chapters.

Use during pregnancy: Pregnancy Risk Assessment Monitoring System (PRAMS)

The Pregnancy Risk Assessment Monitoring System (PRAMS) is a mailed survey of women who recently gave birth. It is sponsored by the Centers for Disease Control and Prevention (CDC). It provides data not available from other sources about pregnancy and the first few months after delivery, and allows CDC and states to monitor changes in maternal and child health indicators, such as unintended pregnancy, prenatal care, breastfeeding, infant health, smoking and alcohol use. In 2014, Colorado added questions about marijuana use before, during and after pregnancy to the state-level PRAMS.

Each of these surveys only collects self-reported information, so there is no way to confirm whether each respondent has answered truthfully. These types of surveys have been validated in various studies, which indicate most people do answer truthfully. Consistency in methodology from year to year for each of the surveys provides confidence that trends over time can be effectively monitored.

Key details about all five surveys

Survey	Population and ages studied	Years	Data collection method
BRFSS	Adults age 18 and up	2014-2015	Telephone survey
CHS	Parents of children age 1-14	2014-2015	Telephone survey
HKCS	Adolescents and young adults age 11-18	1999-2015	In-school paper survey
NSDUH	Adolescents and adults age 12 and up	1971-2015	In-person, at home survey
PRAMS	Pregnant and recently pregnant women	2014	Mailed paper survey

Summary of key findings

The most prominent findings from all surveys are described below. For additional results and details, see the individual chapters for BRFSS (page 9), CHS(page 29), HKCS (page 39) and PRAMS (page 63).

Trends in adult marijuana use in Colorado

In 2015, BRFSS data showed an estimated 13% of Colorado adults ages 18 and up had used marijuana in the past-month. The NSDUH estimate for past-month use differs, at 17%. However, neither survey showed a statistical change from 2014 to 2015. According to NSDUH data, adult use in Colorado continued to be higher than the national average, which was 8%. BRFSS in 2015 showed past-month adult marijuana use in Colorado was highest among those 18-25 years old (26%); males (17%); and those who reported gay, lesbian, bisexual or other sexual orientation (37%). None of these groups saw a statistical change in use between 2014 and 2015. Northwest Colorado saw an increase in past-month use from 2014 (10%) to 2015 (16%), while other regions had no statistical change.

In 2015, 6% of adults reported using marijuana daily or near-daily. This was lower than daily or near-daily alcohol (22%) or tobacco use (16%). Of 18- to 25-year old marijuana users, 50% report using daily or near-daily (13% of all 18- to 25-year olds). Among adult past-month marijuana users, 79% smoke, 30% “vape” and 33% use edibles. Respondents could report using more than one method, which 50% of users did. Finally, approximately 2% of adults drove a vehicle in the past 30 days after using marijuana.

Trends in adolescent marijuana use in Colorado

HKCS results from 2015 indicate approximately 21% of Colorado high school students had used marijuana in the past-month. This is not statistically different from 2013 (20%) and is nearly identical to national estimates from YRBSS (22%). From 2005-2015, past-month use fluctuated between approximately 20% and 25%, with no clear trend. The most recent NSDUH data for high school age adolescents (14- to 17-year olds) is from 2012-2014 and shows 17% past-month use. This compares with the 2013 HKCS estimate of 19%. According to HKCS in 2015, past-month adolescent marijuana use was nearly identical among males and females (21%). Comparing grade levels, use was highest among juniors (26%) and seniors (28%). As with adults, students identifying as gay, lesbian, or bisexual were more likely to report past-month use (35%) than those identifying as heterosexual (20%). Use is higher among Hispanics (24%) and multiple or other races (28%) than among whites (20%).

In 2015, past-month marijuana use among high school students in Colorado (21%) was lower than past-month alcohol use (30%) and higher than past-month tobacco use (9%). Smoking marijuana is the most popular method of use among high school students, with 87% reporting it as their usual method of use. Edibles dropped from 5% in 2013 to 2% in 2015. In 2015, 27% of past-month high school users (more than 5% of all high school students) used daily or near-daily. Concerning age of first use, 41% of high school seniors who had ever used marijuana said they first used it by age 14 or before and another 43% had first used by age 16. 2015 data also showed that 8% of Colorado middle school students had ever used marijuana and 4% used within the past-month.

Marijuana in Colorado homes with children

In 2015, CHS data showed 8% of adults with children 1-14 years old in the home had marijuana or marijuana products in or around the home. In 82% of these homes, marijuana was stored safely, while in 18% it was potentially stored unsafely. It is estimated that approximately 14,000 homes in Colorado with children 1-14 years old had marijuana in the home with potentially unsafe storage.

For 2014 and 2015 together, 3% of adults with children 1-14 years old in the home reported marijuana being used inside the home. Of these, 83% reported the marijuana was smoked, vaporized, or dabbed. It is estimated that approximately 16,000 homes in Colorado had children 1-14 years old with possible exposure to secondhand marijuana smoke or vapor in the home.

Trends in marijuana use during pregnancy and breastfeeding in Colorado

PRAMS results from 2014 show 11% of new mothers had used marijuana shortly before their pregnancy and 6% of new mothers used it during their pregnancy. By comparison, 13% used alcohol and 6% used tobacco during pregnancy. A 2016 article reported use during pregnancy was approximately 4% nationally (see PRAMS chapter for details), an estimate that is not statistically different from PRAMS results for Colorado. According to PRAMS, use during pregnancy in Colorado was statistically higher among women 20-24 years old (13%) than among women 25-34 years old (4%) or women 35 years old or older (3%). It also was higher among women with less than a 12th-grade education (16%) than among women with some college (4%). Use during pregnancy was lower among women who intended to become pregnant (4%) than women with unintended pregnancies (9%). Finally, approximately 5% of new mothers used marijuana after pregnancy when they were also breastfeeding.

Discussion

The citizens of Colorado exhibit behaviors much more complex than any survey can capture. Currently available data cannot answer all the important questions we have about whether or not marijuana use patterns are changing as a result of legalization. The data presented here provide important insights into marijuana use in adults as well as vulnerable populations such as pregnant women; youth; and those with racial, ethnic and sexual orientation disparities.

Encouraging trends

- For adults and adolescents, past-month marijuana use has not changed since legalization either in terms of the number of people using or the frequency of use among users.
- Based on the most comprehensive data available, past-month marijuana use among Colorado adolescents is nearly identical to the national average.
- We have not identified any **new** disparities in marijuana use by age, gender, race, ethnicity or sexual orientation since legalization.
- Daily or near-daily marijuana use among adults is much lower than daily or near-daily alcohol or tobacco use. Among adolescents, past month marijuana use is lower than past month alcohol use.

Trends to continue monitoring

- About 6 percent of pregnant women choose to use marijuana while pregnant. This percentage is higher among those with unintended pregnancies as well as younger mothers or those with less education.
- At least 14,000 children in Colorado are at risk of accidentally eating marijuana products that are not safely stored, and at least 16,000 are at risk of being exposed to secondhand marijuana smoke in the home.

- More than 5 percent of high school students use marijuana daily or near daily. This rate has remained stable since at least 2005.
- Past-month marijuana use among adults in Colorado is higher than the national average. In Colorado, one in four adults ages 18-25 reported past-month marijuana use and one in eight use daily or near-daily. These numbers have been consistent since legalization.
- There continued to be disparities in marijuana use based on race/ethnicity for adolescents and sexual orientation for both adults and adolescents.
- While past-month marijuana use among adults and adolescents was stable for most regions in Colorado, adult use in the Northwest Colorado region increased from 2014 to 2015.
- More than 1-in-3 adolescents who use marijuana first use it by age 14, supporting prevention efforts aimed at children before they enter ninth grade.

Recommendations and future directions

1. Continue assessing prevalence of marijuana use via large Colorado-based surveys including the Pregnancy Risk Assessment Monitoring System, Healthy Kids Colorado Survey, and the Behavioral Risk Factor Surveillance System. Data from surveys identify trends in use patterns that can be used to inform and target education and prevention strategies. National surveys do not have a sufficient Colorado sample size to fully address patterns of use by age, race/ethnicity, and any county or regional catchment. Continued surveys using the same methodology can act as a feedback loop to ensure marijuana policies and education campaigns are effective.
2. Continue to develop, improve and expand tools to monitor marijuana use patterns. Results from the Cannabis Users Survey on Health (CUSH) will be reported in spring 2017. CUSH is a survey created by CDPHE to gather more detailed information about adult marijuana use, including methods, amounts and frequency of use; reasons for using; how it is purchased or obtained; concurrent use with other substances; and any adverse effects experienced. CDPHE is collaborating with other states and national organizations to expand use of this survey to other states.
3. Continue in-depth analyses of existing survey data to assess risk and protective factors for marijuana use, including changes in the perception of harm from marijuana use.
4. Continue collaboration with other state and national agencies to identify data that might add additional detail on use patterns in specific populations or geographic areas in the state.

Section 1

Monitoring Changes in Marijuana Use Patterns

Chapter 1

Behavioral Risk Factor Surveillance System (BRFSS) 2014-2015 Survey Results

Retail Marijuana Public Health Advisory Committee

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The BRFSS survey and marijuana use in Colorado

The Behavioral Risk Factor Surveillance System (BRFSS) collects data on adult, individual-level behavioral health risk factors associated with leading causes of premature mortality and morbidity. It is the nation's premier system of health-related telephone surveys that collect state data about U.S. residents regarding their health-related risk behaviors, chronic health conditions, and safety practices. By collecting behavioral health risk data at the state and local level, BRFSS has become a powerful tool for targeting and building health promotion activities.[1]

Colorado participates in BRFSS using core and optional modules, and it is able to add 'state-added' questions to customize data collection to topics most relevant to Coloradans. In 2014 and 2015 Colorado added questions on marijuana use to the BRFSS (Table 1).[2] These questions have begun to give insight into marijuana use patterns among Colorado's adult population.

For additional survey details and information about analysis methods, see Appendix B.

Survey questions

Table 1. Behavioral Risk Factor Surveillance System questions asked of Colorado adults about marijuana use and methods of marijuana use, 2014-2015.

1.	Have you ever used marijuana or hashish? (all respondents were asked) a. Yes b. No c. Don't Know/Not Sure	2014/2015
2.	How old were you the first time you used marijuana or hashish? (only ever users were asked) a. Age: _____ b. Don't Know/Not Sure	2014/2015
3.	During the past 30 days on how many days did you use marijuana or hashish? (only ever users were asked) a. Number of Days: _____ b. None c. Don't Know/Not Sure	2014/2015
4.	During the past 30 days, how many times did you drive a car or other vehicle when you had been using marijuana or hashish? (only current users were asked) a. Number of days _____ b. Don't Know/Not Sure	2014/2015
5.	On the days that you did use marijuana, how many times per day did you use it on average? (only current users were asked) a. Number of times: _____ b. None c. Don't know/Not sure	2015
6.	During the past 30 days, how did you use marijuana? For each of the following methods please say YES if it does apply or NO if it does not apply or Don't know/Not sure. (only current users were asked) a. Was it vaporized? (e-cigarette-like vaporizer) b. Was it smoked? (in a joint, bong, pipe, blunt) c. Was it eaten in food? (in brownies, cakes, cookies, candy) d. Was it consumed in a beverage? (tea, cola, alcohol) e. Was it dabbed? f. Was it used in some other way? _____ (specify)	2015

The National Survey on Drug Use and Health

The Substance Abuse and Mental Health Services Administration (SAMHSA) tracks national and state level data on tobacco, alcohol, marijuana, and illicit drugs including non-medical use of prescription drugs through the National Survey on Drug Use and Health (NSDUH).[3] National and Colorado past 30 day marijuana use estimates from the NSDUH survey were compared with the Colorado BRFSS past 30 day marijuana use estimate (Figure 2).

Definitions

Current use – having used marijuana or hashish on at least one day in the past 30 days (answered at least '1 day in the past 30 days' on question 3) (Table 1)

Dabbing - a method of marijuana use where a "dab" (small amount) of marijuana concentrate is placed on a pre-heated surface, creating concentrated marijuana vapor to be inhaled.

Daily or near daily use - having used marijuana or hashish on twenty to thirty days in the past 30 days (answered '20-30 days in the past 30 days' on question 3) (Table 1)

Ever use – having used marijuana or hashish at least once in their lifetime (answered 'Yes' on question 1) (Table 1)

Monthly use - having used marijuana or hashish on one to three days in the past 30 days (answered '1-3 days in the past 30 days' on question 3) (Table 1)

Vaping (vaporization of marijuana) - a method of marijuana use where marijuana vapor, rather than smoke, is inhaled. Marijuana flower or concentrate is heated in a vaporizing device (vaporizer) to a temperature below the point of combustion, to produce vapor.

Weekly use - having used marijuana or hashish on four to nineteen days in the past 30 days (answered '4-19 days in the past 30 days' on question 3) (Table 1)

How to interpret survey results

Respondents to the BRFSS survey are a sample of Colorado adults. The percent of survey respondents selecting a specific answer might not be exactly the same as if all adults in Colorado were surveyed. Therefore, the survey results are estimates, and each has a range of possible values (also called margin of error, confidence interval, or 95% CI). These ranges are very important when comparing two estimates, and the following terms are used throughout this report:

'Not statistically different'- Typically, if the ranges of possible values *overlap* for two different survey results (like two different years, or male vs. female), we cannot be confident that there is a true difference between the two (also called 'not statistically significant.') In some cases, an additional statistical test is done to confirm.

'Statistically higher' or 'statistically lower'- If the ranges of possible values *do not overlap* for two different results, we CAN be confident that there is a true difference between the two (also called 'statistically significant.')

On the figures in this report, these ranges of possible values are indicated by black bars. In footnotes, they are referred to by the statistical term '95% CI.'

Results

Results are displayed in Figures 1-13 below.

Trends in marijuana use in Colorado

Ever marijuana use among Colorado adults was estimated at 49.3% in 2015. Survey results indicated that there were no statistical differences in ever marijuana use from 2014 (48.8%) to 2015 (49.3%). Current marijuana use among adults was estimated at 13.4% from 2015 BRFSS (Figure 1). The 2015 NSDUH estimate for current use was statistically higher, at 17.1% (Figure 2). Neither survey showed a statistical difference in current use from 2014 to 2015 (Figure 2). NSDUH estimates of current marijuana use among Colorado adults from 2006-2015 were statistically higher than the national estimates for adult current marijuana use for each year (Figure 2). Monthly, weekly, and daily or near daily marijuana use among adults in 2015 was 3.5%, 3.6%, and 6.3% respectively. In both 2014 and

2015, daily or near daily marijuana use was statistically higher than monthly or weekly marijuana use (Figure 3). Comparing across years within each level of use, there were no statistical differences between 2014 and 2015 (Figure 3). In 2015, 2.1% of adults drove a vehicle in the past 30 days when using marijuana (Figure 4). This was not statistically higher than in 2014 (2.5%).

Current marijuana use in Colorado by age, gender, race & ethnicity, and sexual orientation

In both 2014 and 2015, current marijuana use was lower among adults 35 years and older (9.3%, 10.3%) than among those 18-25 (27.5%, 26.1%) or 26-34 years of age (19.8%, 18.3) (Figure 5). Comparing across years within each age category, there were no statistical differences between 2014 and 2015 (Figure 5). In both 2014 and 2015, current marijuana use was higher among males (17.2%, 16.9%) than females (10.0%, 10.0%) (Figure 6). Comparing across years within each gender, there were no statistical differences in current marijuana use from 2014 to 2015 (Figure 6). There also were no statistical differences in current marijuana use estimates from 2014 to 2015 within any of the race/ethnicity groups: Hispanic, White, Black, Multiracial, or Other Race (Figure 7). In both 2014 and 2015, current marijuana use was higher among those who reported Gay, Lesbian, Bisexual, or Other sexual orientation (30.1%,36.9%) compared to those who reported Heterosexual orientation (12.9%, 12.4%) (Figure 8). Comparing across years within each sexual orientation category, there were no statistical differences in current marijuana use from 2014 to 2015 (Figure 8).

Current marijuana use in Colorado by region

In 2015, the range of current marijuana use was 11.2% to 17.0% across regions compared to 10.3% to 15.1% in 2014. The Northwest region of Colorado had a statistical increase in current marijuana use from 10.3% in 2014 to 16.0% in 2015 (Figure 9). There were no statistical differences in current marijuana use from 2014 to 2015 in all other regions (Figure 9).

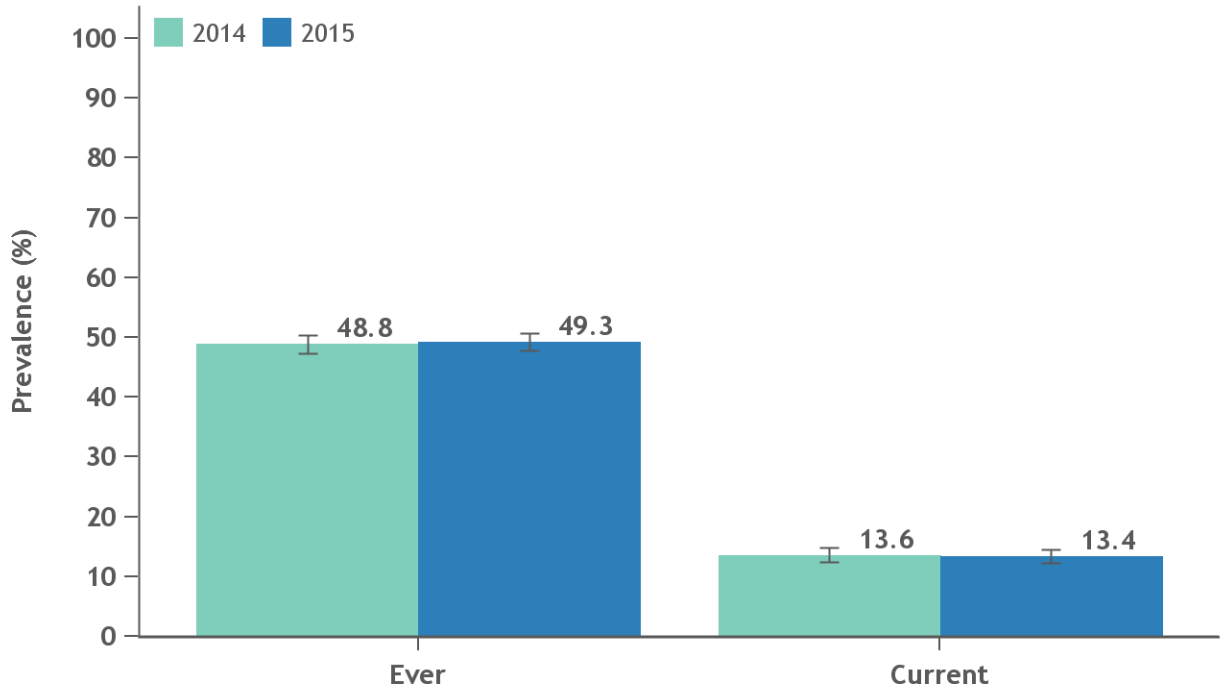
Daily or near daily marijuana use in Colorado

In both 2014 and 2015, daily or near daily marijuana use (6.0%, 6.3%) among adults was lower than daily or near daily alcohol (22.8%, 21.8%) or tobacco use (15.9%, 15.6%) (Figure 10). Comparing across years within each substance, there were no statistical differences between 2014 and 2015 (Figure 10). In both 2014 and 2015, daily or near daily marijuana use was lower among adults 35 years and older (3.6%, 4.8%) than among those 18-25 (13.3%, 13.1%) or 26-34 years of age (9.9%, 8.4%) (Figure 11). Comparing across years within each age group, there were no statistical differences in daily or near daily marijuana use between 2014 and 2015 (Figure 11).

Methods of marijuana use

Data on methods of use were only available for 2015. Dabbing was reported less among current users aged 35 years and older (7.0%) than among those 18-25 (36.0%) or 26-34 (25.2%) years of age (Figure 12). There were no statistical differences between age groups in the number of adults who smoked, vaporized, or ate/drank marijuana (Figure 12). Approximately half of adults who currently use marijuana reported using it through multiple methods (49.9%), which was statistically higher than all other reported methods of marijuana use (Figure 13). Only smoked (40.4%) was the next most commonly reported method of use after multiple methods followed by only vaporized (5.8%), only ate/drank (3.6%) and only dabbed (0.3%) in the past 30 days (Figure 13).

Figure 1. Ever and current marijuana use among Colorado adults (18+ years), 2014-2015.



Produced by: EEOHT, CDPHE 2016.
*Black bars indicate margins of error (95% Confidence Intervals).
†Ever Use was marijuana use at least once in a lifetime. Current Use is defined as marijuana use at least once in the past 30 days.
‡Data Source: Colorado Behavioral Risk Factor Surveillance System 2015.

Major findings

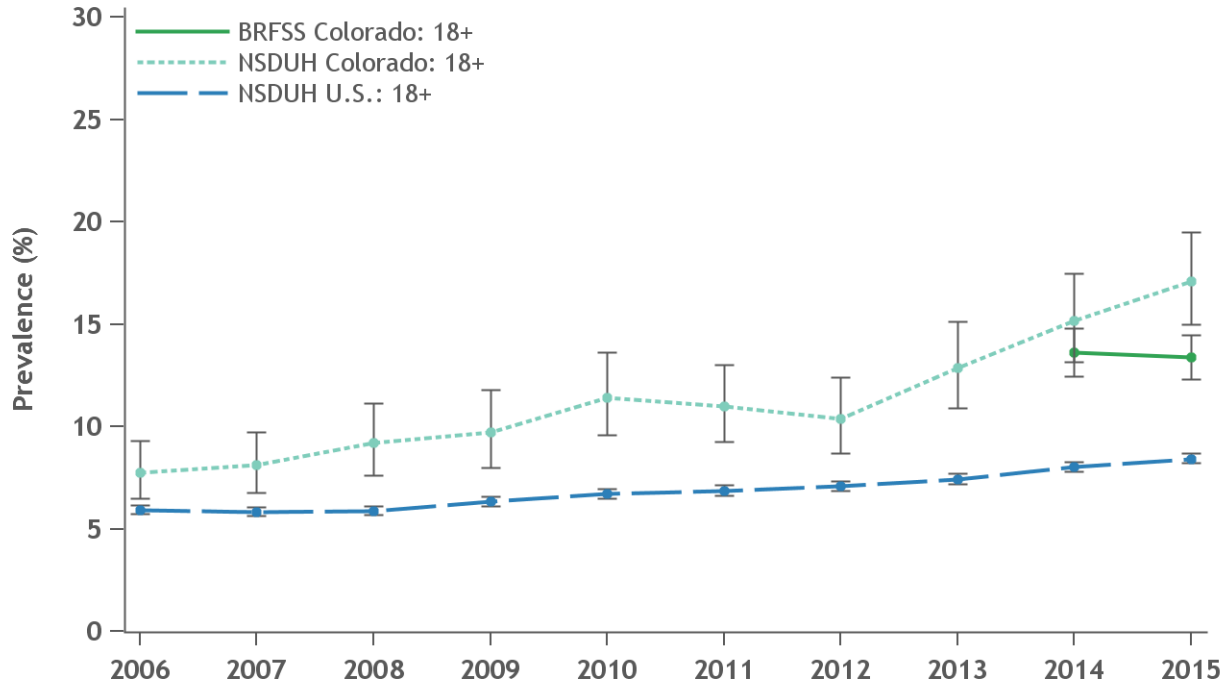
- Ever marijuana use among Colorado adults (18+ years) was not statistically different from 2014 to 2015.[a]
- Current marijuana use (marijuana use at least once in the past 30 days) among adults was not statistically different from 2014 to 2015.[b]

[a] Ever marijuana use 2014 vs. 2015: X^2= 0.15, p=0.7017

[b] Current marijuana use 2014 vs. 2015: X^2= 0.07, p=0.7922

For an explanation of terms, see "How to interpret survey results" above. For statistical methods, see Appendix B. For data, see Appendix B, Table B.1.

Figure 2. Current marijuana use among adults (18+ years): NSDUH 2006-2015 and BRFSS 2014-2015.



Produced by: EEOHT, CDPHE 2016.

*Black bars indicate margins of error (95% Confidence Intervals).

†Daily or Near Daily Use is defined as using 20-30 days in the past 30 days (marijuana or alcohol) or reporting everyday or someday use (smoking tobacco).

‡Data Source: Substance Abuse and Mental Health Services Administration, National Survey on Drug Use and Health (NSDUH) 2006-2014. Colorado Behavioural Risk Factors Surveillance System (BRFSS) 2014-2015

Major findings

- BRFSS estimated current marijuana use among Colorado adults was not statistically different from 2014 to 2015.[c]
- NSDUH estimated current marijuana use among Colorado adults was not statistically different from 2014 to 2015.[d]
- In 2015, the NSDUH estimate for current marijuana use among Colorado adults was statistically higher than the BRFSS estimate.[e]
- NSDUH estimates of current marijuana use among Colorado adults from 2006-2015 were statistically higher than the national estimates for adult current marijuana use for each year.[f]

[c] Current marijuana use (BRFSS): 2014 13.6% (95% CI 12.4-14.8%), 2015 13.4% (95% CI 12.3-14.5%)

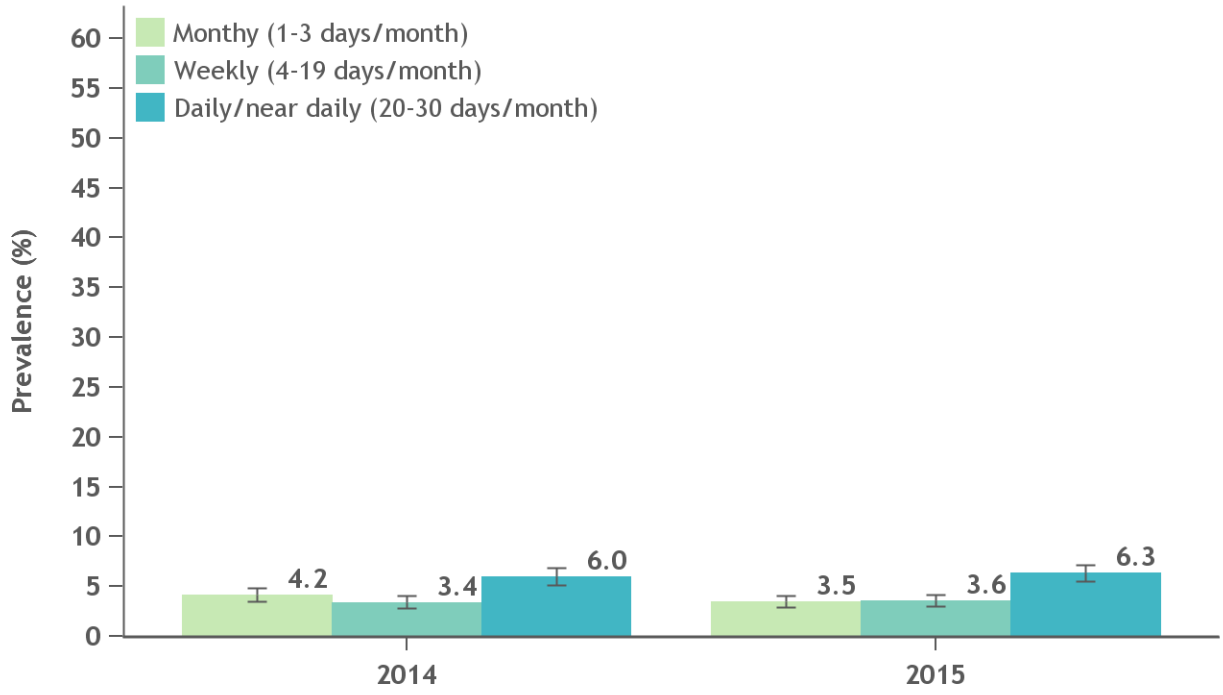
[d] Current marijuana use (NSDUH): 2014 15.2% (95% CI 13.1-17.5%), 2015 17.1% (95% CI 15.0-19.5%)

[e] Current marijuana use: 2014 BRFSS 13.6% (95% CI 12.4-14.8%), 2014 NSDUH 15.2% (95% CI 13.1-17.5%), 2015 BRFSS 13.4% (95% CI 12.3-14.5%), 2015 NSDUH 17.1% (95% CI 15.0-19.5%)

[f] See Appendix B, Table B.2 for Colorado & National NSDUH estimates from 2006-2015

For an explanation of terms, see "How to interpret survey results" above. For statistical methods, see Appendix B. For data, see Appendix B, Table B.2.

Figure 3. Monthy, weekly, and daily or near daily marijuana use among Colorado adults (18+ years), 2014-2015.



Produced by: EEOHT, CDPHE 2016.
*Black bars indicate margins of error (95% Confidence Intervals).
†Monthy use was using marijuana 1-3 days in the past 30 days, weekly use was using marijuana 4-19 days in the past 30 days, and daily or near daily use was using marijuana 20 or more days in the past 30 days.
‡Data Source: Colorado Behavioral Risk Factor Surveillance System 2015.

Major findings

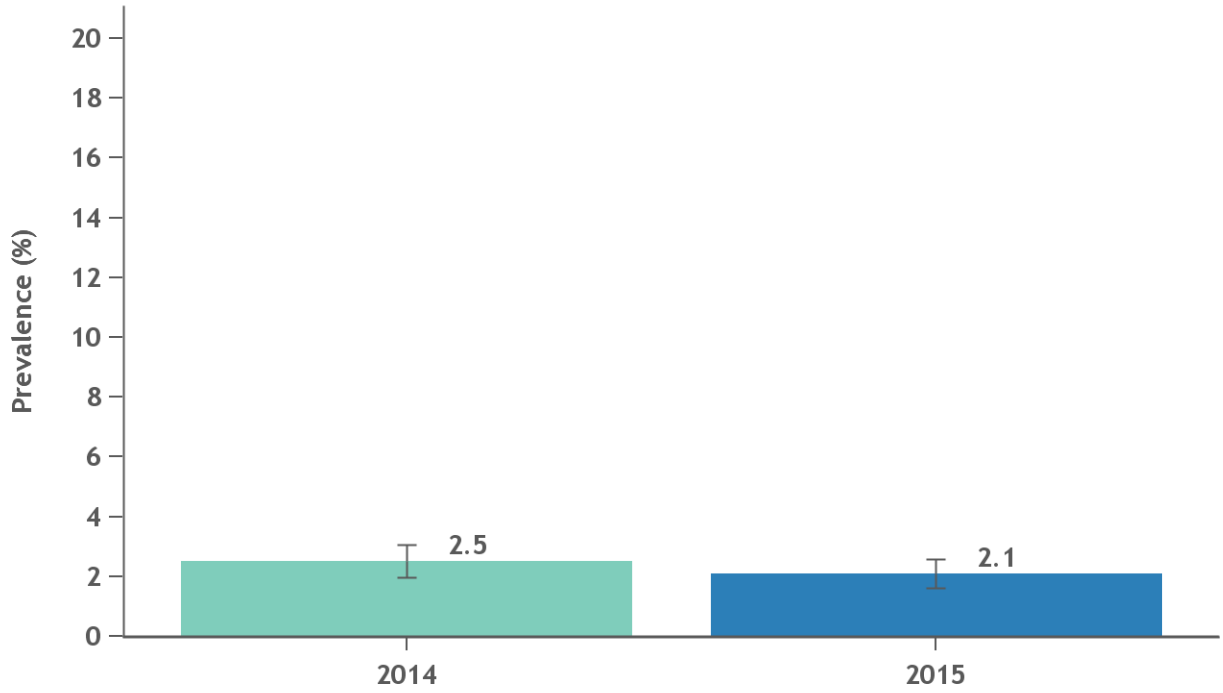
- In both 2014 and 2015, daily or near daily marijuana use among adults was statistically higher than monthly or weekly marijuana use.[g]
- Comparing across years within each level of use, there were no statistical differences between 2014 and 2015.[h]

[g] In 2014: daily/near daily 6.0% (95% CI 5.2-6.9%), monthly 4.2% (95% CI 3.5-4.8%), weekly 3.4% (95% CI: 2.8-4.0%). In 2015: daily/near daily 6.3% (95% CI 5.5-7.2%), monthly 3.5% (95% CI 2.9-4.0%), weekly 3.6 (95% CI 3.0-4.2%).

[h] Monthly, weekly and daily/near daily use 2014 vs. 2015: X^2= 2.56, p=0.4636

For an explanation of terms, see "How to interpret survey results" above. For statistical methods, see Appendix B. For data, see Appendix B, Table B.3.

Figure 4. Colorado adults (18+ years) who drove a vehicle when using marijuana in the past 30 days, 2014-2015.



Produced by: EEOHT, CDPHE 2016.
*Black bars indicate margins of error (95% Confidence Intervals).
†Current Use was marijuana use at least once in the past 30 days.
‡Data Source: Colorado Behavioral Risk Factor Surveillance System 2015.

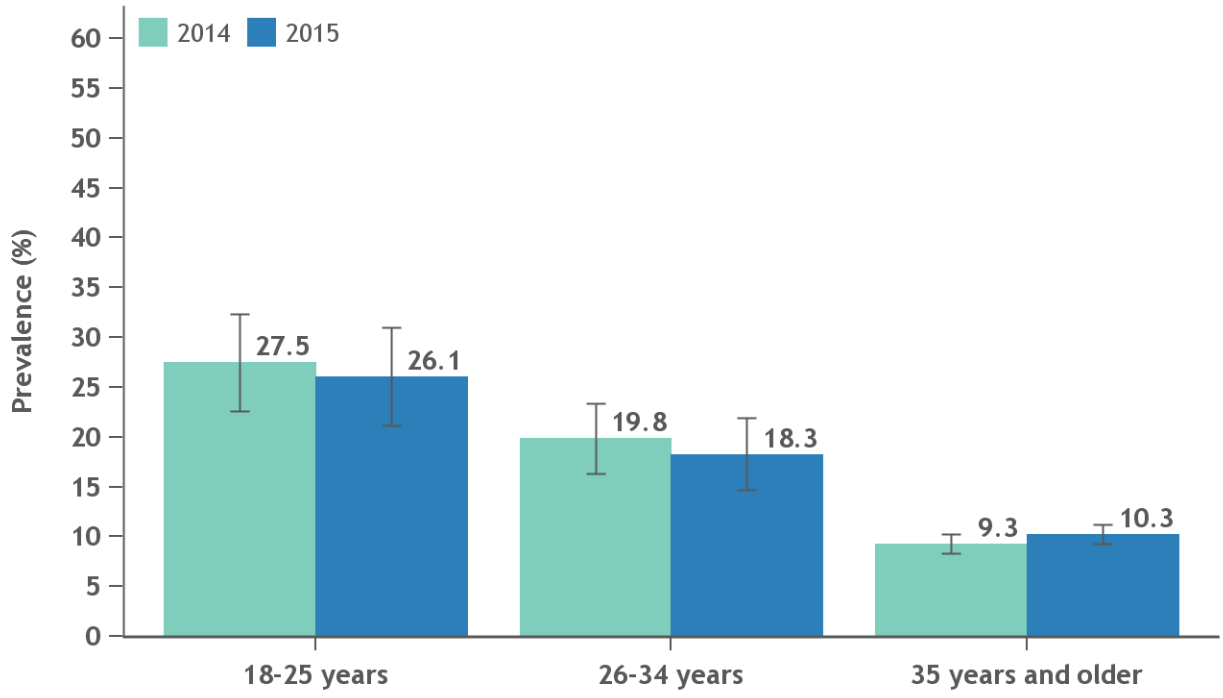
Major findings

- The prevalence of Colorado adults who drove a vehicle when using marijuana in the past 30 days was not statistically different from 2014 to 2015.[i]

[i] Drove a vehicle when using marijuana, 2014 vs. 2015: X^2= 1.26, p=0.2609

For an explanation of terms, see "How to interpret survey results" above. For statistical methods, see Appendix B. For data, see Appendix B, Table B.4.

Figure 5. Current marijuana use among Colorado adults (18+ years) by age categories, 2014-2015.



Produced by: EEOHT, CDPHE 2016.
*Black bars indicate margins of error (95% Confidence Intervals).
†Current Use was marijuana use at least once in the past 30 days.
‡Data Source: Colorado Behavioral Risk Factor Surveillance System 2015.

Major findings

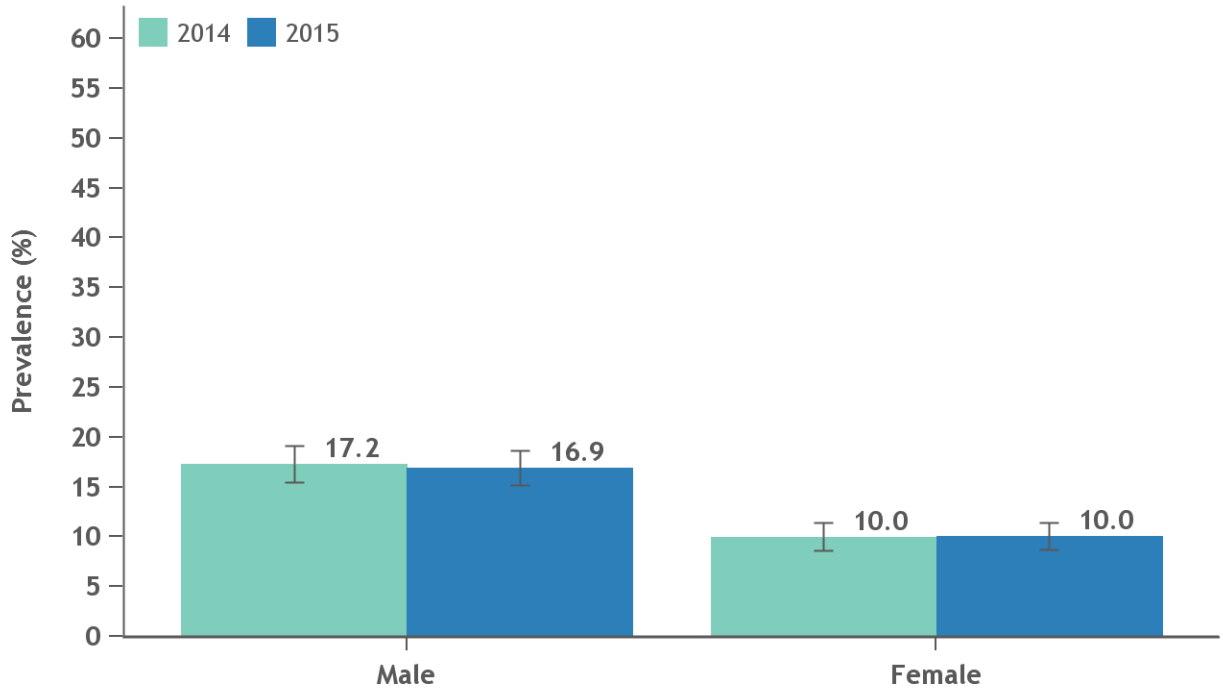
- Current marijuana use was statistically lower among adults 35 years and older than among adults 18-25 years or 26-34 years of age in both 2014 and 2015.[j]
- Comparing across years within each age category, there were no statistical differences between 2014 and 2015.[k]

[j] In 2014: 35+ years 9.3% (95% CI 8.3-10.3%), 26-34 years 19.8% (95% CI 16.3-23.4%), 18-25 years 27.5% (95% CI 22.6-32.3%). In 2015: 35+ years 10.3% (95% CI 9.3-11.2%), 18-25 years 26.1% (95% CI 21.2-31.0%), 26-34 years 18.3% (95% CI 14.7-21.9%).

[k] Current use 2014 vs. 2015: 18-25 years X^2= 0.15, p=0.6974; 26-34 years X^2= 0.36, p=0.5470; 35 years and older X^2= 1.97, p=0.1607.

For an explanation of terms, see "How to interpret survey results" above. For statistical methods, see Appendix B. For data, see Appendix B, Table B.5.

Figure 6. Current marijuana use among Colorado adults (18+ years) by gender, 2014-2015.



Produced by: EEOHT, CDPHE 2016.
*Black bars indicate margins of error (95% Confidence Intervals).
†Current Use was marijuana use at least once in the past 30 days.
‡Data Source: Colorado Behavioral Risk Factor Surveillance System 2015.

Major findings

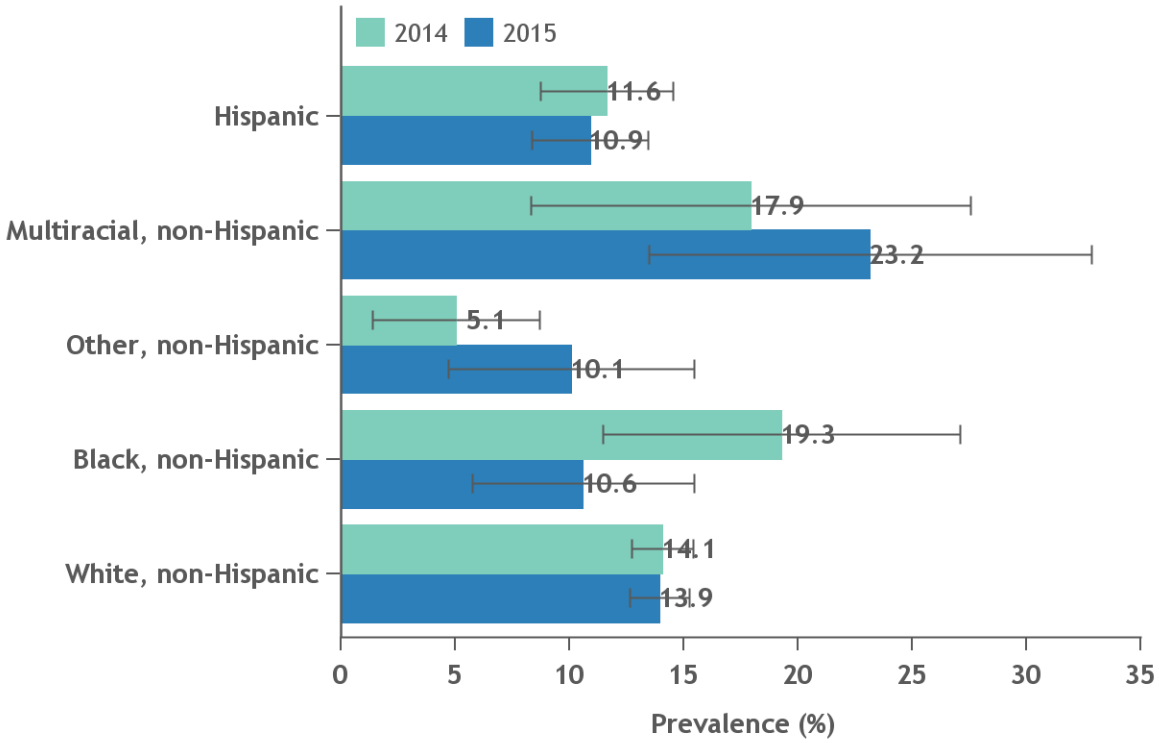
- Current marijuana use was statistically higher among male adults compared to female adults in both 2014 and 2015.[l]
- Comparing across years within each gender, there were no statistical differences in current marijuana use from 2014 to 2015.[m]

[l] In 2014: males 17.2% (95% CI 15.4-19.1%), females 10.0% (95% CI 8.6-11.4%). In 2015: males 16.9% (95% CI 15.1-18.6%), females 10.0% (95% CI 8.7-11.4%).

[m] Current use 2014 vs. 2015: adult males X^2= 0.07, p=0.7846; adult females X^2= 0.003, p=0.9509.

For an explanation of terms, see "How to interpret survey results" above. For statistical methods, see Appendix B. For data, see Appendix B, Table B.6.

Figure 7. Current marijuana use among Colorado adults (18+ years) by race and ethnicity, 2014-2015.



Produced by: EEOHT, CDPHE 2016.
*Black bars indicate margins of error (95% Confidence Intervals).
†Current Use was marijuana use at least once in the past 30 days.
‡Data Source: Colorado Behavioral Risk Factor Surveillance System 2015.

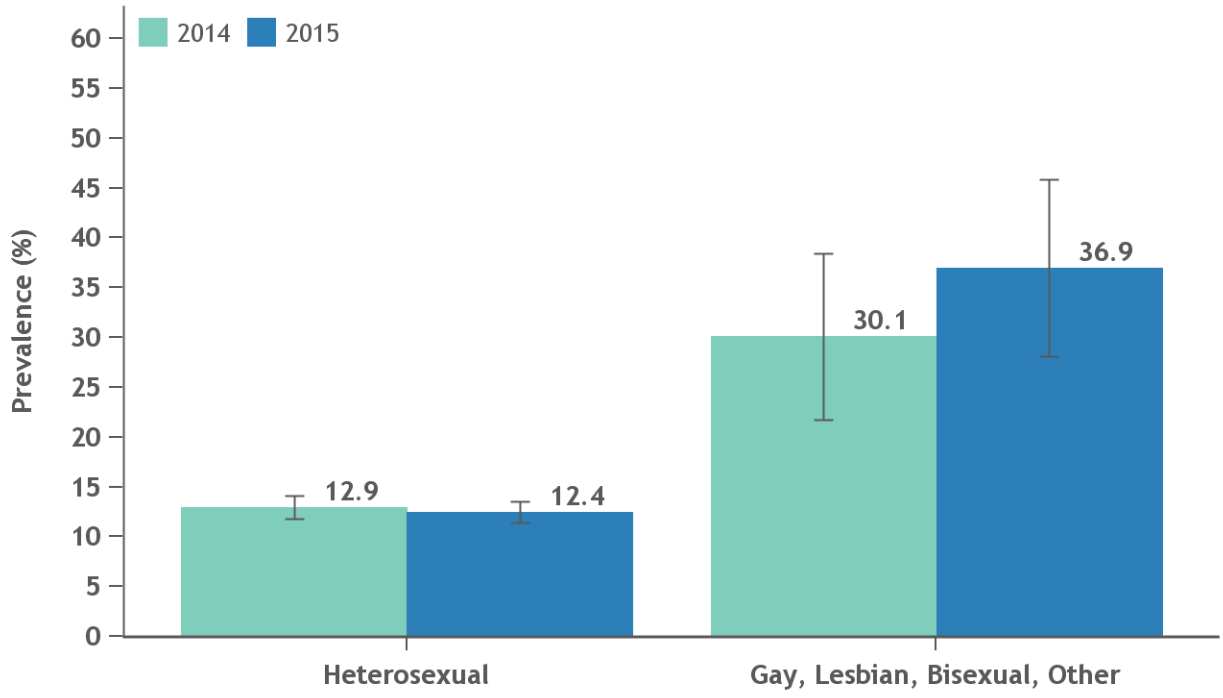
Major findings

- There were no statistical differences in estimates of current marijuana use from 2014 to 2015 within any of the race/ethnicity groups: Hispanic, White, Black, Multiracial, or Other Race.[n]

[n] Current use 2014 vs. 2015: Hispanic X^2= 0.14, p=0.7087; multiracial X^2= 0.57, p=0.4516; other X^2= 2.30, p=0.1298; white non-Hispanic X^2= 0.02, p=0.8845; black X^2 = 3.45, p=0.0633.

For an explanation of terms, see "How to interpret survey results" above. For statistical methods, see Appendix B. For data, see Appendix B, Table B.7.

Figure 8. Current marijuana use among Colorado adults (18+ years) by sexual orientation, 2014-2015.



Produced by: EEOHT, CDPHE 2016.
*Black bars indicate margins of error (95% Confidence Intervals).
†Current Use was marijuana use at least once in the past 30 days.
‡Data Source: Colorado Behavioral Risk Factor Surveillance System 2015.

Major findings

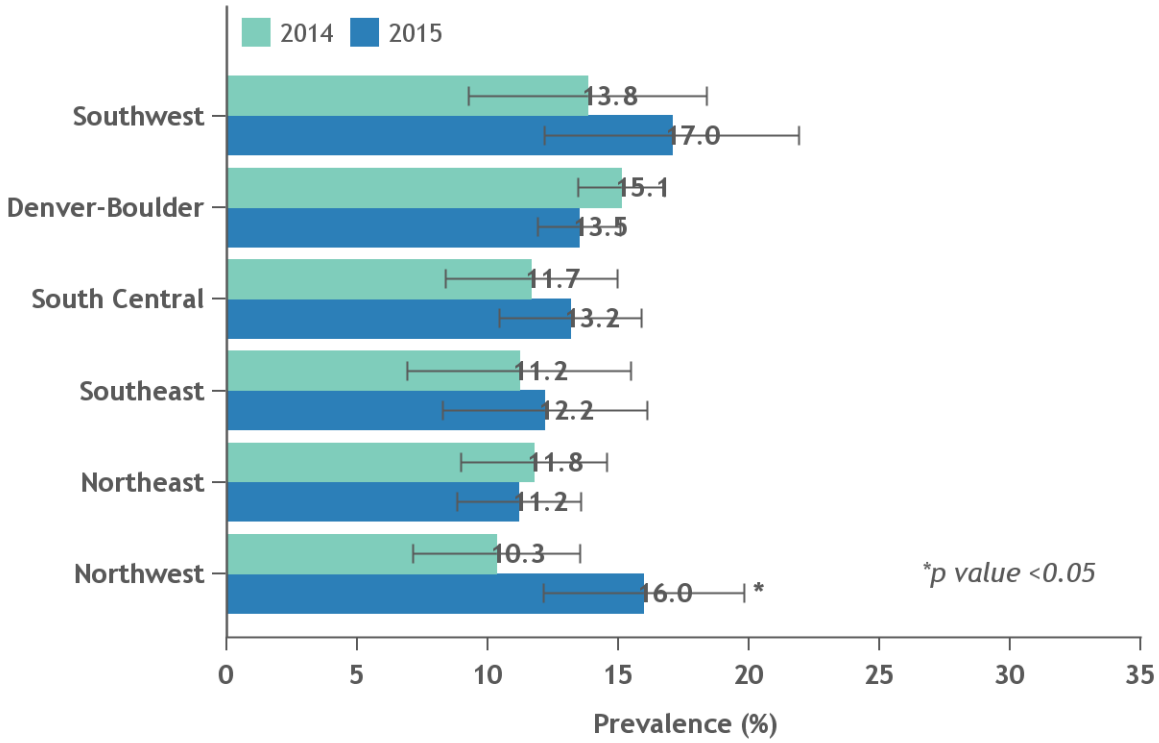
- Current marijuana use was higher among those who reported Gay, Lesbian, Bisexual, or Other sexual orientation compared to those who reported Heterosexual orientation in both 2014 and 2015.[o]
- Comparing across years within each sexual orientation category, there were no statistical differences in current marijuana use from 2014 to 2015.[p]

[o] In 2014: Gay, Lesbian, Bisexual, or Other 30.1% (95% CI 21.7-38.4%), Heterosexual 12.9% (95% CI 11.8-14.1%). In 2015: Gay, Lesbian, Bisexual, or Other 36.9% (95% CI 28.1-45.8%), Heterosexual 12.4% (95% CI 11.4-13.5%).

[p] Current use 2014 vs. 2015: heterosexual adults X^2= 0.41, p=0.5226; gay, lesbian, bisexual, or other sexual orientation adults X^2= 1.23, p=0.2669.

For an explanation of terms, see "How to interpret survey results" above. For statistical methods, see Appendix B. For data, see Appendix B, Table B.8.

Figure 9. Current marijuana use among Colorado adults (18+ years) by regions, 2014-2015.



Produced by: EEOHT, CDPHE 2016.
†Black bars indicate margins of error (95% Confidence Intervals).
‡Current Use was marijuana use at least once in the past 30 days.
§Data Source: Colorado Behavioral Risk Factor Surveillance System 2015.

Major findings

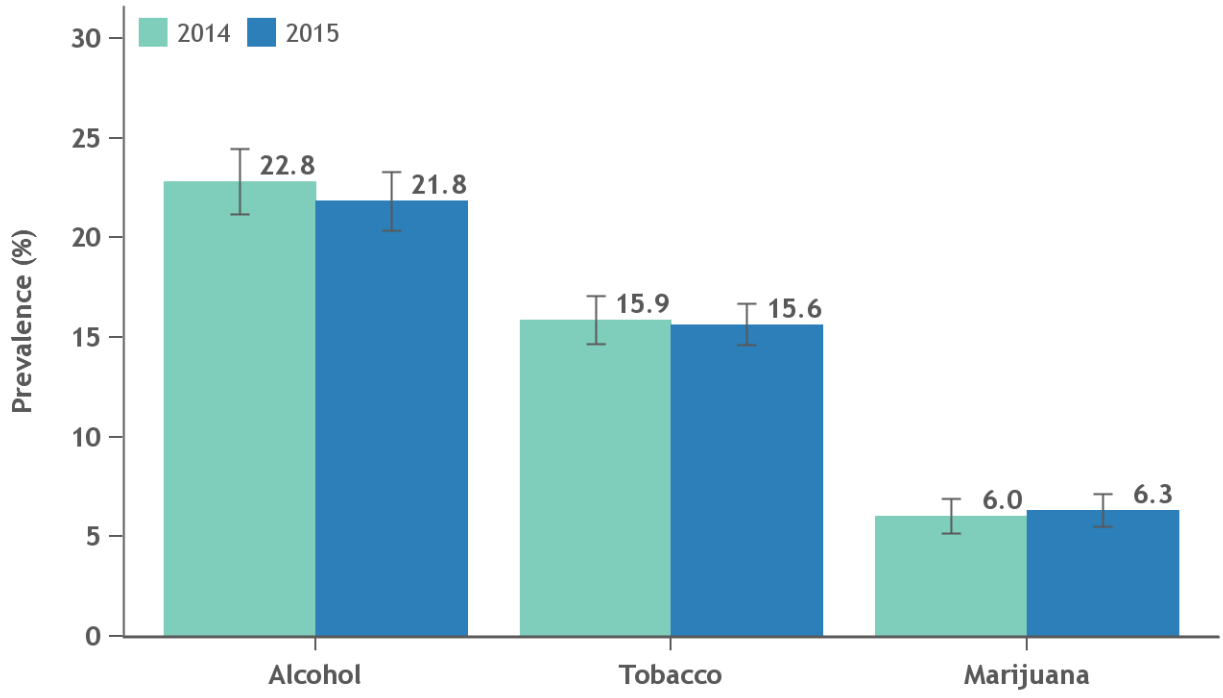
- Current marijuana use among adults in Colorado's Northwest region was statistically higher in 2015 than in 2014.[q]
- There were no statistical differences in estimates of current marijuana use from 2014 to 2015 within the other regions of Colorado: Southwest, Denver-Boulder, South Central, Southeast, or Northeast.[r]

[q] Current use among adults in the Northwest Region in 2014 vs. 2015: X^2= 4.91, p=0.027

[r] Current use 2014 vs. 2015: Southwest Region X^2= 0.89, p=0.3457; Denver-Boulder Region X^2= 1.91 p=0.1664; South Central Region X^2= 0.48, p=0.487; Southeast Region X^2= 0.11, p=0.742; Northeast Region X^2=0.09, p=0.765.

For an explanation of terms, see "How to interpret survey results" above. For statistical methods, see Appendix B. For data, see Appendix B, Table B.9.

Figure 10. Daily or near daily use of alcohol, tobacco, and marijuana among Colorado adults (18+ years) 2014-2015.



Produced by: EEOHT, CDPHE 2016.
*Black bars indicate margins of error (95% Confidence Intervals).
†Daily or Near Daily Use is defined as using 20-30 days in the past 30 days (marijuana or alcohol) or reporting everyday or someday use (smoking tobacco).
‡Data Source: Colorado Behavioral Risk Factor Surveillance System 2015.

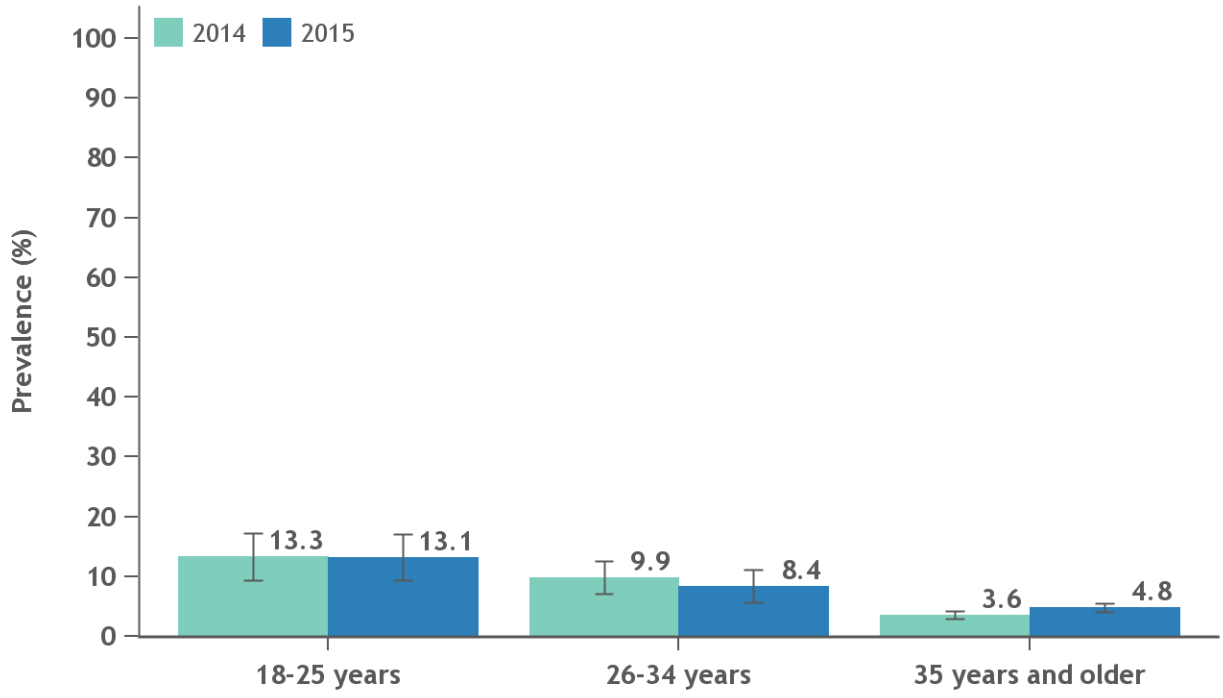
Major findings

- The prevalence of daily or near daily marijuana use among Colorado adults was statistically lower than daily or near daily alcohol or tobacco use in both 2014 and 2015.
- Comparing across years within each substance, there were no statistical differences between 2014 and 2015.[s]

[s] In 2014: Marijuana 6.0% (95% CI 5.2-6.9%), Alcohol 22.8% (95% CI 21.2-24.5%), Tobacco 15.9% (95% CI 14.7-17.1%). In 2015: Marijuana 6.3% (95% CI 5.5-7.2%), Alcohol 21.8% (95% CI 20.4-23.3%), Tobacco 15.6% (95% CI 14.6-16.7%).

For an explanation of terms, see "How to interpret survey results" above. For statistical methods, see Appendix B. For data, see Appendix B, Table B.10.

Figure 11. Daily or near daily marijuana use among Colorado adults (18+ years) by age categories, 2014-2015.



Produced by: EEOHT, CDPHE 2016.
*Black bars indicate margins of error (95% Confidence Intervals).
†Daily or near daily was using marijuana 20 or more days in the past 30 days.
‡Data Source: Colorado Behavioral Risk Factor Surveillance System 2015.

Major findings

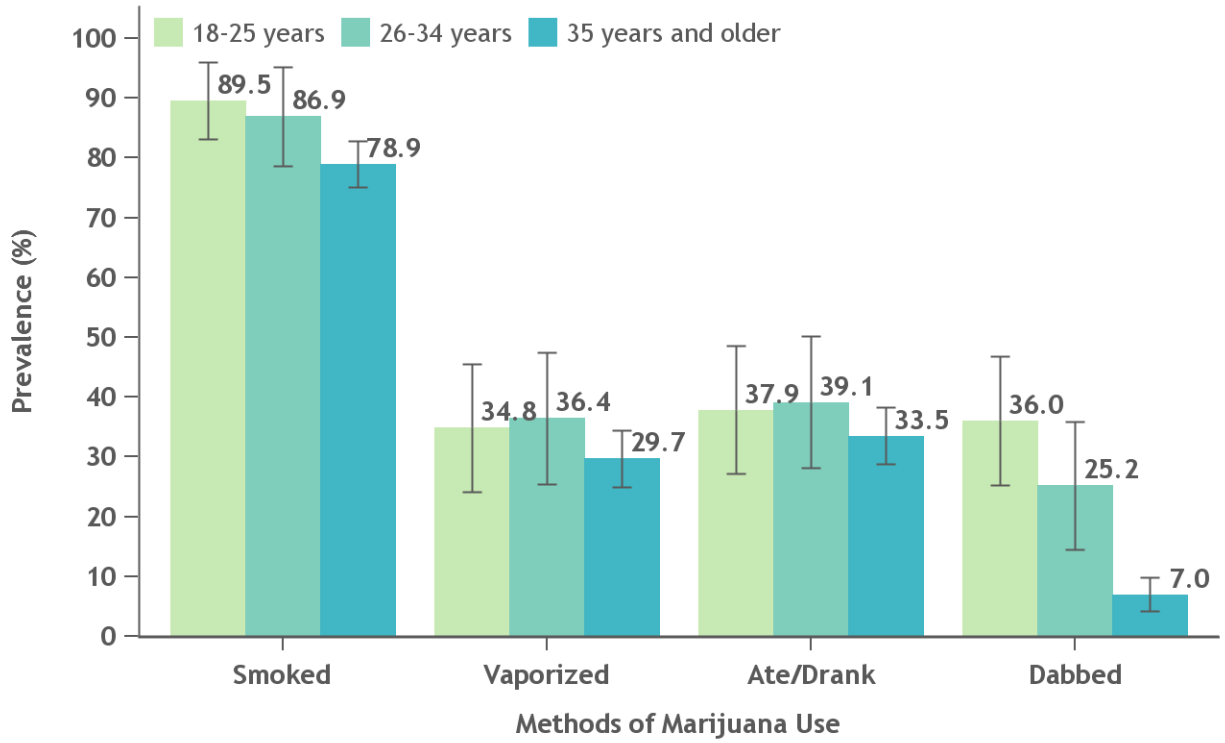
- Daily or near daily marijuana use was statistically lower among adults 35 years and older than among those 18-25 or 26-34 years of age in both 2014 and 2015.[t]
- Comparing across years within each age group, there were no statistical differences in daily or near daily marijuana use between 2014 and 2015.[u]

[t] In 2014: 35+ years 3.6% (95% CI 3.0-4.3%), 18-25 years 13.3% (95% CI 9.4-17.2%), 26-34 years 9.9% (95% CI 7.1-12.6%). In 2015: 35+ years 4.8% (95% CI 4.1-5.5%), 18-25 years 13.1% (95% CI 9.3-17.0%), 26-34 years 8.4% (95% CI 5.7-11.1%).

[u] Current use 2014 vs. 2015: 18-25 years X^2= 0.22, p=0.8991; 26-34 years X^2= 0.63, p=0.729; 35 years and older X^2= 5.86, p=0.0534.

For an explanation of terms, see "How to interpret survey results" above. For statistical methods, see Appendix B. For data, see Appendix B, Table B.11.

Figure 12. Methods of marijuana use among Colorado adults (18+ years) who reported current use, by age categories, 2015.



Produced by: EEOHT, CDPHE 2016.
*Black bars indicate margins of error (95% Confidence Intervals).
†Current Use was marijuana use at least once in the past 30 days. Use of more than one method may have been reported in the past 30 days.
‡Data Source: Colorado Behavioral Risk Factor Surveillance System 2015.

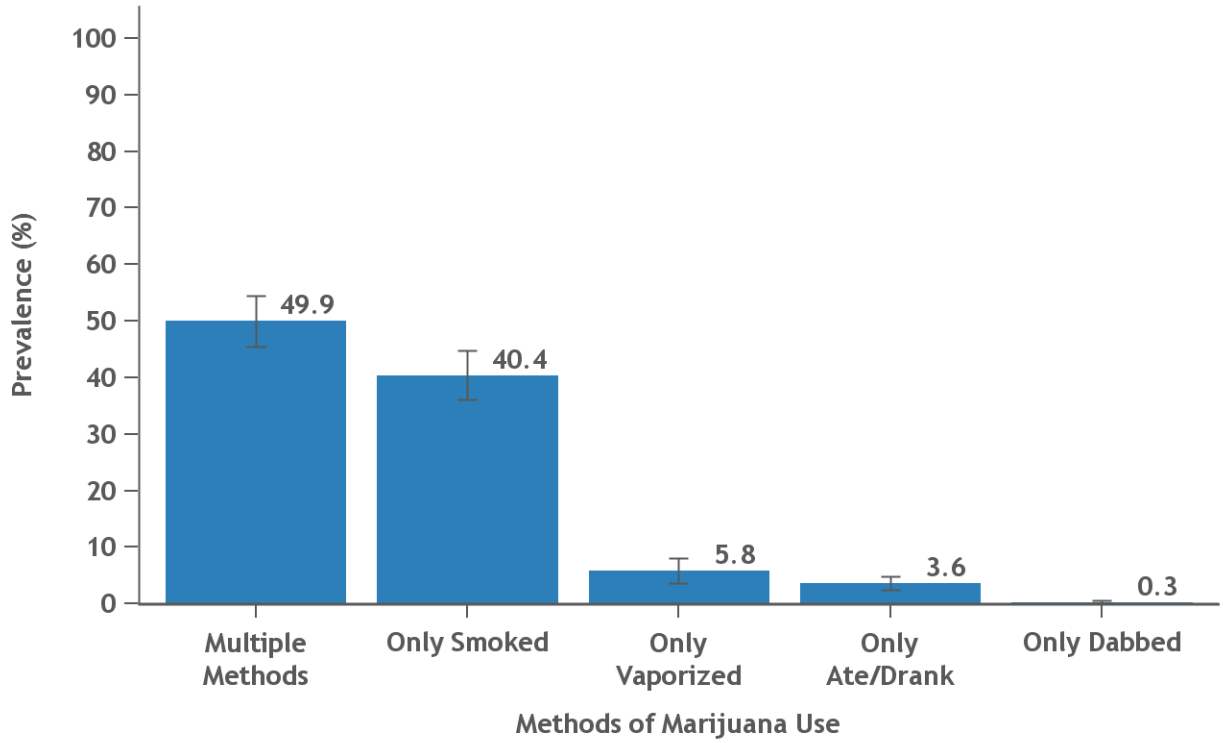
Major findings

- Reported dabbing marijuana in the past 30 days was statistically lower among Colorado adults aged 35 years and older than among those 18-25 or 26-34 years of age.[v]
- There were not statistical differences between age groups within those that smoked, vaporized, or ate/drank marijuana.[w]

[v] Dabbed: 18-25 years 36.0% (95% CI 25.3-46.7%), 26-34 years 25.2% (95% CI 14.5-35.9%), 35+ years 7.0% (95% CI 4.2-9.8%).

[w] Smoked: 18-25 years 89.5% (95% CI 83.1-95.9%), 26-34 years 86.9% (95% CI 78.6-95.2%), 35+ years 78.9% (95% CI 75.1-82.8%). Vaporized: 18-25 years 34.8% (95% CI 24.1-45.5%), 26-34 years 36.4% (95% CI 25.4-47.5%), 35+ years 29.7% (95% CI 25.0-34.5%). Ate/drank: 18-25 years 37.9% (95% CI 27.2-48.6%), 26-34 years 39.1% (95% CI 28.1-50.1%), 35+ years 33.5% (95% CI 28.7-38.2%). For an explanation of terms, see "How to interpret survey results" above. For statistical methods, see Appendix B. For data, see Appendix B, Table B.12.

Figure 13. Methods of marijuana use among Colorado adults (18+ years) who reported current use, 2015.



Produced by: EEOHT, CDPHE 2016.
*Black bars indicate margins of error (95% Confidence Intervals).
†Current Use was marijuana use at least once in the past 30 days.
‡Data Source: Colorado Behavioral Risk Factor Surveillance System 2015.

Major findings

- Approximately half of adults who currently use marijuana use it through multiple methods.
- The prevalence of Colorado adults who used marijuana multiple methods in the past 30 days was statistically higher than those who only smoked, only vaporized, only ate/drank, and only dabbed in the past 30 days.[x]

[x] Multiple methods 49.9% (95% CI 45.4-54.5%), Only Smoked 40.4% (95% CI 36.0-44.8%), Only Vaporized 5.8% (95% CI 3.6-8.0%), Only Ate/Drank 3.6% (95% CI 2.3-4.9%), Only Dabbed 0.3% (95% CI 0.0-0.6%).

For an explanation of terms, see "How to interpret survey results" above. For statistical methods, see Appendix B. For data, see Appendix B, Table B.13.

References

1. Centers for Disease Control and Prevention. Behavioral Risk Factor Surveillance System: Annual Survey Data. http://www.cdc.gov/brfss/annual_data/annual_data.htm. Accessed October 7, 2016.
2. Colorado Department of Public Health and Environment. Colorado Health and Environmental Data: Adult Health Data: Behavioral Risk Factor Surveillance System. http://www.chd.dphe.state.co.us/topics.aspx?q=Adult_Health_Data. Accessed October 7, 2016.
3. Substance Abuse and Mental Health Services Administration. National Survey on Drug Use and Health. https://nsduhweb.rti.org/respweb/homepage.cfm.

Section 1

Monitoring Changes in Marijuana Use Patterns

Chapter 2

Child Health Survey (CHS) 2014-2015 Survey Results

Retail Marijuana Public Health Advisory Committee

COLORADO
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The CHS survey and marijuana-related behaviors in Colorado

Since 2004, the Colorado Department of Public Health and Environment has conducted the Child Health Survey (CHS). This annual survey provides data on a wide range of health issues and risk factors affecting children and youth in Colorado for children ages 1-14. The CHS is conducted as a telephone survey among respondents to the Behavioral Risk Factor Surveillance System (BRFSS) Survey who have children ages 1-14 years old. Data from the CHS help to identify areas where education, resources to assist parents, policy changes or other data-informed actions can improve the health of Colorado's children.[1]

Since 2014, questions about marijuana use and storage in the home have been included in the survey (Table 1). The presence of marijuana in or around the home was evaluated using question 1, and was asked of all survey participants. Participants who answered 'YES' to this question were asked how their marijuana is stored, in question 2. Marijuana being used in the home was evaluated using question 3, and was asked of all survey participants. Participants who answered 'YES' to this question were asked how the marijuana was used inside the home in question 4. Results enable CDPHE to estimate the number of children in Colorado who may be exposed to secondhand marijuana smoke or unintentional ingestion due to unsafe storage of marijuana products in the home.

For additional survey details and information about analysis methods, see Appendix C.

Survey questions

Table 1. Child Health Survey questions about marijuana storage or use in or around the home, 2014-2015.

1. Is there any marijuana or marijuana product in or around your home right now?
   - Yes
   - No

2. Where is the marijuana that is currently in or around your home being stored? For each of the following methods please say yes if it does apply or no if it does not apply.
   - In a childproof container or packaging
   - In a locked container such as a cabinet, drawer or safe
   - In a location your child cannot access (such as out of reach)
   - Someplace else? (specify)

3. During the past 30 days, has anyone- including yourself, used marijuana or hashish inside your home?
   - Yes
   - No

4. How was the marijuana that was used inside your home consumed? For each of the following methods please say yes if it does apply or no if it does not apply.
   - It was vaporized (e-cigarette-like vaporizer)
   - It was smoked (in a joint, bong, pipe, blunt)
   - It was eaten in food (in brownies, cakes, cookies, candy)
   - It was consumed in a beverage (tea, cola, alcohol)
   - It was used in some other way (specify)
   - It was dabbed *(response option was added in 2015)*

Definitions

Dabbing - a method of marijuana use where a "dab" (small amount) of marijuana concentrate is placed on a pre-heated surface, creating concentrated marijuana vapor to be inhaled.

Possible exposure to second-hand marijuana smoke or vapor within the home - defined by combining three responses from question 4: *it was vaporized; it was smoked;* and *it was dabbed*. Dabbing was added as a response in 2015; therefore, this category could be underrepresented in 2014 because respondents who dabbed within the home may have indicated *it was used in some other way*.

Safe storage of marijuana - defined by combining three responses from question 2: *in a childproof container or packaging*; *in a locked container such as a cabinet, drawer, or safe;* and *in a location your child cannot access*. The response *someplace else* was considered potentially unsafe storage and a risk for unintentional ingestion.

Vaping (vaporization of marijuana) - a method of marijuana use where marijuana vapor, rather than smoke, is inhaled. Marijuana flower or concentrate is heated in a vaporizing device (vaporizer) to a temperature below the point of combustion, to produce vapor.

How to interpret survey results

Respondents to the Child Health Survey are a sample of Colorado adults with children 1-14 years old. The percent of survey respondents selecting a specific answer might not be exactly the same as if all adults with children 1-14 years old in Colorado were surveyed. Therefore, the survey results are estimates, and each has a range of possible values (also called margin of error, confidence interval, or 95% CI). These ranges are very important when comparing two estimates, and the following terms are used throughout this report:

'Not statistically different'- Typically, if the ranges of possible values *overlap* for two different survey results (like two different years, or male vs. female), we cannot be confident that there is a true difference between the two (also called 'not statistically significant.') In some cases, an additional statistical test is done to confirm.

'Statistically higher' or 'statistically lower'- If the ranges of possible values *do not overlap* for two different results, we CAN be confident that there is a true difference between the two (also called 'statistically significant.')

On the figures in this report, these ranges of possible values are indicated by black bars. In footnotes, they are referred to by the statistical term '95% CI.'

Results

Results are displayed in Figures 1-3 below.

Marijuana in or around the home and safe storage

In 2015, 7.9% of adults with children 1-14 years old in the home reported having marijuana or marijuana products in or around the home (Figures 1 & 2). In 82.2% of these homes, marijuana was stored safely, while in 17.8% the marijuana was potentially stored unsafely (Figure 2). It was estimated that approximately 14,000 homes in Colorado with children 1-14 years old had marijuana in the home with potentially unsafe storage.

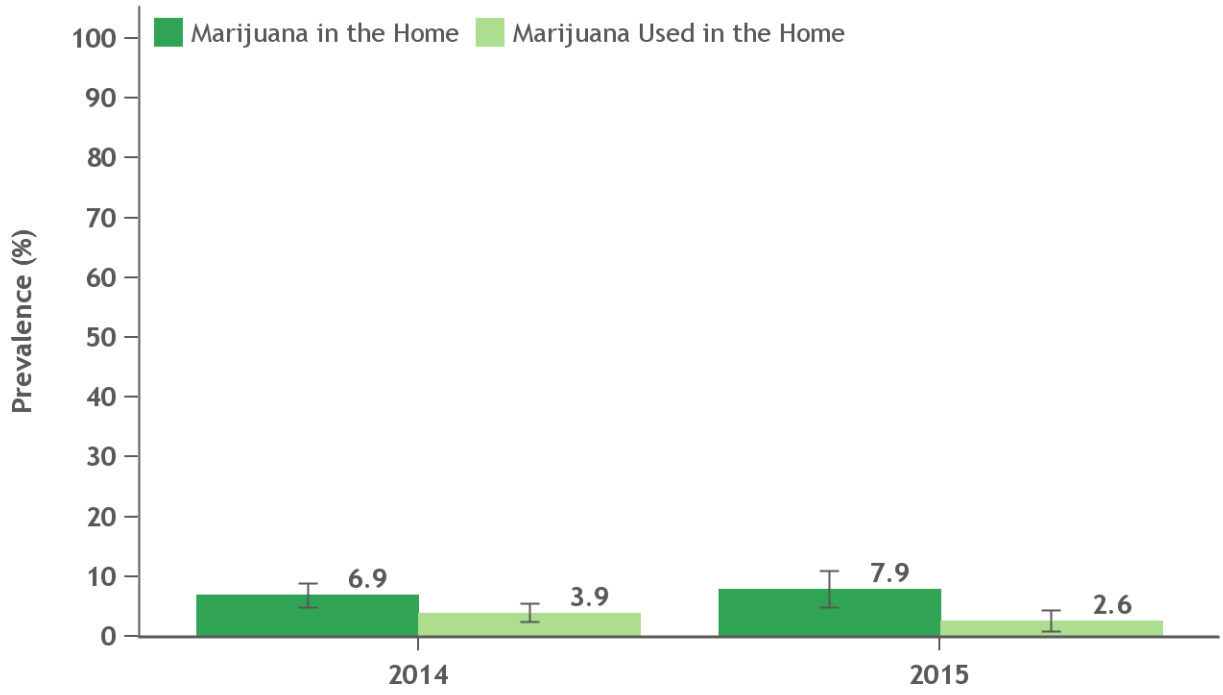
Comparing across years, there were no statistical differences from 2014 to 2015 in the prevalence of marijuana or marijuana products in or around the home (6.9%, 7.9%; Figure 1) or safe storage in homes with marijuana (86.0%, 82.2%; Figure 2). There were no differences in marijuana being in or around the home by child's age, highest household education, or household income, or difference from 2014 to 2015 (data not shown).

Marijuana used inside the home and secondhand smoke exposure

For 2014 and 2015 together, 3.2% of adults with children 1-14 years old in the home reported marijuana being used inside the home (Figure 3). Of these, 83.2% reported the marijuana was smoked, vaporized, or dabbed (Figure 3). It was estimated that approximately 16,000 homes in Colorado had children 1-14 years old with possible exposure to secondhand marijuana smoke or vapor in the home.

Comparing across years, there were no statistical differences from 2014 to 2015 in the prevalence of marijuana being used inside the home (3.9%, 2.6%; Figure 1).

Figure 1. Presence of marijuana in or around the home or used in the home where children live, 2014-2015.



Produced by: EEOHT, CDPHE 2016
*Black bars indicate margins of error (95% Confidence Intervals).
†Data Source: Colorado Child Health Survey 2014-2015 a call-back survey from BRFSS for adults with children 14 years old or younger in the home.

Major findings

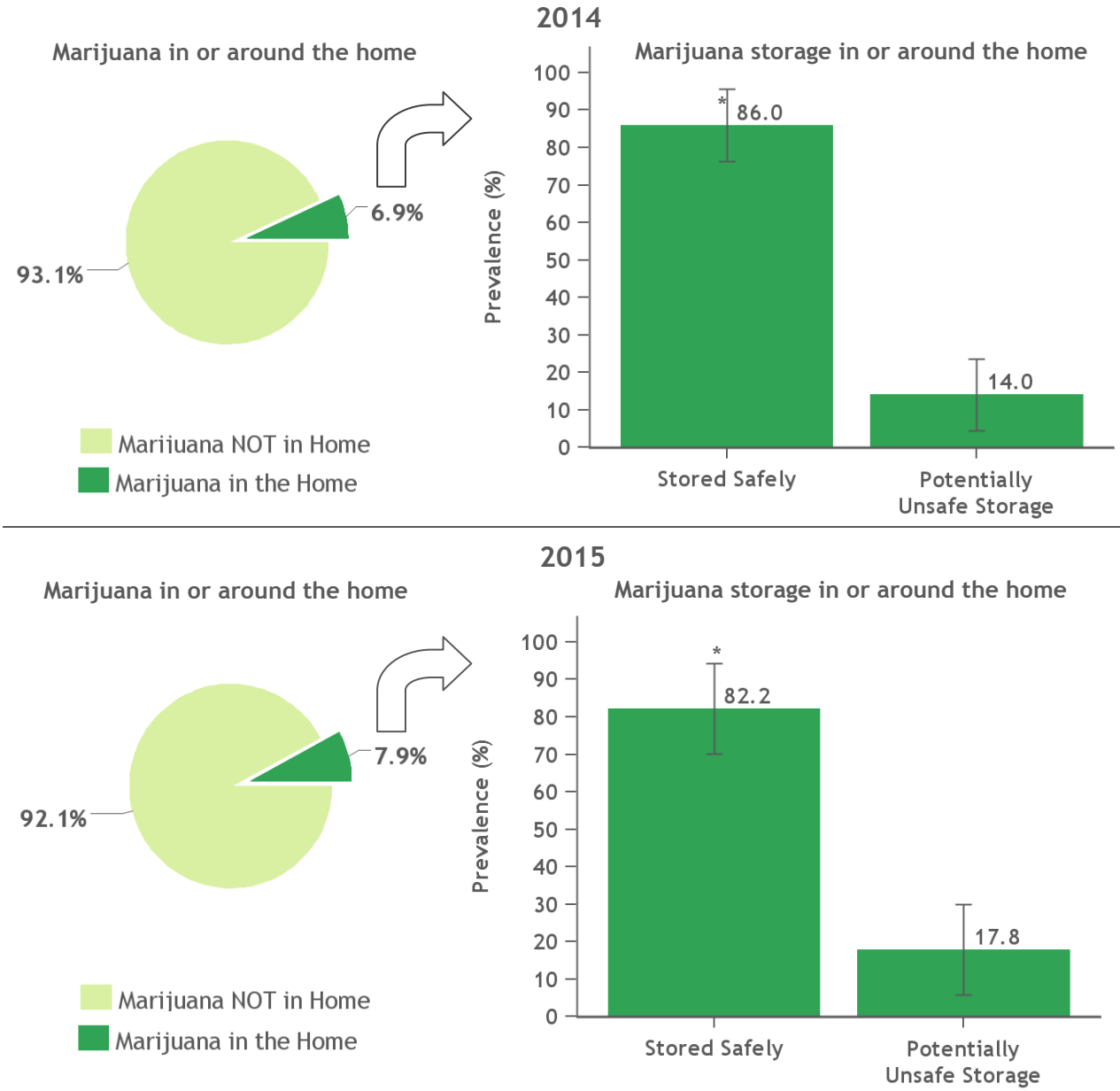
- The prevalence of marijuana or marijuana products in or around homes where children live was not statistically different between 2014 and 2015.[a]
- The prevalence of marijuana being used inside homes where children live was not statistically different between 2014 and 2015.[b]

[a] Marijuana or marijuana products in or around the home: 2014 6.9% (95% CI 4.9-8.9%), 2015 7.9% (95% CI 4.9-10.9%)

[b] Marijuana used inside the home: 2014 3.9% (95% CI 2.4-5.4%), 2015 2.6% (95% CI 0.8-4.4%)

For an explanation of terms, see "How to interpret survey results" above. For statistical methods, see Appendix C. For data, see Appendix C, Table C.1.

Figure 2. Percent of adults with children and marijuana in or around the home who store their marijuana in a safe place, 2014-2015.



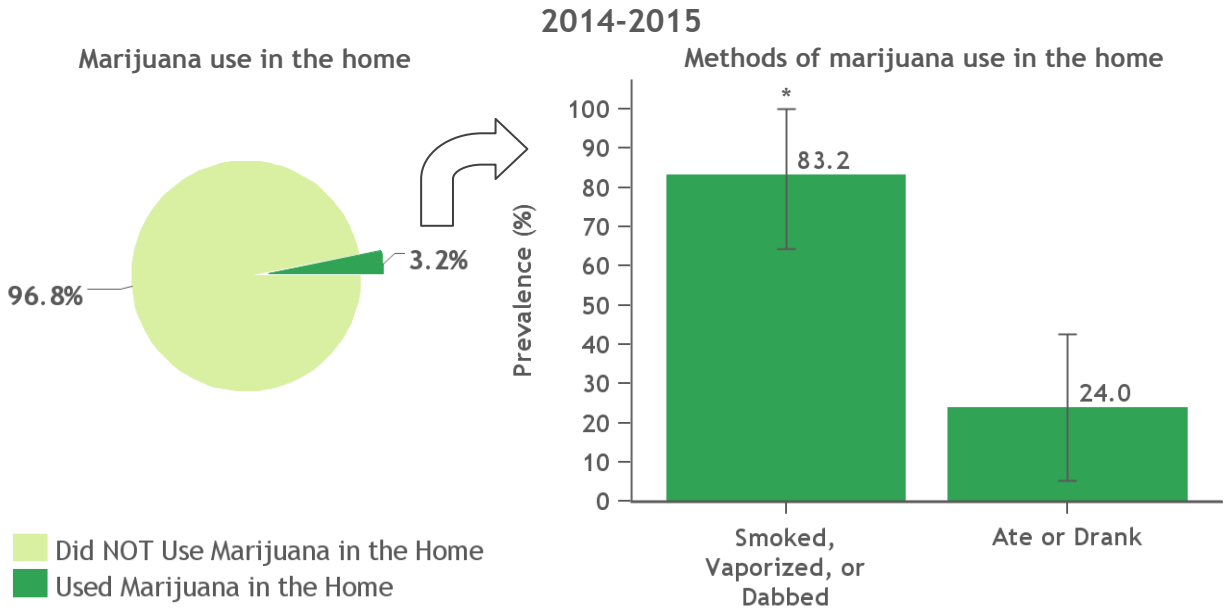
Produced by: EEOHT, CDPHE 2016
*Statistically different due to non overlapping 95% confidence intervals (95% CI).
†Black bars indicate margins of error (95% Confidence Intervals)
‡Data Source: Colorado Child Health Survey 2014-2015 a call-back survey from BRFSS for adults with children 14 years or younger in the home.
§Safe storage included a childproof container, a locked container, or a location a child cannot access.

Major findings:

- The prevalence of marijuana being stored safely in homes where children live was not statistically different between 2014 and 2015.[c]

[c] Marijuana safe storage: 2014 86.0% (95% CI 76.4-95.6%), 2015 82.2% (95% CI 70.1-94.2%)

Figure 3. Methods of marijuana use among adults with children in the home, 2014-2015 (years combined).



Produced by: EEOHT, CDPHE 2016
*Statistically different due to non overlapping 95% confidence intervals (95% CI).
†Black bars indicate margins of error (95% CI)
‡Dabbing was added as a response in 2015.
§ Data Source: Colorado Child Health Survey 2014-2015 a call-back survey from BRFSS for adults with children 14 years or younger in the home.

Major findings

- Among adults who use marijuana in a home where children live, the prevalence of 'smoked, vaporized or dabbed' was statistically higher than 'ate or drank'.[d]

For an explanation of terms, see "How to interpret survey results" above. For statistical methods, see Appendix C. For data, see Appendix C, Table C.2.

[d] For 2014-2015 combined years: smoked, vaporized or dabbed 83.2% (95% CI 64.3-100.0%), ate or drank 24.0% (95% CI 5.2-42.7%)

For an explanation of terms, see "How to interpret survey results" above. For statistical methods, see Appendix C. For data, see Appendix C, Table C.3.

References

1. Colorado Department of Public Health and Environment. Maternal and Child Health Data, Colorado Child Health Survey Data. 2016; http://www.chd.dphe.state.co.us/topics.aspx?q=Maternal_Child_Health_Data. Accessed January 1, 2017.

Section 1

Monitoring Changes in Marijuana Use Patterns

Chapter 3

Healthy Kids Colorado Survey (HKCS) 2005-2015 Survey Results

Retail Marijuana Public Health Advisory Committee

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The HKCS survey and marijuana use in Colorado

The Healthy Kids Colorado Survey (HKCS) collects health information in the fall of odd years from public high school and middle school students. It is a voluntary, anonymous survey, and parents are notified ahead of time. HKCS is a collaboration of the Colorado Department of Public Health and Environment (CDPHE), the Colorado Department of Education, and the Colorado Department of Human Services, who recognized the need to gather critical data while minimizing the student survey requests to Colorado schools. Both state and regional data are available to provide schools and communities with information to support effective strategies to protect the health and promote academic achievement of Colorado youth. This survey also fulfills Colorado's reporting requirement for the CDC-sponsored Youth Risk Behavioral Surveillance Survey (YRBS)[1] and ensures Colorado data can be compared to both national data and data from other states. HKCS provides data on a wide range of health issues and risk factors affecting children and youth including: nutrition, physical activity, safety behaviors, mental health, alcohol, tobacco and other substance use, and sexual behaviors (high school only). The survey has included questions on marijuana since 1999.[2] This report includes results from 2005-2015 for high school and 2011-2015 for middle school.

For additional survey details and information about analysis methods, see Appendix D.

Survey questions

Table 1. Healthy Kids Colorado Survey questions asked of middle school and high school students about whether they use marijuana, when they use it and how they use it, 2005-2015.

Not all questions were included in all years and not all questions were asked of both middle school and high school students.

1. During your life, how many times have you used marijuana?

- 0 times
- 1 or 2 times
- 3 to 9 times
- 10 to 19 times
- 20 to 39 times
- 40 to 99 times
- 100 or more times

2. How old were you when you tried marijuana for the first time?

- I have never tried marijuana
- 8 years old or younger
- 9 or 10 years old
- 11 or 12 years old
- 13 or 14 years old
- 15 or 16 years old
- 17 years old or older

3. During the past 30 days, how many times did you use marijuana?

- 0 times
- 1 or 2 times
- 3 to 9 times
- 10 to 19 times
- 20 to 39 times
- 40 or more times

4. During the past 30 days, how did you use marijuana? (Select all that apply.)

- I did not use marijuana during the past 30 days
- I smoked it
- I ate it (in an edible, candy, tincture or other food)
- I used a vaporizer
- I dabbed it*
- I used it in some other way

5. During the past 30 days, how did you usually use marijuana? (Select only one response.)

- I did not use marijuana during the past 30 days
- I smoked it I ate it (in an edible, candy, tincture or other food)
- I used a vaporizer
- I dabbed it*
- I used it in some other way

*The response option of "I dabbed it" was added in 2015

The National Survey on Drug Use and Health

The Substance Abuse and Mental Health Services Administration (SAMHSA) tracks national and state level data on tobacco, alcohol, marijuana, and illicit drugs including non-medical use of prescription drugs through the National Survey on Drug Use and Health (NSDUH).[3] Colorado past 30 day marijuana use estimates from the NSDUH survey were compared with the Colorado HKCS past 30 day marijuana use estimates (Figure 2).

Definitions

Current use – Having used marijuana at least once in the past 30 days (any answer other than '0 times' on question 3) (Table 1)

Dabbing - a method of marijuana use where a "dab" (small amount) of marijuana concentrate is placed on a pre-heated surface, creating concentrated marijuana vapor to be inhaled.

Ever use – having used marijuana at least once in their lifetime (any answer other than '0 times' on question 1) (Table 1)

Tried marijuana before age 13 - answered '11 or 12 years old', '9 or 10 years old', or '8 years old or younger' on question 2 (Table 1)

Vaping (vaporization of marijuana) - a method of marijuana use in which marijuana vapor, rather than smoke, is inhaled. Marijuana flower or concentrate is heated in a vaporizing device (vaporizer) to a temperature below the point of combustion, to produce vapor.

How to interpret survey results

Respondents to the Healthy Kids Colorado Survey are a sample of Colorado high school and middle school students. The percent of survey respondents selecting a specific answer might not be exactly the same as if every student in Colorado were surveyed. Therefore, the survey results are estimates, and each has a range of possible values (also called margin of error, confidence interval, or 95% CI). These ranges are very important when comparing two estimates, and the following terms are used throughout this report:

'Not statistically different'- Typically, if the ranges of possible values *overlap* for two different survey results (like two different years, or male vs. female), we cannot be confident that there is a true difference between the two (also called 'not statistically significant.') In some cases, an additional statistical test is done to confirm.

'Statistically higher' or 'statistically lower'- If the ranges of possible values *do not overlap* for two different results, we CAN be confident that there is a true difference between the two (also called 'statistically significant.')

On the figures in this report, these ranges of possible values are indicated by black bars. In footnotes, they are referred to by the statistical term '95% CI.'

Results

Results are displayed in Figures 1-13 and Maps 1-2 below.

Trends in marijuana use in Colorado

Survey results from 2015 indicate that approximately 38% of Colorado high school students report having ever used marijuana and 21% report use in the past 30 days (Figures 1 & 3). These estimates are similar to national estimates of ever and current marijuana use among high school students (Figure 1). From 2005-2015, estimates of current marijuana use among Colorado high school students have fluctuated between approximately 20% and 25% (Figures 1 & 3). From 2005 to 2013, the HKCS estimates of current marijuana use among high school students in Colorado were higher than the NSDUH estimates for current marijuana use among high school aged adolescents. However, the difference became smaller in 2013, at 19.7% on HKCS and 17.4% on NSDUH (Figure 2). Among Colorado middle school students in 2015, an estimated 7.6% had ever used marijuana and an estimated 4.4% reported currently using marijuana (Figure 3). Current marijuana use among high school students in Colorado has remained below current alcohol use from 2005 to 2015 and above current tobacco smoking from 2011 to 2015. Current alcohol use and tobacco smoking among high school students in Colorado has trended downward since 2005, while current marijuana use has remained stable (Figure 4). In both 2013 and 2015, current marijuana use among Colorado 9th graders (13.7%, 12.4%) was statistically lower than among 10th graders (19.0%, 18.8%), which was statistically lower than among 11th graders (22.1%, 26.3%) (Figure 5).

Marijuana use among Colorado high school students by gender, race & ethnicity, and sexual orientation

Current marijuana use among male high school students in 2013 (21.5%) was statistically higher than among female students (17.7%), but current use for both genders was nearly identical in 2015 (21.4%, 21.0%) (Figure 6). Current marijuana use among middle school students was not statistically different between males and females in 2013 (5.3%, 4.8%) or 2015 (3.8%, 5.2%) (Figure 7). Prevalence of current marijuana use and age of first use varied among students of different races and ethnicities (Figures 8 & 11). The percent of white non-Hispanic students who tried marijuana before age 13 was statistically lower than among black, Hispanic, or multiple or other race students (Figure 11). Prevalence of marijuana use also varied among students with different sexual orientation. In both 2013 and 2015, estimated current use of marijuana among students identifying as gay, lesbian, or bisexual (39.7%, 34.9%) was statistically higher than the estimated current use among students identifying as heterosexual (17.7%, 19.5%) (Figure 9). In 2015, a large portion of high seniors reported first trying marijuana at ages 13-14 years old (27.0%) and 15-16 years old (43.1%) compared to younger ages and 17 and older (Figure 10).

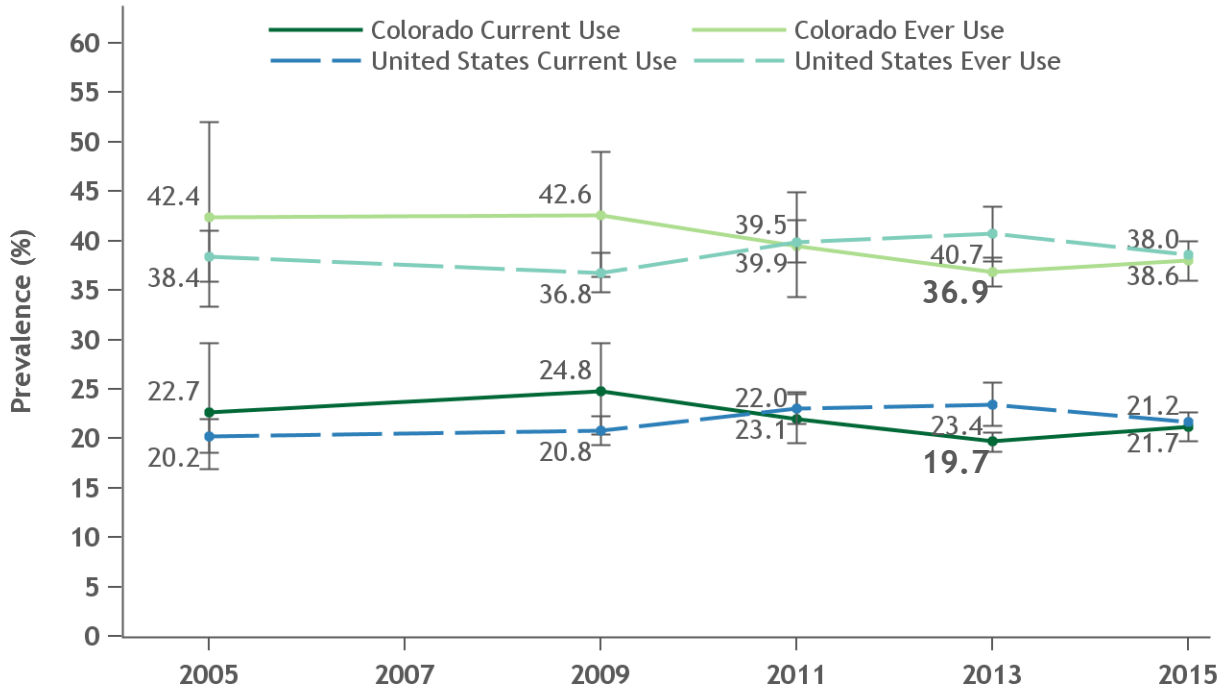
Methods and frequency of marijuana use in Colorado

In 2015, 87% of high school students who currently used marijuana reported that smoking was their usual method of use – much higher than edibles (2%), vaping (5%), or other methods of use (6%) (Figure 12). More than one-third of high school or middle school students who reported current marijuana use in 2015 had used once or twice in the past 30 days, while approximately 27% of high school students and 20% of middle school students had used 20 or more times in the past 30 days (Figure 13). The estimates of marijuana use at each frequency level fluctuated from 2005 to 2015, with no notable trends (Figure 14).

Marijuana use in Colorado by region

Marijuana use also varies greatly by Health Statistics Region (HSR). Some of Colorado's larger counties represent a single HSR, but for smaller or less populated areas, several counties may be represented by a single HSR (Maps 1 & 2). In both 2013 and 2015, health statistics regions 7 (Pueblo County 32.0%, 30.1%) and 9 (Dolores, San Juan, Montezuma, La Plata, and Archuleta Counties 24.6%, 26.2%) were statistically higher than the state prevalence (19.7%, 21.2%) for current marijuana use among high school students. For all but one HSR, current marijuana use among high school students in 2015 was not statistically different from 2013. Health statistics region 10 (Montrose, Delta, Gunnison, Ouray, Hinsdale, and San Miguel Counties) did have statistically lower current marijuana use among high school students in 2015 (17.5%) than in 2013 (26.7%) (Map 2).

Figure 1. Prevalence of ever and current marijuana use for high school students in Colorado (HKCS) compared to the national prevalence (YRBS), 2005-2015.



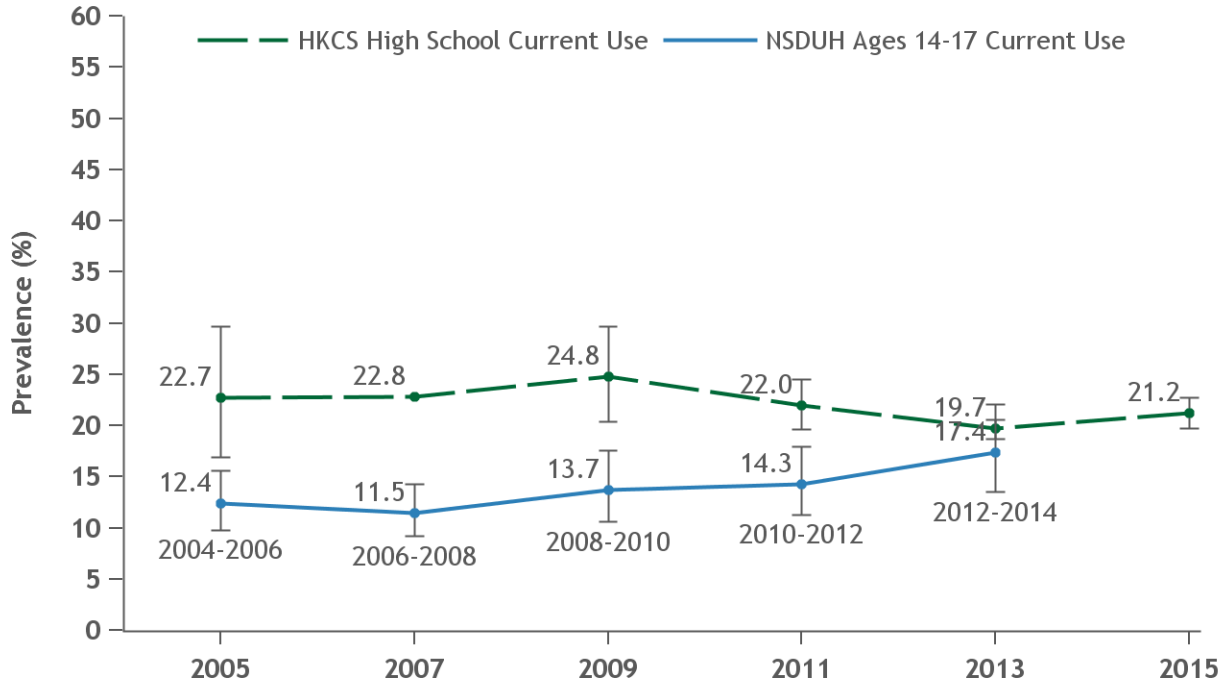
Produced by: EEOHT, CDPHE 2016
*Black bars indicate margins of error (95% Confidence Intervals).
†Ever Use is defined as marijuana use at least one time during a student's lifetime and Current Use is defined as marijuana use at least once in the past 30 days.
‡Data Source: Colorado estimates are from the Healthy Kids Colorado Survey (HKCS) and United States estimates are from the Youth Risk Behavioral Surveillance System survey. Note: Data for the year 2007 was not included due to low sample size.

Major findings

- HKCS estimates for both ever and current marijuana use in Colorado have had no statistical difference from the YRBS national estimates from 2005 through 2015, except for current use in 2013.
- In 2013, the HKCS estimate of current marijuana use among high school students in Colorado was statistically lower than the YRBS national estimate.[a]
- Comparing 2015 HKCS estimates with 2013, there was no statistical difference in current use or ever use among Colorado high school students.[b]
- The 2015 HKCS estimates for both ever and current marijuana use among high school students in Colorado were nearly identical to the 2015 YRBS national estimates.

[a]In 2013: HKCS estimate for Colorado 19.7%, (95% CI 18.7-20.6%), YRBS national estimate 23.4% (95% CI 21.3-25.7%).
[b] Current marijuana use in Colorado (HKCS): 2013 19.7% (95% CI 18.7-20.6%), 2015 21.2% (95% CI 19.7-22.7%). Ever marijuana use in Colorado (HKCS): 2013 36.8% (95% CI 35.4-38.3%), 2015 38.0% (95% CI 36.0-40.0%)
For an explanation of terms, see "How to interpret survey results" above. For statistical methods, see Appendix D. For data, see Appendix D, Table D.1.

Figure 2. Prevalence of current marijuana use for high school aged adolescents in Colorado, 2005-2015.



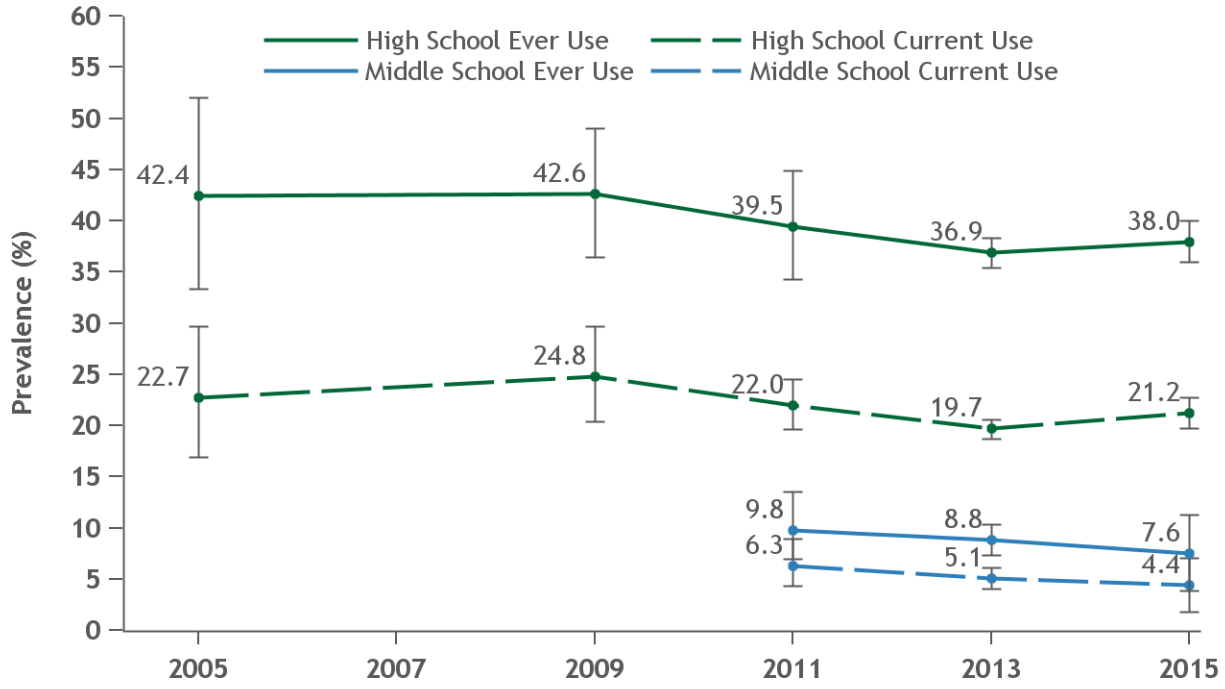
Produced by: EEOHT, CDPHE 2016
*Black bars indicate margins of error (95% Confidence Intervals).
†Current Use is defined as marijuana use at least once in the past 30 days.
‡Data Source: Healthy Kids Colorado Survey (HKCS) prevalence estimates for 2005-2015 and National Survey on Drug Use and Health (NSDUH) for 2004-2014 ages 14-17. Both are for Colorado only.

Major findings

- From 2005 to 2013, the HKCS estimates of current marijuana use among high school students in Colorado were higher than the NSDUH estimates for current marijuana use among high school aged adolescents in Colorado. However, the difference became smaller in 2013.[c]

[c] NSDUH data was a 3-year aggregate 2012-2014. For data, see Appendix D, Table D.2. For statistical methods, see Appendix D.

Figure 3. Prevalence of ever and current marijuana use for high school and middle school students in Colorado, 2005-2015.



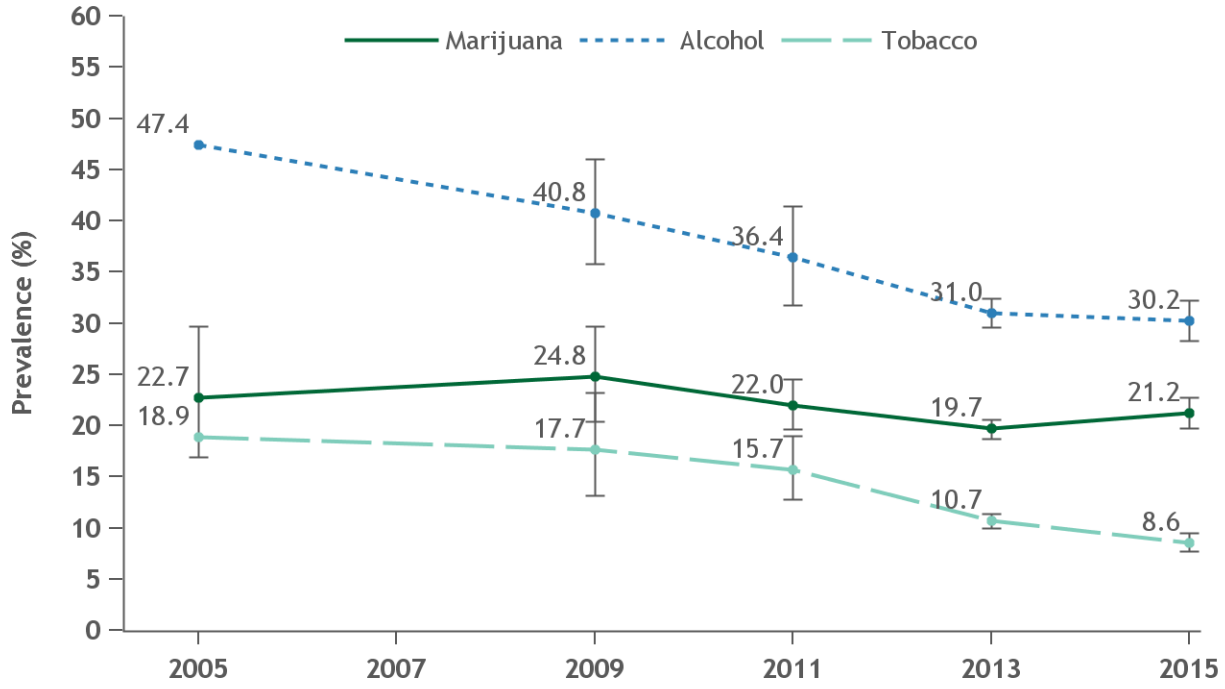
Produced by: EEOHT, CDPHE 2016
*Black bars indicate margins of error (95% Confidence Intervals).
†Ever Use is defined as marijuana use at least one time during a student's lifetime and Current Use is defined as marijuana use at least once in the past 30 days.
‡Data Source: Healthy Kids Colorado Survey (HKCS) prevalence estimates for 2005-2015. Data for the year 2007 was not included due to low sample size. Data for middle school marijuana use was not collected before 2011.

Major findings

- Among Colorado high school students, over the years 2005 to 2015, estimates of current marijuana use have fluctuated between 19.7% and 24.8%. None of these estimates were statistically different from each other.[d]
- Among Colorado high school students, over the years 2005 to 2015, estimates of having ever used marijuana have fluctuated between 36.9% and 42.6%. None of these estimates were statistically different from each other.[d]
- Among Colorado middle school students in 2015, an estimated 4.4% were currently using marijuana and an estimated 7.6% had ever used marijuana. Between 2011 and 2015, none of the estimates were statistically different.[d]

[d] For data, see Appendix D, Table D.3.
For statistical methods, see Appendix D.

Figure 4. Prevalence of current marijuana use for high school students in Colorado compared to current alcohol use and tobacco smoking in Colorado, 2009-2015.



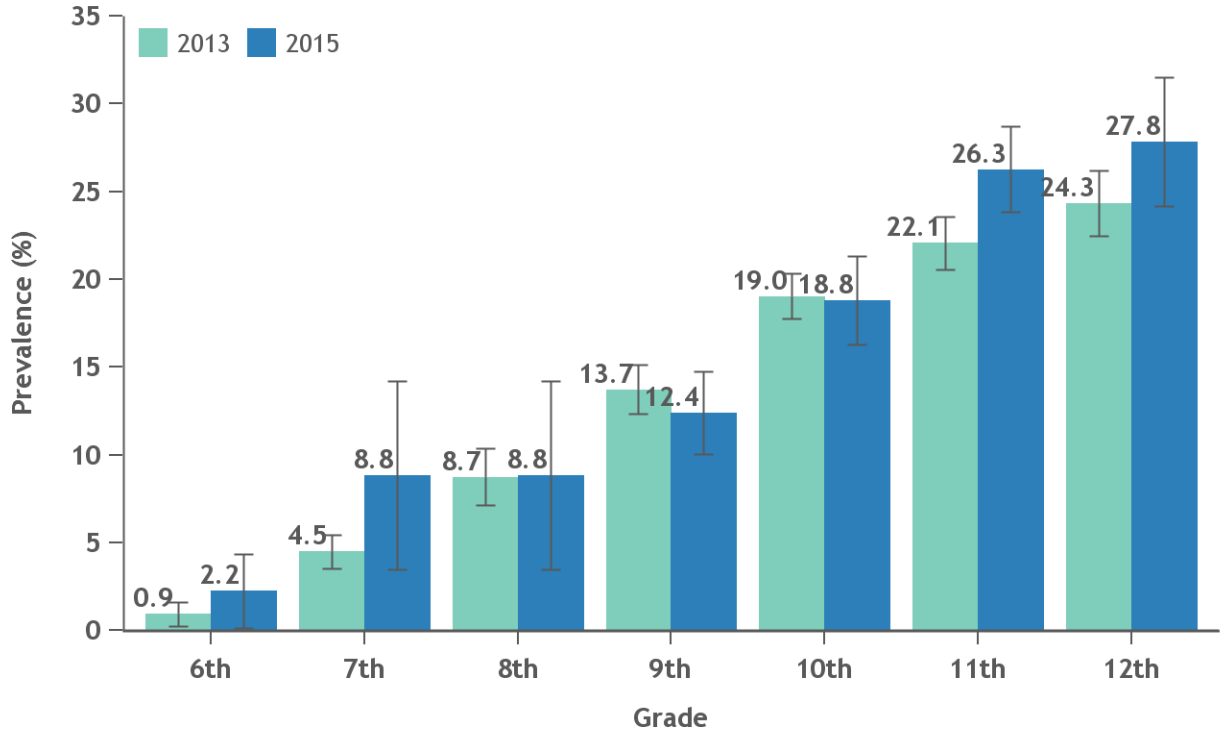
Produced by: EEOHT, CDPHE 2016
*Black bars indicate margins of error (95% Confidence Intervals).
†Current Use is defined as marijuana use at least once in the past 30 days.
‡Data Source: Healthy Kids Colorado Survey (HKCS) prevalence estimates for 2005-2015. Note: Data for the year 2007 was not included due to low sample size.

Major findings

- The prevalence of current marijuana use among high school students in Colorado has remained statistically higher than current tobacco smoking from 2011 through 2015 and has remained statistically lower than current alcohol use from 2009 through 2015.
- Current alcohol use was statistically lower in 2015 compared to 2009.[e]
- Current tobacco smoking was statistically lower in 2015 compared to 2013 and in 2013 compared to 2011.[f]
- Current marijuana use has remained stable from 2009 through 2015 with the prevalence of current marijuana use among high school students ranging from 19.7%-24.8%.

[e] Current alcohol use: 2015 30.2% (95% CI 28.3-32.2%), 2009 40.8% (95% CI 35.8-46.0%)
[f] Current tobacco use: 2015 8.6% (95% CI 7.7-9.5%), 2013 10.7% (95% CI 10.0-11.4%), 2011 15.7% (95% CI 12.8-19.0%)
For an explanation of terms, see "How to interpret survey results" above. For statistical methods, see Appendix D. For data, see Appendix D, Table D.4.

Figure 5. Prevalence of current marijuana use for high school and middle school students in Colorado by grade, 2013-2015.



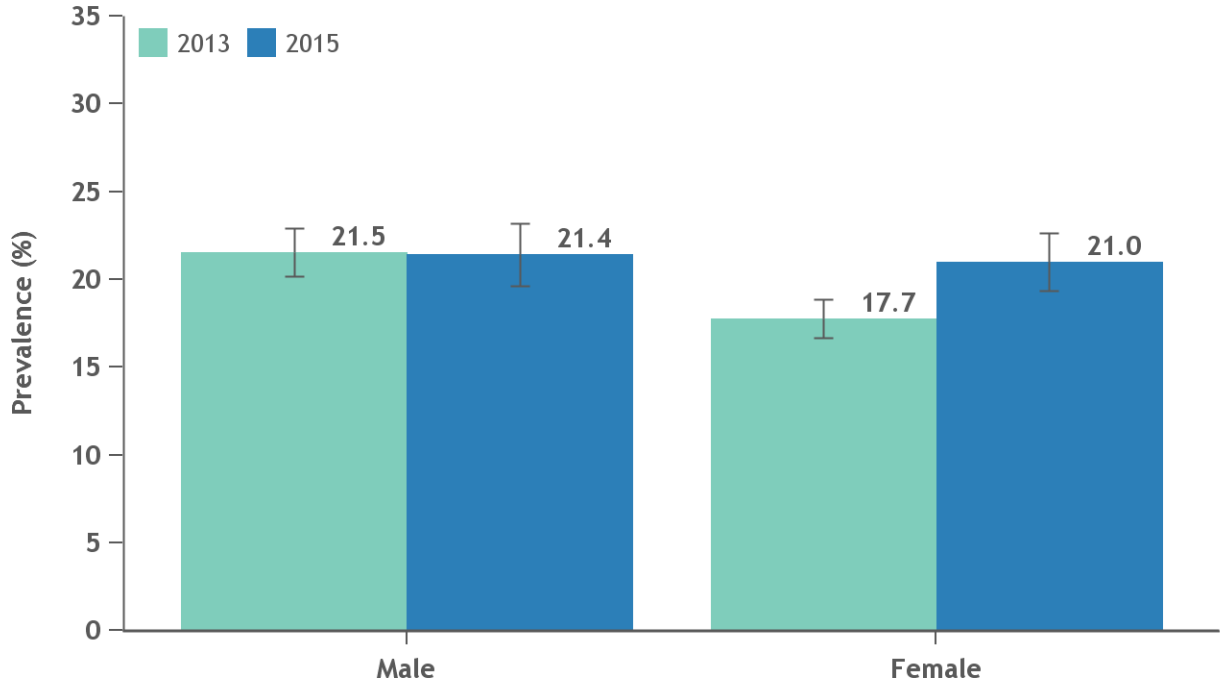
Produced by: EEOHT, CDPHE 2016
*Black bars indicate margins of error (95% Confidence Intervals).
†Current Use is defined as marijuana use at least once in the past 30 days.
‡Data Source: Healthy Kids Colorado Survey (HKCS) prevalence estimates for 2013-2015.

Major findings

- In both 2013 and 2015, estimates of current marijuana use among Colorado students in each grade level trended upward from 6th through 12th grade, with current use higher in older grades than younger grades.
- In both 2013 and 2015, estimated current use among Colorado 9th graders was statistically lower than among 10th graders, and current use among 10th graders was statistically lower than among 11th graders. [g]
- Estimated current use among Colorado 11th graders was statistically higher in 2015 than it was in 2013. There was not a statistical difference in current use among all other grades between 2013 and 2015. [h]

[g] In 2013: 9th graders 13.7% (95% CI 12.3-15.1%), 10th graders 19.0% (95% CI 17.7-20.3%), 11th graders 22.1% (95% CI 20.6-23.5%); In 2015: 9th graders 12.4% (95% CI 10.0-14.7%), 10th graders 18.8% (95% CI 16.3-21.3%), 11th graders 26.3% (95% CI 23.8-28.7%)
[h] Current use among Colorado 11th graders: 2015 26.3% (95% CI 23.8-28.7%), 2013 (22.1%, 95% CI: 20.6%-23.5%).
For an explanation of terms, see "How to interpret survey results" above. For statistical methods, see Appendix D. For data, see Appendix D, Table D.5.

Figure 6. Prevalence of current marijuana use for high school students in Colorado by gender, 2013-2015.



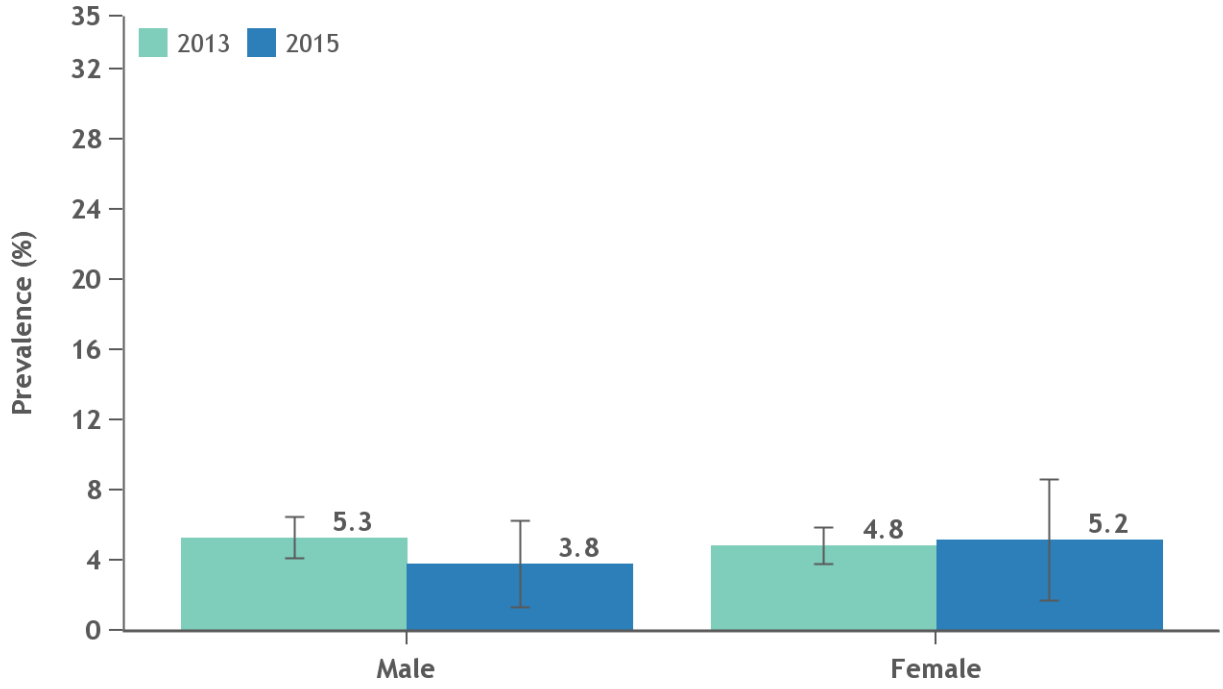
Produced by: EEOHT, CDPHE 2016
*Black bars indicate margins of error (95% Confidence Intervals).
†Current Use is defined as marijuana use at least once in the past 30 days.
‡Data Source: Healthy Kids Colorado Survey (HKCS) prevalence estimates for 2013-2015.

Major findings

- The estimate of female high school students in Colorado who reported current marijuana use in 2015 was statistically higher than in 2013.[i]
- Estimates for current marijuana use among male high school students in Colorado were nearly identical in 2013 and 2015.

[i]Colorado female high school students current marijuana use: 2013 17.7% (95% CI 16.6-18.8%), 2015 21.0% (95% CI 19.3-22.6%) For an explanation of terms, see "How to interpret survey results" above. For statistical methods, see Appendix D. For data, see Appendix D, Table D.6.

Figure 7. Prevalence of current marijuana use for middle school students in Colorado by gender, 2013-2015.



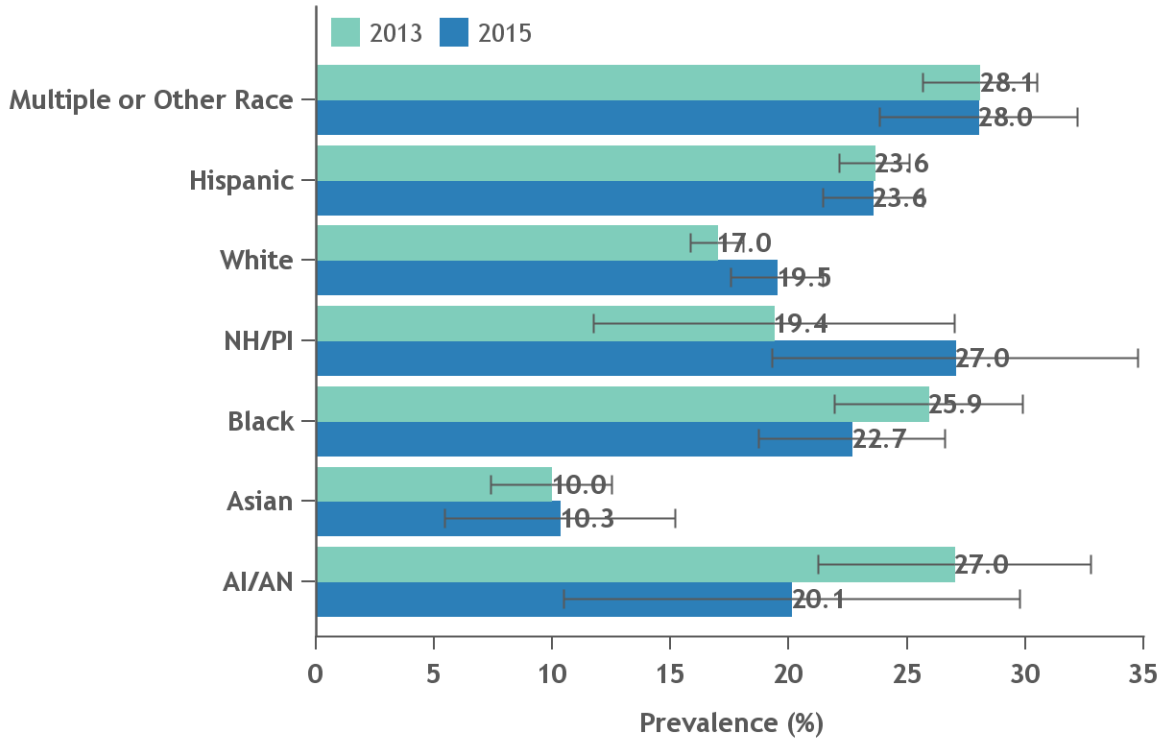
Produced by: EEOHT, CDPHE 2016
*Black bars indicate margins of error (95% Confidence Intervals).
†Current Use is defined as marijuana use at least once in the past 30 days.
‡Data Source: Healthy Kids Colorado Survey (HKCS) prevalence estimates for 2013-2015.

Major findings

- Current marijuana use was not statistically different between 2013 and 2015 for either male or female middle school students in Colorado. [j]

[j] Males: 2013 5.3% (95% CI 4.1-6.5%), 2015 3.8% (95% CI 1.3-6.2%); Females: 2013 4.8% (95% CI 3.8-5.9%), 2015 5.2% (95% CI 1.7-8.6%)
For an explanation of terms, see "How to interpret survey results" above. For statistical methods, see Appendix D. For data, see Appendix D, Table D.7.

Figure 8. Prevalence of current marijuana use for high school students in Colorado by race/ethnicity, 2013-2015.



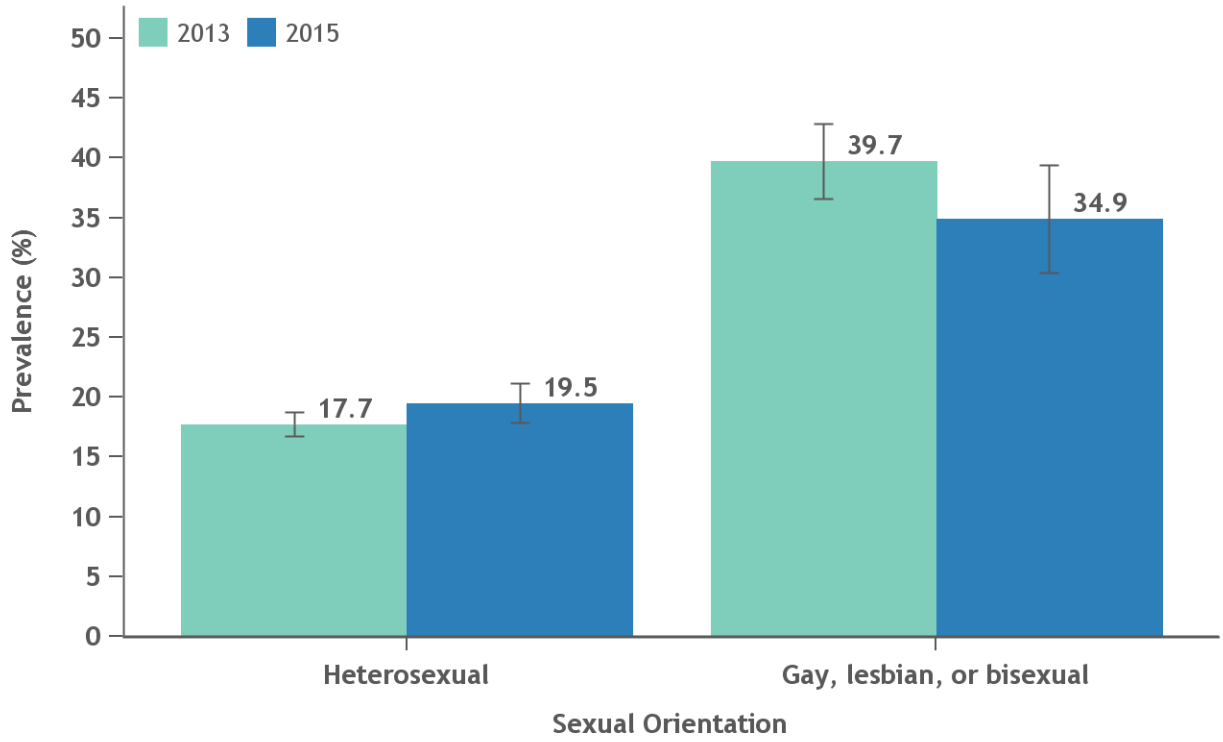
Produced by: EEOHT, CDPHE 2016
*Black bars indicate margins of error (95% Confidence Intervals).
†Current Use is defined as marijuana use at least once in the past 30 days.
‡Hispanic includes respondents who selected "Hispanic" for ethnicity and "white" for race. Those who selected "Hispanic" for ethnicity and a non-white race are included under "multiple or other race".
AI: American Indian, AN: Alaska Native, NH: Native Hawaiian, PI: Pacific Islander.
§Data Source: Healthy Kids Colorado Survey (HKCS) prevalence estimates for 2013-2015.

Major findings

- In both 2013 and 2015, current marijuana use was statistically lower among Asian high school students than among white, Hispanic, black, and multiple or other race students.[k]
- In both 2013 and 2015, current marijuana use was statistically higher among multiple or other race high school students than among white students.[k]
- In 2013, current marijuana use was also statistically higher among Hispanic, black and American Indian/Alaskan Native high school students than among white students.[k]

[k] For data, see Appendix D, Table D.8.
For an explanation of terms, see "How to interpret survey results" above. For statistical methods, see Appendix D.

Figure 9. Prevalence of current marijuana use among high school students in Colorado by sexual orientation, 2013-2015.



Produced by: EEOHT, CDPHE 2016
*Black bars indicate margins of error (95% Confidence Intervals).
†Current Use is defined as marijuana use at least once in the past 30 days.
‡Data Source: Healthy Kids Colorado Survey (HKCS) prevalence estimates for 2013-2015.

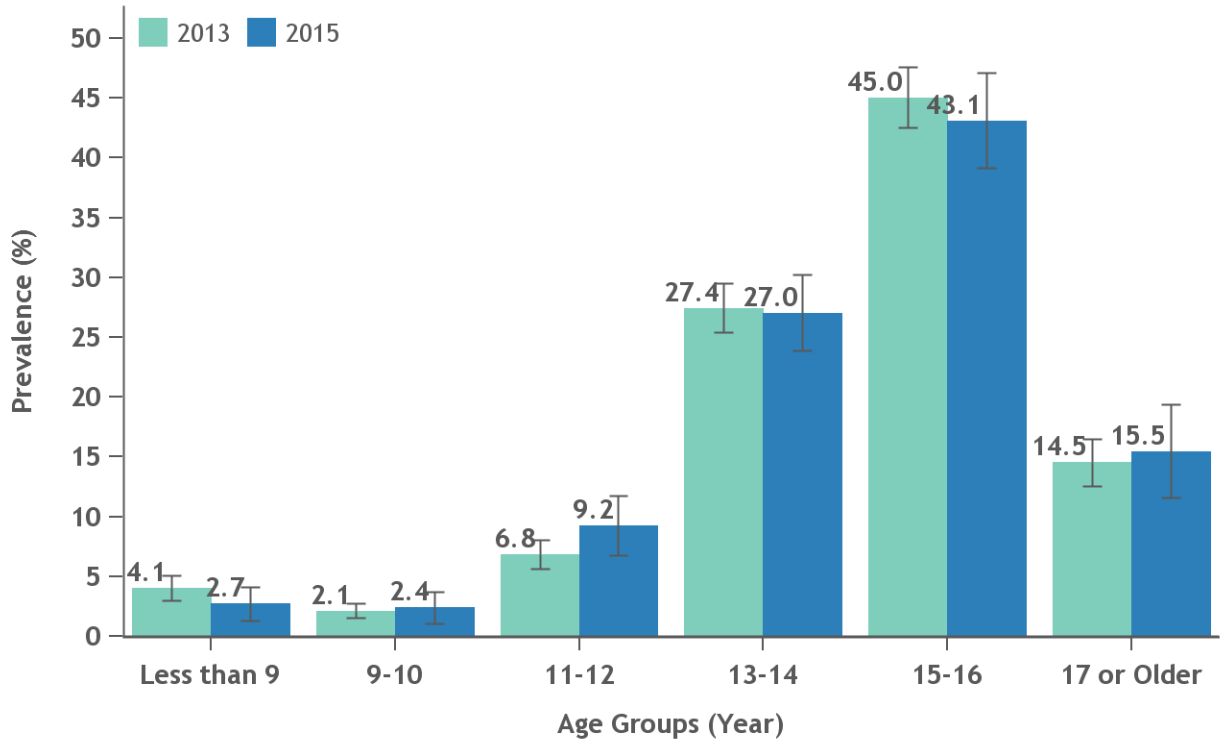
Major findings

- In 2013 and 2015, current use of marijuana among students identifying as gay, lesbian or bisexual, was statistically higher than estimated current use among students identifying as heterosexual. [l]

[l] In 2013: gay, lesbian, or bisexual students 39.7% (95% CI 36.5-42.9%), heterosexual students 17.7% (95% CI 16.7-18.7%). In 2015: gay, lesbian, or bisexual students 34.9% (95% CI 30.4-39.4%), heterosexual students 19.5% (95% CI 17.8-21.1%).

For an explanation of terms, see "How to interpret survey results" above. For statistical methods, see Appendix D. For data, see Appendix D, Table D.9.

Figure 10. Age of first marijuana use among high school seniors in Colorado who reported ever using marijuana, 2013-2015.



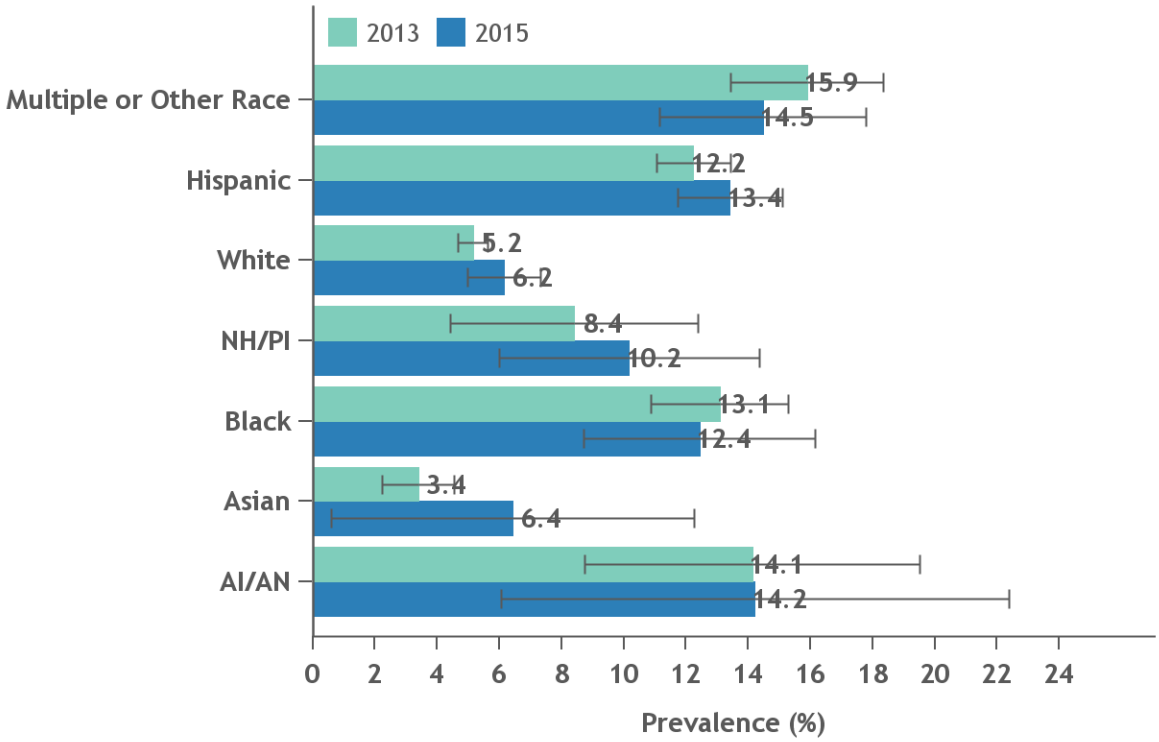
Produced by: EEOHT, CDPHE 2016
*Black bars indicate margins of error (95% Confidence Intervals).
†Current Use is defined as marijuana use at least once in the past 30 days.
‡Data Source: Healthy Kids Colorado Survey (HKCS) prevalence estimates for 2013-2015.

Major findings

- In 2015, among high school seniors who had used marijuana at least once in the past, an estimated 84.4% of them first used by age 16 or before, 41.3% first used by age 14 or before, and 14.3% first used by age 12 or before.[m]
- Age of first marijuana use followed a similar pattern among high school seniors surveyed in 2013 who reported ever using marijuana.

[m] First used by age 12 includes the "Less than 9" (2.7%), "9-10" (2.4%) and "11-12" (9.2%), totaling 14.3%; first used by age 14 includes those plus "13-14" (27.0%), totaling 41.3%; first used by age 16 includes those plus "15-16" (43.1%), totaling 84.4% For data, see Appendix D, Table D.10.

Figure 11. Prevalence of high school students in Colorado who tried marijuana before age 13 by race/ethnicity, 2013-2015.



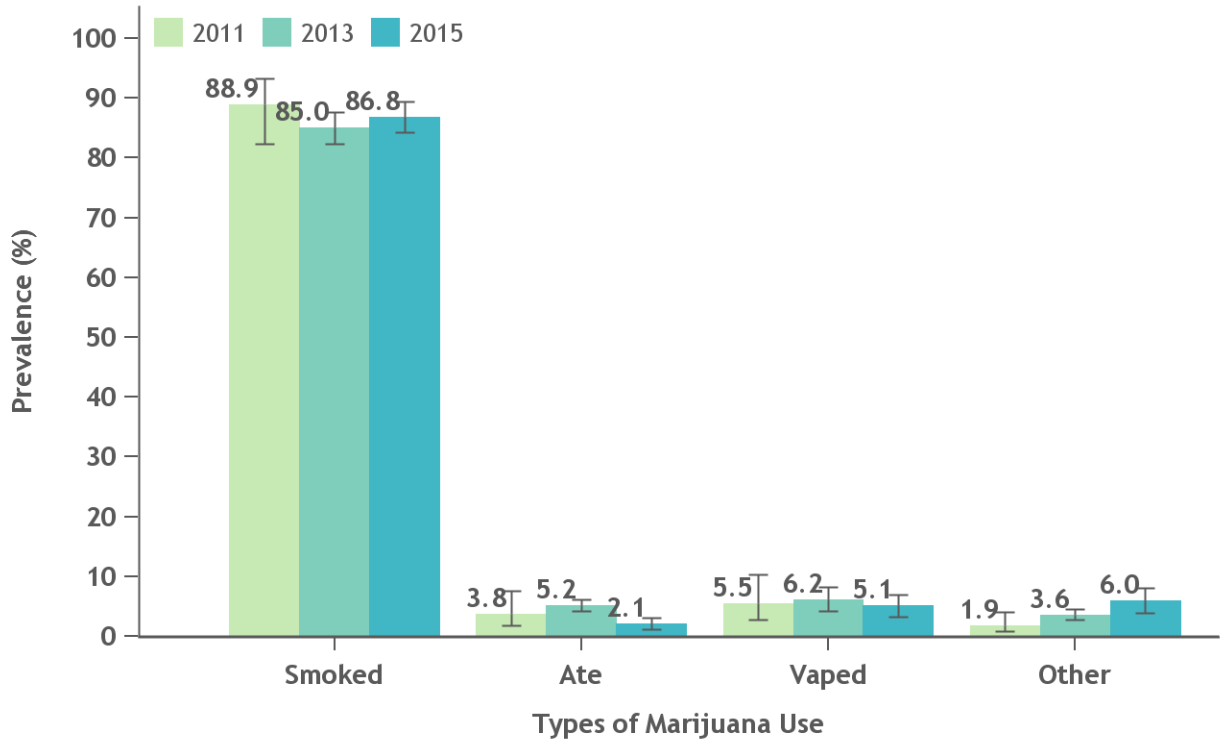
Produced by: EEOHT, CDPHE 2016
*Black bars indicate margins of error (95% Confidence Intervals).
†Hispanic includes respondents who selected "Hispanic" for ethnicity and "white" for race. Those who selected "Hispanic" for ethnicity and a non-white race are included under "multiple or other race".
AI: American Indian, AN: Alaska Native, NH: Native Hawaiian, PI: Pacific Islander.
‡Data Source: Healthy Kids Colorado Survey (HKCS) prevalence estimates for 2013-2015.

Major findings

- In both 2013 and 2015, the estimated percent of white students who first tried marijuana before age 13 was statistically lower than among black, Hispanic, and multiple or other race students. [n]
- In 2013, the estimated percent of Asian students who first tried marijuana before age 13 was statistically lower than among black, Hispanic, American Indian/Alaskan Native and multiple or other race students.[n]

[n] For an explanation of terms, see "How to interpret survey results" above. For statistical methods, see Appendix D. For data, see Appendix D, Table D.11.

Figure 12. Usual methods of marijuana use among high school students in Colorado who reported current marijuana use, 2011-2015.



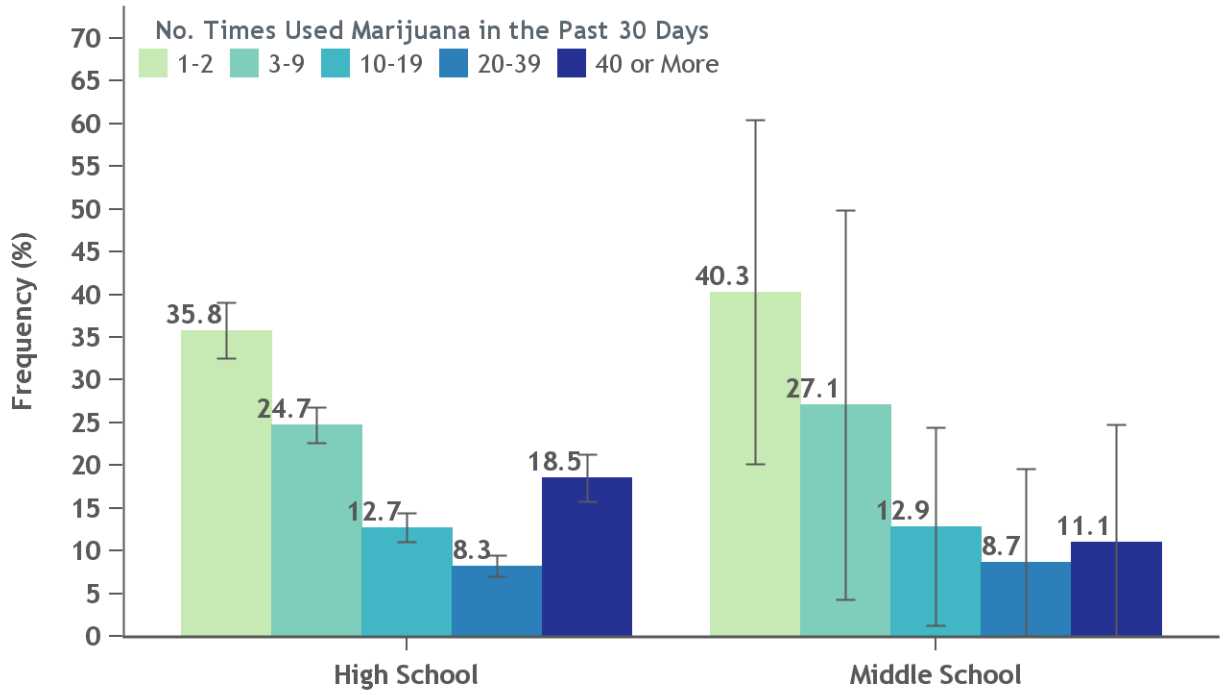
Produced by: EEOHT, CDPHE 2016
*Black bars indicate margins of error (95% Confidence Intervals).
†Current Use is defined as marijuana use at least once in the past 30 days.
‡In 2015 the 'Other' category included 'Other' and 'Dabbing.'
§Data Source: Healthy Kids Colorado Survey (HKCS) prevalence estimates for 2011-2015.

Major findings

- A large majority of high school students who currently use marijuana report that smoking is their usual method of use, as compared to edibles, vaping or other methods of use.
- The percentage of high school students who reported usually using edibles was statistically lower in 2015 compared to 2013.º

º Usually use edibles: 2013 5.2% (95% CI 4.2-6.1%), 2015 2.1% (95% CI 1.2-3.0%)
For an explanation of terms, see "How to interpret survey results" above. For statistical methods, see Appendix D. For data, see Appendix D, Table D.12.

Figure 13. Frequency of marijuana use among high school and middle school students in Colorado who reported current marijuana use, 2015.



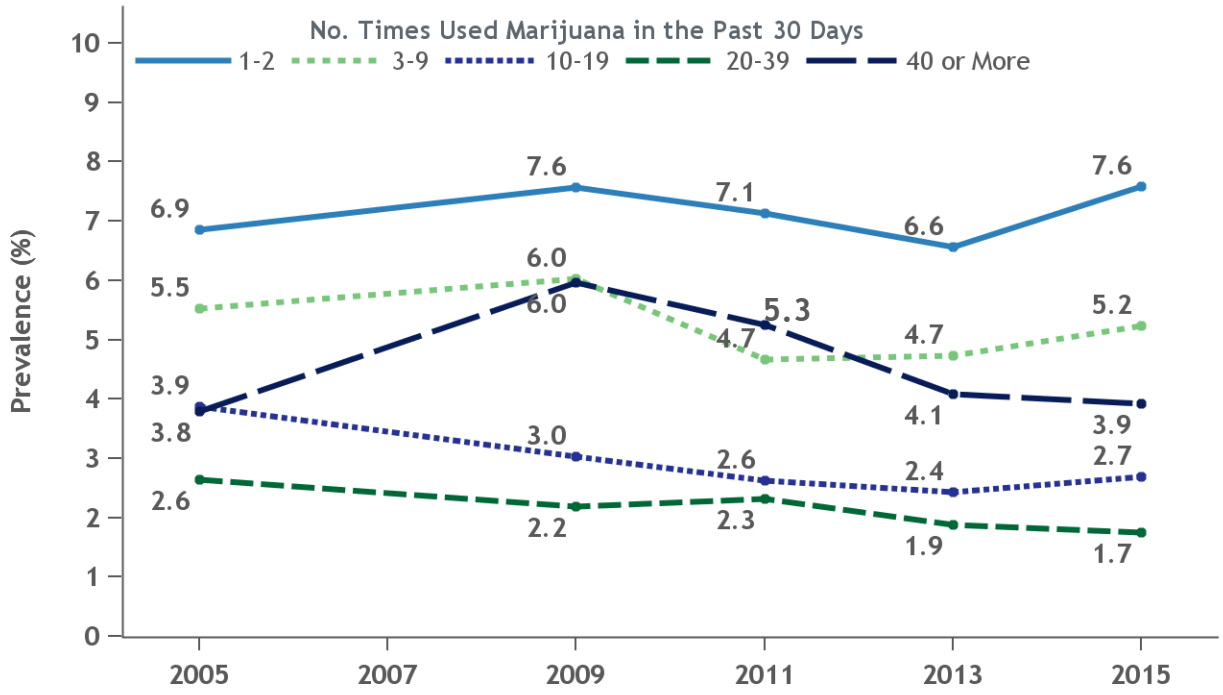
Produced by: EEOHT, CDPHE 2016
*Black bars indicate margins of error (95% Confidence Intervals).
†Current Use is defined as marijuana use at least once in the past 30 days.
‡Data Source: Healthy Kids Colorado Survey (HKCS) prevalence estimates for 2013-2015.

Major findings

- In 2015, among high school students currently using marijuana, an estimated 35.8% used it once or twice in the past 30 days, while 26.8% used it 20 or more times.[p]
- Among middle school students currently using marijuana, an estimated 40.3 % used once or twice in the past 30 days and 19.8% used 20 or more times. [q]

[p] 20 or more times includes "20-39" (8.3%) and "40 or more" (18.5%), totaling 26.8%
[q] 20 or more times includes "20-39" (8.7%) and "40 or more" (11.1%), totaling 19.8%
For statistical methods, see Appendix D. For data, see Appendix D, Table D.13.

Figure 14. Frequency of marijuana use among high school students in Colorado, 2005-2015.



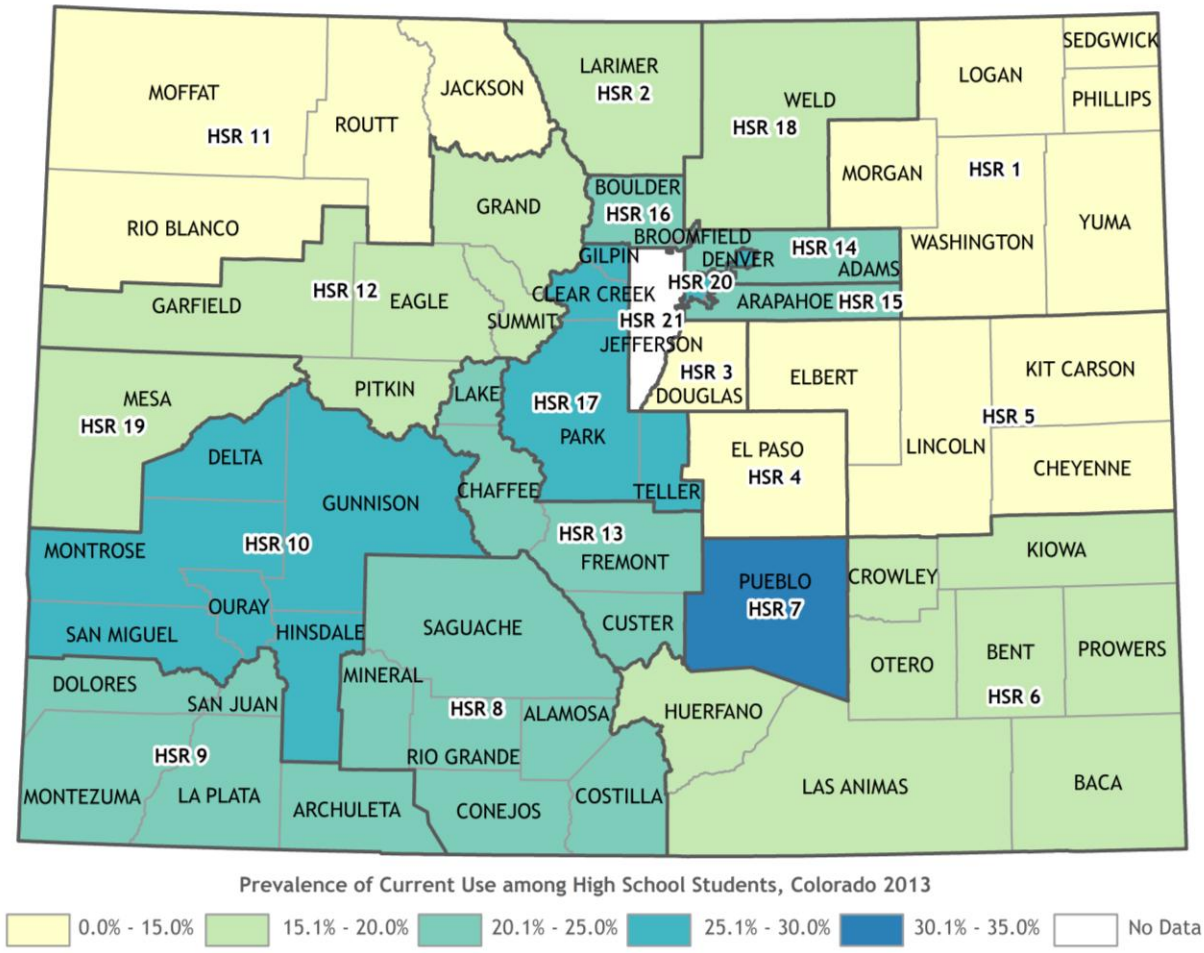
Produced by: EEOHT, CDPHE 2016
*Black bars indicate margins of error (95% Confidence Intervals).
†Current Use is defined as marijuana use at least once in the past 30 days.
‡Data Source: Healthy Kids Colorado Survey (HKCS) prevalence estimates for 2005-2015. Note: Data for the year 2007 was not included due to low sample size.

Major findings

- The estimated percent of Colorado high school students using marijuana at each frequency level fluctuated for surveys from 2005 to 2015, with no notable trends.[r]

[r] For data, see Appendix D, Table D.14.
For statistical methods, see Appendix D.

Map 1. Prevalence of current marijuana use among high school students in Colorado, 2013

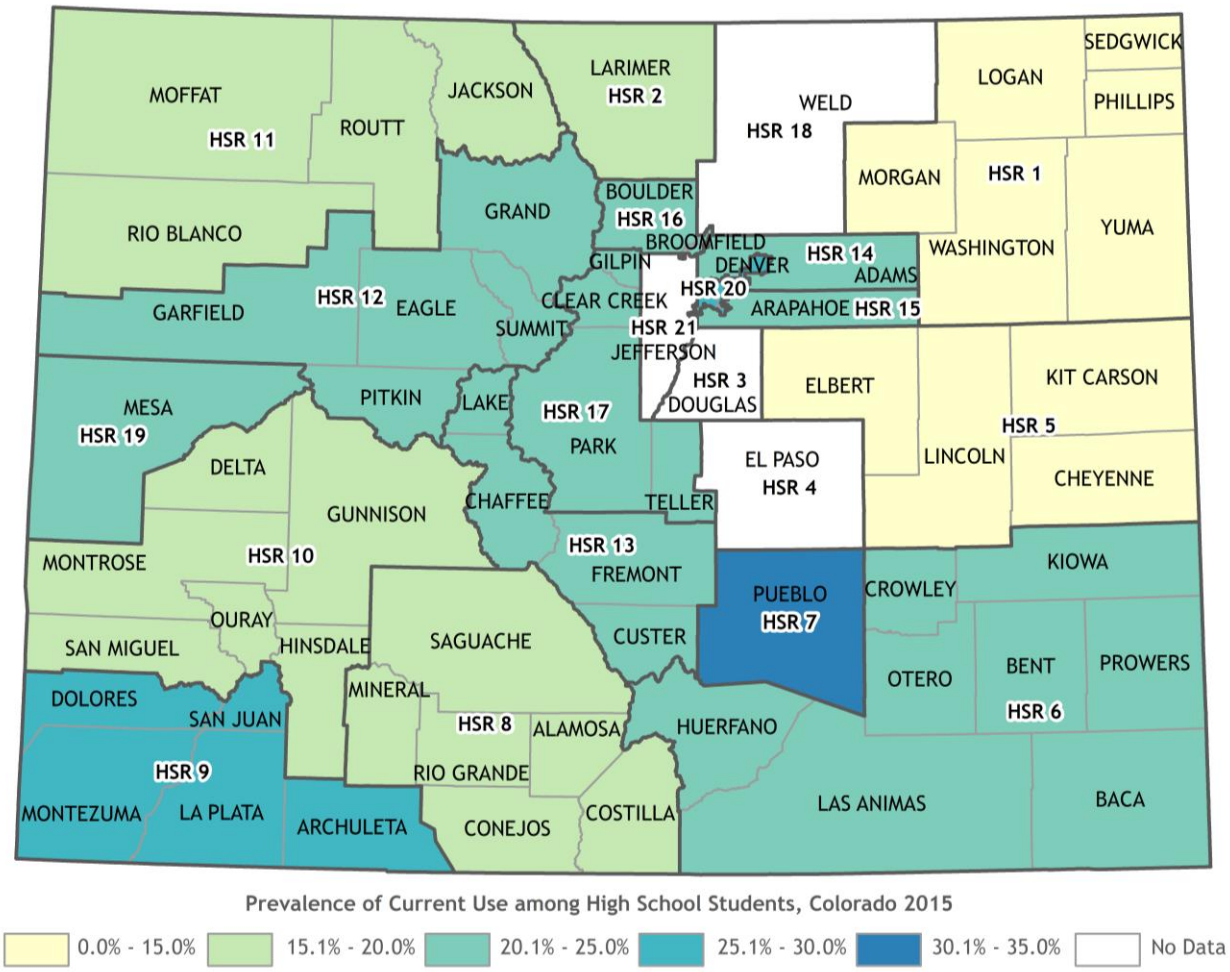


Major findings

- In 2013, health statistic regions 7 (Pueblo County, 32.0%), 10 (Montrose, Delta, Gunnison, Ouray, Hinsdale, and San Miguel Counties, 26.7%), 20 (Denver County, 26.6%), 17 (Gilpin, Clear Creek, Park, and Teller Counties, 25.1%), 9 (Dolores, San Juan, Montezuma, La Plata, and Archuleta Counties, 24.6%), and 13 (Lake, Chaffee, Fremont, and Custer Counties, 22.9%), were statistically higher than the 2013 Colorado state estimate of current use among high school students of 19.7%.[s]

[s] In 2013: HSR 7 - 32.0% (95% CI 25.7-38.4%), HSR 10 - 26.7% (95% CI 22.3-31.0%), HSR 20 - 26.6% (95% CI 22.5-30.8%), HSR 17 - 25.1% (95% CI 21.9-28.3%), HSR 9 - 24.6% (95% CI 20.9-28.3%), HSR 13 – 22.9% (95% CI 21.2-24.7%), all of Colorado - 19.7% (95% CI 18.7-20.6%)
For an explanation of terms, see "How to interpret survey results" above. For statistical methods, see Appendix D.

Map 2. Prevalence of Current Marijuana Use among High School Students in Colorado, 2015



Major findings

- In 2015, health statistics regions 7 (Pueblo County, 30.1%) and 9 (Dolores, San Juan, Montezuma, La Plata, and Archuleta Counties, 26.2%) were statistically higher than the 2015 Colorado state estimate of current use among high school students of 21.2%.[t]
- Current marijuana use in health statistics region 10 (Montrose, Delta, Gunnison, Ouray, Hinsdale, and San Miguel Counties) was statistically lower in 2015 (17.5%) than it was in 2013 (26.7%).[u]
- For all other health statistics regions, current use in 2015 was not statistically different from current use in 2013.

[t] In 2015: HSR 7 - 30.1% (95% CI 27.1-33.2%), HSR 9 - 26.2% (95% CI 24.7-37.7%), all of Colorado - 21.2% (95% CI 19.7-22.7%)
[u] HSR 10: 2013 - 26.7% (95% CI 22.3-31.0%), 2015 - 17.5% (95% CI12.7-22.3%)
For an explanation of terms, see "How to interpret survey results" above. For statistical methods, see Appendix D.

References

1. Centers for Disease Control and Prevention. Youth Risk Behavioral Surveillance System. *Adolescent and School Health* http://www.cdc.gov/healthyyouth/data/yrbs/.
2. Colorado Department of Public Health and Environment. Adolescent Health Data, Healthy Kids Colorado Survey. *Colorado Health and Environmental Data* 2015; http://www.chd.dphe.state.co.us/topics.aspx?q=Adolescent_Health_Data, 2016.
3. Substance Abuse and Mental Health Services Administration. Population Data / NSDUH. https://www.samhsa.gov/data/population-data-nsduh/2015.

Section 1

Monitoring Changes in Marijuana Use Patterns

Chapter 4

Pregnancy Risk Assessment Monitoring System (PRAMS) 2014 Survey Results

Retail Marijuana Public Health Advisory Committee

COLORADO
Department of Public Health & Environment

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The PRAMS survey and marijuana use in Colorado

The Pregnancy Risk Assessment Monitoring System (PRAMS) is a survey sponsored by the Centers for Disease Control and Prevention (CDC). The survey asks new mothers questions about their pregnancy and their new baby. It provides data not available from other sources about pregnancy and the first few months after delivery, and allows CDC and the states to monitor changes in maternal and child health indicators, such as unintended pregnancy, prenatal care, breastfeeding, infant health, smoking and alcohol use. These data can be used to identify groups of women and infants at high risk for health problems, to monitor changes in health status, and to measure progress toward goals in improving the health of mothers and infants.[1] In 2014, PRAMS in Colorado asked about marijuana use before, during and after pregnancy (Table 1).[2]

For additional survey details and information about analysis methods, see Appendix E.

Survey questions

Table 1. Pregnancy Risk Assessment Monitoring System question about marijuana use, 2014.

1. During any of the following time periods, did you use marijuana or hashish (hash)? For each time period, say No if you did not use then or say Yes if you did.

    a. During the 3 months before I got pregnant.
    b. During the first 3 months of my pregnancy.
    c. During the last 3 months of my pregnancy.
    d. At any time during my most recent pregnancy.
    e. Since my baby was born.
    f. Don't know/don't remember

Definitions

Using marijuana during pregnancy was defined by combining three responses: *during the first 3 months of my pregnancy; during the last 3 months of my pregnancy;* and *at any time during my most recent pregnancy*.

Using marijuana and breastfeeding after delivery was defined as answering 'Yes' to using marijuana *since my baby was born* AND answering 'Yes' to one of two breastfeeding questions: *Did you ever breastfeed or pump breastmilk to feed your new baby;* or *Are you currently breastfeeding or feeding pumped milk to your new baby*.

How to interpret survey results

Respondents to the PRAMS survey are a sample of Colorado women who recently gave birth. The percent of survey respondents selecting a specific answer might not be exactly the same as if all Colorado women who recently gave birth were surveyed. Therefore, the survey results are estimates, and each has a range of possible values (also called margin of error, confidence interval, or 95% CI). These ranges are very important when comparing two estimates, and the following terms are used throughout this report:

'Not statistically different'- Typically, if the ranges of possible values *overlap* for two different survey results (like two different years, or male vs. female), we cannot be confident that there is a true difference between the two (also called 'not statistically significant.') In some cases, an additional statistical test is done to confirm.

'Statistically higher' or 'statistically lower'- If the ranges of possible values *do not overlap* for two different results, we CAN be confident that there is a true difference between the two (also called 'statistically significant.')

On the figures in this report, these ranges of possible values are indicated by black bars. In footnotes, they are referred to by the statistical term '95% CI.'

Results

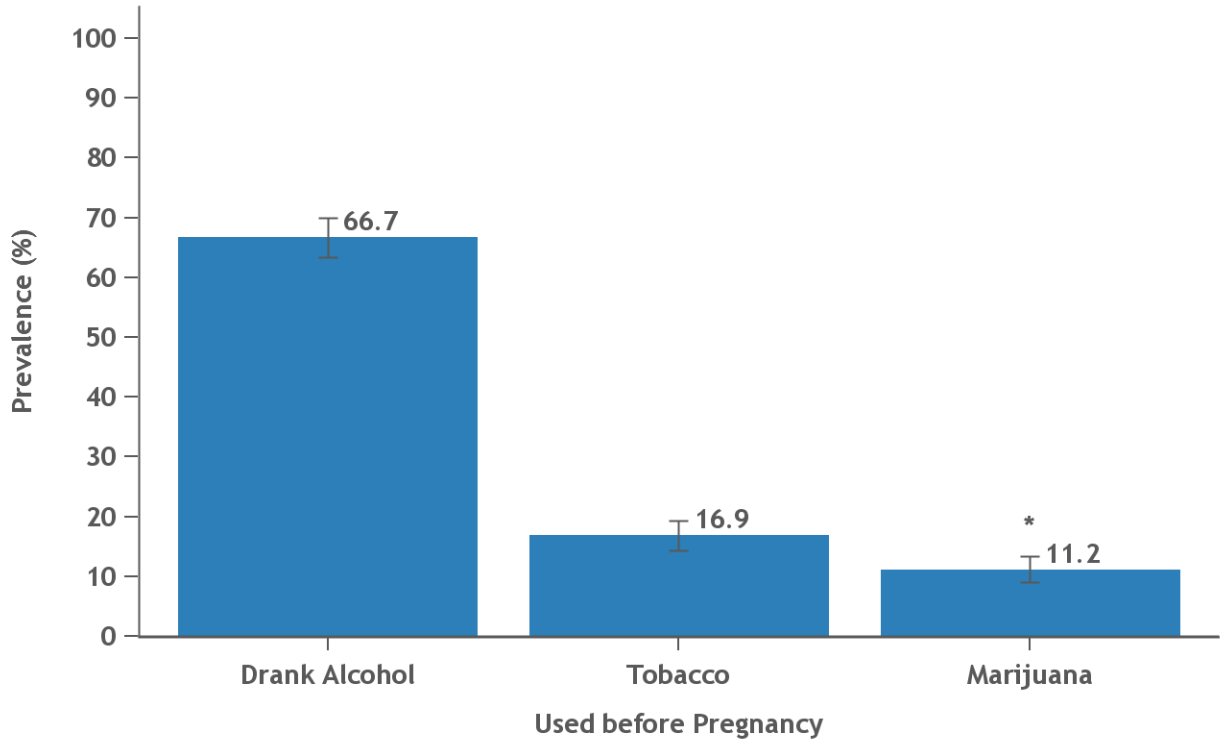
Results are displayed in Figures 1-5 below.

In 2014, among new mothers in Colorado, marijuana use before pregnancy (11.2%) was statistically lower than use of tobacco (16.9%) or alcohol (66.7%) before pregnancy (Figure 1). During pregnancy, alcohol use (12.8%) was statistically higher than use of tobacco (6.4%) or marijuana (5.7%) (Figure 2). A 2016 article estimated that 3.9% of pregnant women in the United States overall used marijuana during pregnancy (data not shown).[3] This was not statistically different from the PRAMS estimate of 5.7% for Colorado.

Marijuana use before pregnancy (11.2%) was statistically higher than use during pregnancy (5.7%) or use by breastfeeding mothers after delivery (4.5%) (Figure 3). There was no statistical difference between use during pregnancy and use by breastfeeding mothers after delivery. Marijuana use during pregnancy was statistically higher among women with an unintended pregnancy (9.1%) than among women who intended to become pregnant (4.0%) (Figure 4).

When marijuana use during pregnancy was compared among different demographics, both education and age showed statistical differences, while race/ethnicity did not. Use during pregnancy was statistically higher among women with less than a 12th grade education (15.7%) than among women with some college (4.1%) (Figure 5). It was also statistically higher among women 20-24 years old (12.6%) than among women 25-34 years old (4.3%) or women 35 years old or older (2.7%) (Figure 5). There were no statistical differences in marijuana use during pregnancy by race/ethnicity (Figure 5).

Figure 1. Colorado women who reported using substances before pregnancy, 2014.



Produced by: EEOHT, CDPHE 2016
*95% confidence intervals do not overlap.
†Black bars indicate margins of error (95% Confidence Intervals).
‡Data Source: Colorado Pregnancy Risk Assessment Monitoring System 2014.

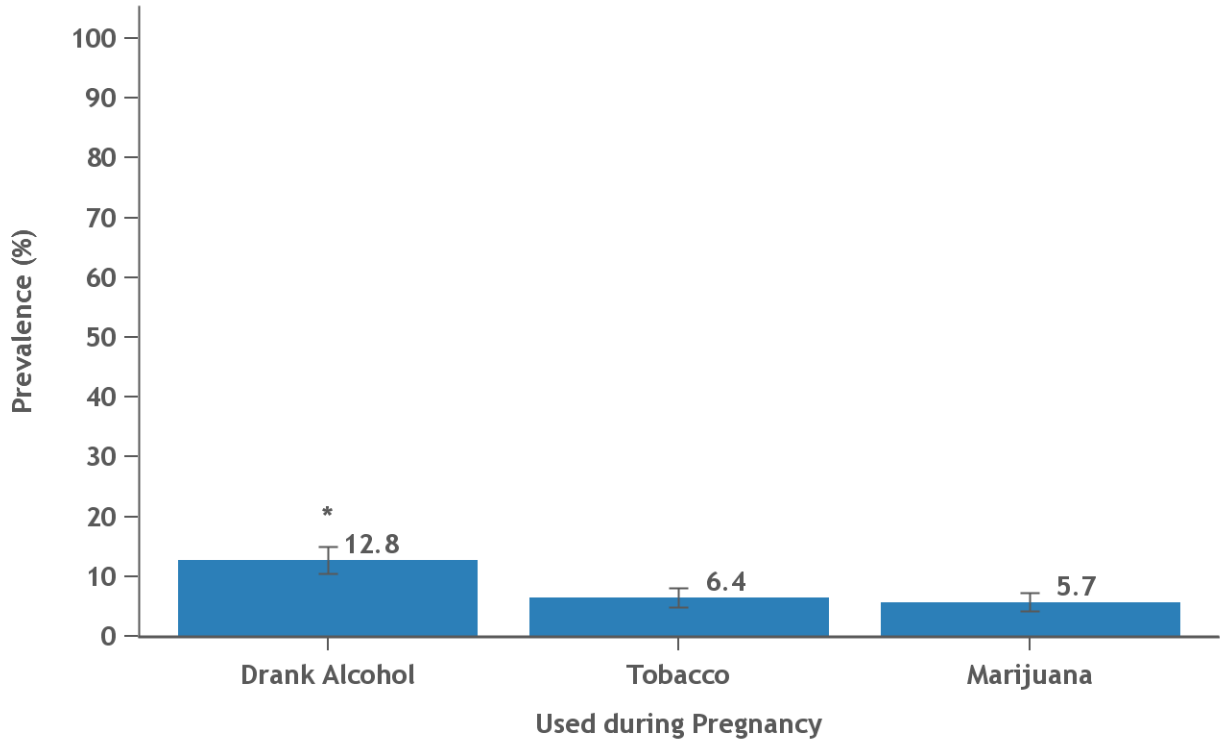
Major findings

- The prevalence of marijuana use before pregnancy among women who recently gave birth was statistically lower than use of tobacco or alcohol before pregnancy.[a]

[a] 2014 substance use before pregnancy: alcohol 66.7% (95% CI 63.4-69.9%), tobacco 14.4% (95% CI 14.4-19.4%), marijuana 11.2% (95% CI 9.0-13.3%)

For an explanation of terms, see "How to interpret survey results" above. For statistical methods, see Appendix E. For data, see Appendix E, Table E.1.

Figure 2. Colorado women who reported using substances during pregnancy, 2014.



Produced by: EEOHT, CDPHE 2016
*95% confidence intervals do not overlap.
†Black bars indicate margins of error (95% Confidence Intervals).
‡Tobacco and alcohol use was during the last 3 months of pregnancy.
§Data Source: Colorado Pregnancy Risk Assessment Monitoring System 2014.

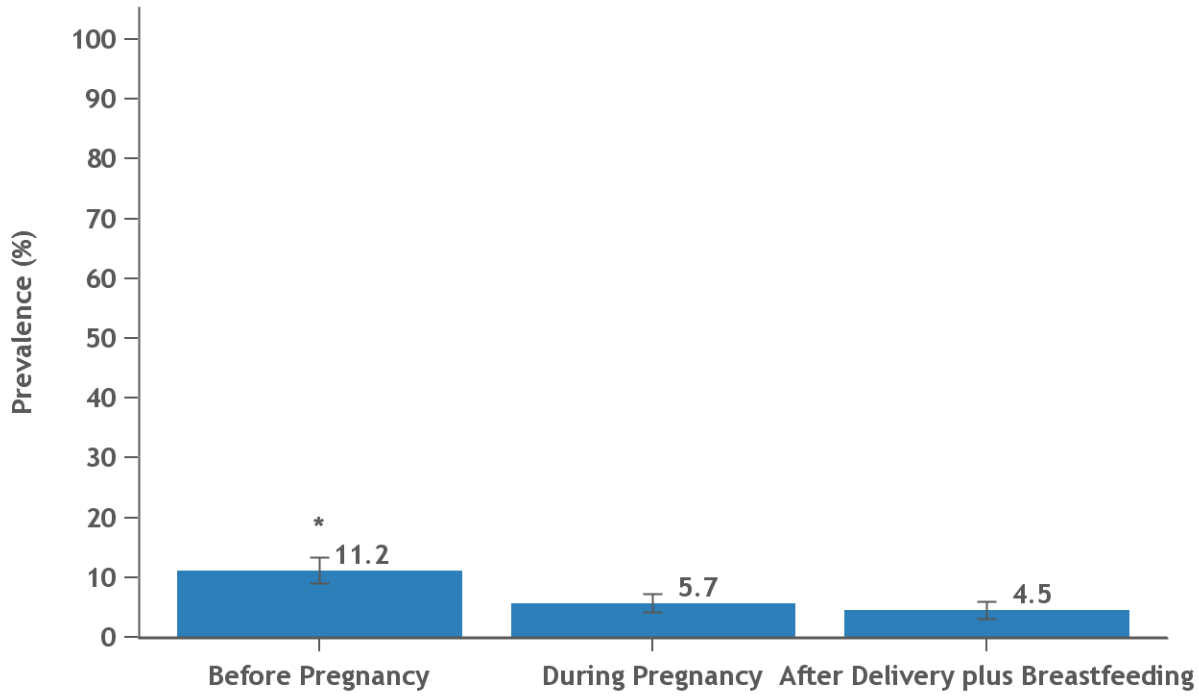
Major findings

- The prevalence of alcohol use during pregnancy was statistically higher than use of tobacco or marijuana during pregnancy. The use of marijuana was not statistically different from use of tobacco.[b]

[b] 2014 substance use during pregnancy: alcohol 12.8% (95% CI 10.5-15.0%), tobacco 6.4% (95% CI 4.8-8.1%), marijuana 5.7% (95% CI 4.2-7.2%)

For an explanation of terms, see "How to interpret survey results" above. For statistical methods, see Appendix E. For data, see Appendix E, Table E.2.

Figure 3. Colorado women who reported using marijuana before, during, and after pregnancy, 2014.



Produced by: EEOHT, CDPHE 2016
*95% confidence intervals do not overlap.
†Black bars indicate margins of error (95% Confidence Intervals).
‡Data Source: Colorado Pregnancy Risk Assessment Monitoring System 2014.

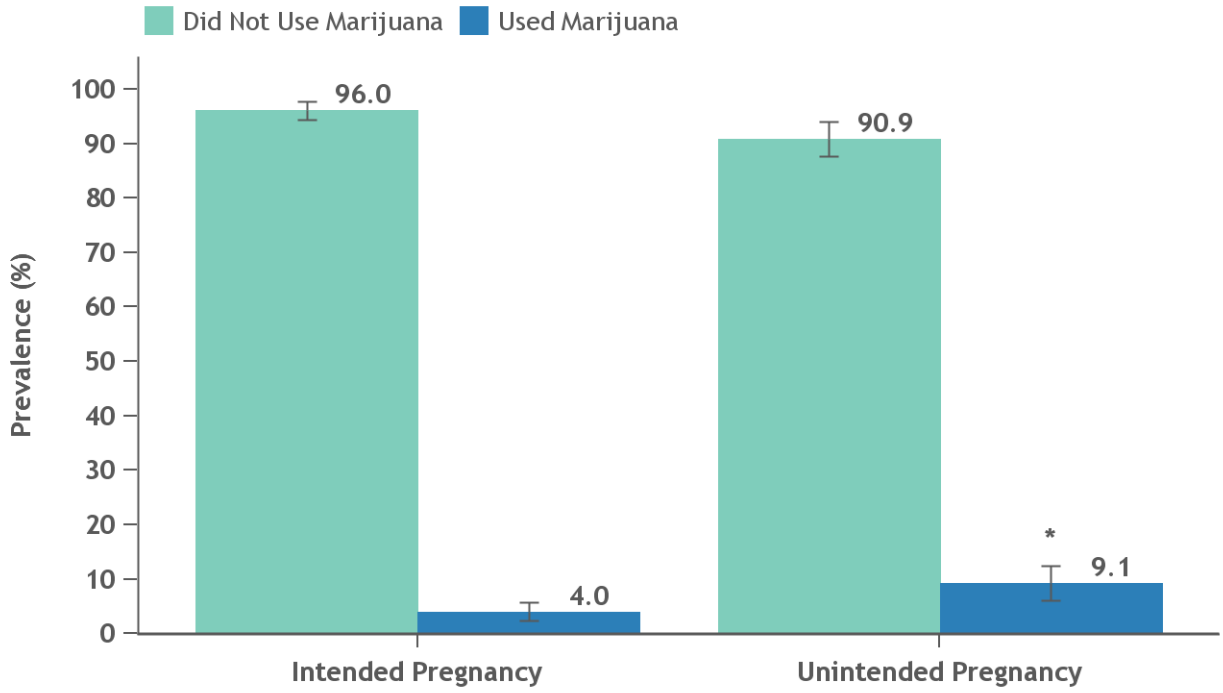
Major findings

- The prevalence of marijuana use before pregnancy was statistically higher than use during pregnancy or use by breastfeeding mothers after delivery. There was no statistical difference between use during pregnancy and use by breastfeeding mothers after delivery.[c]

[c] 2014 marijuana use: before pregnancy 11.2% (95% CI 9.0-13.3%), during pregnancy 5.7% (95% CI 4.2-7.2%), by breastfeeding mothers after delivery 4.5% (95% CI 3.1-5.9%)

For an explanation of terms, see "How to interpret survey results" above. For statistical methods, see Appendix E. For data, see Appendix E, Table E.3.

Figure 4. Colorado women who reported using marijuana during pregnancy by intention to become pregnant, 2014.



Produced by: EEOHT, CDPHE 2016
*95% confidence intervals do not overlap.
†Black bars indicate margins of error (95% Confidence Intervals).
‡Data Source: Colorado Pregnancy Risk Assessment Monitoring System 2014.

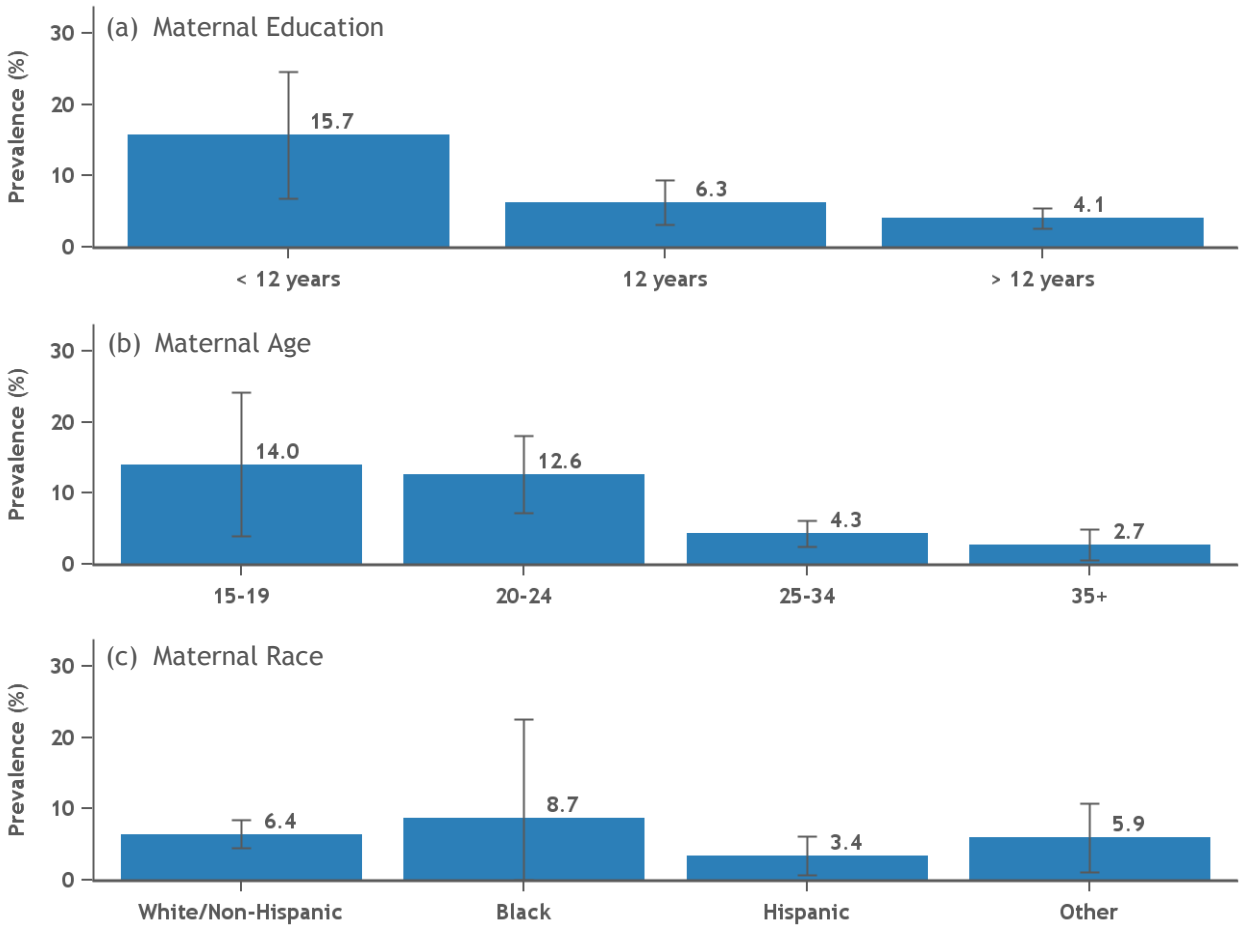
Major findings

- The prevalence of marijuana use during pregnancy was statistically higher among women with an unintended pregnancy than among women who intended to become pregnant.[d]

[d] 2014 marijuana use during pregnancy, by intention to become pregnant: intended pregnancy 4.0% (95% CI 2.3-5.7%), unintended pregnancy 9.1% (95% CI 6.0-12.3%)

For an explanation of terms, see "How to interpret survey results" above. For statistical methods, see Appendix E. For data, see Appendix E, Table E.4.

Figure 5. Colorado women who reported using marijuana during pregnancy by maternal education (a), age (b), and race (c), 2014.



Produced by: EEOHT, CDPHE 2016
†Black bars indicate margins of error (95% Confidence Intervals).
‡Data Source: Colorado Pregnancy Risk Assessment Monitoring System 2014.

Major Findings

- The prevalence of marijuana use during pregnancy was statistically higher among women with less than a 12th grade education than among women with some college.[e]
- The prevalence of marijuana use during pregnancy was statistically higher among women 20-24 years old than among women 25-34 years old or women 35 years old or older.[f]
- There were no statistical differences in marijuana use during pregnancy by race/ethnicity.[g]

[e] 2014 marijuana use during pregnancy, by education: <12 years 15.7% (95% CI 6.9-24.5%), 12 years 6.3% (95% CI 3.2-9.5%), >12 years 4.1% (95% CI 2.6-5.5%)

[f] 2014 marijuana use during pregnancy, by maternal age: 15-19 years old 14.0% (95% CI 3.9-24.1%), 20-24 years old 12.6% (95% CI 7.2-18.0%), 25-34 years old 4.3% (95% CI 2.5-6.1%), 35 years or older 2.7% (95% CI 0.6-4.9%)

[g] 2014 marijuana use during pregnancy, by race/ethnicity: White/non-Hispanic 6.4% (95% CI 4.4-8.4%), Black 8.7% (95% CI 0.0-22.5%), Hispanic 3.4% (95% CI 0.7-6.2%), Other 5.9% (95% CI 1.1-10.8%)

For an explanation of terms, see "How to interpret survey results" above. For statistical methods, see Appendix E. For data, see Appendix E, Table E.5.

References

1. Centers for Disease Control and Prevention. PRAMS. 2016; https://www.cdc.gov/prams/, https://www.cdc.gov/prams/.
2. Colorado Department of Public Health and Environment. Pregnancy Risk Assessment Monitoring System. https://www.colorado.gov/pacific/cdphe/pregnancysurvey.
3. Volkow ND, Compton WM, Wargo EM. The Risks of Marijuana Use During Pregnancy. *JAMA*. 2017;317(2):129-130.

Section 2

Scientific Literature Review on Potential Health Effects of Marijuana Use

Retail Marijuana Public Health Advisory Committee

COLORADO
Department of Public Health & Environment

Background

The Colorado Department of Public Health and Environment (CDPHE) was given statutory (25-1.5-110, C.R.S.) responsibility to:

- "…monitor changes in drug use patterns, broken down by county and race and ethnicity, and the emerging science and medical information relevant to the health effects associated with marijuana use."

- "…appoint a panel of health care professionals with expertise in cannabinoid physiology to monitor the relevant information."

Based on this charge, CDPHE appointed a 14-member committee, the Retail Marijuana Public Health Advisory Committee, to review scientific literature on the health effects of marijuana. Members of this committee (see Appendix, Retail Marijuana Public Health Advisory Committee Membership Roster) are individuals in the fields of public health, medicine, epidemiology, and medical toxicology who demonstrate expertise related to marijuana through their work, training or research. This committee was charged with the duties as outlined in 25-1.5-110 C.R.S. to "...establish criteria for studies to be reviewed, review studies and other data, and make recommendations, as appropriate, for policies intended to protect consumers of marijuana or marijuana products and the general public."

The committee has met since May 2014 to complete these duties. The overall goal was to implement an unbiased and transparent process for evaluating scientific literature and data on marijuana use and health outcomes. The committee was particularly interested in ensuring quality information is shared about the known physical and mental health effects associated with marijuana use – and also about what is unknown at present. The official bylaws of this committee are included in Appendix A, Retail Marijuana Public Health Advisory Committee By-laws.

The committee used a standardized systematic literature review process to search and grade the existing scientific literature on health effects of marijuana. Findings were synthesized into evidence statements that summarize the quantity and quality of scientific evidence supporting an association between marijuana use and a health outcome. These evidence statements were classified as follows:

- **Substantial evidence** - indicates robust scientific findings that support an association between marijuana use and the outcome.
- **Moderate evidence** - indicates scientific findings support an association between marijuana use and the outcome, but these findings have some limitations.
- **Limited evidence** - indicates modest scientific findings that support an association between marijuana use and the outcome, but these findings have significant limitations.
- **Mixed evidence** - indicates both supporting and non-supporting scientific findings for an association between marijuana use and the outcome, with neither direction dominating.
- **Body of research failing to show an association** - indicates the topic has been researched without evidence of an association; is further classified as a **limited**, **moderate** or **substantial** body of research.
- **Insufficient evidence** - indicates the outcome has not been sufficiently studied to conclude whether or not there is an association between marijuana use and the outcome.

The committee also translated these evidence statements into plain language so they are understandable to the general public for future use in public health messaging. In addition, the committee was asked to develop public health recommendations based on potential concerns identified through the review process and to articulate research gaps based on common limitations of existing research. All these were presented to the full committee during open public meetings with opportunities for stakeholder input. Final statements, recommendations and research gaps were formally approved by a majority vote of the committee.

The topics for review were originally chosen in 2014 based on recently published peer-reviewed publications outlining the potential health effects of marijuana use, and public health priorities identified from key informant interviews of local public health officials across Colorado, including in urban, rural, and resort communities. Additional topics added in 2015 and 2016 were based on committee and stakeholder suggestions. Key findings for each topic are presented below. More detailed findings including literature citations are included in each of the individual chapters.

An important note for all key findings is the available research evaluated the **association** between marijuana use and potential adverse health outcomes. This **association** does not prove the marijuana use alone **caused** the effect. Despite the best efforts of researchers to account for confounding factors, there may be other important factors related to **causality** that were not identified. In addition, marijuana use was illegal everywhere in the United States prior to 1996. Research funding, when appropriated, was commonly sought to identify adverse effects from marijuana use. This legal fact introduces both funding bias and publication bias into the body of literature related to marijuana use. Another limitation of the available research data is that most studies did not or could not measure the THC level (potency) of marijuana used by subjects, nor which other cannabinoids were present. There are diverse products now available in Colorado, many of which are likely higher in potency than the marijuana used by study subjects for much of the literature reviewed.

The Retail Marijuana Public Health Advisory Committee recognizes the limitations and biases inherent in the published literature and made efforts to ensure the information reviewed and synthesized is reflective of the current state of medical knowledge. Where information was lacking – for whatever reason – the committee identified this knowledge gap and recommended further research. This information will be updated as new research becomes available.

Summary of key findings

Marijuana use among adolescents and young adults

The committee reviewed the relationships between adolescent and young adult marijuana use and cognitive abilities, academic performance, mental health and future substance use. Weekly marijuana use by adolescents is associated with impaired learning, memory, math and reading, even 28 days after last use. Weekly use is also associated with failure to graduate from high school. Adolescents and young adults who use marijuana are more likely to experience psychotic symptoms as adults, such as hallucinations, paranoia, delusional beliefs and feeling emotionally unresponsive. Evidence shows marijuana users can become addicted to marijuana and treatment for marijuana addiction can decrease use and dependence. Additionally, marijuana users who quit have lower risks of cognitive and mental health outcomes than those who continue to use.

Marijuana use and cancer

The committee reviewed different forms of cancer relative to marijuana use, as well as the chemicals released in marijuana smoke and vapor. Strong evidence shows marijuana smoke contains many of the same cancer-causing chemicals found in tobacco smoke. However, there is conflicting research for whether or not a higher cumulative level of marijuana smoking is associated with lung cancer. Limited evidence suggests an association between marijuana use and both testicular and prostate cancers. On the other hand, the limited evidence available concerning cancers of the bladder, head and neck suggests that they might not have any association with marijuana use.

Marijuana use and cardiovascular effects

The committee reviewed myocardial infarction, stroke and death from cardiovascular causes, relative to marijuana use. There is a moderate level of scientific evidence that marijuana use increases risk for some forms of stroke in individuals younger than 55, and more limited evidence that marijuana use may increase risk for heart attack. Research is lacking concerning other cardiovascular events and conditions, including death.

Marijuana dose and drug interactions

The committee reviewed THC (tetrahydrocannabinol, the main psychoactive component of marijuana) levels relative to marijuana dose and method of use, the effects of secondhand marijuana smoke, drug-drug interactions involving marijuana, and relationships between marijuana and opioid use. One important finding is that it can take up to four hours after consuming an edible marijuana product to reach the peak THC blood concentration and feel the full effects. There is credible evidence of clinically important drug-drug interactions between marijuana and multiple medications, including some anti-seizure medications and a common blood-thinner. Data about potential interactions are lacking for many drugs at this time and likely to evolve substantially over coming years. Finally, there is some evidence that opioid pain medication overdose deaths are lower in states with legal medical marijuana than would be expected based on trends in states without legal medical marijuana. There is conflicting evidence for whether or not marijuana use is associated with a decrease in opioid use among chronic pain patients or individuals with a history of problem drug use.

Marijuana use and driving

The committee reviewed driving impairment and motor vehicle crash risk relative to marijuana use, as well as evidence indicating how long it takes for impairment to resolve after marijuana use. It found the risk of a motor vehicle crash increases among drivers with recent marijuana use. Furthermore, the higher the blood THC level, the higher the motor vehicle crash risk. In addition, using alcohol and marijuana together increases impairment and the risk of a motor vehicle crash more than using either substance alone. For less-than-weekly marijuana users, using marijuana containing 10 milligrams or more of THC is likely to impair the ability to safely drive, bike or perform other safety-sensitive activities. Less-than-weekly users should wait at least six hours after smoking or eight hours after eating or drinking marijuana to allow time for impairment to resolve.

Marijuana use and gastrointestinal or reproductive effects

The committee reviewed gastrointestinal diseases, particularly cyclic vomiting, and infertility or abnormal reproductive function. Evidence shows that long-time, daily or near daily marijuana use is associated with cyclic vomiting. This condition has been called cannabinoid hyperemesis syndrome. In such cases, stopping marijuana use may relieve the vomiting. There is conflicting research for whether or not marijuana use is associated with male infertility or abnormal reproductive function, and research is lacking on female reproductive function related to marijuana use.

Marijuana use and injury

The committee reviewed workplace, recreational and other non-driving injuries, burns from hash-oil extraction or failed electronic smoking devices, and physical dating violence. Evidence shows marijuana use may increase the risk of workplace injury while impaired, but is unclear for other types of non-driving related injury. There have been many reports of severe burns resulting from home-extraction of butane hash oil leading to explosions, and cases of electronic smoking devices exploding, leading to trauma and burns. Concerning dating violence, adolescent girls who use marijuana may be more likely to commit physical violence against their dating partners, and adolescent boys who use marijuana may be more likely to be victims of physical dating violence.

Marijuana use and neurological, cognitive and mental health effects

The committee reviewed the potential relationships between marijuana use and cognitive impairment, mental health disorders and substance abuse. Strong evidence shows that daily or near daily marijuana users are more likely to have impaired memory lasting a week or more after quitting. An important acute effect of THC is psychotic symptoms, such as hallucinations, paranoia and delusional beliefs during intoxication. These symptoms are worse with higher doses. Daily or near daily marijuana use is associated with developing a psychotic disorder such as schizophrenia. Finally, evidence shows marijuana users can become addicted to marijuana and treatment for marijuana addiction can decrease use and dependence.

Marijuana use during pregnancy and breastfeeding

The committee reviewed adverse birth outcomes, effects of prenatal marijuana use on exposed offspring later in childhood or adolescence and effects of marijuana use by a breastfeeding mother. Biological evidence shows THC passes through the placenta to the fetus, so the unborn child is exposed to THC if the mother uses marijuana, and THC passes through breast milk to a breastfeeding child. Marijuana use during pregnancy may be associated with an increased risk of heart defects or stillbirth. Stronger evidence was found for effects that are seen months or years after birth if a child's mother used marijuana while pregnant with the child. These include decreased growth and impaired cognitive function and attention. Decreased academic ability or increased depression symptoms may also occur.

Marijuana use and respiratory effects

The committee reviewed respiratory diseases such as chronic obstructive pulmonary disorder (COPD), chronic bronchitis and asthma, respiratory infections and lung function relative to smoked marijuana. It also reviewed potential health effects of vaporized marijuana. Strong evidence shows an association between daily or near-daily marijuana use and chronic bronchitis. Additionally, daily or near daily marijuana use may be associated with bullous lung disease and pneumothorax in individuals younger than 40 years of age. Research is lacking concerning any possible association between marijuana use and COPD, emphysema or respiratory infections. Smokers who switch from marijuana smoking to marijuana vaporizing may have fewer respiratory symptoms and improved pulmonary function. Finally, a notable effect of acute use is a short-term improvement in lung airflow.

Unintentional marijuana exposures in children

The committee reviewed unintentional marijuana exposure relative to marijuana legalization and child-resistant packaging. They found strong evidence that more unintentional marijuana exposures of children occur in states with increased legal access to marijuana, and that the exposures can lead to significant clinical effects requiring hospitalization. Additionally, evidence shows child resistant packaging prevents exposure to children from potentially harmful substances, such as THC.

The following table includes the committee's most prominent findings from reviews of scientific literature on marijuana use and potential health effects.

Table 1. Substantial and moderate findings from systematic literature review

Marijuana use among adolescents and young adults (p.97)		
	Substantial	**Moderate**
Cognitive and academic	Less high school graduation	Impaired cognitive abilities and academic performance after 28 days abstinence
Mental health	Psychotic symptoms in adulthood	Psychotic disorder in adulthood (daily or near-daily users)
Substance use, abuse and addiction	Can develop marijuana addiction‡	Increased marijuana use and addiction‡ after adolescence
	Other illicit drug use and addiction‡ after adolescence	Alcohol or tobacco use and addiction‡ after adolescence
Benefits of quitting	Treatment for marijuana addiction‡ can reduce use and dependence	Quitting marijuana lowers risk of cognitive and mental health effects
Marijuana use and cancer (p.113)		
	Substantial	**Moderate**
Chemicals in MJ smoke or vapor	Marijuana smoke contains same cancer-causing chemicals as tobacco smoke	
Cancer and pre-cancerous lesions	Pre-cancerous lesions with daily or near-daily use	Failure to show association with lung cancer for less than 10 joint-years cumulative use
Marijuana use and cardiovascular effects (p.123)		
	Substantial	**Moderate**
		Increased risk of ischemic stroke in individuals younger than 55

‡ In this document, the term marijuana addiction is considered equivalent to cannabis use disorder (and addiction to another substance is considered equivalent to use disorder for that substance).

Table 1. (continued) Substantial and moderate findings from systematic literature review

Marijuana dose and drug interaction (p.131) → = results in/produces.		
	Substantial	**Moderate**
THC levels	Smoking >10 mg THC produces blood THC level near or > 5 ng/mL within 10 minutes	Ingesting ≥15 mg THC may → blood THC level > 5 ng/mL
	Time to peak blood THC level is up to four hours post ingestion	Inhaling vaporized THC→ blood THC level similar to smoking the same dose
Secondhand exposure	Typical secondhand exposure → NO positive drug screen by urine or blood	

Marijuana use and driving (p.149) * = applies only to less-than-weekly users. → = results in/produces.		
	Substantial	**Moderate**
Impairment and crash risk	Increased motor vehicle crash risk with recent use	THC blood level and motor vehicle crash risk
	Increased risk of driving impairment at blood THC of 2-5 ng/mL*	Higher blood THC in impaired drivers now than in the past
	Smoking >10 mg THC leads to driving impairment*	
	Orally ingesting >10 mg THC leads to driving impairment*	
	Combined use with alcohol increases crash risk	
Time to wait before driving	Waiting ≥ 6 hrs after smoking < 18 mg → driving impairment resolves/nearly resolves*	Waiting ≥ 6 hrs after smoking about 35 mg → driving impairment resolves/nearly resolves*
	Waiting ≥ 8 hrs after orally ingesting < 18 mg → driving impairment resolves/nearly resolves*	

*** = applies only to less-than-weekly users.**
→ = results in/produces.
There were no substantial or moderate findings for Marijuana Use and Injury

Table 1. (continued) Substantial and moderate findings from systematic literature review

Marijuana use and gastrointestinal and reproductive effects (p.161)		
	Substantial	**Moderate**
		Cyclic vomiting with long-time, daily or near-daily use (cannabinoid hyperemesis syndrome)
Marijuana use and neurological, cognitive, mental health effects (p.183)		
	Substantial	**Moderate**
Cognitive effects	Impaired memory for at least 7 days (daily or near-daily users)	
Mental health effects	Acute psychotic symptoms during intoxication	Psychotic disorder in adulthood (daily or near-daily users)
Substance use and addiction	Can develop marijuana addiction‡	
	Daily or near-daily users may experience withdrawal symptoms	
	Treatment of marijuana addiction‡ can reduce use and dependence	
Marijuana use during pregnancy and breastfeeding (p.197)		
	Substantial	**Moderate**
Effects on exposed offspring		Attention problems
		Decreased IQ scores in young children
		Decreased cognitive function
		Decreased growth

There were no substantial or moderate findings for Marijuana Use and Injury

Table 1. (continued) Substantial and moderate findings from systematic literature review

Marijuana use and respiratory effects (p.213)		
	Substantial	**Moderate**
Smoked marijuana	Chronic bronchitis with cough/wheeze/ sputum	
	Acute use improves airflow	
Unintentional marijuana exposures in children (p.225)		
	Substantial	**Moderate**
	Legal marijuana access increases unintentional marijuana exposures in children	Child-resistant packaging reduces unintentional pediatric poisonings

Public Health Recommendations

It is important to continue improving data quality by systematically collecting information on the frequency, amount, potency and method of marijuana use in both public health surveillance and medical care settings. During hospitalizations and emergency department visits, marijuana use should be a standard question, and follow-up questions should clarify timing and amount of last use. Improved testing methods and documentation are needed in relation to motor vehicle crashes and driving under the influence of drugs (DUID).

Questions regarding marijuana use should be continued on population-based surveys such as the Behavioral Risk Factors Surveillance System (BRFSS), the Healthy Kids Colorado Survey (HKCS) and Pregnancy Risk Assessment Monitoring System (PRAMS). Surveillance methods should continue to be expanded to collect more detailed information, such as quantity and methods of use, perceptions of risk, reasons for using and adverse effects experienced. To better assess potential health impacts, data on hospitalizations and emergency department visits related to marijuana should be further explored.

Public education on potential health effects of marijuana is important, particularly related to the effects of use during pregnancy, adolescent use, driving after using and unsafe storage around children. Dispensaries and industry should continue to partner with public health in disseminating education about these topics of highest concern. Education for health care providers on the known health effects of marijuana use may encourage more open dialog between providers and patients.

Research Gaps

Important research gaps related to the population-based health effects of marijuana use were identified during the literature and data review process. These research gaps were based on common limitations of existing research, exposures or outcomes not sufficiently studied, or issues important to public education or policymaking. These research gaps provide an important framework for continuing to prioritize research related to marijuana use and public health. The committee strongly recommends Colorado support research to fill these important gaps in public health knowledge. While outside the scope of this committee's duties, the committee also recognizes more research is needed on the potential therapeutic benefits of marijuana.

A common theme among the research gaps was the need for studies with better defined marijuana-use histories and practices. This should include frequency, amount, potency, and method of marijuana use; length of abstinence; and a standardized method for documenting cumulative lifetime marijuana exposure. A particularly important need is the evaluation of effects separately for less frequent users versus daily or near-daily users. Researchers should consider evaluating separately by age group, gender or other characteristics when the health effect being studied could differ among groups - for example, by age for cardiovascular effects or by gender for mental health effects.

Research gaps particularly important to public health and safety include the need for: 1) additional research using marijuana with THC levels consistent with currently available products; 2) research on impairment in marijuana users who use more than weekly and may have developed tolerance; 3) research to identify improved testing methods for impairment either through alternate biological testing methods or physical tests of impairment; and 4) research to better characterize the pharmacokinetics/pharmacodynamics, potential drug interactions, health effects, and impairment related to newer methods of marijuana use such as edibles and vaporizing as well as other cannabinoids such as cannabidiol (CBD).

Section 2

Scientific Literature Review on Potential Health Effects of Marijuana Use

Chapter 1

Systematic Literature Review Process

Retail Marijuana Public Health Advisory Committee

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Committee objectives

The RMPHAC was appointed in April 2014, had its first organizational meeting in May 2014, and began the scientific review process in June 2014. The committee established these objectives:

- Develop well-designed, systematic, unbiased criteria for selecting and evaluating studies
- Systematically review the scientific literature currently available on health effects of marijuana use
- Judge and openly discuss the science using expert scientific and medical opinion.
- Establish committee consensus on population health effects of marijuana use based on current science
- Establish committee consensus on translation of the science into public health messages
- Recommend public health-related policies based on the current science and expert medical discussion
- Recommend public health surveillance activities to address any gaps in knowledge discovered
- Identify and prioritize gaps in science important to public health
- Create a framework to add emerging evidence and update committee findings

The committee also selected and prioritized review topics based on recently published peer-reviewed publications outlining the potential health effects of marijuana use, and public health priorities identified from key informant interviews of Colorado public health officials. These topics included:

- Marijuana Use During Pregnancy and Breastfeeding
- Neurological and Mental Health Effects
- Effects on Youth and Unintentional Poisonings
- Marijuana Dose and Drug Interactions
- Extrapulmonary Effects and Injuries
- Respiratory Effects and Lung Cancer

Within each of these topics, Colorado Department of Public Health and Environment (CDPHE) staff established specific research questions to ensure that the relevant public health issues were covered in the literature review process.

The overall goal of the committee was to implement an unbiased and transparent process for evaluating scientific literature. The official committee bylaws included procedures for disclosing potential conflicts of interest, including financial relationships with companies in the marijuana industry; financial relationships with companies engaged in the treatment of patients for marijuana-related health effects; funding support from the National Institute on Drug Abuse; and personal or political beliefs that may prevent an unbiased recommendation.

Outside technical experts were recruited from CDPHE staff, the University of Colorado School of Medicine, and the Colorado School of Public Health to search the scientific literature and summarize and present findings to the full committee. All committee members were provided access to the summary findings and the full-text literature for review before each committee meeting.

Overview of systematic review process

The committee utilized a PRISMA framework to ensure an unbiased and complete systematic literature review.[1] The following are the general steps that were followed for each review topic:

1. Search: Conduct a broad search of peer-reviewed publications (Medline).
2. Review: Download articles from search and relevant cited articles.
3. Rate the findings: Each finding in the articles is rated as a high, medium, or low quality finding based on the strengths and limitations of the methods. Evaluation of the strengths and limitations was based on criteria in the GRADE system, which is a well-accepted method for evaluating the quality of scientific evidence.
4. Group related findings: Each finding is categorized based on population, exposure, and outcome (health effect).
5. Weigh the evidence: Draft evidence statements that summarize the quantity and quality of evidence.
6. Translate the evidence: Draft public health statements that translate the evidence statements into lay language understandable by the general public.
7. Synthesize the evidence: Draft public health recommendations based on potential concerns identified through the review process.
8. Identify research gaps: Draft statements to articulate the research gaps identified during the review process.
9. Present to committee: Findings, evidence statements, public health statements, public health recommendations, and research gaps are formally presented to committee for review and revision during open public meetings.
10. Public comment: During the open public meetings, interested stakeholders and members of the general public are invited to provide comments relevant to the topic presented.
11. Reach consensus: Committee members come to consensus on findings, evidence statements, public health statements, public health recommendations, and research gaps.
12. Officially adopt summary statements: Committee votes to officially accept findings, evidence statements, public health statements, public health recommendations, and research gaps.

Searching the literature

Literature review methods were approved by the full committee. Medline was the priority research database used to obtain articles for the review, though the Embase biomedical database and gray literature were secondarily reviewed when references in included articles were not included in the initial Medline search. Relevant articles cited in reviews or other primary studies also were included. Studies of marijuana use in humans were the primary focus of the review. Review of animal studies was reserved for specific topics with limited human research. In general, highly specialized research, such as brain imaging studies not directly associated with measurable clinical outcomes, was not evaluated in-depth unless an appropriately experienced reviewer was available. Research databases other than Medline were searched primarily when time allowed though very little additional data was found via these additional searches. All available peer-reviewed literature on a given topic identified through these methods was reviewed, regardless of positive or negative findings.

For Medline searches, the appropriate Medical Subject Heading (MeSH) terms were chosen for each topic and used for the search. To find newer articles relevant to the topic (those without MeSH yet

applied), a list of specific terms was established for each topic area. For example, the general search string used for marijuana was: "Cannabis [mesh] OR Cannabis OR Marijuana OR Marihuana OR Ganja OR Hashish OR Hemp OR Bhang OR Tetrahydrocannabinol."

Rating the findings

Findings were rated as a high, medium, or low quality based on the strengths and limitations of the methods. Evaluation of the strengths and limitations was based on criteria in the "GRADE approach to evaluating the quality of evidence."[2] The GRADE system is a well-established method for systematic literature review and has been used by the Cochrane Collaboration, British Medical Journal, American College of Physicians, World Health Organization, and many others.[2]

High quality

The official definition is: "We are very confident that the true effect lies close to that of the estimate of the effect outlined in the study." High quality findings originate from well-designed and well-controlled studies with few limitations. In the context of observational epidemiology studies, which was the most common study type in this systematic review, high quality does not necessarily imply causation. High quality implies that an observed association persists between an exposure and effect in an appropriately-sized study population after adjusting for the appropriate confounders.

Medium quality

The official definition is: "We are moderately confident in the effect estimate outlined in the study. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different." Moderate quality findings originate from studies that may be well designed, but have limitations that affect the interpretation of the results. In the context of observational epidemiology studies, moderate quality implies the finding of an observed association with an interpretation that may be limited by a small study population or insufficient adjustment for important confounders.

Low quality

The official definition is: "Our confidence in the effect estimate outlined in the study is limited. The true effect may be substantially different from the estimate of the effect." Low quality findings originate from studies with significant methodological limitations that affect the interpretation of the results. In the context of observational epidemiology studies, low quality implies the finding of an observed association with an interpretation that is significantly restricted by major study limitations.

When critically reviewing the literature, all findings were initially considered medium quality and subsequently adjusted up or down in quality based on the strengths and limitations of the methodology. Quality ratings were applied to individual outcomes; therefore, it was possible for a single study to have multiple findings of differing quality. Criteria for evaluating strengths and limitations for this literature review included:

- Methods of selecting exposed and comparison groups
- Relevance of study population to the population of interest
- Method for describing extent of exposure or marijuana use (e.g., ever vs. never, frequency measured by days used, measured by number of times used, etc.)
- Method for measuring exposure (self-report or other methods)
- Adequacy of exposure and outcome group sizes

- Methods for measurement of outcome (validated tools, blinded if subjective, etc.)
- Adequacy of adjustment for confounders (e.g., tobacco smoking, other drug use, education level, etc.) for both positive effects and lack of positive effect
- Full vs. selective outcome reporting
- Effect size and width of confidence intervals
- Temporal relationship between exposure and effect
- Completeness of follow-up
- Adequacy of sample size for assessing lack of positive effect

Grouping the findings and weighing the evidence

Findings from individual studies were grouped together to facilitate weighing the overall scientific evidence. Findings were usually grouped based on outcome (health effect). However, in specific situations, findings could be further subdivided based on factors such as: age group of the exposed population, special subject circumstances such as pregnancy or breastfeeding, level or method of marijuana use, and time period since last use of marijuana. Standardized definitions of level of use and age groups were established to help facilitate the grouping of findings:

Levels of marijuana use

- Daily or near daily use: 5-7 days/week.
- Weekly use: 1-4 days/week.
- Less-than-weekly use: less than 1 day/week.
- Acute use: Used within the last few hours, such that the short-term effects or symptoms are still being experienced.

Age groups

- Child: up to 9 years of age.
- Adolescent: 9 through 17 years of age.
- Young Adult: 18 through 24 years of age.
- Adult: 25 through 64 years of age.
- Older Adult: 65 years of age and older.

Once findings were appropriately grouped, evidence statements (e.g., “We found moderate evidence that adolescents who regularly use marijuana are less likely than non-users to graduate high school.”) were drafted based on the following criteria which were approved by the committee:

Substantial evidence refers to:

1. Robust scientific findings that support the outcome with no credible opposing scientific evidence. This was defined as any of the following:
    - At least one high quality positive finding, plus supporting findings at least one of which is medium quality, with no opposing findings (must include studies of at least two cohorts)
    - At least three medium quality positive findings from studies of at least two cohorts, with no opposing findings
    - Many high and medium quality positive findings from studies of at least two cohorts that heavily outweigh opposing findings
    - At least two high quality positive findings from systematic reviews or meta-analyses published within the past 10 years
2. A robust body of scientific literature that has examined the outcome and failed to demonstrate a positive finding. This was defined as any of the following:
    - At least one high quality study lacking a positive finding, plus at least one medium quality supporting study, and no opposing findings (must include studies of at least two cohorts)
    - At least three medium quality studies lacking a positive finding from studies of at least two cohorts, and no opposing findings
    - Many high and medium quality studies lacking a positive finding that heavily outweigh opposing findings
    - At least two high quality systematic reviews or meta-analyses published within the past 10 years lacking positive findings

Moderate evidence refers to:

1. Strong scientific findings that support the outcome, but these findings have some limitations. This was defined as any of the following:
    - A single high quality positive finding , with no opposing findings
    - At least one medium quality positive finding, plus supporting findings with no opposing findings; supporting findings can include animal studies
    - Many medium and low quality positive findings from studies of at least two cohorts that heavily outweigh opposing findings
    - A single high quality positive finding from a systematic review or meta-analysis published within the past 10 years
2. A strong body of scientific literature that has examined the outcome and failed to demonstrate a positive finding. This was defined as any of the following:
    - A single high quality study lacking a positive finding, and no opposing findings
    - At least one medium quality study lacking a positive finding, plus supporting findings, and no opposing findings
    - Many medium and low quality studies lacking positive findings from studies of at least two cohorts that heavily outweigh opposing findings
    - A single high quality systematic review or meta-analysis published within the past 10 years lacking positive findings

Limited evidence refers to:

1. Modest scientific findings that support the outcome, but these findings have significant limitations. This was defined as any of the following:
    - A single medium quality positive finding
    - Two or more low quality positive findings from studies of at least two cohorts
    - One low quality positive finding supported by animal studies
    - Many low quality positive findings from studies of at least two cohorts that outweigh opposing findings
2. Modest scientific finding that have examined the outcome and failed to demonstrate a positive finding. This was defined as any of the following:
    - A single medium quality study lacking a positive finding
    - Two or more low quality studies lacking positive findings from studies of at least two cohorts
    - One low quality study lacking a positive finding supported by animal studies
    - Many low quality studies lacking positive findings from studies of at least two cohorts that outweigh opposing findings

Mixed evidence refers to:

Both supporting and non-supporting scientific findings for the outcome with neither direction dominating. This was defined as the following:

- Mixed findings, with neither direction dominating

Insufficient evidence refers to:

The outcome has not been sufficiently studied. This was defined as any of the following:

- A single low quality positive finding with no supporting findings
- There are no studies examining the outcome or relevant parameters

These criteria were translated into evidence statements using the following guidelines:

- Substantial positive evidence becomes: “We found substantial evidence…”
- Substantial lack of positive evidence becomes: “We found a substantial body of research that failed to show an association…”
- Moderate positive evidence becomes: “We found moderate evidence…”
- Moderate lack of positive evidence becomes: “We found a moderate body of research that failed to show an association…”
- Limited evidence becomes: “We found limited evidence…”
- Limited lack of positive evidence becomes: “We found a limited body of research that failed to show an association…”
- Mixed evidence becomes: “We found mixed evidence for whether or not…”
- Insufficient evidence becomes: “There is insufficient evidence to determine…”

Evidence statements were drafted by CDPHE technical staff, revised based on committee review and feedback from technical advisors and public stakeholders, and finally approved by a vote of the committee.

Translating the evidence statements into public health statements

Evidence Statements were translated into Public Health Statements using a standardized convention to ensure traceability back to the scientific literature. Public Health Statements were designed to accurately reflect the evidence statements using language that could be understood by the general public. The goals of the committee were to ensure that the Public Health Statements: 1) conveyed the volume and quality of research related to the outcome; 2) provided a generalized framework to allow consistent language for all findings regardless of topic; and 3) allowed the statement to stand on its own without context. These statements were drafted by CDPHE technical staff, revised based on comments from the committee, technical advisors and public stakeholders, and finally approved by a vote of the committee. The standardized convention used for the translation is shown below:

Standardized convention: <level of> marijuana use <by specific group> <strength of relationship> associated with <outcome>, <specific circumstances>.

A specific example: “Regular marijuana use by adolescents and young adults is strongly associated with impaired learning, memory, math and reading achievement, even after 28 days or more since last use.”

Standard language was chosen for the “strength of relationship,” corresponding to the level of evidence from the Evidence Statements:

- Substantial positive evidence becomes “is strongly associated”
- Substantial research lacking positive evidence becomes “an association is unlikely”
- Moderate positive evidence becomes “is associated”
- Moderate research lacking positive evidence becomes “an association appears unlikely”
- Limited evidence becomes “may be associated”
- Limited research lacking positive evidence becomes “might not be associated"
- Mixed evidence becomes “There is conflicting evidence for whether or not ___ is associated”

The wording “associated with” was specifically chosen to represent epidemiologic (i.e., statistical) associations, and NOT to imply causality.

Synthesizing the evidence: public health recommendations and research gaps

Based on the literature review, public health recommendations were drafted. The committee recommendations were separated into data quality issues, surveillance, and education recommendations. Data quality issues were defined as recommendations to improve current data collection deficiencies at the clinical or governmental level that prevent full analysis of public health outcomes related to marijuana use. Public health surveillance recommendations were based on improving capacity to detect an acute public health danger (e.g., real-time emergency department surveillance for detection of poisonings from contaminated products); the ability to characterize chronic public health dangers to support policy and other intervention decisions (e.g., surveillance of marijuana-related traffic fatalities or skiing injuries); or the ability to generate epidemiologic data (e.g. BRFSS survey questions), to contribute to planning and evaluating population level interventions. Education recommendations were included to ensure health-based information on marijuana use is provided to the appropriate target audiences.

In addition to public health recommendations, important research gaps related to the population-based health effects of marijuana use were identified during the literature review process. These research gaps were based on common limitations of existing research (e.g., not enough focus on occasional marijuana use, distinct from regular or heavy use); exposures not sufficiently studied (e.g., dabbing or edibles); outcomes not sufficiently studied; or issues important to public education or policymaking (e.g., impairment in frequent users). These research gaps provide an important framework for prioritizing research related to marijuana use and public health. Statements articulating the public health recommendations and research gaps were initially drafted by CDPHE technical staff, revised based on comments from the committee, technical advisors and public stakeholders, and finally approved by a vote of the committee.

Consensus and approval by the committee

CDPHE technical staff formally presented findings, evidence statements, public health statements, public health recommendations and research gaps to the committee for review and revision during open public meetings. During these open public meetings, interested stakeholders and members of the general public were invited to provide comments relevant to the topic presented. The committee chair facilitated a consensus process to ensure all committee members could agree on the scientific evaluation and wording. Once consensus was achieved, the committee voted to officially accept these statements and recommendations.

Procedures for reviewing and updating documents

The Retail Marijuana Public Health Advisory Committee will continue to meet quarterly throughout 2017 and 2018. All approved evidence statements, public health statements, public health recommendations, and research gaps will be reviewed and updated if needed on a two-year cycle. The committee also will expand the reviewed literature to include new topics as new research becomes available or new public health concerns arise.

References

1. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *J Clin Epidemiol*. 2009;62(10):1006-1012.
2. GRADE guidelines - best practices using the GRADE framework. *GRADE working group* http://training.cochrane.org/path/grade-approach-evaluating-quality-evidence-pathway, 2014.

Section 2

Scientific Literature Review on Potential Health Effects of Marijuana Use

Chapter 2

Marijuana Use Among Adolescents and Young Adults

Retail Marijuana Public Health Advisory Committee

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Introduction

The Retail Marijuana Public Health Advisory Committee identified many important public health topics related to marijuana and has reviewed the scientific evidence currently available regarding those topics. This chapter includes reviews of potential health effects among adolescents and young adults who use marijuana. In particular, the relationships between marijuana use and cognitive abilities, academic performance, mental health and future substance use were reviewed.

Adolescence through young adulthood is a critical window for social and emotional development and for neurocognitive functioning. It also is a time that has an increased risk of developing mental health disorders, including depression and anxiety. In Colorado, almost 23 percent of students who started high school in 2011 did not graduate by 2015.[1] Almost 30 percent of Colorado high school students in 2015 felt sad or hopeless almost every day for two weeks or more, an indicator for depression, and 6 percent attempted suicide.[2]

A growing body of literature suggests parts of the brain continue to develop well into a person's twenties.[3] Alcohol use is known to affect this development and have negative cognitive, mental health and social consequences.[4,5] This raises concern that marijuana use may do the same. The impact of marijuana use on brain development, and on future cognitive abilities and mental health, has been the subject of much public debate. A recent example is the claim that marijuana use lowers IQ[6] and the counterclaim that it does not.[7] While most health effects of interest are long-term, there is also concern that marijuana's acute health effects, which include fragmented thinking and anxiety,[8] might lead to rash decisions or abnormal behavior. One prominent case in Colorado was a 19-year-old college student who behaved strangely and fell to his death after using marijuana.[9]

Analyses of 2015 Behavioral Risk Factor Surveillance System data, completed for this report, estimated that 26 percent of young adults in Colorado ages 18-25 have used marijuana within the last month. About half of them use daily or near-daily. 2015 Healthy Kids Colorado Survey data, also analyzed for this report, estimate that 21 percent of Colorado high school students used marijuana within the last month. With that many adolescents and young adults using marijuana at least monthly, the potential adverse health effects are a significant public health concern. It is of critical importance to evaluate what the scientific literature says about the health effects of marijuana use among adolescents and young adults.

Definitions

Age groups

- Adolescents: 9 to 17 years of age.
- Young adults: 18 to 24 years of age.

Levels of marijuana use

- Daily or near-daily use: 5-7 days/week.
- Weekly use: 1-4 days/week.
- Less-than-weekly use: less than 1 day/week.

Cannabis use disorder – a formal diagnosis indicating two or more of these factors: hazardous use, social/interpersonal problems related to use, neglects major roles in order to use, legal problems, withdrawal, tolerance, uses more or longer than planned, repeated attempts to quit or reduce use, much time is spent using, physical or psychological problems related to use, and/or gives up activities in order to use;[10] commonly called addiction.

Cognitive abilities - brain-based skills we need to carry out any task from the simplest to the most complex, which include retrieving information from memory, using logic to solve problems, communicating through language, mentally visualizing a concept, and focusing attention when distractions are present.

Illicit drugs – fall into two categories: 1) Those drugs that are illegal to process, sell, and consume; includes cocaine, methamphetamine, ecstasy and heroin. 2) Those drugs that are legal to process, sell, and consume when prescribed by a physician, but are then misused or used without a prescription; includes prescription pain medication and prescription sedatives.

Intelligence quotient (IQ) - a number used to express the apparent relative intelligence of a person, determined by one's performance on a standardized intelligence test relative to the average performance of others of the same age.

Marijuana addiction - an informal term which is more commonly used than cannabis use disorder, but the two are considered equivalent by the committee and many mental health professionals.

Psychotic disorders – these include schizophrenia, schizoaffective, schizophreniform, schizotypal, and delusional disorders. These formal diagnoses are made when a combination of psychotic symptoms are present (possibly combined with other mental health symptoms), the symptoms cause significant problems with work, relationships or self-care and they have been present for six months or longer.[10]

Psychotic symptoms - these include auditory or visual hallucinations, difficulty separating real from imagined, perception that self or others can read minds, perceived ability to predict the future, feeling that an outside force is controlling thoughts or actions, fear that someone intends to harm them, belief they have supernatural gifts, apathy, social withdrawal, absent or blunted emotions, occurrences of unclear speech or inability to speak or difficulty organizing thoughts to complete activities.[10]

Key findings

The committee's strongest findings are related to reduced cognitive abilities and academic achievement, problem use or addiction[‡] to marijuana or other substances after adolescence and experiencing psychotic symptoms or diagnoses. Weekly marijuana use by adolescents is associated with impaired learning, memory, math and reading, even 28 days after last use. Weekly use is also associated with failure to graduate from high school and may be associated with failure to attain a college degree. Adolescents and young adults who use marijuana are more likely to experience psychotic symptoms as adults, such as hallucinations, paranoia, delusional beliefs and feeling emotionally unresponsive. Daily or near-daily use is associated with developing a psychotic disorder such as schizophrenia in adulthood.

Concerning future substance use, marijuana use among adolescents and young adults is associated with future tobacco and illicit drug use and high-risk use of alcohol. In addition, marijuana users can develop addiction[‡] to marijuana. Strong evidence shows that treatment for marijuana addiction[‡] can decrease use and dependence. Additionally, marijuana users who quit have lower risks of cognitive and mental health outcomes than those who continue to use. Finally, the committee found conflicting evidence regarding the potential effect of adolescent marijuana use on future IQ.

An important note for all key findings is that the available research evaluated the **association** between marijuana use and potential adverse health outcomes. This **association** does not prove that the marijuana use alone **caused** the effect. Despite the best efforts of researchers to account for confounding factors, there may be other important factors related to **causality** that were not identified. In addition, marijuana use was illegal everywhere in the United States prior to 1996. Research funding, when appropriated, was commonly sought to identify adverse effects from marijuana use. This legal fact introduces both funding bias and publication bias into the body of literature related to marijuana use. The Retail Marijuana Public Health Advisory Committee recognizes the limitations and biases inherent in the published literature and made efforts to ensure the information reviewed and synthesized is reflective of the current state of medical knowledge. Where information was lacking – for whatever reason – the committee identified this knowledge gap and recommended further research. This information will be updated as new research becomes available.

[‡] In this document, the term marijuana addiction is considered equivalent to cannabis use disorder (and addiction to another substance is considered equivalent to use disorder for that substance).

Recommendations

A number of important public health recommendations were identified. There were significant limitations in the reviewed literature regarding the characterization of marijuana use. To facilitate future study of the effects of marijuana, it is important to improve data quality by systematically collecting information on the frequency, amount, potency, and method of marijuana use in both public health surveillance and clinical settings.

It also is important to better characterize the prevalence of marijuana use among Colorado adolescents and young adults. Questions regarding marijuana use should be added (or continued) on population-based surveys such as the Behavioral Risk Factors Surveillance System (BRFSS), the Healthy Kids Colorado Survey (HKCS) and the National College Health Assessment (NCHS). In order to better assess potential adverse outcomes, adolescent and young adult hospitalizations and emergency department visits related to marijuana should be monitored using de-identified data available from the Colorado Hospital Association. Addiction[‡] treatment admissions should be monitored using data from the Colorado Office of Behavioral Health, and the prevalence of addiction[‡] among different groups should be obtained.

Public education on the potential effects of marijuana use also is important and should be designed for adolescents and young adults themselves as well as parents and caregivers. Educational materials for schools and colleges should be accurate and could be combined with other behavioral education. Education should include information on what addiction looks like. Finally, availability and access to treatment should be promoted.

The committee also identified a number of important research gaps. A common theme among the research gaps was the need for studies with better defined marijuana-use histories, including frequency, amount, potency, and method of marijuana use and length of abstinence. A particular need was identified for evaluation of effects separately for less-than-weekly users versus daily or near-daily users. Studies of psychological outcomes suggest a possible difference between males and females, and future studies should evaluate them separately. Finally, more studies are needed that examine marijuana use as a predictor of risk behaviors, especially among adolescents, college attending young adults and non-college attending young adults.

[‡] In this document, the term marijuana addiction is considered equivalent to cannabis use disorder (and addiction to another substance is considered equivalent to use disorder for that substance).

Table 1 Findings summary: Marijuana use among adolescents and young adults

For information on the classifications "Substantial," "Moderate," etc., see Chapter 7. Systematic literature review process.

	Substantial	Moderate	Limited	Insufficient	Mixed
Cognitive and academic	Less high school graduation	Impaired cognitive abilities and academic performance after 28 days abstinence	Less likely to earn college degree	Lower IQ after brief abstinence	Lower future IQ scores
Mental health	Psychotic symptoms in adulthood	Psychotic disorder in adulthood (daily or near-daily users)			Depression or anxiety after adolescence
					Suicidal thoughts or attempts
Substance use, abuse and addiction	Can develop marijuana addiction‡	Increased marijuana use and addiction‡ after adolescence			
		Alcohol or tobacco use and addiction‡ after adolescence			
	Other illicit drug use and addiction‡ after adolescence				
Benefits of quitting	Treatment for marijuana addiction‡ can reduce use and dependence	Quitting marijuana lowers risk of cognitive and mental health effects			

‡ In this document, the term marijuana addiction is considered equivalent to cannabis use disorder (and addiction to another substance is considered equivalent to use disorder for that substance).

Evidence statements

Evidence statements are based on systematic scientific literature reviews performed by Colorado Department of Public Health and Environment staff with oversight and approval by the Retail Marijuana Public Health Advisory Committee. For an explanation of the classifications "Substantial," "Moderate," etc., see Chapter 7. Systematic literature review process. For details about the studies reviewed, see Appendix F.

Cognitive and academic

1. We found **MODERATE** evidence that adolescents and young adults who use marijuana weekly or more frequently are more likely than non-users to have ongoing impairment of cognitive and academic abilities for at least 28 days after last use.[11-14]
2. We found **INSUFFICIENT** evidence to determine whether or not adolescents who use marijuana are more likely than non-users to score lower on IQ tests after brief abstinence.[15,16] (Revised*)
3. We found **MIXED** evidence for whether or not adolescent marijuana use affects future IQ scores.[17-19] (Added*)
4. We found **SUBSTANTIAL** evidence that adolescents who use marijuana weekly or more frequently are less likely than non-users to graduate from high school.[20-24] (Revised*)
5. We found **LIMITED** evidence that adolescents and young adults who use marijuana weekly or more frequently are less likely than non-users to attain a college degree.[23,25-27]

Mental health

6. We found **SUBSTANTIAL** evidence that adolescents and young adults who use marijuana are more likely than non-users to develop psychotic symptoms in adulthood, and this likelihood increases with more frequent use.[28-32] (Revised*)
7. We found **MODERATE** evidence that adolescents and young adults who use marijuana daily or near-daily are more likely than non-users to develop psychotic disorders like schizophrenia in adulthood.[28,33-35] (Revised*)
8. We found **MIXED** evidence for whether or not adolescent and young adult marijuana users are more likely than non-users to have symptoms or a diagnosis of anxiety in adulthood.[33,36-39]
9. We found **MIXED** evidence for whether or not adolescent and young adult marijuana users are more likely than non-users to have symptoms or a diagnosis of depression in adulthood.[32,33,36-42]
10. We found **MIXED** evidence for whether or not adolescent and young adult marijuana users are more likely than non-users to have suicidal thoughts or attempt suicide.[42-46]

* Revised = the statement has been adjusted since the 2014 edition of the report, due to new evidence. Added = the statement is new since the 2014 edition of the report. See Appendix F for dates of most recent literature review.

Substance use, abuse and addiction[‡]

11. We found SUBSTANTIAL evidence that marijuana users can develop cannabis use disorder, including adolescent and young adult users.[47,48] (Added*)
12. We found MODERATE evidence that adolescent and young adult marijuana users are more likely than non-users to increase their use and to develop cannabis use disorder in adulthood.[21,22,49]
13. We found MODERATE evidence that adolescent and young adult marijuana users are more likely than non-users to use and be addicted[‡] to alcohol or tobacco in adulthood.[21,22,50,51]
14. We found SUBSTANTIAL evidence that adolescent and young adult marijuana users are more likely than non-users to use and be addicted[‡] to illicit drugs in adulthood.[21,26,38,50,52-56]

Benefits of quitting

15. We found MODERATE evidence that adolescent and young adult marijuana users who quit have lower risks of cognitive and mental health outcomes than those who continue to use.[15,16,41,50]
16. We found SUBSTANTIAL evidence that some adolescent and young adult marijuana users who receive treatment for cannabis use disorder (including cognitive behavioral therapy, motivational enhancement/interviewing, multidimensional family therapy and/or abstinence-based contingency management) can decrease their marijuana use and dependence.[57-61] (Added*)

[‡] In this document, the term marijuana addiction is considered equivalent to cannabis use disorder (and addiction to another substance is considered equivalent to use disorder for that substance).

* Revised = the statement has been adjusted since the 2014 edition of the report, due to new evidence. Added = the statement is new since the 2014 edition of the report. See Appendix F for dates of most recent literature review.

Public health statements

Public health statements are plain language translations of the major findings (Evidence Statements) from the systematic literature reviews. These statements have been officially approved by the Retail Marijuana Public Health Advisory Committee.

Cognitive and academic

1. Weekly or more frequent marijuana use by adolescents and young adults is associated with impaired learning, memory, math and reading achievement, even 28 days after last use.
    a. These impairments increase with more frequent marijuana use.
2. There is conflicting evidence on whether or not adolescent marijuana use is associated with changes in future IQ scores. (Added*)
3. Weekly or more frequent marijuana use by adolescents is strongly associated with failure to graduate from high school. (Revised*)
4. Weekly or more frequent marijuana use by adolescents and young adults may be associated with not attaining a college degree.

Mental health

5. Marijuana use by adolescents and young adults is strongly associated with developing psychotic symptoms in adulthood, such as hallucinations, paranoia and delusional beliefs. (Revised*)
    a. This risk is higher with more frequent marijuana use.
    b. This risk may be higher among those who start using marijuana at a younger age.
6. Daily or near-daily marijuana use by adolescents and young adults is associated with developing a psychotic disorder such as schizophrenia in adulthood. (Revised*)

Substance use, abuse and addiction‡

7. Some marijuana users become addicted‡ to marijuana. Starting marijuana use during adolescence or young adulthood is associated with future marijuana addiction‡. (Revised*)
8. Marijuana use by adolescents and young adults - even less-than-weekly use - is associated with future high-risk use of alcohol, tobacco, and other drugs like cocaine, ecstasy, opioids and methamphetamine.

Benefits of quitting

9. Adolescents and young adults who quit marijuana use have a lower risk of developing cognitive impairment or mental health disorders than those who continue to use.
10. There are treatments for marijuana addiction‡ that can reduce use and dependence. (Added*)

‡ In this document, the term marijuana addiction is considered equivalent to cannabis use disorder (and addiction to another substance is considered equivalent to use disorder for that substance).

* Revised = the statement has been adjusted since the 2014 edition of the report, due to new evidence. Added = the statement is new since the 2014 edition of the report. See Appendix F for dates of most recent literature review.

Public health recommendations

Public health recommendations have been suggested and approved by the Retail Marijuana Public Health Advisory Committee with the goals of: 1) Improving knowledge regarding population-based health effects of retail marijuana use and 2) Developing and targeting public health education and prevention strategies for high-risk sub-populations.

Data quality

- Standardization of data collection on frequency, amount, potency, and method of marijuana use in medical records and other surveillance data sources.
- Specify marijuana use as separate from other drug use in medical records and other surveillance data sources.

Surveillance

- Monitor adolescent use and the factors associated with adolescents initiating use, through surveys such as the Healthy Kids Colorado Survey (HKCS).
- Monitor young adult use and the factors associated with initiation of use, through surveys such as the Behavioral Risk Factor Surveillance Survey (BRFSS).
- Monitor National College Health Assessment data, Colorado and national, for comparisons related to college students.
- Monitor adolescent and young adult marijuana-related hospitalizations (both psychiatric and non-psychiatric) and emergency department visits.
- Monitor adolescent and young adult cannabis use disorder treatment rates.
- Evaluate prevalence of cannabis use disorder among adolescents and young adults and monitor trends.

Education

- Public education for adolescents, young adults, parents and caregivers, using optimal methods including social media.
- Develop accurate educational materials for schools and colleges, either stand-alone or integrated with other behavioral education.
- Promote accurate information about cannabis use disorder.
- Promote availability and access to treatment for cannabis use disorder.

Research gaps

The Retail Marijuana Public Health Advisory Committee identifies important gaps in the scientific literature that may impact public health policies and prevention strategies. Colorado should support unbiased research to help fill the following research gaps identified by the committee.

- Research studies on all outcomes should evaluate different levels of use separately, such as daily or near-daily, weekly and less-than-weekly use.
- Research studies on all outcomes should include former users and continuing users with comparable prior use frequency and age of onset to help separate long-term effects from the effects of current use.
- Additional studies with more varied time periods of abstinence are needed to assess the duration of cognitive impact of marijuana use.
- Studies evaluating the potential psychological outcomes of marijuana use should have separate evaluations of males and females.
- Increase the number of studies that examine marijuana use as a predictor of risk behaviors, especially among adolescents, college attending young adults and non-college attending young adults.
- More studies are needed to assess the risk of increasing use or developing cannabis use disorder among groups with different levels of use, especially for less-than-weekly use. These should also assess this risk based on different ages of initiating use.
- Studies are needed to compare the factors associated with adolescents initiating use between states with different legal status. These studies should include specific factors such as parental influences, marijuana marketing and marijuana merchandising.
- Better studies are needed to assess causality rather than only association, which may be confounded by other factors.

References

1. Colorado Department of Education. Graduation Statistics. 2016; https://www.cde.state.co.us/cdereval/gradcurrent,.
2. Colorado Department of Public Health and Environment. Adolescent Health Data, Healthy Kids Colorado Survey. *Colorado Health and Environmental Data* 2015; http://www.chd.dphe.state.co.us/topics.aspx?q=Adolescent_Health_Data, 2016.
3. Johnson SB, Blum RW, Giedd JN. Adolescent maturity and the brain: the promise and pitfalls of neuroscience research in adolescent health policy. *J Adolesc Health*. 2009;45(3):216-221.
4. Skala K, Walter H. Adolescence and Alcohol: a review of the literature. *Neuropsychiatr*. 2013;27(4):202-211.
5. White A, Hingson R. The burden of alcohol use: excessive alcohol consumption and related consequences among college students. *Alcohol Res*. 2013;35(2):201-218.
6. Bradberry T. Study Shows Heavy Adolescent Pot Use Permanently Lowers IQ. *Forbes*, http://www.forbes.com/sites/travisbradberry/2015/02/10/new-study-shows-smoking-pot-permanently-lowers-iq/#7d2d0562185c2015.
7. Ingraham C. No, marijuana use doesn't lower your IQ. *The Washington Post*. October 22, 2014, 2014.
8. Grotenhermen F. Pharmacokinetics and pharmacodynamics of cannabinoids. *Clin Pharmacokinet*. 2003;42(4):327-360.
9. Nicholson K. Man who plunged from Denver balcony ate 6x recommended amount of pot cookie. *The Denver Post*. April 17, 2014, 2014.
10. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed. Washington , DC2013.
11. Pope HG, Jr., Gruber AJ, Hudson JI, Cohane G, Huestis MA, Yurgelun-Todd D. Early-onset cannabis use and cognitive deficits: what is the nature of the association? *Drug Alcohol Depend*. 2003;69(3):303-310.
12. Bolla KI, Brown K, Eldreth D, Tate K, Cadet JL. Dose-related neurocognitive effects of marijuana use. *Neurology*. 2002;59(9):1337-1343.
13. Medina KL, Hanson KL, Schweinsburg AD, Cohen-Zion M, Nagel BJ, Tapert SF. Neuropsychological functioning in adolescent marijuana users: subtle deficits detectable after a month of abstinence. *J Int Neuropsychol Soc*. 2007;13(5):807-820.
14. Hooper SR, Woolley D, De Bellis MD. Intellectual, neurocognitive, and academic achievement in abstinent adolescents with cannabis use disorder. *Psychopharmacology (Berl)*. 2014;231(8):1467-1477.
15. Fried PA, Watkinson B, Gray R. Neurocognitive consequences of marihuana--a comparison with pre-drug performance. *Neurotoxicol Teratol*. 2005;27(2):231-239.
16. Fried P, Watkinson B, James D, Gray R. Current and former marijuana use: preliminary findings of a longitudinal study of effects on IQ in young adults. *CMAJ*. 2002;166(7):887-891.
17. Jackson NJ, Isen JD, Khoddam R, et al. Impact of adolescent marijuana use on intelligence: Results from two longitudinal twin studies. *Proc Natl Acad Sci U S A*. 2016;113(5):E500-508.
18. Meier MH, Caspi A, Ambler A, et al. Persistent cannabis users show neuropsychological decline from childhood to midlife. *Proc Natl Acad Sci U S A*. 2012;109(40):E2657-2664.

19. Mokrysz C, Landy R, Gage SH, Munafo MR, Roiser JP, Curran HV. Are IQ and educational outcomes in teenagers related to their cannabis use? A prospective cohort study. *J Psychopharmacol*. 2016;30(2):159-168.

20. Fergusson DM, Horwood LJ, Beautrais AL. Cannabis and educational achievement. *Addiction*. 2003;98(12):1681-1692.

21. Lynne-Landsman SD, Bradshaw CP, Ialongo NS. Testing a developmental cascade model of adolescent substance use trajectories and young adult adjustment. *Dev Psychopathol*. 2010;22(4):933-948.

22. Brook JS, Balka EB, Whiteman M. The risks for late adolescence of early adolescent marijuana use. *Am J Public Health*. 1999;89(10):1549-1554.

23. Horwood LJ, Fergusson DM, Hayatbakhsh MR, et al. Cannabis use and educational achievement: findings from three Australasian cohort studies. *Drug Alcohol Depend*. 2010;110(3):247-253.

24. Stiby AI, Hickman M, Munafo MR, Heron J, Yip VL, Macleod J. Adolescent cannabis and tobacco use and educational outcomes at age 16: birth cohort study. *Addiction*. 2015;110(4):658-668.

25. Fergusson DM, Boden JM. Cannabis use and later life outcomes. *Addiction*. 2008;103(6):969-976; discussion 977-968.

26. Fergusson DM, Horwood LJ. Does cannabis use encourage other forms of illicit drug use? *Addiction*. 2000;95(4):505-520.

27. Baggio S, Iglesias K, Deline S, et al. Not in Education, Employment, or Training status among young Swiss men. Longitudinal associations with mental health and substance use. *J Adolesc Health*. 2015;56(2):238-243.

28. van Os J, Bak M, Hanssen M, Bijl RV, de Graaf R, Verdoux H. Cannabis use and psychosis: a longitudinal population-based study. *Am J Epidemiol*. 2002;156(4):319-327.

29. Kuepper R, van Os J, Lieb R, Wittchen HU, Hofler M, Henquet C. Continued cannabis use and risk of incidence and persistence of psychotic symptoms: 10 year follow-up cohort study. *Bmj*. 2011;342:d738.

30. Henquet C, Krabbendam L, Spauwen J, et al. Prospective cohort study of cannabis use, predisposition for psychosis, and psychotic symptoms in young people. *Bmj*. 2005;330(7481):11.

31. Fergusson DM, Horwood LJ, Ridder EM. Tests of causal linkages between cannabis use and psychotic symptoms. *Addiction*. 2005;100(3):354-366.

32. Arseneault L, Cannon M, Witton J, Murray RM. Causal association between cannabis and psychosis: examination of the evidence. *Br J Psychiatry*. 2004;184:110-117.

33. Bechtold J, Simpson T, White HR, Pardini D. Chronic Adolescent Marijuana Use as a Risk Factor for Physical and Mental Health Problems in Young Adult Men. *Psychol Addict Behav*. 2015;10.1037/adb0000103.

34. Di Forti M, Marconi A, Carra E, et al. Proportion of patients in south London with first-episode psychosis attributable to use of high potency cannabis: a case-control study. *Lancet Psychiatry*. 2015;2(3):233-238.

35. Zammit S, Allebeck P, Andreasson S, Lundberg I, Lewis G. Self reported cannabis use as a risk factor for schizophrenia in Swedish conscripts of 1969: historical cohort study. *Bmj*. 2002;325(7374):1199.

36. Miettunen J, Murray GK, Jones PB, et al. Longitudinal associations between childhood and adulthood externalizing and internalizing psychopathology and adolescent substance use. *Psychol Med*. 2013;10.1017/S0033291713002328:1-12.

37. Degenhardt L, Coffey C, Romaniuk H, et al. The persistence of the association between adolescent cannabis use and common mental disorders into young adulthood. *Addiction*. 2013;108(1):124-133.

38. Zaman T, Malowney M, Knight J, Boyd JW. Co-Occurrence of Substance-Related and Other Mental Health Disorders Among Adolescent Cannabis Users. *J Addict Med*. 2015;10.1097/adm.0000000000000138.

39. Gage SH, Hickman M, Heron J, et al. Associations of cannabis and cigarette use with depression and anxiety at age 18: findings from the Avon Longitudinal Study of Parents and Children. *PLoS One*. 2015;10(4):e0122896.

40. Horwood LJ, Fergusson DM, Coffey C, et al. Cannabis and depression: an integrative data analysis of four Australasian cohorts. *Drug Alcohol Depend*. 2012;126(3):369-378.

41. Pahl K, Brook JS, Koppel J. Trajectories of marijuana use and psychological adjustment among urban African American and Puerto Rican women. *Psychol Med*. 2011;41(8):1775-1783.

42. Rasic D, Weerasinghe S, Asbridge M, Langille DB. Longitudinal associations of cannabis and illicit drug use with depression, suicidal ideation and suicidal attempts among Nova Scotia high school students. *Drug Alcohol Depend*. 2013;129(1-2):49-53.

43. Kokkevi A, Richardson C, Olszewski D, Matias J, Monshouwer K, Bjarnason T. Multiple substance use and self-reported suicide attempts by adolescents in 16 European countries. *Eur Child Adolesc Psychiatry*. 2012;21(8):443-450.

44. Consoli A, Peyre H, Speranza M, et al. Suicidal behaviors in depressed adolescents: role of perceived relationships in the family. *Child Adolesc Psychiatry Ment Health*. 2013;7(1):8.

45. Spears M, Montgomery AA, Gunnell D, Araya R. Factors associated with the development of self-harm amongst a socio-economically deprived cohort of adolescents in Santiago, Chile. *Soc Psychiatry Psychiatr Epidemiol*. 2014;49(4):629-637.

46. Zhang X, Wu LT. Suicidal ideation and substance use among adolescents and young adults: a bidirectional relation? *Drug Alcohol Depend*. 2014;142:63-73.

47. Schuermeyer J, Salomonsen-Sautel S, Price RK, et al. Temporal trends in marijuana attitudes, availability and use in Colorado compared to non-medical marijuana states: 2003-11. *Drug Alcohol Depend*. 2014;140:145-155.

48. Hasin DS, Saha TD, Kerridge BT, et al. Prevalence of Marijuana Use Disorders in the United States Between 2001-2002 and 2012-2013. *JAMA Psychiatry*. 2015;72(12):1235-1242.

49. Swift W, Coffey C, Carlin JB, Degenhardt L, Patton GC. Adolescent cannabis users at 24 years: trajectories to regular weekly use and dependence in young adulthood. *Addiction*. 2008;103(8):1361-1370.

50. Swift W, Coffey C, Degenhardt L, Carlin JB, Romaniuk H, Patton GC. Cannabis and progression to other substance use in young adults: findings from a 13-year prospective population-based study. *J Epidemiol Community Health*. 2012;66(7):e26.

51. Rubinstein ML, Rait MA, Prochaska JJ. Frequent marijuana use is associated with greater nicotine addiction in adolescent smokers. *Drug Alcohol Depend*. 2014;141:159-162.

52. Fergusson DM, Boden JM, Horwood LJ. Cannabis use and other illicit drug use: testing the cannabis gateway hypothesis. *Addiction*. 2006;101(4):556-569.

53. Schepis TS, Krishnan-Sarin S. Characterizing adolescent prescription misusers: a population-based study. *J Am Acad Child Adolesc Psychiatry*. 2008;47(7):745-754.

54. Fiellin LE, Tetrault JM, Becker WC, Fiellin DA, Hoff RA. Previous use of alcohol, cigarettes, and marijuana and subsequent abuse of prescription opioids in young adults. *J Adolesc Health*. 2013;52(2):158-163.

55. Nakawaki B, Crano WD. Predicting adolescents' persistence, non-persistence, and recent onset of nonmedical use of opioids and stimulants. *Addict Behav*. 2012;37(6):716-721.

56. Moss HB, Chen CM, Yi HY. Early adolescent patterns of alcohol, cigarettes, and marijuana polysubstance use and young adult substance use outcomes in a nationally representative sample. *Drug Alcohol Depend*. 2014;136:51-62.

57. Stanger C, Ryan SR, Scherer EA, Norton GE, Budney AJ. Clinic- and home-based contingency management plus parent training for adolescent cannabis use disorders. *J Am Acad Child Adolesc Psychiatry*. 2015;54(6):445-453 e442.

58. Stanger C, Budney AJ, Kamon JL, Thostensen J. A randomized trial of contingency management for adolescent marijuana abuse and dependence. *Drug Alcohol Depend*. 2009;105(3):240-247.

59. Rigter H, Henderson CE, Pelc I, et al. Multidimensional family therapy lowers the rate of cannabis dependence in adolescents: a randomised controlled trial in Western European outpatient settings. *Drug Alcohol Depend*. 2013;130(1-3):85-93.

60. Hendriks V, van der Schee E, Blanken P. Treatment of adolescents with a cannabis use disorder: main findings of a randomized controlled trial comparing multidimensional family therapy and cognitive behavioral therapy in The Netherlands. *Drug Alcohol Depend*. 2011;119(1-2):64-71.

61. Dennis M, Godley SH, Diamond G, et al. The Cannabis Youth Treatment (CYT) Study: main findings from two randomized trials. *J Subst Abuse Treat*. 2004;27(3):197-213.

Section 2

Scientific Literature Review on Potential Health Effects of Marijuana Use

Chapter 3

Marijuana Use and Cancer

Retail Marijuana Public Health Advisory Committee

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Introduction

The Retail Marijuana Public Health Advisory Committee identified many important public health topics related to marijuana use and has reviewed the scientific evidence currently available regarding those topics. This chapter includes reviews of different forms of cancer relative to marijuana use, as well as the chemicals released in marijuana smoke and vapor.

Cancer is a disease that affects all ages and demographics. More than 20,000 Coloradoans are diagnosed with cancer each year,[1] with nearly one-third eventually dying from it.[2] Many behavioral factors are known to increase cancer risk, including tobacco smoking,[3] alcohol use,[4] and poor diet.[5] This raises concern that marijuana use may also increase cancer risk. It is important to identify any cancer-causing chemicals that marijuana users are exposed to and to investigate possible connections between marijuana use and various forms of cancer.

Definitions

Cancer-causing chemicals – chemicals known to cause cancer in humans, including polycyclic aromatic hydrocarbons

Combustion by-products – chemicals produced when a material is burned. These chemicals including carbon monoxide and polycyclic aromatic hydrocarbons.

Marijuana combustion - the heating of marijuana flower or concentrate by applying a direct heat source of 230 degrees Celsius or above in order to produce smoke for inhalation. Combustion methods include burning a joint, blunt, pipe, or bong bowl.

Mainstream smoke – also known as firsthand smoke, it is the smoke that a smoker inhales from a lit cigarette, pipe, or joint and then exhales.

Polycyclic aromatic hydrocarbons - a group of more than 100 different chemicals released from burning coal, oil, gasoline, trash, tobacco, wood, or other organic substances.

Sidestream smoke – the smoke that wafts off the end of a lit cigarette, pipe or joint into the surrounding air.

Secondhand smoke – the smoke that is inhaled by non-smokers when near to a person smoking, also known as passive exposure.

Vaporization of marijuana (vaping) - a method of marijuana use in which marijuana vapor, rather than smoke, is inhaled. Marijuana flower or concentrate is heated in a vaporizing device (vaporizer) to a temperature below the point of combustion, to produce vapor.

Water pipe - a pipe for smoking tobacco, marijuana, etc., that draws the smoke through water to cool it. Examples are a hookah and a bong.

Key findings

Strong evidence shows that marijuana smoke contains many of the same cancer-causing chemicals found in tobacco smoke. Marijuana smoke from water pipes or bongs may contain more cancer-causing chemicals than smoke from a marijuana joint. On the other hand, marijuana vapor may contain fewer cancer-causing chemicals than smoke from a marijuana joint.

Most lung cancer studies have used the concept of "joint-years" as a measure of total cumulative marijuana smoking. A "joint-year" is the equivalent of smoking one joint per day for a year. Levels of cumulative use in these studies tended to divide into people who have smoked more than 10 joint-years and people who have smoked fewer than 10 joint years. There is conflicting research for whether or not smoking *more* than 10 joint-years is associated with lung cancer. For those who have smoked *fewer* than 10 joint-years, an association appears unlikely.

Limited evidence suggests an association between marijuana use and both testicular (nonseminoma) and prostate cancers. On the other hand, the limited evidence available concerning cancers of the bladder, head and neck suggests that they might not have any association with marijuana use.

An important note for all key findings is that the available research evaluated the **association** between marijuana use and potential adverse health outcomes. This **association** does not prove that the marijuana use alone **caused** the effect. Despite the best efforts of researchers to account for confounding factors, there may be other important factors related to **causality** that were not identified. In addition, marijuana use was illegal everywhere in the United States prior to 1996. Research funding, when appropriated, was commonly sought to identify adverse effects from marijuana use. This legal fact introduces both funding bias and publication bias into the body of literature related to marijuana use. The Retail Marijuana Public Health Advisory Committee recognizes the limitations and biases inherent in the published literature and made efforts to ensure the information reviewed and synthesized is reflective of the current state of medical knowledge. Where information was lacking – for whatever reason – the committee identified this knowledge gap and recommended further research. This information will be updated as new research becomes available.

Recommendations

The committee recommends improved documentation of cumulative lifetime marijuana use history for individuals diagnosed with cancer, including methods of use. Public health should monitor the prevalence of relevant cancers through the Colorado Central Cancer Registry, and educate the public on the potential for additive risks to lung health related to smoking both tobacco and marijuana.

Additional study is needed about the possible associations between marijuana use and various types of cancer. These should include improved methods to assess cumulative marijuana exposure to facilitate comparisons between studies and relevance to the clinical setting. They should include older age groups separately, due to the increased risk of cancer. Finally, they should include adequate numbers of non-tobacco smokers, to eliminate the confounding introduced by tobacco smoking.

Table 1 Findings summary: Marijuana use and cancer

For an explanation of the classifications "Substantial," "Moderate," etc., see Chapter 7. Systematic literature review process.

	Substantial	Moderate	Limited	Insufficient	Mixed
Chemicals in MJ smoke or vapor	Marijuana smoke contains same cancer-causing chemicals as tobacco smoke		Water-pipe smoke has more cancer-causing chemicals than smoke from joints		
			Vaporized marijuana has fewer cancer-causing chemicals than smoke from joints		
Cancer and pre-cancerous lesions	Pre-cancerous lesions with daily or near-daily use	Failure to show association with lung cancer for less than 10 joint-years cumulative use	Increased risk of nonseminoma testicular cancer		Association with lung cancer for more than 10 joint-years cumulative use
			Increased risk of prostate cancer		
			Failure to show association with bladder cancer		
			Failure to show association with head and neck cancer		

Evidence statements

Evidence statements are based on systematic scientific literature reviews performed by Colorado Department of Public Health and Environment staff with oversight and approval by the Retail Marijuana Public Health Advisory Committee. For an explanation of the classifications "Substantial," "Moderate," etc., see Chapter 7. Systematic literature review process. For details about the studies reviewed, see Appendix G.

Chemical content of marijuana smoke or vapor

1. We found **SUBSTANTIAL** evidence that marijuana smoke, both mainstream and sidestream, contains many of the same cancer-causing chemicals as tobacco smoke.[6-10]
2. We found **LIMITED** evidence from simulated smoking studies that smoke from water pipes or bongs contains more cancer-causing chemicals per milligram of THC compared to smoke from unfiltered joints.[6,11]
3. We found **LIMITED** evidence that marijuana vaporizers produce fewer combustion by-products, including carbon monoxide and polycyclic aromatic hydrocarbons, compared with smoking marijuana.[10,12,13] (Added*)

Cancer and pre-cancerous lesions

4. We found **SUBSTANTIAL** evidence that daily or near-daily marijuana smoking is associated with pre-malignant lesions in the airway.[14-16]
5. We found **MIXED** evidence for whether or not cumulative levels of marijuana smoking greater than the equivalent of one joint per day for 10 years are associated with lung cancer.[17-21] (Revised*)
6. We found a **MODERATE** body of research that failed to show an association between cumulative levels of marijuana smoking less than the equivalent of one joint per day for 10 years and lung cancer.[17-22] (Revised*)
7. We found **LIMITED** evidence that marijuana use among adult males increases risk of nonseminoma testicular cancer.[23-25]
8. We found **LIMITED** evidence [1]that marijuana use among adult males increases risk of prostate cancer.[22]
9. We found a **LIMITED** body of research that failed to show an association between marijuana use by adults and transitional cell carcinoma of the bladder.[22,26,27] (Revised*)
10. We found a **LIMITED** body of research that failed to show an association between marijuana use by adults and head and neck cancer.[28] (Added*)

*Revised = the statement has been adjusted since the 2014 edition of the report, due to new evidence. Added = the statement is new since the 2014 edition of the report. See Appendix G for dates of most recent literature review.

Public health statements

Public health statements are plain language translations of the major findings (Evidence Statements) from the systematic literature reviews. These statements have been officially approved by the Retail Marijuana Public Health Advisory Committee.

1. Marijuana smoke, both firsthand and secondhand, contains many of the same cancer-causing chemicals as tobacco smoke.
2. Marijuana smoke from water pipes or bongs may contain more cancer-causing chemicals than smoke from a joint.
3. Vaporized marijuana may contain fewer cancer-causing chemicals than smoke from a joint. (Added*)
4. Daily or near-daily marijuana smoking is strongly associated with pre-malignant lesions that may lead to cancer in the airways of your lungs.
5. There is conflicting research on whether or not smoking marijuana more than a joint per day for 10 years is associated with lung cancer. (Revised*)
6. An association appears unlikely between marijuana smoking and lung cancer when used less than a joint per day for 10 years. (Revised*)
7. Marijuana use may be associated with prostate cancer or nonseminoma testicular cancer.

Public health recommendations

Public health recommendations have been suggested and approved by the Retail Marijuana Public Health Advisory Committee with the goals of: 1) Improving knowledge regarding population-based health effects of retail marijuana use and 2) Developing and targeting public health education and prevention strategies for high-risk sub populations.

Data quality

- Improved documentation of cumulative lifetime marijuana use history for individuals diagnosed with cancer, including methods of use.

Surveillance

- Monitor the prevalence of relevant cancers through the Colorado Central Cancer Registry.

Education

- Educate the public on the [2]potential for additive risks to lung health related to smoking both tobacco and marijuana.

*Revised = the statement has been adjusted since the 2014 edition of the report, due to new evidence. Added = the statement is new since the 2014 edition of the report. See Appendix G for dates of most recent literature review.

Research gaps

The Retail Marijuana Public Health Advisory Committee identifies important gaps in the scientific literature that may impact public health policies and prevention strategies. Colorado should support unbiased research to help fill the following research gaps identified by the committee.

- Improved studies assessing the risk of lung and oropharyngeal cancers related to marijuana use, especially including adequate numbers of non-tobacco smokers, assessment of cumulative marijuana exposure, and older age groups.
- Additional, high quality studies assessing the risk of relevant non-respiratory-tract cancers related to marijuana use, using good methods to assess cumulative marijuana exposure.

References

1. Colorado Department of Public Health and Environment. *Cancer in Colorado 2003-2012, Statistical Tables and Highlights All Cancers Combined Number of Diagnosed Cancers and Average Annual Age-Adjusted Incidence Rates per 100,000 by Sex, County/Region, Time Period, Colorado 2003-2009 and 2010-2012*. 2015.
2. Colorado Department of Public Health and Environment. *Cancer in Colorado 2003-2012, Statistical Tables and Highlights All Cancers Combined Number of Cancers Deaths and Average Annual Age-Adjusted Mortality Rates per 100,000 by Sex, County/Region, Time Period, Colorado 2003-2009 and 2010-2012*. 2015.
3. American Cancer Society. Health Risks of Smoking Tobacco. 2015; http://www.cancer.org/cancer/cancercauses/tobaccocancer/health-risks-of-smoking-tobacco. Accessed December 28, 2016, http://www.cancer.org/cancer/cancercauses/tobaccocancer/health-risks-of-smoking-tobacco.
4. National Cancer Institute. Alcohol and Cancer Risk. 2013; https://www.cancer.gov/about-cancer/causes-prevention/risk/alcohol/alcohol-fact-sheet#q2. Accessed December 28, 2016.
5. Cancer Research UK. Diet Facts and Evidence. 2016; http://www.cancerresearchuk.org/about-cancer/causes-of-cancer/diet-and-cancer/diet-facts-and-evidence. Accessed December 28, 2016.
6. Gieringer D. Waterpipe Study. *Multidisciplinary Assocation for Psycheldelic Studies (MAPS)*. 1996;6(3).
7. Lee ML, Novotny M, Bartle KD. Gas chromatography/mass spectrometric and nuclear magnetic resonance spectrometric studies of carcinogenic polynuclear aromatic hydrocarbons in tobacco and marijuana smoke condensates. *Anal Chem*. 1976;48(2):405-416.
8. Moir D, Rickert WS, Levasseur G, et al. A comparison of mainstream and sidestream marijuana and tobacco cigarette smoke produced under two machine smoking conditions. *Chem Res Toxicol*. 2008;21(2):494-502.
9. Sparacino CM, Hyldburg PA, Hughes TJ. Chemical and Biological Analysis of Marijuana Smoke Condensate. In: Services USDoHaH, ed, 1990.
10. Gieringer D, St. Laurent J, Goodrich S. Cannabis Vaporizer Combines Efficient Delivery of THC with Effective Suppression of Pyrolytic Compounds. *Journal of Cannabis Therapeutics*. 2004;4(1).
11. Gowing LR, Ali RL, White JM. Respiratory harms of smoked cannabis. In: Australia DaASCS, ed. *DASC Monograph No. 8, Research Series*, 2000.
12. Abrams DI, Vizoso HP, Shade SB, Jay C, Kelly ME, Benowitz NL. Vaporization as a smokeless cannabis delivery system: a pilot study. *Clin Pharmacol Ther*. 2007;82(5):572-578.
13. Pomahacova B, Van der Kooy F, Verpoorte R. Cannabis smoke condensate III: the cannabinoid content of vaporised Cannabis sativa. *Inhal Toxicol*. 2009;21(13):1108-1112.
14. Barsky SH, Roth MD, Kleerup EC, Simmons M, Tashkin DP. Histopathologic and molecular alterations in bronchial epithelium in habitual smokers of marijuana, cocaine, and/or tobacco. *J Natl Cancer Inst*. 1998;90(16):1198-1205.
15. Fligiel SE, Roth MD, Kleerup EC, Barsky SH, Simmons MS, Tashkin DP. Tracheobronchial histopathology in habitual smokers of cocaine, marijuana, and/or tobacco. *Chest*. 1997;112(2):319-326.
16. Gong H, Jr., Fligiel S, Tashkin DP, Barbers RG. Tracheobronchial changes in habitual, heavy smokers of marijuana with and without tobacco. *Am Rev Respir Dis*. 1987;136(1):142-149.

17. Aldington S, Harwood M, Cox B, et al. Cannabis use and risk of lung cancer: a case-control study. *Eur Respir J*. 2008;31(2):280-286.

18. Callaghan RC, Allecbeck P, Sidorchuk A. Marijuana use and risk of lung cancer: a 40-year cohort study. *Cancer Causes Control*. 2013;24:1811-1820.

19. Han B, Gfroerer JC, Colliver JD. Associations between duration of illicit drug use and health conditions: results from the 2005-2007 national surveys on drug use and health. *Ann Epidemiol*. 2010;20(4):289-297.

20. Hashibe M, Morgenstern H, Cui Y, et al. Marijuana use and the risk of lung and upper aerodigestive tract cancers: results of a population-based case-control study. *Cancer Epidemiol Biomarkers Prev*. 2006;15(10):1829-1834.

21. Zhang LR, Morgenstern H, Greenland S, et al. Cannabis smoking and lung cancer risk: Pooled analysis in the International Lung Cancer Consortium. *Int J Cancer*. 2014;10.1002/ijc.29036.

22. Sidney S, Jr CPQ, Friedman GD, Tekawa IS. Marijuana use and cancer incidence (California, United States). *Cancer Causes & Control*. 1997;8(5):722-728.

23. Trabert B, Sigurdson AJ, Sweeney AM, Strom SS, McGlynn KA. Marijuana use and testicular germ cell tumors. *Cancer*. 2011;117(4):848-853.

24. Daling JR, Doody DR, Sun X, et al. Association of marijuana use and the incidence of testicular germ cell tumors. *Cancer*. 2009;115(6):1215-1223.

25. Lacson JCA, Carroll JD, Tuazon E, Castelao EJ, Bernstein L, Cortessis VK. Population-based case-control study of recreational drug use and testis cancer risk confirms an association between marijuana use and nonseminoma risk. *Cancer*. 2012;118(21):5374-5383.

26. Chacko Ja, Heiner JG, Siu W, Macy M, Terris MK. Association between marijuana use and transitional cell carcinoma. *Urology*. 2006;67(1):100-104.

27. Thomas AA, Wallner LP, Quinn VP, et al. Association between cannabis use and the risk of bladder cancer: results from the California Men's Health Study. *Urology*. 2015;85(2):388-392.

28. de Carvalho MF, Dourado MR, Fernandes IB, Araujo CT, Mesquita AT, Ramos-Jorge ML. Head and neck cancer among marijuana users: a meta-analysis of matched case-control studies. *Arch Oral Biol*. 2015;60(12):1750-1755.

Section 2

Scientific Literature Review on Potential Health Effects of Marijuana Use

Chapter 4

Marijuana Use and Cardiovascular Effects

Retail Marijuana Public Health Advisory Committee

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Introduction

The Retail Marijuana Public Health Advisory Committee identified many important public health topics related to marijuana use and has reviewed the scientific evidence currently available regarding those topics. This chapter includes reviews of myocardial infarction, stroke and death from cardiovascular causes, relative to marijuana use.

Cardiovascular disease is the leading cause of death for both men and women in the United States and is responsible for one in four deaths.[1] The financial cost in the United States is over $200 billion each year.[1] Tobacco smoking is a major risk factor and causes one of every three deaths from heart disease.[2] There is concern that marijuana smoking may contribute to heart disease in ways similar to tobacco smoking. Marijuana use often causes a faster heart rate, elevated blood pressure, and an increased need for oxygen[3] in the hours immediately after use, all of which are effects that can contribute to cardiovascular disease or be dangerous in a person who already has cardiovascular disease. With approximately 13 percent of Colorado adults using marijuana, it is important to identify any potential connections between marijuana use and the development or worsening of cardiovascular disease.

Definitions

Acute marijuana use – marijuana used within the past few hours, such that the short-term effects or symptoms are still being experienced.

Cardiovascular disease – a disease of the heart and/or blood vessels, including both heart disease and stroke.

Heart disease – encompasses several conditions that affect the heart, including coronary heart disease, myocardial infarction (heart attack), heart failure, arrhythmias and heart valve problems.

Myocardial infarction – the medical term for a "heart attack," which occurs when blood flow to the heart is blocked, causing injury to part of the heart muscle. This can cause a life-threatening change in heart rhythm (arrhythmia).

Stroke – an event that blocks blood flow to part of the brain or causes bleeding into the brain, causing permanent damage.

Key findings

There is a moderate level of scientific evidence that marijuana use increases risk for some forms of stroke in individuals younger than age 55 years, and more limited evidence that marijuana use may increase risk for heart attack. Research is lacking for other cardiovascular events and conditions, including death.

An important note for all key findings is that the available research evaluated the **association** between marijuana use and potential adverse health outcomes. This **association** does not prove that the marijuana use alone **caused** the effect. Despite the best efforts of researchers to account for confounding factors, there may be other important factors related to **causality** that were not identified. In addition, marijuana use was illegal everywhere in the United States prior to 1996. Research funding, when appropriated, was commonly sought to identify adverse effects from marijuana use. This legal fact introduces both funding bias and publication bias into the body of literature related to marijuana use. The Retail Marijuana Public Health Advisory Committee recognizes the limitations and biases inherent in the published literature and made efforts to ensure the information reviewed and synthesized is reflective of the current state of medical knowledge. Where information was lacking – for whatever reason – the committee identified this knowledge gap and recommended further research. This information will be updated as new research becomes available.

Recommendations

The committee recommends that health care systems and providers improve the documentation of marijuana use history during hospitalizations and emergency department visits, including timing, potency and amount of last marijuana use and measures of cumulative lifetime use. Public health should monitor and analyze this data for possible associations between marijuana use and cardiovascular events. Educational programs for adult users, their families, and health care providers who care for them should be developed to ensure more information is shared about the known health effects of marijuana use, as well as what is unknown at present.

Additional research on critical cardiovascular events is needed. This research should seek good data on timing, potency and amount of last marijuana use, in order to evaluate potential acute associations. Similarly, better data on cumulative lifetime use is important when evaluating potential long-term associations. Prospective studies enlisting groups of marijuana users and non-users should be done, and observed outcomes should include both the development of chronic cardiovascular disease and the occurrence of acute cardiovascular events.

Table 1 Findings summary: Marijuana use and cardiovascular effects
For an explanation of the classifications "Substantial," "Moderate," etc., see Chapter 7. Systematic literature review process.

Substantial	Moderate	Limited	Insufficient	Mixed
	Increased risk of ischemic stroke in individuals younger than 55	Increased risk of myocardial infarction (heart attack) with acute use	Death due to cardiovascular cause with acute or long-term use	

Evidence statements

Evidence statements are based on systematic scientific literature reviews performed by Colorado Department of Public Health and Environment staff with oversight and approval by the Retail Marijuana Public Health Advisory Committee. For an explanation of the classifications "Substantial," "Moderate," etc., see Chapter 7. Systematic literature review process. For details about the studies reviewed, see Appendix H.

1. We found **MODERATE** evidence that marijuana use increases risk of ischemic stroke in individuals younger than 55 years of age.[4-9] (Revised*)
2. We found **LIMITED** evidence that acute marijuana use increases risk of myocardial infarction.[10,11]
3. We found **INSUFFICIENT** evidence to determine whether or not marijuana use changes the risk of death related to a cardiovascular event, either acutely or over time.[12-14]

Public health statements

Public health statements are plain language translations of the major findings (Evidence Statements) from the systematic literature reviews. These statements have been officially approved by the Retail Marijuana Public Health Advisory Committee.

1. Marijuana use is associated with increased risk of stroke in individuals younger than 55 years of age. (Revised*)
2. Acute marijuana use may be associated with increased risk of heart attack among adults.

*Revised = the statement has been adjusted since the 2014 edition of the report, due to new evidence. Added = the statement is new since the 2014 edition of the report. See Appendix H for dates of most recent literature review.

Public health recommendations

Public health recommendations have been suggested and approved by the Retail Marijuana Public Health Advisory Committee with the goals of: 1) Improving knowledge regarding population-based health effects of retail marijuana use and 2) Developing and targeting public health education and prevention strategies for high-risk sub populations.

Data quality

- Improved documentation of marijuana use history during hospitalizations and emergency department visits, including timing, potency and amount of last marijuana use and measures of cumulative lifetime use.

Surveillance

- Monitor and analyze emergency department and hospitalization data for possible associations between marijuana use and cardiovascular events.

Education

- Public education about the potential cardiovascular risks of cannabis use.

Research gaps

The Retail Marijuana Public Health Advisory Committee identifies important gaps in the scientific literature that may impact public health policies and prevention strategies. Colorado should support unbiased research to help fill the following research gaps identified by the committee.

- Additional studies of critical cardiovascular events, with improved data on timing, potency and amount of last marijuana use (for potential acute associations) and cumulative lifetime use (for potential long-term associations).
- Prospective studies of cohorts of marijuana users and non-users for possible associations with the development of chronic cardiovascular disease or with acute cardiovascular events.

References

1. Mozaffarian D, Benjamin EJ, Go AS, et al. Heart Disease and Stroke Statistics-2016 Update: A Report From the American Heart Association. *Circulation*. 2016;133(4):e38-360.
2. U.S. Department of Health & Human Services. *The Health Consequences of Smoking - 50 Years of Progress, A Report of the Surgeon General*. 2014.
3. Grotenhermen F. Pharmacokinetics and pharmacodynamics of cannabinoids. *Clin Pharmacokinet*. 2003;42(4):327-360.
4. Geller T, Loftis L, Brink DS. Cerebellar infarction in adolescent males associated with acute marijuana use. *Pediatrics*. 2004;113(4):e365-370.
5. Barber PA, Pridmore HM, Krishnamurthy V, et al. Cannabis, ischemic stroke, and transient ischemic attack: a case-control study. *Stroke*. 2013;44(8):2327-2329.
6. Wolff V, Armspach J-P, Lauer V, et al. Cannabis-related stroke: myth or reality? *Stroke*. 2013;44(2):558-563.
7. Hackam DG. Cannabis and stroke: systematic appraisal of case reports. *Stroke*. 2015;46(3):852-856.
8. Rumalla K, Reddy AY, Mittal MK. Recreational marijuana use and acute ischemic stroke: A population-based analysis of hospitalized patients in the United States. *J Neurol Sci*. 2016;364:191-196.
9. Thanvi BR, Treadwell SD. Cannabis and stroke: is there a link? *Postgrad Med J*. 2009;85(1000):80-83.
10. Mittleman Ma, Lewis Ra, Maclure M, Sherwood JB, Muller JE. Triggering Myocardial Infarction by Marijuana. *Circulation*. 2001;103(23):2805-2809.
11. Jouanjus E, Lapeyre-Mestre M, Micallef J, French Association of the Regional A, Dependence Monitoring Centres Working Group on Cannabis C. Cannabis use: signal of increasing risk of serious cardiovascular disorders. *J Am Heart Assoc*. 2014;3(2):e000638.
12. Mukamal KJ, Maclure M, Muller JE, Mittleman Ma. An exploratory prospective study of marijuana use and mortality following acute myocardial infarction. *American Heart Journal*. 2008;155(3):465-470.
13. Frost L, Mostofsky E, Rosenbloom JI, Mukamal KJ, Mittleman Ma. Marijuana use and long-term mortality among survivors of acute myocardial infarction. *American Heart Journal*. 2013;165(2):170-175.
14. Sidney S, Beck JE, Tekawa IS, Quesenberry CP, Friedman GD. Marijuana use and mortality. *Am J Public Health*. 1997;87(4):585-590.

Section 2

Scientific Literature Review on Potential Health Effects of Marijuana Use

Chapter 5

Marijuana Dose and Drug Interactions

Retail Marijuana Public Health Advisory Committee

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Introduction

The Retail Marijuana Public Health Advisory Committee identified many important public health topics related to marijuana and has reviewed the scientific evidence currently available regarding those topics. This chapter includes reviews of THC levels relative to marijuana dose and method of use, the effects of secondhand marijuana smoke, drug-drug interactions involving marijuana, and relationships between marijuana and opioid use.

In an era of legalized marijuana, it is possible that more individuals will drive or work while under the influence of marijuana. Many employers are creating new marijuana policies and need accurate and easily interpretable marijuana testing. The Colorado State Patrol also is working to improve its marijuana testing.[1] As a result, it is important to have good information about marijuana testing methods and THC levels that can be expected relative to different types and amounts of use.

Another prominent public health question about marijuana is the health effects secondhand marijuana smoke may have, especially on children. Secondhand tobacco smoke is known to be associated with many diseases and health problems for both children and adults.[2] Many argue that marijuana smoke may be just as harmful. Analysis of 2014 and 2015 Colorado Child Health Survey data, completed for this report, estimated that approximately 16,000 homes in Colorado had children 1-14 years old with possible exposure to secondhand marijuana smoke or vapor in the home. While current public health education already advises against using marijuana around children, it is important to investigate the potential health effects of secondhand marijuana smoke.

About 1 percent of hospital admissions are due to drug-drug interactions, which occur when the effects of one medication are changed by the use of another medication or drug.[3] With an aging population, many of whom use multiple medications, these interactions are a growing concern.[4] Many medications have been found to have such interactions with alcohol or tobacco, raising reasonable concern for interactions with marijuana.[5,6] In 2014, about 3 percent of adults 65 years and older used marijuana.[7] Drug-drug interactions can be minimized if prescribers are aware of which medications and drugs affect each other, so they can adjust or change patients' medications appropriately. Therefore, it is important to identify any drug-drug interactions involving marijuana and inform the medical community.

Opioid abuse has increased dramatically in the United States over the past 15 years and has been declared an epidemic by the U.S. Department of Health & Human Services, causing more than 28,000 deaths in 2014.[8] In Colorado, 5 percent of people 12 years and older misused prescription pain relievers (primarily opioids) in 2013 and 2014.[9] The possibility that marijuana use can reduce opioid use and abuse is a prominent claim.[10] Others argue that marijuana use makes using opioids and other drugs more likely. It is important to clarify the relationships between marijuana use and opioid use.

Definitions

Levels of marijuana use

- Daily or near-daily use: 5-7 days/week
- Weekly use: 1-4 days/week
- Less-than-weekly use: less than 1 day/week

Analgesic – a medication used to relieve pain.

Dabbing - a method of marijuana use where a "dab" (small amount) of marijuana concentrate is placed on a pre-heated surface, creating concentrated marijuana vapor to be inhaled.

Drug-drug interaction – a potentially dangerous interaction that occurs when the effects of one medication are changed by the use of another medication or drug. An example is when a person taking a blood thinner starts a new medication or drug that causes an increase in the blood thinner, leading to bleeding. Similar interactions can occur with many medications.

Opioid - one of many medications or street drugs including heroin, opium and prescription pain medications such as morphine, hydrocodone (Vicodin, Norco, Lortab), oxycodone (Percocet, OxyContin), hydromorphone (Dilaudid), fentanyl and methadone.

Pharmacokinetic / pharmacodynamic - the absorption, distribution, metabolism and excretion of a drug and the effect the drug has on the body.

Secondhand marijuana smoke exposure - the smoke that is inhaled by non-smokers when near to a person smoking marijuana, also known as passive exposure.

- Typical conditions: exposure at or below the level of smoke present in a small ventilated room (such as with open windows or an exhaust fan) with multiple people smoking marijuana.
- Extreme conditions: exposure at or above the level of smoke present in a small room (or a vehicle) without ventilation and with multiple people smoking marijuana.

Tetrahydrocannabinol (THC) - the main psychoactive component of marijuana.

Thirdhand marijuana smoke exposure – residual contamination left in rooms and on clothes after marijuana smoking.

Vaporization of marijuana (vaping) – a method of marijuana use in which marijuana vapor, rather than smoke, is inhaled. Marijuana flower or concentrate is heated in a vaporizing device (vaporizer) to a temperature below the point of combustion, to produce vapor.

Key findings

Multiple studies have measured blood THC levels following marijuana use. One important finding is that it can take up to four hours after consuming an edible marijuana product to reach the peak THC blood concentration and feel the full effects. This has important implications for the time to wait between doses or prior to safety-sensitive activities like driving. Smoking or vaporizing more than 10mg THC, or consuming an edible marijuana product with more than 15mg THC can lead to a blood THC level above 5ng/mL, which can be used to support a conviction for driving under the influence.

Regarding secondhand marijuana exposure, evidence shows that individuals passively exposed under usual conditions would not test above standard cutoffs for marijuana on a workplace urine test or driving impairment blood test. There is some evidence that secondhand exposure under extreme conditions can cause psychomotor impairment and increased heart rate.

Much has been said about the relationship between marijuana use and opioid use, but research remains limited. There is some evidence that opioid analgesic overdose deaths are lower in states with legal medical marijuana than would be expected based on trends in states without legal medical marijuana. There is conflicting evidence for whether or not marijuana use is associated with a decrease in opioid use among chronic pain patients or individuals with a history of problem drug use.

Clinical and pharmacokinetic data about potential drug-drug interactions with marijuana are currently lacking for many drugs and are likely to evolve substantially over coming years. There is credible evidence of clinically important drug-drug interactions with marijuana including the following: chlorpromazine, clobazam, clozapine, CNS depressants (e.g. barbiturates, benzodiazepines), disulfiram, hexobarbital, hydrocortisone, ketoconazole, MAO inhibitors, phenytoin, protease inhibitors (indinavir, nelfinavir), theophylline, tricyclic antidepressants and warfarin (see Table 2 for additional details). The lack of a cited interaction with other medications does not preclude the possibility that drug interactions exist; it simply means no studies have yet reported an interaction with that particular drug.

An important note for all key findings is that the available research evaluated the **association** between marijuana use and potential adverse health outcomes. This **association** does not prove that the marijuana use alone **caused** the effect. Despite the best efforts of researchers to account for confounding factors, there may be other important factors related to **causality** that were not identified. In addition, marijuana use was illegal everywhere in the United States prior to 1996. Research funding, when appropriated, was commonly sought to identify adverse effects from marijuana use. This legal fact introduces both funding bias and publication bias into the body of literature related to marijuana use. The Retail Marijuana Public Health Advisory Committee recognizes the limitations and biases inherent in the published literature and made efforts to ensure the information reviewed and synthesized is reflective of the current state of medical knowledge. Where information was lacking – for whatever reason – the committee identified this knowledge gap and recommended further research. This information will be updated as new research becomes available.

Recommendations

The committee recommends continued data collection efforts to assess marijuana use patterns among Colorado users, including better characterization of method, amount, potency and frequency. Data on the THC content of Colorado products is also needed. Data collected in relation to impairment should include type, amount, potency and timing of marijuana used. The public should be educated on possible unwanted interactions between marijuana and medications and the potential effects of secondhand marijuana smoke.

Further research is needed to identify potential interactions between marijuana and medications. Secondhand and thirdhand marijuana smoke should be further studied, including identification of biomarkers of exposure and evaluation of health effects, especially in children. The relationship between marijuana use and opioid use remains unclear, and further research is needed, especially at the individual level. Research is also needed to better characterize the pharmacokinetics/pharmacodynamics of cannabinoids.

Table 1 Findings summary: Marijuana dose and drug interaction

All statements apply only to less-than-weekly users. → = results in/produces. For an explanation of the classifications "Substantial," "Moderate," etc., see Chapter 7. Systematic literature review process.

	Substantial	Moderate	Limited	Insufficient	Mixed
THC levels	Smoking >10 mg THC produces blood THC level near or > 5 ng/mL within 10 minutes	Ingesting ≥15 mg THC may → blood THC level > 5 ng/mL			
	Time to peak blood THC level is up to four hours post ingestion	Inhaling vaporized THC→ blood THC level similar to smoking the same dose			
Secondhand exposure	Typical secondhand exposure → NO positive drug screen by urine or blood		Extreme secondhand exposure →psychomotor impairment and increased heart rate	Secondhand exposure → positive drug screen by oral fluid	
				Health effects of secondhand exposure on children	
				Health effects of third-hand exposure	
				Health effects of secondhand vapor	

Table 1 (continued) Findings summary: marijuana dose and drug interaction

All statements apply only to less-than-weekly users. → = results in/produces. For an explanation of the classifications "Substantial," "Moderate," etc., see Chapter 7. Systematic literature review process.

	Substantial	Moderate	Limited	Insufficient	Mixed
Marijuana and opioids			Less opioid overdose deaths than expected in states with legal medical marijuana	Association between legal medical marijuana and opioid use	Marijuana use and reduction in opioid use by chronic pain patients
					Marijuana use and reduction in opioid use by individuals with a history of problem drug use
Alternate methods				Dabbing and tolerance or withdrawal	

Evidence statements

Evidence statements are based on systematic scientific literature reviews performed by Colorado Department of Public Health and Environment staff with oversight and approval by the Retail Marijuana Public Health Advisory Committee. For an explanation of the classifications "Substantial," "Moderate," etc., see Chapter 7. Systematic literature review process. For details about the studies reviewed, see Appendix J.

THC levels resulting from different exposures

1. We found **SUBSTANTIAL** evidence that smoking more than about 10 mg THC (or part of a currently available marijuana cigarette) is likely to yield whole blood THC concentrations near or above 5 ng/mL within 10 minutes.[11-14]
2. We found **MODERATE** evidence that ingesting more than about 15 mg THC is capable of yielding a whole blood THC concentration above 5 ng/mL.[15-20]
3. We found **MODERATE** evidence that inhaling vaporized marijuana yields blood THC levels that are similar to those produced by smoking the same dose.[21,22]
4. We found **SUBSTANTIAL** evidence that it takes up to 4 hours after ingesting marijuana to reach peak blood THC concentrations.[15,16,18,19]

Secondhand (passive) exposure

5. We found **SUBSTANTIAL** evidence that an individual passively exposed to marijuana smoke (up to approximately 10% THC) under typical passive exposure conditions would NOT test above standard cutoffs for marijuana on a urine screening test or a blood test (given the current federal screening cutoff of 50 ng/mL for urine cannabinoid metabolites and the current Colorado limit for driving of 5 ng/mL whole blood THC).[23-35]
6. We found **INSUFFICIENT** evidence to determine whether individuals passively exposed to marijuana smoke would test above standard cutoffs by oral fluid testing because it has not yet been established which analyte or analytes to measure and which cutoff(s) to use.[23,24,36-39]
7. We found **LIMITED** evidence that individuals passively exposed to marijuana smoke under extreme passive exposure conditions (such as spending one hour in an unventilated space with individuals smoking marijuana of 11% potency) experience psychomotor impairment and increased heart rate in the hour immediately following exposure. [34,35] (Added*)
8. We found **INSUFFICIENT** evidence to determine the health effects of secondhand marijuana smoke in children. (Added*)
9. We found **INSUFFICIENT** evidence to determine the health effects of thirdhand marijuana smoke (the residual smoke that lingers in a room or on clothes). (Added*)
10. We found **INSUFFICIENT** evidence to determine whether or not secondhand marijuana vapor exposure is associated with adverse health effects. (Added*)

*Revised = the statement has been adjusted since the 2014 edition of the report, due to new evidence. Added = the statement is new since the 2014 edition of the report. See Appendix J for dates of most recent literature review.

Drug-drug interactions

11. There is credible evidence of clinically important drug-drug interactions between marijuana and the following medications: chlorpromazine, clobazam, clozapine, CNS depressants (e.g. barbiturates, benzodiazepines), disulfiram, hexobarbital, hydrocortisone, ketoconazole, MAO inhibitors, phenytoin, protease inhibitors (indinavir, nelfinavir), theophylline, tricyclic antidepressants and warfarin. The lack of a cited interaction does not preclude the possibility that drug interactions exist; it simply means no studies have yet reported an interaction with that particular drug.[22,40-56] (Revised*)

Marijuana and opioids

12. We found **INSUFFICIENT** evidence to determine whether or not there is an association between the availability of legal medical marijuana and the prevalence of opioid use.[57,58] (Added*)
13. We found **LIMITED** evidence that states with legal medical marijuana had a lower rate of opioid analgesic overdose deaths than would be expected based on trends in states without legal medical marijuana.[59] (Added*)
14. We found **MIXED** evidence for whether or not marijuana use is associated with a reduction in the number of patients using opioids or the amount of opioid use among chronic pain patients.[60,61] (Added*)
15. We found **MIXED** evidence for whether or not marijuana use is associated with a reduction in opioid use among individuals with a history of opioid addiction treatment or injection drug use.[62,63] (Added*)

Alternate methods of use

16. We found **INSUFFICIENT** evidence to determine whether dabbing concentrated marijuana is associated with an increase in marijuana tolerance or more severe withdrawal upon cessation of use compared to smoking marijuana.[64] (Added*)

*Revised = the statement has been adjusted since the 2014 edition of the report, due to new evidence. Added = the statement is new since the 2014 edition of the report. See Appendix J for dates of most recent literature review.

Public health statements

Public health statements are plain language translations of the major findings (Evidence Statements) from the systematic literature reviews. These statements have been officially approved by the Retail Marijuana Public Health Advisory Committee.

THC levels resulting from different exposures

1. It takes up to 4 hours after consuming an edible marijuana product to reach maximum blood levels of THC and feel the full effects. It is important to delay consuming another THC-containing product or engaging in safety-sensitive activities like driving until the effects from the first edible serving are known, especially for new or less-than-weekly users.
2. Smoking or vaporizing more than 10mg THC, or consuming an edible marijuana product with more than 15mg THC can lead to a blood THC level above 5ng/mL, which can be used to support a conviction for driving under the influence.

Secondhand (passive) exposure

3. Typical secondhand exposure to marijuana smoke is unlikely to result in a failed workplace urine test or a failed driving impairment blood test.
4. Extreme secondhand exposure to marijuana smoke (such as one hour of exposure in an unventilated space), may be associated with psychomotor impairment and an increase in heart rate. (Added*)

Drug-drug interactions

5. Use caution when taking medications and marijuana at the same time. Some medications have known interactions with marijuana, and others may have interactions that have not yet been identified.

Marijuana and opioids

6. Rates of overdose death from opioid pain relievers may be reduced in states with legal medical marijuana compared to states without. (Added*)
7. There is conflicting research on whether or not marijuana use is associated with a decrease in opioid use by chronic pain patients. (Added*)
8. There is conflicting research on whether or not marijuana use is associated with a decrease in opioid use by individuals with a history of opioid addiction treatment or injection drug use.(Added*)

*Revised = the statement has been adjusted since the 2014 edition of the report, due to new evidence. Added = the statement is new since the 2014 edition of the report. See Appendix J for dates of most recent literature review.

Public health recommendations

Public health recommendations have been suggested and approved by the Retail Marijuana Public Health Advisory Committee with the goals of: 1) Improving knowledge regarding population-based health effects of retail marijuana use and 2) Developing and targeting public health education and prevention strategies for high-risk sub populations.

Data quality issues

- Monitor data on THC content of marijuana products in Colorado.
- Monitor airborne THC/cannabinoid/by-products in future test chamber studies.
- Increase sample size in future pharmacologic studies.

Surveillance

- Monitor type, amount, potency and timing of marijuana consumed in correlation with impairment.
- Monitor health effects of secondhand marijuana smoke exposure.
- Add method of use questions (including vaporization and dabbing) to existing population-based surveys.
- Conduct targeted surveys of marijuana users (non-population-based surveys), including detailed questions on method, amount, potency and frequency of use.

Education

- Educate the public on potential interactions when using marijuana with medications.
- Educate the public about the potential effects of secondhand marijuana smoke and encourage safe and responsible use.
- Ensure marijuana smoking is prohibited in all venues where tobacco smoking is not permitted.

Research gaps

The Retail Marijuana Public Health Advisory Committee identifies important gaps in the scientific literature that may impact public health policies and prevention strategies. Colorado should support unbiased research to help fill the following research gaps identified by the committee.

- More research to identify interactions between marijuana and prescription drugs.
- Research to better characterize the pharmacokinetics/pharmacodynamics of cannabinoids, via various methods of marijuana use.
- Study possible differences in health effects of different methods of marijuana use.
- Analysis of chemicals released or produced by different methods of marijuana use.
- Identify biomarkers to assess secondhand marijuana smoke exposures.
- Further research on potential short-term and long-term health effects of secondhand marijuana smoke exposure, particularly in children.
- Impacts of secondhand marijuana vapor.
- Research on the relationship between marijuana use and opioid use at the individual level, both in the general population and in relevant subpopulations.

Table 2

Specific drug/drug classes with published clinical evidence of interactions with marijuana. Some drugs with published clinical evidence of a lack of interaction with marijuana are also included. These are marked with *. (Y=Yes, N= No, P=Possible)

Concomitant Drug/Drug Class	Description of Interaction	Contra-indicated	Increased THC Effect	Increased CNS Depressant Effect	Increased Concomitant Drug Effect	Decreased Concomitant Drug Effect
Chlorpromazine	Marijuana smoking increased clearance of chlorpromazine, as did tobacco smoking.[41]	N				P
Clobazam	In subjects taking cannabidiol (CBD), mean clobazam levels were about 60-80% higher, and nCLB levels 300-500% higher. A decrease in the clobazam dose was required in subjects taking CBD.[55]	N		Y	P	
Clozapine	Possible increased clozapine metabolism by marijuana induction of CYP1A2 (similar to tobacco). Therefore cessation may lead to increased clozapine levels and toxicity. Single case report of clozapine toxicity after tobacco and marijuana cessation.[43]	N			P	P
CNS depressants	Additive drowsiness and CNS depression Includes: alcohol, opioids, sedative-hypnotics, barbiturates, benzodiazepine, buspirone, antihistamines, muscles relaxants, and many more.[22,40,42]	N		Y		
Disulfiram	Possible hypomanic/psychotic reaction.[40,42]	N	P			
Fluoxetine*	No change in fluoxetine efficacy and no serious adverse reactions in a 12 week clinical study of fluoxetine vs. placebo for marijuana-related depression.[45]	N				
Hexobarbital	May enhance CNS depressant effect. CBD decreased metabolism of hexabarbital but did not change its clinical effects.[44]	N		Y	P	
Hydrocortisone	THC increased serum cortisol, but effect is blunted in frequent users. Theoretical possibility of cushingoid syndrome.[46]	N			P	
Ketoconazole	Peak THC concentration was increased by 27%.[53]	N	P	P		
MAO Inhibitors	Possible enhancement of orthostatic hypotension.[40]	N				
Phenytoin	May enhance CNS depressant effect. In vitro, decreased phenytoin levels due to induction of metabolism by THC. Therefore, phenytoin levels may rise rapidly after THC cessation, causing toxicity. Intermittent THC use may cause transient subtherapeutic phenytoin levels. Case report of phenytoin toxicity after recreational use of phenytoin concomitantly with EtOH and marijuana.[40,48,51]	N		Y	P	P
Protease inhibitors	Statistically significant decrease in peak concentration of indinavir and nelfinavir with THC use.[47]	N				P
Theophylline	Smoked marijuana lowers theophylline concentrations, similar to tobacco. Unclear if only a smoking-related effect. No studies of oral marijuana/THC.[49,52]	N				P
Tricyclic antidepressants	May cause transient cognitive changes, delirium, or tachycardia.[56]	N	P		P	
Warfarin	Possible enhanced anticoagulant effect.[40,50,54]	N			P	

References

1. Hernandez E. Pilot program eyes pot-DUI devices. *The Denver Post*. January 9, 2016, 2016.
2. Cao S, Yang C, Gan Y, Lu Z. The Health Effects of Passive Smoking: An Overview of Systematic Reviews Based on Observational Epidemiological Evidence. *PLoS One*. 2015;10(10):e0139907.
3. Dechanont S, Maphanta S, Butthum B, Kongkaew C. Hospital admissions/visits associated with drug-drug interactions: a systematic review and meta-analysis. *Pharmacoepidemiol Drug Saf*. 2014;23(5):489-497.
4. Kantor ED, Rehm CD, Haas JS, Chan AT, Giovannucci EL. Trends in Prescription Drug Use Among Adults in the United States From 1999-2012. *JAMA*. 2015;314(17):1818-1831.
5. Chan LN, Anderson GD. Pharmacokinetic and pharmacodynamic drug interactions with ethanol (alcohol). *Clin Pharmacokinet*. 2014;53(12):1115-1136.
6. Zevin S, Benowitz NL. Drug interactions with tobacco smoking. An update. *Clin Pharmacokinet*. 1999;36(6):425-438.
7. Colorado Department of Public Health and Environment. Adult Health Data, Behavioral Risk Factor Surveillance System. *Colorado Health and Environmental Data* 2015; http://www.chd.dphe.state.co.us/topics.aspx?q=Adult_Health_Data.
8. U.S. Department of Health & Human Services. Opioids: The Prescription Drug & Heroin Overdose Epidemic. 2016; https://www.hhs.gov/opioids/. Accessed December 21, 2016.
9. Substance Abuse and Mental Health Services Administration. National Survey on Drug Use and Health: Comparison of 2012-2013 and 2013-2014 Population Percentages (50 States and the District of Columbia). https://www.samhsa.gov/data/sites/default/files/NSDUHsaeShortTermCHG2014/NSDUHsaeShortTermCHG2014.htm2015.
10. Sifferlin A. Can Medical Marijuana Help End the Opioid Epidemic? *Time*, http://time.com/4419003/can-medical-marijuana-help-end-the-opioid-epidemic/ 2016.
11. Berghaus G, Sticht G, Grellner W. *Meta-analysis of empirical studies concerning the effects of medicines and illegal drugs including pharmacokinetics on safe driving*. Center for Traffic Sciences at the University of Wurzburg;2011.
12. Huestis MA, Sampson AH, Holicky BJ, Henningfield JE, Cone EJ. Characterization of the absorption phase of marijuana smoking. *Clin Pharmacol Ther*. 1992;52(1):31-41.
13. Ramaekers JG, Moeller MR, van Ruitenbeek P, Theunissen EL, Schneider E, Kauert G. Cognition and motor control as a function of Delta9-THC concentration in serum and oral fluid: limits of impairment. *Drug Alcohol Depend*. 2006;85(2):114-122.
14. Reeve VC, Grant JD, Robertson W, Gillespie HK, Hollister LE. Plasma concentrations of delta-9-tetrahydrocannabinol and impaired motor function. *Drug Alcohol Depend*. 1983;11(2):167-175.
15. Bosker WM, Kuypers KP, Theunissen EL, et al. Medicinal Delta(9) -tetrahydrocannabinol (dronabinol) impairs on-the-road driving performance of occasional and heavy cannabis users but is not detected in Standard Field Sobriety Tests. *Addiction*. 2012;107(10):1837-1844.
16. Curran HV, Brignell C, Fletcher S, Middleton P, Henry J. Cognitive and subjective dose-response effects of acute oral Delta 9-tetrahydrocannabinol (THC) in infrequent cannabis users. *Psychopharmacology (Berl)*. 2002;164(1):61-70.
17. Huestis MA. Human cannabinoid pharmacokinetics. *Chem Biodivers*. 2007;4(8):1770-1804.
18. Lile JA, Kelly TH, Charnigo RJ, Stinchcomb AL, Hays LR. Pharmacokinetic and pharmacodynamic profile of supratherapeutic oral doses of Delta(9) -THC in cannabis users. *J Clin Pharmacol*. 2013;53(7):680-690.

19. Menetrey A, Augsburger M, Favrat B, et al. Assessment of driving capability through the use of clinical and psychomotor tests in relation to blood cannabinoids levels following oral administration of 20 mg dronabinol or of a cannabis decoction made with 20 or 60 mg Delta9-THC. *J Anal Toxicol*. 2005;29(5):327-338.

20. Perez-Reyes M, Lipton MA, Timmons MC, Wall ME, Brine DR, Davis KH. Pharmacology of orally administered 9 -tetrahydrocannabinol. *Clin Pharmacol Ther*. 1973;14(1):48-55.

21. Abrams DI, Vizoso HP, Shade SB, Jay C, Kelly ME, Benowitz NL. Vaporization as a smokeless cannabis delivery system: a pilot study. *Clin Pharmacol Ther*. 2007;82(5):572-578.

22. Abramovici H. Information for Health Care Professionals. In: Canada H, ed, 2013.

23. Niedbala RS, Kardos KW, Fritch DF, et al. Passive cannabis smoke exposure and oral fluid testing. II. Two studies of extreme cannabis smoke exposure in a motor vehicle. *J Anal Toxicol*. 2005;29(7):607-615.

24. Niedbala S, Kardos K, Salamone S, Fritch D, Bronsgeest M, Cone EJ. Passive cannabis smoke exposure and oral fluid testing. *J Anal Toxicol*. 2004;28(7):546-552.

25. Rohrich J, Schimmel I, Zorntlein S, et al. Concentrations of delta9-tetrahydrocannabinol and 11-nor-9-carboxytetrahydrocannabinol in blood and urine after passive exposure to Cannabis smoke in a coffee shop. *J Anal Toxicol*. 2010;34(4):196-203.

26. Cone EJ, Johnson RE. Contact highs and urinary cannabinoid excretion after passive exposure to marijuana smoke. *Clin Pharmacol Ther*. 1986;40(3):247-256.

27. Cone EJ, Johnson RE, Darwin WD, et al. Passive inhalation of marijuana smoke: urinalysis and room air levels of delta-9-tetrahydrocannabinol. *J Anal Toxicol*. 1987;11(3):89-96.

28. Morland J, Bugge A, Skuterud B, Steen A, Wethe GH, Kjeldsen T. Cannabinoids in blood and urine after passive inhalation of Cannabis smoke. *J Forensic Sci*. 1985;30(4):997-1002.

29. Law B, Mason PA, Moffat AC, King LJ, Marks V. Passive inhalation of cannabis smoke. *J Pharm Pharmacol*. 1984;36(9):578-581.

30. Mason AP, Perez-Reyes M, McBay AJ, Foltz RL. Cannabinoids in plasma after passive inhalation of marijuana smoke. *JAMA*. 1983;249(4):475-476.

31. Mule SJ, Lomax P, Gross SJ. Active and realistic passive marijuana exposure tested by three immunoassays and GC/MS in urine. *J Anal Toxicol*. 1988;12(3):113-116.

32. Perez-Reyes M, di Guiseppi S, Davis KH. Passive inhalation of marijuana smoke and urinary excretion cannabinoids. *JAMA*. 1983;249(4):475.

33. Norchem Lab. Urine Drug Test Information Sheet: Marijuana. http://www.norchemlab.com/wp-content/uploads/2011/10/marijuana.pdf. Accessed 8/8/2014.

34. Herrmann ES, Cone EJ, Mitchell JM, et al. Non-smoker exposure to secondhand cannabis smoke II: Effect of room ventilation on the physiological, subjective, and behavioral/cognitive effects. *Drug Alcohol Depend*. 2015;151:194-202.

35. Cone EJ, Bigelow GE, Herrmann ES, et al. Non-smoker exposure to secondhand cannabis smoke. I. Urine screening and confirmation results. *J Anal Toxicol*. 2015;39(1):1-12.

36. Moore C. Response to "Is THCCOOH a useful determinant for passive inhalation in oral fluid THC testing?". *J Anal Toxicol*. Vol 36. United States2012:358.

37. Moore C, Coulter C, Uges D, et al. Cannabinoids in oral fluid following passive exposure to marijuana smoke. *Forensic Sci Int*. 2011;212(1-3):227-230.

38. Walsh JM, Cone EJ, Crouch DJ, Caplan YH. Is THC-COOH a useful determinant for passive inhalation in oral fluid THC testing? *J Anal Toxicol*. Vol 36. United States2012:291.

39. Cone EJ, Bigelow GE, Herrmann ES, et al. Nonsmoker Exposure to Secondhand Cannabis Smoke. III. Oral Fluid and Blood Drug Concentrations and Corresponding Subjective Effects. *J Anal Toxicol*. 2015;39(7):497-509.
40. Lexi-Comp Online. *Interaction Lookup*, http://www.uptodate.com.hsl-ezproxy.ucdenver.edu/.
41. Chetty M, Miller R, Moodley SV. Smoking and body weight influence the clearance of chlorpromazine. *Eur J Clin Pharmacol*. 1994;46(6):523-526.
42. Unimed Pharmaceuticals. Marinol (Dronabinol) package insert. 2004.
43. Zullino DF, Delessert D, Eap CB, Preisig M, Baumann P. Tobacco and cannabis smoking cessation can lead to intoxication with clozapine or olanzapine. *Int Clin Psychopharmacol*. 2002;17(3):141-143.
44. Benowitz NL, Nguyen TL, Jones RT, Herning RI, Bachman J. Metabolic and psychophysiologic studies of cannabidiol-hexobarbital interaction. *Clin Pharmacol Ther*. 1980;28(1):115-120.
45. Cornelius JR, Bukstein OG, Douaihy AB, et al. Double-blind fluoxetine trial in comorbid MDD-CUD youth and young adults. *Drug Alcohol Depend*. 2010;112(1-2):39-45.
46. D'Souza DC, Ranganathan M, Braley G, et al. Blunted psychotomimetic and amnestic effects of delta-9-tetrahydrocannabinol in frequent users of cannabis. *Neuropsychopharmacology*. 2008;33(10):2505-2516.
47. Kosel BW, Aweeka FT, Benowitz NL, et al. The effects of cannabinoids on the pharmacokinetics of indinavir and nelfinavir. *Aids*. 2002;16(4):543-550.
48. Bland TM, Haining RL, Tracy TS, Callery PS. CYP2C-catalyzed delta9-tetrahydrocannabinol metabolism: kinetics, pharmacogenetics and interaction with phenytoin. *Biochem Pharmacol*. 2005;70(7):1096-1103.
49. Gardner MJ, Tornatore KM, Jusko WJ, Kanarkowski R. Effects of tobacco smoking and oral contraceptive use on theophylline disposition. *Br J Clin Pharmacol*. 1983;16(3):271-280.
50. Ge B, Zhang Z, Zuo Z. Updates on the clinical evidenced herb-warfarin interactions. *Evid Based Complement Alternat Med*. 2014;2014:957362.
51. Jessen K. Recreational use of phenytoin, marijuana, and alcohol: a case report. *Neurology*. 2004;62(12):2330.
52. Jusko WJ, Gardner MJ, Mangione A, Schentag JJ, Koup JR, Vance JW. Factors affecting theophylline clearances: age, tobacco, marijuana, cirrhosis, congestive heart failure, obesity, oral contraceptives, benzodiazepines, barbiturates, and ethanol. *J Pharm Sci*. 1979;68(11):1358-1366.
53. Stott C, White L, Wright S, Wilbraham D, Guy G. A Phase I, open-label, randomized, crossover study in three parallel groups to evaluate the effect of Rifampicin, Ketoconazole, and Omeprazole on the pharmacokinetics of THC/CBD oromucosal spray in healthy volunteers. *Springerplus*. 2013;2(1):236.
54. Yamreudeewong W, Wong HK, Brausch LM, Pulley KR. Probable interaction between warfarin and marijuana smoking. *Ann Pharmacother*. 2009;43(7):1347-1353.
55. Geffrey AL, Pollack SF, Bruno PL, Thiele EA. Drug-drug interaction between clobazam and cannabidiol in children with refractory epilepsy. *Epilepsia*. 2015;56(8):1246-1251.
56. Wilens TE, Biederman J, Spencer TJ. Case study: adverse effects of smoking marijuana while receiving tricyclic antidepressants. *J Am Acad Child Adolesc Psychiatry*. 1997;36(1):45-48.
57. Kim JH, Santaella-Tenorio J, Mauro C, et al. State Medical Marijuana Laws and the Prevalence of Opioids Detected Among Fatally Injured Drivers. *Am J Public Health*. 2016;106(11):2032-2037.
58. Bradford AC, Bradford WD. Medical Marijuana Laws Reduce Prescription Medication Use In Medicare Part D. *Health Aff (Millwood)*. 2016;35(7):1230-1236.

59. Bachhuber MA, Saloner B, Cunningham CO, Barry CL. Medical cannabis laws and opioid analgesic overdose mortality in the United States, 1999-2010. *JAMA Intern Med*. 2014;174(10):1668-1673.

60. Boehnke KF, Litinas E, Clauw DJ. Medical Cannabis Use Is Associated With Decreased Opiate Medication Use in a Retrospective Cross-Sectional Survey of Patients With Chronic Pain. *J Pain*. 2016;17(6):739-744.

61. Haroutounian S, Ratz Y, Ginosar Y, et al. The Effect of Medicinal Cannabis on Pain and Quality-of-Life Outcomes in Chronic Pain: A Prospective Open-label Study. *Clin J Pain*. 2016;32(12):1036-1043.

62. Kral AH, Wenger L, Novak SP, et al. Is cannabis use associated with less opioid use among people who inject drugs? *Drug and Alcohol Dependence*. 2015;153:236-241.

63. Scavone JL, Sterling RC, Weinstein SP, Van Bockstaele EJ. Impact of cannabis use during stabilization on methadone maintenance treatment. *Am J Addict*. 2013;22(4):344-351.

64. Loflin M, Earleywine M. A new method of cannabis ingestion: the dangers of dabs? *Addict Behav*. 2014;39(10):1430-1433.

Section 2

Scientific Literature Review on Potential Health Effects of Marijuana Use

Chapter 6

Marijuana Use and Driving

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Introduction

The Retail Marijuana Public Health Advisory Committee identified many important public health topics related to marijuana and has reviewed the scientific evidence currently available regarding those topics. This chapter includes reviews of driving impairment and motor vehicle crash risk relative to amounts of marijuana used and to blood THC levels. It also includes reviews of evidence indicating how long it takes after marijuana use for impairment to resolve.

There are more than 80 crashes in Colorado each day, on average, and 12 percent of them cause injuries or fatalities.[1] Motor vehicle crashes are the leading cause of death among 10-24 year olds.[2] About 30 percent of all driving fatalities in Colorado are alcohol related.[3] Marijuana legalization has raised concern about the impact it may have on motor vehicle crashes. Marijuana is known to cause slowed reaction time and poorer motor coordination and attention.[4] In 2014, more than 18 percent of current marijuana users reported driving after using marijuana.[5] A Denver initiative passed in November 2016, allowing businesses to obtain marijuana use permits, has further raised concern for marijuana-impaired driving.[6] The different methods of marijuana use, such as edibles and vaporizing, complicate matters further because they may lead to different levels of impairment and require different wait times to allow the impairment to resolve. It is extremely important to investigate these topics to determine the impact marijuana use has on driving impairment and motor vehicle crashes and how it is affected by different methods of use, amounts used, and time since using.

Definitions

Levels of marijuana use

- Daily or near-daily use: 5-7 days/week.
- Weekly use: 1-4 days/week.
- Less-than-weekly use: less than 1 day/week.

Tetrahydrocannabinol (THC) - the main psychoactive component of marijuana.

Vaporization of marijuana (vaping) - a method of marijuana use in which marijuana vapor, rather than smoke, is inhaled. Marijuana flower or concentrate is heated in a vaporizing device (vaporizer) to a temperature below the point of combustion, to produce vapor.

Key findings

The committee found that the risk of a motor vehicle crash increases among drivers with recent marijuana use. Furthermore, the higher the blood THC level, the higher the motor vehicle crash risk. In addition, using alcohol and marijuana together increases impairment and the risk of a motor vehicle crash even more than using either substance alone. For less-than-weekly marijuana users, using marijuana containing 10 milligrams or more of THC is likely to impair the ability to safely drive, bike, or perform other safety-sensitive activities. This applies to smoking, eating, or drinking the marijuana or marijuana product. Waiting at least six hours after smoking marijuana containing less than 35 milligrams of THC likely will allow sufficient time for the impairment to resolve among less-than-weekly users. The waiting time is longer for eating or drinking marijuana products. It is necessary for marijuana users who use it less-than-weekly to wait at least eight hours for impairment to resolve after eating or drinking less than 18 milligrams of THC. Data on doses that cause impairment and time for impairment to resolve is lacking for frequent marijuana users.

An important note for all key findings is that the available research evaluated the **association** between marijuana use and potential adverse health outcomes. This **association** does not prove that the marijuana use alone **caused** the effect. Despite the best efforts of researchers to account for confounding factors, there may be other important factors related to **causality** that were not identified. In addition, marijuana use was illegal everywhere in the United States prior to 1996. Research funding, when appropriated, was commonly sought to identify adverse effects from marijuana use. This legal fact introduces both funding bias and publication bias into the body of literature related to marijuana use. The Retail Marijuana Public Health Advisory Committee recognizes the limitations and biases inherent in the published literature and made efforts to ensure the information reviewed and synthesized is reflective of the current state of medical knowledge. Where information was lacking – for whatever reason – the committee identified this knowledge gap and recommended further research. This information will be updated as new research becomes available.

Recommendations

The committee recommended improved testing and documentation of marijuana involvement in motor vehicle crashes and impaired driving encounters. This includes testing for THC and its metabolites in drivers, and accurately recording the timing of blood testing relative to the time impairment was suspected. If such data becomes more consistent, research should use blood THC levels rather than self-reported use, when possible. Centralized reporting of these levels would help both with surveillance and research. There are significant intervention opportunities for public education on marijuana-related impairment, including the dangers of driving after using marijuana, especially when combined with alcohol, and the amount of time a person should wait after using various types and doses of marijuana products before driving. However, in order to measure the impact of these educational interventions over time, additional questions are needed on population-based surveys such as the Behavioral Risk Factor Surveillance System (BRFSS) to measure self-reported impaired driving behaviors and perceptions of risk associated with impaired driving.

The committee identified several research gaps including the need for more research on the relationship of THC levels in saliva, blood and urine, and how these biomarkers relate to measures of functional impairment. Research focusing on impairment in daily or near-daily marijuana users is needed, as the relationship between timing of use, THC levels and impairment may differ from these effects in less-than-weekly users. Improved testing methods for impairment should be researched further, in order to develop best methods, either using alternate biological testing or physical and cognitive tests of impairment.

Table 1 Findings summary: Marijuana use and driving

* = applies only to less-than-weekly users. → = results in/produces. For an explanation of the classifications "Substantial," "Moderate," etc., see Chapter 7. Systematic literature review process.

	Substantial	Moderate	Limited	Insufficient	Mixed
Impairment and crash risk	Increased motor vehicle crash risk with recent use	THC blood level and motor vehicle crash risk		Risk of motor vehicle crash differs based on frequency of use	
	Increased risk of driving impairment at blood THC of 2-5 ng/mL*	Higher blood THC in impaired drivers now than in the past			
	Smoking >10 mg THC leads to driving impairment*				
	Orally ingesting >10 mg THC leads to driving impairment*				
	Combined use with alcohol increases crash risk				
Time to wait before driving		Waiting ≥ 6 hrs after smoking about 35 mg → driving impairment resolves/nearly resolves*		How long to wait after smoking ≥ 35 mg for impairment to resolve	
	Waiting ≥ 6 hrs after smoking < 18 mg → driving impairment resolves/nearly resolves*			How long daily or near-daily users should wait before driving	
	Waiting ≥ 8 hrs after orally ingesting < 18 mg → driving impairment resolves/nearly resolves*			How long to wait after vaporizing, dermal application, or other methods of use	

Evidence statements

Evidence statements are based on systematic scientific literature reviews performed by Colorado Department of Public Health and Environment staff with oversight and approval by the Retail Marijuana Public Health Advisory Committee. For an explanation of the classifications "Substantial," "Moderate," etc., see Chapter 7. Systematic literature review process. For details about the studies reviewed, see Appendix K.

Impairment and crash risk

1. We found **SUBSTANTIAL** evidence that recent marijuana use by a driver increases their risk of motor vehicle crash.[7-11](Revised*)
2. We found **MODERATE** evidence for a positive relationship between THC blood level and motor vehicle crash risk.[12-15] (Revised*)
3. We found **SUBSTANTIAL** evidence that for marijuana users who use less-than-weekly, there is meaningful driving impairment with a whole blood THC of 2-5 ng/mL.[8,16-18]
4. We found **SUBSTANTIAL** evidence that for marijuana users who use less-than-weekly, smoking more than about 10 mg THC (or part of a currently available marijuana cigarette) is likely to meaningfully impair driving ability.[16,17,19-30]
5. We found **SUBSTANTIAL** evidence that for marijuana users who use less-than-weekly, orally ingesting 10 mg or more of THC is likely to meaningfully impair driving ability.[17,20,31,32]
6. We found **MODERATE** evidence that blood THC levels of marijuana-impaired drivers are higher now than in the past.[33]
7. We found **INSUFFICIENT** evidence to determine whether or not motor vehicle crash risk differs for users who use less-than-weekly compared to daily or near-daily users.[34-37]

Combined marijuana and alcohol use

8. We found **SUBSTANTIAL** evidence that the combined use of marijuana and alcohol increases impairment and motor vehicle crash risk more than use of either substance alone.[12,14,15,38-42]

Time to wait before driving

9. We found **SUBSTANTIAL** evidence that delaying driving for at least 6 hours after smoking less than 18 mg THC allows THC-induced impairment to resolve or nearly resolve for users who use less-than-weekly.[8,16,17,19,26,43]
10. We found **MODERATE** evidence that delaying driving at least 6 hours after smoking about 35 mg THC allows THC-induced impairment to resolve or nearly resolve for users who use less-than-weekly.[22,25,26]
11. We found **SUBSTANTIAL** evidence that delaying driving at least 8 hours after oral ingestion of less than 18 mg THC allows THC-induced impairment to resolve or nearly resolve for users who use less-than-weekly.[17,20,32,44]

* Revised = the statement has been adjusted since the 2014 edition of the report, due to new evidence. Added = the statement is new since the 2014 edition of the report. See Appendix K for dates of most recent literature review.

12. We found **INSUFFICIENT** evidence to determine the amount of time necessary to wait after smoking more than 35 mg THC to allow THC-induced impairment to resolve for users who use less-than-weekly.[17,22,45]
13. We found **INSUFFICIENT** evidence to determine the amount of time necessary to delay driving to allow THC-induced impairment to resolve or nearly resolve for daily or near-daily users after using marijuana.[8,21,25,29,46,47]
14. We found **INSUFFICIENT** evidence to determine the amount of time to delay driving after other methods of marijuana use (such as vaporizing or application of dermal or mucosal preparations).

Public health statements

Public health statements are plain language translations of the major findings (Evidence Statements) from the systematic literature reviews. These statements have been officially approved by the Retail Marijuana Public Health Advisory Committee.

1. Driving soon after using marijuana increases the risk of a motor vehicle crash. (Revised*)
2. Using alcohol and marijuana together increases impairment and the risk of a motor vehicle crash more than using either substance alone.
3. The typical marijuana cigarette or joint in Colorado contains approximately 0.5 grams of marijuana, and the THC content in marijuana ranges from 12-23% THC; therefore, a typical joint contains between 60-115 mg THC. The standard serving size for a marijuana edible is 10 mg.
    a) For less-than-weekly marijuana users, smoking, eating, or drinking marijuana containing 10 mg or more of THC is likely to cause impairment that affects your ability to drive, bike, or perform other safety-sensitive activities.
    b) Wait at least 6 hours after smoking marijuana containing less than 35 mg THC before driving, biking, or performing other safety-sensitive activities. If you have smoked more than 35 mg, wait longer.
    c) Wait at least 8 hours after eating or drinking marijuana containing less than 18 mg THC before driving, biking, or performing other safety-sensitive activities. If you have consumed more than 18 mg, wait longer.
4. Use caution when driving, biking, or performing other safety-sensitive activities after using any form of marijuana or marijuana product.

* Revised = the statement has been adjusted since the 2014 edition of the report, due to new evidence. Added = the statement is new since the 2014 edition of the report. See Appendix K for dates of most recent literature review.

Public health recommendations

Public health recommendations have been suggested and approved by the Retail Marijuana Public Health Advisory Committee with the goals of: 1) Improving knowledge regarding population-based health effects of retail marijuana use and 2) Developing and targeting public health education and prevention strategies for high-risk sub populations.

Data quality

- Use better quality measures of marijuana use exposure, for example, blood THC levels instead of self-reported cannabis use, for studies of impairment and accidents.
- Increase testing for THC and its metabolites in drivers, especially fatally injured drivers and at-fault drivers.
- Accurately record timing of THC blood testing relevant to motor vehicle crashes and driving under the influence of drugs (DUID).

Surveillance

- Monitor perceptions of the risk associated with driving after using marijuana and self-report of personally doing so.
- Centralize reporting of blood THC levels (not just presence/absence of THC) for driving under the influence of drugs (DUID).
- Monitor method of use and dose of marijuana consumed in correlation with impairment.

Education

- Educate the public on marijuana-related impairment (driving, biking, and safety sensitive activities), including riding with impaired drivers.
- Educate the public on minimum time to wait before driving, biking, or participating in safety sensitive activities after using various types and doses of marijuana products.
- Educate the public on the combined effects and increased risk when using marijuana with alcohol or other substances.

Research gaps

The Retail Marijuana Public Health Advisory Committee identifies important gaps in the scientific literature that may impact public health policies and prevention strategies. Colorado should support unbiased research to help fill the following research gaps identified by the committee.

- Research to further clarify the relationship of saliva and urine levels to blood levels and relationship of all biomarkers to measures of functional impairment.
- Study the difference in impairment based on frequency of use/tolerance.
- Pharmacokinetic/pharmacodynamic and impairment research using doses consistent with the THC content of currently available marijuana products.
- Research on duration of driving impairment after oral marijuana and after high-dose smoked marijuana.
- Research to improve road-side marijuana testing.
- Research to identify reliable methods of assessing tolerance to marijuana in frequent users and to determine the extent to which tolerance affects impairment.
- Identification of better methods for measuring meaningful impairment.
- Research to determine whether THC metabolite ratios may be helpful in defining a better biomarker for impairment.
- Research to determine impairment after other methods of marijuana use (vaporizing, mucosal and dermal preparations).

References

1. Colorado State Patrol. Traffic Safety Statistics. 2016; https://www.colorado.gov/pacific/csp/traffic-safety-statistics. Accessed December 28, 2016.
2. CDC WONDER. Multiple Causes of Death Files, 1999-2014. http://wonder.cdc.gov/ucd-icd10.html: Centers for Disease Control and Prevention; 2016.
3. Colorado Task Force on Drunk & Impaired Driving. *Colorado Task Force on Drunk & Impaired Driving 2015 Annual Report*. 2016.
4. Hall W, Degenhardt L. Adverse health effects of non-medical cannabis use. *Lancet*. 2009;374(9698):1383-1391.
5. New data show 13.6 percent of Colorado adults use marijuana [press release]. June 15, 2015.
6. Baca R. Initiative 300: Everything you need to know about Denver's social cannabis use measure. *The Denver Post*2016.
7. Asbridge M, Hayden JA, Cartwright JL. Acute cannabis consumption and motor vehicle collision risk: Systematic review of observational studies and meta-analysis. *Bmj*. 2012;344:e536.
8. Hartman RL, Huestis MA. Cannabis effects on driving skills. *Clin Chem*. 2013;59(3):478-492.
9. Lowenstein SR, Koziol-McLain J. Drugs and traffic crash responsibility: A study of injured motorists in Colorado. *The Journal of Trauma: Injury, Infection, and Critical Care*. 2001;50(2):313-320.
10. Gjerde H, Strand MC, Morland J. Driving under the influence of non-alcohol drugs--An update Part I: Epidemiological Studies. *Forensic Sci Rev*. 2015;27(2):89-113.
11. Rogeberg O, Elvik R. The effects of cannabis intoxication on motor vehicle collision revisited and revised. *Addiction*. 2016;111(8):1348-1359.
12. Drummer OH, Gerostamoulos J, Batziris H, et al. The involvement of drugs in drivers of motor vehicles killed in Australian road traffic crashes. *Accident Analysis & Prevention*. 2004;36(2):239-248.
13. Kuypers KP, Legrand SA, Ramaekers JG, Verstraete AG. A case-control study estimating accident risk for alcohol, medicines and illegal drugs. *PLoS One*. 2012;7(8):e43496.
14. Laumon B, Gadegbeku B, Martin JL, Biecheler MB, Group SAM. Cannabis intoxication and fatal road crashes in France: population based case-control study. *Bmj*. 2005;331(7529):1371.
15. Poulsen H, Moar R, Pirie R. The culpability of drivers killed in New Zealand road crashes and their use of alcohol and other drugs. *Accid Anal Prev*. 2014;67:119-128.
16. Berghaus G, Scheer N, Schmidt P. Effects of cannabis on psychomotor skills and driving performance - a metaanalysis of experimental studies. 1995; http://casr.adelaide.edu.au/T95/paper/s16p2.html. Accessed 8/31/2014.
17. Berghaus G, Sticht G, Grellner W. *Meta-analysis of empirical studies concerning the effects of medicines and illegal drugs including pharmacokinetics on safe driving*. Center for Traffic Sciences at the University of Wurzburg;2011.
18. Grotenhermen F, Leson G, Berghaus G, et al. Developing limits for driving under cannabis. *Addiction*. 2007;102(12):1910-1917.
19. Ramaekers JG, Moeller MR, van Ruitenbeek P, Theunissen EL, Schneider E, Kauert G. Cognition and motor control as a function of Delta9-THC concentration in serum and oral fluid: limits of impairment. *Drug Alcohol Depend*. 2006;85(2):114-122.
20. Curran HV, Brignell C, Fletcher S, Middleton P, Henry J. Cognitive and subjective dose-response effects of acute oral Delta 9-tetrahydrocannabinol (THC) in infrequent cannabis users. *Psychopharmacology (Berl)*. 2002;164(1):61-70.

21. Hart CL, van Gorp W, Haney M, Foltin RW, Fischman MW. Effects of acute smoked marijuana on complex cognitive performance. *Neuropsychopharmacology*. 2001;25(5):757-765.

22. Hunault CC, Mensinga TT, Bocker KB, et al. Cognitive and psychomotor effects in males after smoking a combination of tobacco and cannabis containing up to 69 mg delta-9-tetrahydrocannabinol (THC). *Psychopharmacology (Berl)*. 2009;204(1):85-94.

23. Kelly TH, Foltin RW, Emurian CS, Fischman MW. Performance-based testing for drugs of abuse: dose and time profiles of marijuana, amphetamine, alcohol, and diazepam. *J Anal Toxicol*. 1993;17(5):264-272.

24. Lenne MG, Dietze PM, Triggs TJ, Walmsley S, Murphy B, Redman JR. The effects of cannabis and alcohol on simulated arterial driving: Influences of driving experience and task demand. *Accid Anal Prev*. 2010;42(3):859-866.

25. Ramaekers JG, Kauert G, Theunissen EL, Toennes SW, Moeller MR. Neurocognitive performance during acute THC intoxication in heavy and occasional cannabis users. *J Psychopharmacol*. 2009;23(3):266-277.

26. Ramaekers JG, Kauert G, van Ruitenbeek P, Theunissen EL, Schneider E, Moeller MR. High-potency marijuana impairs executive function and inhibitory motor control. *Neuropsychopharmacology*. 2006;31(10):2296-2303.

27. Ronen A, Chassidim HS, Gershon P, et al. The effect of alcohol, THC and their combination on perceived effects, willingness to drive and performance of driving and non-driving tasks. *Accid Anal Prev*. 2010;42(6):1855-1865.

28. Ronen A, Gershon P, Drobiner H, et al. Effects of THC on driving performance, physiological state and subjective feelings relative to alcohol. *Accid Anal Prev*. 2008;40(3):926-934.

29. Schwope DM, Bosker WM, Ramaekers JG, Gorelick DA, Huestis MA. Psychomotor performance, subjective and physiological effects and whole blood Delta(9)-tetrahydrocannabinol concentrations in heavy, chronic cannabis smokers following acute smoked cannabis. *J Anal Toxicol*. 2012;36(6):405-412.

30. Weinstein A, Brickner O, Lerman H, et al. A study investigating the acute dose-response effects of 13 mg and 17 mg Delta 9- tetrahydrocannabinol on cognitive-motor skills, subjective and autonomic measures in regular users of marijuana. *J Psychopharmacol*. 2008;22(4):441-451.

31. Bosker WM, Kuypers KP, Theunissen EL, et al. Medicinal Delta(9) -tetrahydrocannabinol (dronabinol) impairs on-the-road driving performance of occasional and heavy cannabis users but is not detected in Standard Field Sobriety Tests. *Addiction*. 2012;107(10):1837-1844.

32. Menetrey A, Augsburger M, Favrat B, et al. Assessment of driving capability through the use of clinical and psychomotor tests in relation to blood cannabinoids levels following oral administration of 20 mg dronabinol or of a cannabis decoction made with 20 or 60 mg Delta9-THC. *J Anal Toxicol*. 2005;29(5):327-338.

33. Vindenes V, Strand DH, Kristoffersen L, Boix F, Morland J. Has the intake of THC by cannabis users changed over the last decade? Evidence of increased exposure by analysis of blood THC concentrations in impaired drivers. *Forensic Sci Int*. 2013;226(1-3):197-201.

34. Blows S, Ivers RQ, Connor J, Ameratunga S, Woodward M, Norton R. Marijuana use and car crash injury. *Addiction (Abingdon, England)*. 2005;100(5):605-611.

35. Chipman ML, Macdonald S, Mann RE. Being "at fault" in traffic crashes: does alcohol, cannabis, cocaine, or polydrug abuse make a difference? *Inj Prev*. 2003;9(4):343-348.

36. Mann RE, Adlaf E, Zhao J, et al. Cannabis use and self-reported collisions in a representative sample of adult drivers. *J Safety Res*. 2007;38(6):669-674.

37. Pulido J, Barrio G, Lardelli P, Bravo MJ, Regidor E, de la Fuente L. Association between cannabis and cocaine use, traffic injuries and use of protective devices. *Eur J Public Health*. 2011;21(6):753-755.

38. Mura P, Kintz P, Ludes B, et al. Comparison of the prevalence of alcohol, cannabis and other drugs between 900 injured drivers and 900 control subjects: results of a French collaborative study. *Forensic Sci Int*. 2003;133(1-2):79-85.

39. Sewell RA, Poling J, Sofuoglu M. The effect of cannabis compared with alcohol on driving. *Am J Addict*. 2009;18(3):185-193.

40. Dubois S, Mullen N, Weaver B, Bedard M. The combined effects of alcohol and cannabis on driving: Impact on crash risk. *Forensic Sci Int*. 2015;248:94-100.

41. Fierro I, González-Luque JC, Álvarez FJ. The relationship between observed signs of impairment and THC concentration in oral fluid. *Drug and Alcohol Dependence*. 2014;144:231-238.

42. Hartman RL, Brown TL, Milavetz G, et al. Controlled vaporized cannabis, with and without alcohol: Subjective effects and oral fluid-blood cannabinoid relationships. *Drug Test Anal*. 2015;10.1002/dta.1839.

43. Cone EJ, Johnson RE. Contact highs and urinary cannabinoid excretion after passive exposure to marijuana smoke. *Clin Pharmacol Ther*. 1986;40(3):247-256.

44. Huestis MA. Human cannabinoid pharmacokinetics. *Chem Biodivers*. 2007;4(8):1770-1804.

45. Hunault CC, Bocker KB, Stellato RK, Kenemans JL, de Vries I, Meulenbelt J. Acute subjective effects after smoking joints containing up to 69 mg Delta9-tetrahydrocannabinol in recreational users: a randomized, crossover clinical trial. *Psychopharmacology (Berl)*. 2014;231(24):4723-4733.

46. Bosker WM, Karschner EL, Lee D, et al. Psychomotor function in chronic daily Cannabis smokers during sustained abstinence. *PLoS One*. 2013;8(1):e53127.

47. Wolff K, Johnston A. Cannabis use: a perspective in relation to the proposed UK drug-driving legislation. *Drug Test Anal*. 2014;6(1-2):143-154.

Section 2

Scientific Literature Review on Potential Health Effects of Marijuana Use

Chapter 7

Marijuana Use and Gastrointestinal and Reproductive Effects

Retail Marijuana Public Health Advisory Committee

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Introduction

The Retail Marijuana Public Health Advisory Committee identified many important public health topics related to marijuana use and has reviewed the scientific evidence currently available regarding those topics. This chapter includes reviews of gastrointestinal diseases, particularly cyclic vomiting, and infertility or abnormal reproductive function.

Gastrointestinal diseases affect 60 to 70 million people in the United States,[1] and caused more than 20 million hospitalizations in 2010.[2] Both tobacco and alcohol contribute to some of these diseases, and it is possible marijuana could as well. One condition of concern, reported by emergency department providers, is cyclic vomiting among long-time, frequent marijuana users. Analysis of 2015 data from the Behavioral Risk Factor Surveillance System (BRFSS), completed for this report, estimated that 6 percent of adults in Colorado use marijuana daily or near-daily. Potential connections between marijuana use and cyclic vomiting or other gastrointestinal diseases are important to clarify.

Many women who want to become pregnant are unable. Eleven percent of women 15-44 years of age in the United States have used infertility services,[3] often at great expense. Many men also have conditions that can prevent a desired pregnancy, such as low sperm count. Because normal reproductive function is dependent on so many factors, any substance that has effects throughout the body could potentially contribute to infertility. Marijuana use in Colorado is highest among individuals of reproductive age. Analysis of 2015 data from the BRFSS, completed for this report, estimated that 26 percent of 18-25 year olds and 18 percent of 26-34 year olds in Colorado were current marijuana users. It is important to evaluate possible associations between infertility and marijuana use.

Definitions

Cannabinoid hyperemesis syndrome - a term currently used by some medical professionals to describe cyclic vomiting occurring in long-time marijuana users. A formal medical definition, including clinical diagnostic criteria, has not yet been established.

Cyclic vomiting - episodes of severe, repeated vomiting.

Abnormal male reproductive function - abnormal sperm count, concentration, motility or structure, or abnormal reproductive hormone levels.

Abnormal female reproductive function - abnormal ovulation, implantation, placenta formation, or reproductive hormone levels.

Levels of marijuana use

- Daily or near-daily use: 5-7 days/week.
- Weekly use: 1-4 days/week.
- Less-than-weekly use: less than 1 day/week.

Key findings

Evidence shows that long-time, daily or near-daily marijuana use is associated with cyclic vomiting. This condition has been called cannabinoid hyperemesis syndrome. In such cases, stopping marijuana use may relieve the vomiting. There is conflicting research on whether or not marijuana use is associated with male infertility or abnormal reproductive function, and research is lacking on female reproductive function related to marijuana use.

An important note for all key findings is that the available research evaluated the **association** between marijuana use and potential adverse health outcomes. This **association** does not prove that the marijuana use alone **caused** the effect. Despite the best efforts of researchers to account for confounding factors, there may be other important factors related to **causality** that were not identified. In addition, marijuana use was illegal everywhere in the United States prior to 1996. Research funding, when appropriated, was commonly sought to identify adverse effects from marijuana use. This legal fact introduces both funding bias and publication bias into the body of literature related to marijuana use. The Retail Marijuana Public Health Advisory Committee recognizes the limitations and biases inherent in the published literature and made efforts to ensure the information reviewed and synthesized is reflective of the current state of medical knowledge. Where information was lacking – for whatever reason – the committee identified this knowledge gap and recommended further research. This information will be updated as new research becomes available.

Recommendations

The committee recommends that health care systems and providers improve the documentation of marijuana use history during hospitalizations and emergency department visits, including timing, potency and amount of last marijuana use and measures of cumulative lifetime use. Because cannabinoid hyperemesis syndrome is an emerging medical concern, public health should assess and monitor its prevalence among marijuana users, and educate the public about the potential for cyclic vomiting with long-time, daily or near-daily marijuana use.

It is also important to reach a consensus on diagnostic criteria for cannabinoid hyperemesis syndrome. Treatment of the condition should be studied using randomized, controlled trials, including an assessment of the effectiveness of marijuana cessation. High-quality observational research is needed to further assess the effects of marijuana use on reproductive function.

Table 1 Findings summary: Marijuana use and gastrointestinal and reproductive effects

For an explanation of the classifications "Substantial," "Moderate," etc., see Chapter 7. Systematic literature review process.

Substantial	Moderate	Limited	Insufficient	Mixed
	Cyclic vomiting with long-time, daily or near-daily use (cannabinoid hyperemesis syndrome)	Relief from cyclic vomiting by stopping marijuana use	Female infertility or altered reproductive function	Male infertility or altered reproductive function

Evidence statements

Evidence statements are based on systematic scientific literature reviews performed by Colorado Department of Public Health and Environment staff with oversight and approval by the Retail Marijuana Public Health Advisory Committee. For an explanation of the classifications "Substantial," "Moderate," etc., see Chapter 7. Systematic literature review process. For details about the studies reviewed, see Appendix L.

1. We found **MODERATE** evidence that long-time, daily or near-daily marijuana use is associated with cases of cyclic vomiting (some medical experts have called this cannabinoid hyperemesis syndrome).[4-8] (Added*)
2. We found **LIMITED** evidence that marijuana users who experience cyclic vomiting have found relief by stopping marijuana use.[6,8,9] (Added*)
3. We found **MIXED** evidence for whether or not marijuana use is associated with male infertility or abnormal reproductive function (such as abnormal sperm count, concentration, motility or structure, or abnormal reproductive hormone levels).[10-13] (Revised*)
4. We found **INSUFFICIENT** evidence to determine whether or not marijuana use is associated with female infertility or abnormal reproductive function (such as abnormal ovulation, implantation, placenta formation, or reproductive hormone levels).[14] (Added*)

* Revised = the statement has been adjusted since the 2014 edition of the report, due to new evidence. Added = the statement is new since the 2014 edition of the report. See Appendix L for dates of most recent literature review.

Public health statements

Public health statements are plain language translations of the major findings (Evidence Statements) from the systematic literature reviews. These statements have been officially approved by the Retail Marijuana Public Health Advisory Committee.

1. Long-time, daily or near-daily marijuana use is associated with cyclic vomiting, which some medical experts have called cannabinoid hyperemesis syndrome. (Added*)
2. Marijuana users who experience cyclic vomiting may find relief by stopping marijuana use. (Added*)
3. There is conflicting research on whether or not marijuana use is associated with male infertility or reproductive function.

Public health recommendations

Public health recommendations have been suggested and approved by the Retail Marijuana Public Health Advisory Committee with the goals of: 1) Improving knowledge regarding population-based health effects of retail marijuana use and 2) Developing and targeting public health education and prevention strategies for high-risk sub populations.

Data quality

- Improved documentation of marijuana use history during hospitalizations and emergency department visits, including timing, potency and amount of last marijuana use and measures of cumulative lifetime use.

Surveillance

- Population based analyses to evaluate the prevalence of cannabinoid hyperemesis syndrome or cyclic vomiting among marijuana users, including separate rates for medical versus recreational users.

Education

- Public education about the potential for cyclic vomiting with long-time, daily or near-daily marijuana use.

* Revised = the statement has been adjusted since the 2014 edition of the report, due to new evidence. Added = the statement is new since the 2014 edition of the report. See Appendix L for dates of most recent literature review.

Research gaps

The Retail Marijuana Public Health Advisory Committee identifies important gaps in the scientific literature that may impact public health policies and prevention strategies. Colorado should support unbiased research to help fill the following research gaps identified by the committee.

- High quality studies assessing reproductive function related to marijuana use.
- Consensus diagnostic criteria for cannabinoid hyperemesis syndrome (CHS) to be used in subsequent research.
- Determination of the molecular etiology of CHS.
- Clinical studies of CHS treatment, including the effectiveness of marijuana cessation.

References

1. National Institute of Diabetes and Digestive and Kidney Diseases. *Opportunities & Challenges in Digestive Diseases Research: Recommendations of the National Commission on Digestive Diseases*. National Institutes of Health;2009.
2. National Center for Health Statistics. National Hosptial Discharge Survey, United States 2010 https://www.cdc.gov/nchs/fastats/hospital.htm: Centers for Disease Control and Prevention.
3. National Center for Health Statistics. Key Statistics from the National Survey of Family Growth. https://www.cdc.gov/nchs/nsfg/key_statistics.htm. Accessed December 27, 2016.
4. Wallace EA, Andrews SE, Garmany CL, Jelley MJ. Cannabinoid hyperemesis syndrome: literature review and proposed diagnosis and treatment algorithm. *South Med J*. 2011;104(9):659-664.
5. Soriano-Co M, Batke M, Cappell MS. The cannabis hyperemesis syndrome characterized by persistent nausea and vomiting, abdominal pain, and compulsive bathing associated with chronic marijuana use: a report of eight cases in the United States. *Dig Dis Sci*. 2010;55(11):3113-3119.
6. Simonetto Da, Oxentenko AS, Herman ML, Szostek JH. Cannabinoid hyperemesis: a case series of 98 patients. *Mayo Clinic Proceedings*. 2012;87(2):114-119.
7. Kim HS, Anderson JD, Saghafi O, Heard KJ, Monte AA. Cyclic vomiting presentations following marijuana liberalization in Colorado. *Acad Emerg Med*. 2015;22(6):694-699.
8. Allen JH, de Moore GM, Heddle R, Twartz JC. Cannabinoid hyperemesis: cyclical hyperemesis in association with chronic cannabis abuse. *Gut*. 2004;53(11):1566-1570.
9. Namin F, Patel J, Lin Z, et al. Clinical, psychiatric and manometric profile of cyclic vomiting syndrome in adults and response to tricyclic therapy. *Neurogastroenterol Motil*. 2007;19(3):196-202.
10. Pacey AA, Povey AC, Clyma JA, et al. Modifiable and non-modifiable risk factors for poor sperm morphology. *Hum Reprod*. 2014;29(8):1629-1636.
11. Povey AC, Clyma JA, McNamee R, et al. Modifiable and non-modifiable risk factors for poor semen quality: a case-referent study. *Hum Reprod*. 2012;27(9):2799-2806.
12. Block RI, Farinpour R, Schlechte JA. Effects of chronic marijuana use on testosterone, luteinizing hormone, follicle stimulating hormone, prolactin and cortisol in men and women. *Drug Alcohol Depend*. 1991;28(2):121-128.
13. Gundersen TD, Jorgensen N, Andersson AM, et al. Association Between Use of Marijuana and Male Reproductive Hormones and Semen Quality: A Study Among 1,215 Healthy Young Men. *Am J Epidemiol*. 2015;182(6):473-481.
14. Mueller BA, Daling JR, Weiss NS, Moore DE. Recreational drug use and the risk of primary infertility. *Epidemiology*. 1990;1(3):195-200.

Section 2

Scientific Literature Review on Potential Health Effects of Marijuana Use

Chapter 8

Marijuana Use and Injury

Retail Marijuana Public Health Advisory Committee

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(2014)

Introduction

The Retail Marijuana Public Health Advisory Committee identified many important public health topics related to marijuana and has reviewed the scientific evidence currently available regarding those topics. This chapter includes reviews of workplace, recreational and other non-driving injuries (driving-related injuries are described in Chapter 12. Marijuana use and driving), burns from hash oil extraction or failed electronic smoking devices, and physical dating violence.

In Colorado, thousands of people are injured on the job each year, and a work-related death occurs every three to four days.[1] Outdoor recreational activities are extremely popular in Colorado, drawing participation from about two-thirds of residents annually,[2] and recreational injuries are common. Additionally, many of the tourists visiting Colorado - 64 million in 2013[3] – come to enjoy outdoor recreation. Unintentional injuries, excluding motor vehicle crashes, are responsible for 17 percent of all deaths among persons 10-24 years of age in the United States.[4] Marijuana use can cause unsteady gait, slower reaction time, impaired motor coordination, and impaired attention,[5,6] which are all factors that contribute to accidental injuries.

Analyses of 2015 Behavioral Risk Factor Surveillance System data, completed for this report, estimated that 26 percent of 18-25 year olds and 18 percent of 26-34 year olds in Colorado have used marijuana within the last month. These age groups make up a large portion of the workforce. Recreational activities are common among these 18-34 year olds, as well as adolescents. 2015 Healthy Kids Colorado Survey data, also analyzed for this report, estimate that 21 percent of Colorado high school students used marijuana within the last month. It is important to investigate possible associations between marijuana use and workplace, recreational and other non-driving injuries.

Recently, there have been increased reports of explosions related to hash oil extraction. In 2014, there were 32 hash oil extraction explosions in Colorado, which injured 30 people (most often burns).[7] Another emerging topic of concern has been the explosion of electronic smoking devices[8,9], which are used for both marijuana and nicotine. The devices have grown in popularity, and injuries resulting from explosions are increasing.[10] These topics should be evaluated.

Approximately 10 percent of U.S. high school students report having experienced physical dating violence,[11] and the prevalence is similar among college students.[12] The consequences of this violence are serious. Those who are victimized are at increased risk for a range of negative outcomes including poor health outcomes, depressive symptoms, unhealthy eating behavior, academic difficulties, and physical injury.[13-15] Alcohol use has been clearly linked with intimate partner violence,[16,17] and some have argued that marijuana use is also a contributing factor. It is important to identify factors that may contribute to dating violence, including examination of possible associations with marijuana use.

Definitions

Age groups

- Adolescent: 12 to 17 years of age.
- Young adult: 18 to 24 years of age.
- Adult: 25 years or older.
- Older adult: 65 years of age and older.

Electronic smoking device (vaporizer or e-cigarette) - a vaporizing device with a rechargeable battery that heats material such as marijuana flower (bud) or liquids containing THC or nicotine to produce vapor for inhalation. Used as an alternative to smoking marijuana or tobacco.

Hash oil extraction - a technique that removes THC (the psychoactive component of marijuana) from the plant material in a concentrated form. This concentrate can then be smoked, vaporized, mixed into food or drink, or used on the skin. A very common method of extraction uses butane, which is highly flammable.

Physical dating violence - physically aggressive behavior among current or former romantic, sexual/intimate, or dating partners, including hitting, kicking, choking, slapping, etc. Psychological, emotional, verbal or sexual violence were not included, nor were threats of violence.

Physical dating violence victimization (PDVV) - to be harmed by physical violence committed by a partner.

Physical dating violence perpetration (PDVP) - to commit physical violence against a partner.

Tetrahydrocannabinol (THC) - the main psychoactive component of marijuana.

Key findings

There is some evidence that marijuana use increases the risk of workplace injury. Evidence is conflicting for other types of non-driving injury, including marijuana use alone or in combination with alcohol. There have been many cases of severe burns resulting from explosions that occurred during home-extraction of hash oil through the use of butane. There also have been cases of electronic smoking devices exploding, leading to trauma and burns. Concerning dating violence, marijuana use by adolescent girls may be associated with their committing physical violence against their dating partners, and marijuana use by adolescent boys may be associated with their being victims of physical violence from their dating partners.

An important note for all key findings is that the available research evaluated the **association** between marijuana use and potential adverse health outcomes. This **association** does not prove that the marijuana use alone **caused** the effect. Despite the best efforts of researchers to account for confounding factors, there may be other important factors related to **causality** that were not identified. In addition, marijuana use was illegal everywhere in the United States prior to 1996. Research funding, when appropriated, was commonly sought to identify adverse effects from marijuana use. This legal fact introduces both funding bias and publication bias into the body of literature related to marijuana use. The Retail Marijuana Public Health Advisory Committee recognizes the limitations and biases inherent in the published literature and made efforts to ensure the information reviewed and synthesized is reflective of the current state of medical knowledge. Where information was lacking – for whatever reason – the committee identified this knowledge gap and recommended further research. This information will be updated as new research becomes available.

Recommendations

The committee recommended more consistent collection of blood samples following recreational, workplace or any other injury requiring medical attention, including accurately recording the timing of testing, and specifying marijuana use as distinct from other substances. Improved collection of information on individual marijuana use history by amount, potency, frequency, and method is also important. The link between exposure to marijuana and adverse health outcomes, in both injury and chronic disease medical settings, cannot be adequately assessed until consistent, standardized data on individual marijuana use is collected during encounters with medical care settings, mental health settings and, when necessary, law enforcement. Collecting accurate exposure (or dose) information and injury outcome data will permit analysis of the data to determine the severity of injury and its possible relationship with marijuana use.

Surveillance or monitoring systems currently in place (e.g., hospitalization and emergency department data from the Colorado Hospital Association) can be interrogated to assess injuries potentially related to marijuana use. The committee recommended additional small-scale pilot projects to determine the relationship between marijuana use and injury in focused settings including recreational, workplaces, and where services are provided for the elderly. Monitoring the incidence of injuries caused by electronic device explosions and hash oil extraction explosions is also recommended.

Educational programs for adult users, their families, and health care providers are needed to ensure more information is shared about the potential risks of marijuana use and injury. Such information also should be available and distributed to customers at marijuana dispensaries. Education about the potential explosion of electronic smoking devices and at-home hash oil extractions is important.

The committee identified several research gaps including the need for more research on the relationship of THC levels in saliva, blood and urine, and how these biomarkers relate to measures of functional impairment. Research is also needed on differences in impairment levels based on marijuana use frequency and tolerance in daily or near-daily users versus other levels of use. More publicly accessible product safety research is needed for electronic smoking devices. Finally, more studies are needed that examine marijuana use as a predictor of risk behaviors, especially among adolescents, college attending young adults and non-college attending young adults.

Table 1 Findings summary: Marijuana use and injury

For an explanation of the classifications "Substantial," "Moderate," etc., see Chapter 7. Systematic literature review process.

	Substantial	Moderate	Limited	Insufficient	Mixed
Non-driving injury			Increased risk of workplace injury		Marijuana use and risk of non-driving injury
					Combined marijuana and alcohol use and non-driving injury
					Marijuana use and risk of recreational injury
Burns			Severe burns and hospitalization from hash oil extraction	Marijuana use and burns	
			Serious injury from exploding electronic smoking devices		
Physical Dating Violence			Physical dating violence perpetration by adolescent girls	Physical dating violence victimization in young adults	Physical dating violence perpetration by adolescent boys
			Physical dating violence victimization in adolescent boys		Physical dating violence victimization in adolescent girls
			Failure to show physical dating violence perpetration by young adult women or men		

Evidence statements

Evidence statements are based on systematic scientific literature reviews performed by Colorado Department of Public Health and Environment staff with oversight and approval by the Retail Marijuana Public Health Advisory Committee. For an explanation of the classifications "Substantial," "Moderate," etc., see Chapter 7. Systematic literature review process. For details about the studies reviewed, see Appendix M.

Workplace, recreational, other non-driving

1. We found **LIMITED** evidence that marijuana use increases workplace injury risk (non-driving injury).[18-20]
2. We found **MIXED** evidence for whether or not adults who use marijuana are at a higher risk of non-driving related injuries.[20-27]
3. We found **MIXED** evidence for whether or not adults who use marijuana and alcohol combined are at a higher risk of non-driving related injury than those who use either substance alone.[23,24,27-29]
4. We found **MIXED** evidence for whether or not adults who use marijuana are at a higher risk of injury due to recreational activity.[28,30,31]

Burns

5. We found **LIMITED** evidence that home extraction of hash oil has resulted in cases of severe burns requiring hospitalization.[32-36] (Added*)
6. We found **LIMITED** evidence that electronic smoking devices have failed (exploded), resulting in cases of trauma and burn injury.[37-39] (Added*)
7. We found **INSUFFICIENT** evidence to determine whether or not there is an association between marijuana-use in the past 30-days and burn injury.[40] (Added*)

Physical dating violence

8. We found **LIMITED** evidence that marijuana use is associated with physical dating violence perpetration (PDVP) by adolescent girls.[41-44] (Added*)
9. We found **LIMITED** evidence that marijuana use is associated with physical dating violence victimization (PDVV) among adolescent boys.[45-47] (Added*)
10. We found **MIXED** evidence for whether or not marijuana use is associated with physical dating violence perpetration (PDVP) by adolescent boys.[43,44] (Added*)
11. We found **MIXED** evidence for whether or not marijuana use is associated with physical dating violence victimization (PDVV) among adolescent girls .[41,45,46] (Added*)
12. We found a **LIMITED** body of research that failed to show an association between marijuana use and physical dating violence perpetration (PDVP) by young adult men.[48,49] (Added*)
13. We found a **LIMITED** body of research that failed to show an association between marijuana use and physical dating violence perpetration (PDVP) by young adult women.[41,48,50,51] (Added*)
14. We found **INSUFFICIENT** evidence to determine whether or not marijuana use is associated with physical dating violence victimization (PDVV) among young adults.[52] (Added*)

* Revised = the statement has been adjusted since the 2014 edition of the report, due to new evidence. Added = the statement is new since the 2014 edition of the report. See Appendix M for dates of most recent literature review

Public health statements

Public health recommendations have been suggested and approved by the Retail Marijuana Public Health Advisory Committee with the goals of: 1) Improving knowledge regarding population-based health effects of retail marijuana use and 2) Developing and targeting public health education and prevention strategies for high-risk sub populations.

1. Marijuana use may be associated with increased risk of non-driving related workplace injuries.
2. There is conflicting research on whether or not marijuana use alone or combined with alcohol increases the risk of other non-driving related injury among adults.
3. Use caution when driving, biking, or performing other safety-sensitive activities after using any form of marijuana or marijuana product.
4. Electronic smoking or vaporizing devices can explode, causing serious injury. (Added*)
5. Extracting hash oil yourself with flammable substances can cause severe burns requiring hospitalization. (Added*)
6. Marijuana use by adolescent girls may be associated with a higher risk of committing physical violence against their dating partners. Marijuana use by adolescent boys may be associated with a higher risk of being the victim of physical violence from their dating partners.

* *Revised = the statement has been adjusted since the 2014 edition of the report, due to new evidence. Added = the statement is new since the 2014 edition of the report. See Appendix M for dates of most recent literature review.

Public health recommendations

Public health recommendations have been suggested and approved by the Retail Marijuana Public Health Advisory Committee with the goals of: 1) improving knowledge regarding population-based health effects of retail marijuana use, 2) developing and targeting public health education and prevention strategies for high-risk subpopulations.

Data quality

- Accurately record timing of THC blood testing, relevant to recreational, workplace or any other injury requiring medical attention, and specify marijuana use as distinct from other substances.
- Use better quality measure of marijuana use exposure, for example, blood THC levels instead of self-reported marijuana use, for studies of impairment and accidents.
- Ensure quality description of burns related to marijuana use or production.
- Improve the measures of marijuana exposure used in population-based studies.
- Report measures of association separately by age group (e.g. adolescent, young adult), sex, and other characteristics that may lead to differing findings.

Surveillance

- Improve and centralize reporting of blood THC levels (not just presence/absence of THC) for trauma and workplace injury surveillance.
- Develop small-scale surveillance projects to assess the use of marijuana among those injured in recreational activities.
- Monitor incidence of recreational injuries related to marijuana use.
- Monitor incidence of workplace injuries related to marijuana production or use.
- Monitor the prevalence of marijuana use and incidence of fall-related injuries among older adults.
- Monitor incidence of injuries caused by electronic device explosions and hash oil extraction explosions.

Education

- Educate the public on marijuana-related impairment, including related risks of recreational injuries, workplace injuries and falls in older adults.
- Educate the public about the potential hazards of exploding electronic smoking devices.
- Educate the public on the hazards and laws pertaining to at-home hash oil extraction.
- Expand public education about the link between marijuana use and risk behaviors among adolescents and young adults.

Research gaps

The Retail Marijuana Public Health Advisory Committee identifies important gaps in the scientific literature that may impact public health policies and prevention strategies. Colorado should support unbiased research to help fill the following research gaps identified by the committee.

- Research to further clarify the relationship of saliva and urine levels to blood levels and relationship of all biomarkers to measures of functional impairment.
- Study differences in impairment based on frequency of use/tolerance.
- Develop studies to evaluate risk of burn injuries among marijuana users.
- Study consumer product safety of electronic smoking devices.
- Increase the number of studies that examine marijuana use as a predictor of risk behaviors, especially among adolescents, college attending young adults and non-college attending young adults.
- Identify the independent effect of marijuana use on adolescent risk behaviors, adjusting for alcohol use and other potential confounders.

References

1. Colorado Department of Public Health and Environment. Workplace safety data and reports. 2016; https://www.colorado.gov/pacific/cdphe/workplace-safety-data-and-reports. Accessed December 27, 2016.
2. Outdoor Industry Association. *The Outdoor Recreation Economy: Colorado*. 2012.
3. Development Research Partners Inc. and Progress Colorado. Tourism continues as state's economic cornerstone. 2015; http://progressco.org/recreation-tourism-overview/. Accessed December 28, 2016.
4. CDC WONDER. About Underlying Cause of Death, 1999-2015. http://wonder.cdc.gov/ucd-icd10.html: Centers for Disease Control and Prevention.
5. Grotenhermen F. Pharmacokinetics and pharmacodynamics of cannabinoids. *Clin Pharmacokinet*. 2003;42(4):327-360.
6. Hall W, Degenhardt L. Adverse health effects of non-medical cannabis use. *Lancet*. 2009;374(9698):1383-1391.
7. Rocky Mountain High Intensity Drug Trafficing Area. *The Legalization of Marijuana in Colorado: The Impact*. September 2015 2015.
8. Whaley M. Some Colorado smokers burned by exploding e-cigarettes. *The Denver Post*. February 7, 2016, 2016.
9. Glaser A. Vape Pens and E-Cigs Are Blowing Up. Like, Literally. *Wired*, https://www.wired.com/2016/02/exploding-e-cigs-and-vape-pens/2016.
10. Eltman F. E-cigarette fires and injuries are on the rise, with faulty batteries suspected. *The Denver Post*. December 14, 2016, 2016.
11. Rothman EF, Xuan Z. Trends in Physical Dating Violence Victimization Among U.S. High School Students, 1999-2011. *J Sch Violence*. 2014;13(3):277-290.
12. Black MC, Basile, K.C., Breiding, M.J., Smith, S.G., Walters, M.L., Merrick, M.T., Chen, J., & Stevens, M.R. *The National Intimate Partner and Sexual Violence Survey (NISVS): 2010 Summary Report*. Atlanta, GA: National Center for Injury Prevention and Control, Centers for Disease Control and Prevention;2011.
13. Fletcher J. The effects of intimate partner violence on health in young adulthood in the United States. *Soc Sci Med*. 2010;70(1):130-135.
14. Bonomi AE, Anderson ML, Nemeth J, Rivara FP, Buettner C. History of dating violence and the association with late adolescent health. *BMC Public Health*. 2013;13:821.
15. Ackard DM, Eisenberg ME, Neumark-Sztainer D. Long-term impact of adolescent dating violence on the behavioral and psychological health of male and female youth. *J Pediatr*. 2007;151(5):476-481.
16. Foran HM, O'Leary KD. Alcohol and intimate partner violence: a meta-analytic review. *Clin Psychol Rev*. 2008;28(7):1222-1234.
17. Leonard KE. Alcohol and intimate partner violence: when can we say that heavy drinking is a contributing cause of violence? *Addiction*. 2005;100(4):422-425.
18. Shipp EM, Tortolero SR, Cooper SP, Baumler EG, Weller NF. Substance use and occupational injuries among high school students in South Texas. *Am J Drug Alcohol Abuse*. 2005;31(2):253-265.
19. Price JW. Marijuana and workplace safety: an examination of urine drug tests. *J Addict Dis*. 2014;33(1):24-27.

20. Wadsworth EJK, Moss SC, Simpson Sa, Smith aP. A community based investigation of the association between cannabis use, injuries and accidents. *Journal of psychopharmacology (Oxford, England)*. 2006;20(1):5-13.

21. Polen MR, Sidney S, Tekawa IS, Sadler M, Friedman GD. Health care use by frequent marijuana smokers who do not smoke tobacco. *West J Med*. 1993;158(6):596-601.

22. Barrio G, Jiménez-Mejías E, Pulido J, Lardelli-Claret P, Bravo MJ, de la Fuente L. Association between cannabis use and non-traffic injuries. *Accid Anal Prev*. 2012;47:172-176.

23. Gerberich S. Marijuana Use and Injury Events Resulting in Hospitalization. *Annals of Epidemiology*. 2003;13(4):230-237.

24. Gmel G, Kuendig H, Rehm J, Schreyer N, Daeppen J-B. Alcohol and cannabis use as risk factors for injury--a case-crossover analysis in a Swiss hospital emergency department. *BMC Public Health*. 2009;9(1):40-40.

25. Tait RJ, Anstey KJ, Butterworth P. Incidence of self-reported brain injury and the relationship with substance abuse: findings from a longitudinal community survey. *BMC Public Health*. 2010;10(1):171-171.

26. Braun BL, Tekawa IS, Gerberich SG, Sidney S. Marijuana Use and Medically Attended Injury Events. *Ann Emerg Med*. 1998;32(3):353-360.

27. Vinson DC. Marijuana and other illicit drug use and the risk of injury: A case-control study. *Mo Med*. 2006;103(2):152-156.

28. Asbridge M, Mann R, Cusimano MD, Tallon JM, Pauley C, Rehm J. Cycling-related crash risk and the role of cannabis and alcohol: a case-crossover study. *Preventive Medicine*. 2014;66:80-86.

29. Woolard R, Nirenberg TD, Becker B, et al. Marijuana Use and Prior Injury among Injured Problem Drinkers. *Academic Emergency Medicine*. 2003;10(1):43-51.

30. Siwani R, Tombers NM, Rieck KL, Cofer SA. Comparative analysis of fracture characteristics of the developing mandible: the Mayo Clinic experience. *International journal of pediatric otorhinolaryngology*. 2014;78(7):1066-1070.

31. Chiolero A, Schmid H. Repeated self-reported injuries and substance use among young adolescents: the case of Switzerland. *Sozial- und Präventivmedizin*. 2002;47(5):289-297.

32. Bell C, Slim J, Flaten HK, Lindberg G, Arek W, Monte AA. Butane Hash Oil Burns Associated with Marijuana Liberalization in Colorado. *J Med Toxicol*. 2015;11(4):422-425.

33. Jensen G, Bertelotti R, Greenhalgh D, Palmieri T, Maguina P. Honey oil burns: a growing problem. *J Burn Care Res*. 2015;36(2):e34-37.

34. Porter CJ, Armstrong JR. Burns from illegal drug manufacture: case series and management. *J Burn Care Rehabil*. 2004;25(3):314-318.

35. Schneberk T, Valenzuela RG, Sterling G, Mallon WK. Hot Wax. *JEMS*. 2015;40(9):44-47, 52.

36. Williams GD. Hash-oil manufacture: an important factor in the occurrence of adult burns in Jamaica. *West Indian Med J*. 1988;37(4):210-214.

37. Colaianni CA, Tapias LF, Cauley R, Sheridan R, Schulz JT, Goverman J. Injuries Caused by Explosion of Electronic Cigarette Devices. *Eplasty*. 2016;16:ic9.

38. Roger JM, Abayon M, Elad S, Kolokythas A. Oral Trauma and Tooth Avulsion Following Explosion of E-Cigarette. *J Oral Maxillofac Surg*. 2016;10.1016/j.joms.2015.12.017.

39. United States Fire Administration. Electronic Cigarette Fires and Explosions. October 2014.

40. Jehle CC, Jr., Nazir N, Bhavsar D. The rapidly increasing trend of cannabis use in burn injury. *J Burn Care Res*. 2015;36(1):e12-17.

41. Epstein-Ngo QM, Cunningham RM, Whiteside LK, et al. A daily calendar analysis of substance use and dating violence among high risk urban youth. *Drug Alcohol Depend*. 2013;130(1-3):194-200.

42. Foshee VA, Reyes HL, Ennett ST. Examination of Sex and Race Differences in Longitudinal Predictors of the Initiation of Adolescent Dating Violence Perpetration. *J Aggress Maltreat Trauma*. 2010;19(5):492-516.

43. McNaughton Reyes HL, Foshee VA, Bauer DJ, Ennett ST. Proximal and time-varying effects of cigarette, alcohol, marijuana and other hard drug use on adolescent dating aggression. *J Adolesc*. 2014;37(3):281-289.

44. Rothman EF, Johnson RM, Azrael D, Hall DM, Weinberg J. Perpetration of physical assault against dating partners, peers, and siblings among a locally representative sample of high school students in Boston, Massachusetts. *Arch Pediatr Adolesc Med*. 2010;164(12):1118-1124.

45. Eaton DK, Davis KS, Barrios L, Brener ND, Noonan RK. Associations of dating violence victimization with lifetime participation, co-occurrence, and early initiation of risk behaviors among U.S. high school students. *J Interpers Violence*. 2007;22(5):585-602.

46. Shorey RC, Fite PJ, Choi H, Cohen JR, Stuart GL, Temple JR. Dating Violence and Substance Use as Longitudinal Predictors of Adolescents' Risky Sexual Behavior. *Prev Sci*. 2015;16(6):853-861.

47. Yan FA, Howard DE, Beck KH, Shattuck T, Hallmark-Kerr M. Psychosocial correlates of physical dating violence victimization among Latino early adolescents. *J Interpers Violence*. 2010;25(5):808-831.

48. Nabors EL. Drug use and intimate partner violence among college students: an in-depth exploration. *J Interpers Violence*. 2010;25(6):1043-1063.

49. Shorey RC, Stuart GL, McNulty JK, Moore TM. Acute alcohol use temporally increases the odds of male perpetrated dating violence: a 90-day diary analysis. *Addict Behav*. 2014;39(1):365-368.

50. Shorey RC, Stuart GL, Moore TM, McNulty JK. The temporal relationship between alcohol, marijuana, angry affect, and dating violence perpetration: A daily diary study with female college students. *Psychol Addict Behav*. 2014;28(2):516-523.

51. Testa M, Hoffman JH, Leonard KE. Female intimate partner violence perpetration: stability and predictors of mutual and nonmutual aggression across the first year of college. *Aggress Behav*. 2011;37(4):362-373.

52. Melander LA, Noel H, Tyler KA. Bidirectional, unidirectional, and nonviolence: a comparison of the predictors among partnered young adults. *Violence Vict*. 2010;25(5):617-630.

Section 2

Scientific Literature Review on Potential Health Effects of Marijuana Use

Chapter 9

Marijuana Use and Neurological, Cognitive and Mental Health Effects

Retail Marijuana Public Health Advisory Committee

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Introduction

The Retail Marijuana Public Health Advisory Committee identified many important public health topics related to marijuana and has reviewed the scientific evidence currently available regarding those topics. This chapter includes reviews of the potential relationships between marijuana use and cognitive impairment, mental health disorders and substance abuse.

Many adults in the United States suffer from some form of mental illness. In 2015, approximately 18 percent of the adult U.S. population (43 million people), had a diagnosable mental, behavioral, or emotional disorder, according to the National Survey on Drug Use and Health.[1] While the effects of these disorders can range from mild impairment to severe disability, all have a detrimental individual impact. In addition, these disorders place a considerable financial burden on our health care system. The extent and impact of cognitive impairment is difficult to measure among the general adult population. Many adults may not realize if they have a cognitive impairment. Those who do may downplay and attempt to compensate for it, but cognitive impairments can greatly affect a person's quality of life.

Some researchers have suggested that marijuana use can cause lasting cognitive impairment or mental health disorders such as anxiety, depression, and psychosis. Known acute effects of marijuana use include fragmented thinking, disturbed memory, reduced motor coordination, anxiety and distorted awareness.[2,3] It is conceivable that ongoing marijuana use might cause some of these effects to be long-lasting. Many adults in Colorado use marijuana. Analysis of 2015 survey data, completed for this report, estimated that 13 percent of Colorado adults 18 years and older have used marijuana within the last month. About 6 percent use marijuana daily or near-daily. With at least one in 10 adults using marijuana, nearly one in five having a mental health disorder, and an uncertain number with cognitive impairment; it is extremely important to investigate the relationships between marijuana use, cognitive functioning and mental health.

Definitions

Levels of marijuana use

- Daily or near-daily use: 5-7 days/week.
- Weekly use: 1-4 days/week.
- Less-than-weekly use: less than 1 day/week.
- Acute use: used within the past few hours, such that the short-term effects or symptoms are still being experienced.

Cannabis use disorder - a formal diagnosis indicating two or more of these factors: hazardous use, social/interpersonal problems related to use, neglects major roles in order to use, legal problems, withdrawal, tolerance, uses more or longer than planned, repeated attempts to quit or reduce use, much time is spent using, physical or psychological problems related to use, and/or gives up activities in order to use;[4] commonly called addiction.

Dabbing - a method of marijuana use where a "dab" (small amount) of marijuana concentrate is placed on a pre-heated surface, creating concentrated marijuana vapor to be inhaled.

Marijuana addiction - an informal term which is more commonly used than cannabis use disorder, but the two are considered equivalent by the committee and many mental health professionals.

Psychotic disorders – these include schizophrenia, schizoaffective, schizophreniform, schizotypal, and delusional disorders. These formal diagnoses are made when a combination of psychotic symptoms are

present (possibly combined with other mental health symptoms), the symptoms cause significant problems with work, relationships or self-care, and they have been present for six months or longer.[4]

Psychotic symptoms - these include auditory or visual hallucinations, difficulty separating real from imagined, perception that self or others can read minds, perceived ability to predict the future, feeling that an outside force is controlling thoughts or actions, fear that someone intends to harm them, belief they have supernatural gifts, apathy, social withdrawal, absent or blunted emotions, occurrences of unclear speech or inability to speak, or difficulty organizing thoughts to complete activities.[4]

Tetrahydrocannabinol (THC) - the main psychoactive component of marijuana.

Key findings

Strong evidence shows that daily or near-daily marijuana users are more likely to have impaired memory lasting a week or more after quitting. Evidence regarding other cognitive effects is either lacking or the results are mixed. An important acute effect of THC, the primary psychoactive component of marijuana, is psychotic symptoms, such as hallucinations, paranoia, delusional beliefs and feeling emotionally unresponsive during intoxication. These symptoms are worse with higher doses. Furthermore, daily or near-daily marijuana use is associated with developing a psychotic disorder such as schizophrenia. There is limited evidence that use of more potent marijuana is also associated with developing a psychotic disorder. Finally, marijuana users can develop cannabis use disorder (addiction‡) and daily or near-daily marijuana users can experience withdrawal symptoms when abstaining from marijuana. Evidence also shows there are treatments for marijuana addiction‡ that can reduce use and dependence.

An important note for all key findings is that the available research evaluated the **association** between marijuana use and potential adverse health outcomes. This **association** does not prove that the marijuana use alone **caused** the effect. Despite the best efforts of researchers to account for confounding factors, there may be other important factors related to **causality** that were not identified. In addition, marijuana use was illegal everywhere in the United States prior to 1996. Research funding, when appropriated, was commonly sought to identify adverse effects from marijuana use. This legal fact introduces both funding bias and publication bias into the body of literature related to marijuana use. The Retail Marijuana Public Health Advisory Committee recognizes the limitations and biases inherent in the published literature and made efforts to ensure the information reviewed and synthesized is reflective of the current state of medical knowledge. Where information was lacking – for whatever reason – the committee identified this knowledge gap and recommended further research. This information will be updated as new research becomes available.

Recommendations

Several important public health recommendations were identified. To facilitate future study on the effects of marijuana, it is important to improve data quality by systematically collecting information on the frequency, amount, potency, and method of marijuana use in both public health surveillance and clinical settings. To that end, improved measures of marijuana use and cumulative marijuana exposure should be developed and standardized. It also is important to better characterize the prevalence and patterns of marijuana use among Colorado adults, including breakdowns by age and other demographics. To better assess potential adverse outcomes, adult hospitalizations and emergency department visits related to marijuana use should be monitored using de-identified data available from the Colorado Hospital Association. Addiction[‡] treatment admissions should be monitored using data from the Colorado Office of Behavioral Health.

High-quality educational materials on the potential cognitive and mental health effects of marijuana use should be developed and distributed, including the risk specific to daily or near-daily marijuana use and use of high potency marijuana. The public should also be educated on the signs of marijuana abuse and addiction[‡] and treatment should be made available and accessible.

The committee also identified a number of important research gaps. Long-term studies on mental health and cognitive effects of marijuana use would help assess temporality and clarify associations. These should have well defined marijuana-use histories and evaluation of study groups with different levels or methods of marijuana use. Research should thoroughly identify potential confounding variables and measure and adjust for them. Studies using longer periods of abstinence are needed to evaluate the potential long-term effects in former users. Of special importance in Colorado, research studies are needed to determine the potential effects of higher potency marijuana and the effects of different methods of use (e.g., dabbing, edibles). Finally, there is no literature examining the potential adverse effects of other important cannabinoids such as cannabidiol (CBD).

[‡] In this document, the term marijuana addiction is considered equivalent to cannabis use disorder (and addiction to another substance is considered equivalent to use disorder for that substance).

Table 1 Findings summary: Marijuana use and neurological, cognitive, and mental health effects

For an explanation of the classifications "Substantial," "Moderate," etc., see Chapter 7. Systematic literature review process.

	Substantial	Moderate	Limited	Insufficient	Mixed
Cognitive effects	Impaired memory for at least 7 days (daily or near-daily users)		Impaired decision-making up to 2 days after last use (weekly users)		Impaired executive functioning after short abstinence
					Cognitive impairment for at least 28 days (daily or near-daily users)
Mental health effects	Acute psychotic symptoms during intoxication	Psychotic disorder in adulthood (daily or near-daily users)	Diagnosis of psychotic disorder with use of potent marijuana	Bipolar Disorder diagnosis	Depression or Anxiety symptoms or diagnosis
			Failure to show psychotic symptoms or disorder with less-than-weekly use		
Substance use and addiction	Can develop marijuana addiction‡				
	Daily or near-daily users may experience withdrawal symptoms				
	Treatment of marijuana addiction‡ can reduce use and dependence				

‡In this document, the term marijuana addiction is considered equivalent to cannabis use disorder (and addiction to another substance is considered equivalent to use disorder for that substance).

Evidence statements

Evidence statements are based on systematic scientific literature reviews performed by Colorado Department of Public Health and Environment staff with oversight and approval by the Retail Marijuana Public Health Advisory Committee. For an explanation of the classifications "Substantial," "Moderate," etc., see Chapter 7. Systematic literature review process. For details about the studies reviewed, see Appendix N.

Cognitive effects

1. We found **SUBSTANTIAL** evidence that adults who use marijuana daily or near-daily are more likely than non-users to have memory impairments for at least seven days after last use.[5-13]

2. We found **LIMITED** evidence that adults who use marijuana weekly are more likely than non-users to have impaired decision-making lasting up to two days after last use. [11,14]

3. We found **MIXED** evidence for whether or not adults who use marijuana are more likely than non-users to have impaired executive functioning, after not using for a short time.[5,6,8,9]

4. We found **MIXED** evidence for whether or not adults who use marijuana daily or near-daily are more likely than non-users to have impairment of memory or other cognitive functions for at least 28 days after last use.[6,8,15-17]

Mental health effects

5. We found **MIXED** evidence for whether or not adults who use marijuana are more likely than non-users to have symptoms or diagnosis of depression or anxiety.[18-25] (Revised*)

6. We found **INSUFFICIENT** evidence to determine whether or not adults who use marijuana are more likely than non-users to have symptoms or diagnosis of bipolar disorder.[21,22] (Added*)

7. We found **SUBSTANTIAL** evidence that THC intoxication can cause acute psychotic symptoms, which are worse with higher doses.[26-31]

8. We found **MODERATE** evidence that adults who use marijuana daily or near-daily are more likely than non-users to be diagnosed with a psychotic disorder, such as schizophrenia.[32-34] (Revised*)

9. We found **LIMITED** evidence that individuals who use more potent marijuana (>10% THC) are more likely than non-users to be diagnosed with a psychotic disorder, such as schizophrenia.[32,33] (Added*)

10. We found a **LIMITED** body of research that failed to show an association between less-than-weekly marijuana use and psychotic symptoms or disorders.[30,31,35] (Added*)

* Revised = the statement has been adjusted since the 2014 edition of the report, due to new evidence. Added = the statement is new since the 2014 edition of the report. See Appendix N for dates of most recent literature review.

Substance use, abuse and addiction

11. We found **SUBSTANTIAL** evidence that marijuana users can develop cannabis use disorder.[36-38] (Added*)
12. We found **SUBSTANTIAL** evidence that individuals who use marijuana daily or near-daily can experience withdrawal symptoms when abstaining from marijuana.[39-46] (Added*)
13. We found **SUBSTANTIAL** evidence that some marijuana users who receive treatment for cannabis use disorder (including cognitive behavioral therapy, motivational enhancement/interviewing, multidimensional family therapy, and/or abstinence-based contingency management) can decrease their marijuana use and dependence.[47-54] (Added*)

Public health statements

Public health statements are plain language translations of the major findings (Evidence Statements) from systematic literature reviews. These statements have been officially approved by the Retail Marijuana Public Health Advisory Committee.

1. Daily or near-daily use of marijuana is strongly associated with impaired memory, persisting a week or more after quitting.
2. THC, a component of marijuana, can cause acute psychotic symptoms such as hallucinations, paranoia, delusional beliefs, and feeling emotionally unresponsive during intoxication. These symptoms are worse with higher doses.
3. Daily or near-daily use of marijuana is associated with development of psychotic disorders such as schizophrenia. (Added*)
4. Marijuana users can become addicted‡ to marijuana. (Added*)
5. Daily or near-daily marijuana users can experience withdrawal symptoms when abstaining. (Added*)
6. There are treatments for marijuana addiction‡ that can reduce use and dependence. (Added*)

* Revised = the statement has been adjusted since the 2014 edition of the report, due to new evidence. Added = the statement is new since the 2014 edition of the report. See Appendix N for dates of most recent literature review.
‡ In this document, the term marijuana addiction is considered equivalent to cannabis use disorder (and addiction to another substance is considered equivalent to use disorder for that substance).

Public health recommendations

Public health recommendations have been suggested and approved by the Retail Marijuana Public Health Advisory Committee with the goals of: 1) Improving knowledge regarding population-based health effects of retail marijuana use and 2) Developing and targeting public health education and prevention strategies for high-risk sub populations.

Data quality issues

- Standardize and improve data collection on potency, amount, frequency and method of marijuana use in medical records and other surveillance data sources.
- Specify marijuana use as separate from other drug use in medical records and other surveillance data sources.
- Improved measures to determine levels of marijuana use and cumulative marijuana exposure.
- Provide power calculations for smaller studies.

Surveillance

- Monitor adult patterns of use through surveys such as the Behavioral Risk Factor Surveillance Survey (BRFSS), including breakdowns by age and other demographics.
- Population-based monitoring of mental health conditions through surveys such as the Behavioral Risk Factor Surveillance System (BRFSS)
- Monitor marijuana-related hospitalizations and emergency department visits.
- Evaluate prevalence of cannabis use disorder and monitor trends and treatment rates, including breakdowns by age and other demographics.
- Evaluate prevalence of schizophrenia and monitor trends, including breakdowns by age and other demographics.

Education

- Public education concerning the potential cognitive and mental health effects of marijuana use.
- Communicate potential risks associated with daily or near-daily use and use of potent marijuana.
- Promote accurate information about cannabis use disorder.
- Promote availability and access to treatment for cannabis use disorder.

Research gaps

The Retail Marijuana Public Health Advisory Committee identifies important gaps in the scientific literature that may impact public health policies and prevention strategies. Colorado should support unbiased research to help fill the following research gaps identified by the committee.

- Longitudinal studies on mental health and cognitive effects to assess temporality.
- Expand evaluation of covariates and make proper statistical adjustments to account for their effects.
- Evaluate and provide information on the potency of marijuana in future studies and if different potencies are involved, categorize them and conduct separate analyses.
- Effects of higher potency marijuana, especially dabbing (high-dose rate).
- Effects of different methods of marijuana use.
- Effects of other cannabinoids, especially cannabidiol (CBD).
- More on duration of impact (after various lengths of abstinence).
- More studies are needed to assess the risk of increasing use or developing cannabis use disorder among groups with different levels of use, especially among users who use less-than-weekly.

References

1. United States Department of Health and Human Services; Substance Abuse and Mental Health Services Administration. *Key Substance Use and Mental Health Indicators in the United States: Results from the 2015 National Survey on Drug Use and Health*. September 2016.
2. Grotenhermen F. Pharmacokinetics and pharmacodynamics of cannabinoids. *Clin Pharmacokinet*. 2003;42(4):327-360.
3. Hall W, Degenhardt L. Adverse health effects of non-medical cannabis use. *Lancet*. 2009;374(9698):1383-1391.
4. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed. Washington , DC2013.
5. Solowij N. Cognitive Functioning of Long-term Heavy Cannabis Users Seeking Treatment. *JAMA*. 2002;287(9):1123-1123.
6. Bolla KI, Brown K, Eldreth D, Tate K, Cadet JL. Dose-related neurocognitive effects of marijuana use. *Neurology*. 2002;59(9):1337-1343.
7. Roebke PV, Vadhan NP, Brooks DJ, Levin FR. Verbal learning in marijuana users seeking treatment: a comparison between depressed and non-depressed samples. *Am J Drug Alcohol Abuse*. 2014;10.3109/00952990.2013.875551:1-6.
8. Thames AD, Arbid N, Sayegh P. Cannabis use and neurocognitive functioning in a non-clinical sample of users. *Addict Behav*. 2014;39(5):994-999.
9. Sanchez-Torres AM, Basterra V, Rosa A, et al. Lifetime cannabis use and cognition in patients with schizophrenia spectrum disorders and their unaffected siblings. *European Archives of Psychiatry and Clinical Neuroscience*. 2013;263(8):643-653.
10. Rodgers J, Buchanan T, Scholey AB, Heffernan TM, Ling J, Parrott A. Differential effects of Ecstasy and cannabis on self-reports of memory ability: a web-based study. *Hum Psychopharmacol*. 2001;16(8):619-625.
11. Tamm L, Epstein JN, Lisdahl KM, et al. Impact of ADHD and cannabis use on executive functioning in young adults. *Drug Alcohol Depend*. 2013;133(2):607-614.
12. Pope HG, Jr., Gruber AJ, Hudson JI, Huestis MA, Yurgelun-Todd D. Neuropsychological performance in long-term cannabis users. *Arch Gen Psychiatry*. 2001;58(10):909-915.
13. Schoeler T, Kambeitz J, Behlke I, Murray R, Bhattacharyya S. The effects of cannabis on memory function in users with and without a psychotic disorder: findings from a combined meta-analysis. *Psychol Med*. 2016;46(1):177-188.
14. Fridberg DJ, Queller S, Ahn WY, et al. Cognitive Mechanisms Underlying Risky Decision-Making in Chronic Cannabis Users. *J Math Psychol*. 2010;54(1):28-38.
15. Pope HG, Gruber AJ, Hudson JI, Huestis MA, Yurgelun-Todd D. Neuropsychological Performance in Long-term Cannabis Users. *Arch Gen Psychiatry*. 2001;58(10):909-909.
16. Smith MJ, Cobia DJ, Wang L, et al. Cannabis-related working memory deficits and associated subcortical morphological differences in healthy individuals and schizophrenia subjects. *Schizophr Bull*. 2014;40(2):287-299.
17. Bayrakci A, Sert E, Zorlu N, Erol A, Saricicek A, Mete L. Facial emotion recognition deficits in abstinent cannabis dependent patients. *Compr Psychiatry*. 2015;58:160-164.
18. Lev-Ran S, Roerecke M, Le Foll B, George TP, McKenzie K, Rehm J. The association between cannabis use and depression: a systematic review and meta-analysis of longitudinal studies. *Psychol Med*. 2014;44(4):797-810.

19. Pacek LR, Martins SS, Crum RM. The bidirectional relationships between alcohol, cannabis, co-occurring alcohol and cannabis use disorders with major depressive disorder: results from a national sample. *J Affect Disord*. 2013;148(2-3):188-195.

20. Choi NG, DiNitto DM, Marti CN. Risk Factors for Self-reported Driving Under the Influence of Alcohol and/or Illicit Drugs Among Older Adults. *Gerontologist*. 2014;10.1093/geront/gnu070.

21. Cougle JR, Hakes JK, Macatee RJ, Chavarria J, Zvolensky MJ. Quality of life and risk of psychiatric disorders among regular users of alcohol, nicotine, and cannabis: An analysis of the National Epidemiological Survey on Alcohol and Related Conditions (NESARC). *J Psychiatr Res*. 2015;66-67:135-141.

22. Feingold D, Weiser M, Rehm J, Lev-Ran S. The association between cannabis use and mood disorders: A longitudinal study. *J Affect Disord*. 2015;172:211-218.

23. Huijbregts SC, Griffith-Lendering MF, Vollebergh WA, Swaab H. Neurocognitive moderation of associations between cannabis use and psychoneuroticism. *J Clin Exp Neuropsychol*. 2014;36(8):794-805.

24. Schuler MS, Vasilenko SA, Lanza ST. Age-varying associations between substance use behaviors and depressive symptoms during adolescence and young adulthood. *Drug Alcohol Depend*. 2015;157:75-82.

25. Kedzior KK, Laeber LT. A positive association between anxiety disorders and cannabis use or cannabis use disorders in the general population- a meta-analysis of 31 studies. *BMC Psychiatry*. 2014;14(1):136.

26. D'Souza DC, Perry E, MacDougall L, et al. The psychotomimetic effects of intravenous delta-9-tetrahydrocannabinol in healthy individuals: implications for psychosis. *Neuropsychopharmacology*. 2004;29(8):1558-1572.

27. Morrison PD, Zois V, McKeown DA, et al. The acute effects of synthetic intravenous Delta9-tetrahydrocannabinol on psychosis, mood and cognitive functioning. *Psychol Med*. 2009;39(10):1607-1616.

28. Morrison PD, Stone JM. Synthetic delta-9-tetrahydrocannabinol elicits schizophrenia-like negative symptoms which are distinct from sedation. *Hum Psychopharmacol*. 2011;26(1):77-80.

29. Englund A, Atakan Z, Kralj A, Tunstall N, Murray R, Morrison P. The effect of five day dosing with THCV on THC-induced cognitive, psychological and physiological effects in healthy male human volunteers: A placebo-controlled, double-blind, crossover pilot trial. *J Psychopharmacol*. 2016;30(2):140-151.

30. Mason O, Morgan CJ, Dhiman SK, et al. Acute cannabis use causes increased psychotomimetic experiences in individuals prone to psychosis. *Psychol Med*. 2009;39(6):951-956.

31. Morgan CJ, Rothwell E, Atkinson H, Mason O, Curran HV. Hyper-priming in cannabis users: a naturalistic study of the effects of cannabis on semantic memory function. *Psychiatry Res*. 2010;176(2-3):213-218.

32. van Os J, Bak M, Hanssen M, Bijl RV, de Graaf R, Verdoux H. Cannabis use and psychosis: a longitudinal population-based study. *Am J Epidemiol*. 2002;156(4):319-327.

33. Di Forti M, Marconi A, Carra E, et al. Proportion of patients in south London with first-episode psychosis attributable to use of high potency cannabis: a case-control study. *Lancet Psychiatry*. 2015;2(3):233-238.

34. Giordano GN, Ohlsson H, Sundquist K, Sundquist J, Kendler KS. The association between cannabis abuse and subsequent schizophrenia: a Swedish national co-relative control study. *Psychol Med*. 2015;45(2):407-414.

35. Van Dam NT, Earleywine M, DiGiacomo G. Polydrug use, cannabis, and psychosis-like symptoms. *Hum Psychopharmacol*. 2008;23(6):475-485.

36. Hasin DS, Saha TD, Kerridge BT, et al. Prevalence of Marijuana Use Disorders in the United States Between 2001-2002 and 2012-2013. *JAMA Psychiatry*. 2015;72(12):1235-1242.

37. Lopez-Quintero C, Perez de los Cobos J, Hasin DS, et al. Probability and predictors of transition from first use to dependence on nicotine, alcohol, cannabis, and cocaine: results of the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC). *Drug Alcohol Depend*. 2011;115(1-2):120-130.

38. Schuermeyer J, Salomonsen-Sautel S, Price RK, et al. Temporal trends in marijuana attitudes, availability and use in Colorado compared to non-medical marijuana states: 2003-11. *Drug Alcohol Depend*. 2014;140:145-155.

39. Budney AJ, Moore BA, Vandrey RG, Hughes JR. The time course and significance of cannabis withdrawal. *J Abnorm Psychol*. 2003;112(3):393-402.

40. Budney AJ, Novy PL, Hughes JR. Marijuana withdrawal among adults seeking treatment for marijuana dependence. *Addiction*. 1999;94(9):1311-1322.

41. Budney AJ, Radonovich KJ, Higgins ST, Wong CJ. Adults seeking treatment for marijuana dependence: a comparison with cocaine-dependent treatment seekers. *Exp Clin Psychopharmacol*. 1998;6(4):419-426.

42. Budney AJ, Vandrey RG, Hughes JR, Moore BA, Bahrenburg B. Oral delta-9-tetrahydrocannabinol suppresses cannabis withdrawal symptoms. *Drug Alcohol Depend*. 2007;86(1):22-29.

43. Budney AJ, Vandrey RG, Hughes JR, Thostenson JD, Bursac Z. Comparison of cannabis and tobacco withdrawal: severity and contribution to relapse. *J Subst Abuse Treat*. 2008;35(4):362-368.

44. Vandrey R, Budney AJ, Kamon JL, Stanger C. Cannabis withdrawal in adolescent treatment seekers. *Drug Alcohol Depend*. 2005;78(2):205-210.

45. Vandrey RG, Budney AJ, Hughes JR, Liguori A. A within-subject comparison of withdrawal symptoms during abstinence from cannabis, tobacco, and both substances. *Drug Alcohol Depend*. 2008;92(1-3):48-54.

46. Vandrey RG, Budney AJ, Moore BA, Hughes JR. A cross-study comparison of cannabis and tobacco withdrawal. *Am J Addict*. 2005;14(1):54-63.

47. Budney AJ, Higgins ST, Radonovich KJ, Novy PL. Adding voucher-based incentives to coping skills and motivational enhancement improves outcomes during treatment for marijuana dependence. *J Consult Clin Psychol*. 2000;68(6):1051-1061.

48. Copeland J, Swift W, Roffman R, Stephens R. A randomized controlled trial of brief cognitive-behavioral interventions for cannabis use disorder. *J Subst Abuse Treat*. 2001;21(2):55-64; discussion 65-56.

49. Dennis M, Godley SH, Diamond G, et al. The Cannabis Youth Treatment (CYT) Study: main findings from two randomized trials. *J Subst Abuse Treat*. 2004;27(3):197-213.

50. Hendriks V, van der Schee E, Blanken P. Treatment of adolescents with a cannabis use disorder: main findings of a randomized controlled trial comparing multidimensional family therapy and cognitive behavioral therapy in The Netherlands. *Drug Alcohol Depend*. 2011;119(1-2):64-71.

51. Rigter H, Henderson CE, Pelc I, et al. Multidimensional family therapy lowers the rate of cannabis dependence in adolescents: a randomised controlled trial in Western European outpatient settings. *Drug Alcohol Depend*. 2013;130(1-3):85-93.

52. Rooke S, Copeland J, Norberg M, Hine D, McCambridge J. Effectiveness of a self-guided web-based cannabis treatment program: randomized controlled trial. *J Med Internet Res*. 2013;15(2):e26.

53. Stanger C, Budney AJ, Kamon JL, Thostensen J. A randomized trial of contingency management for adolescent marijuana abuse and dependence. *Drug Alcohol Depend*. 2009;105(3):240-247.

54. Stanger C, Ryan SR, Scherer EA, Norton GE, Budney AJ. Clinic- and home-based contingency management plus parent training for adolescent cannabis use disorders. *J Am Acad Child Adolesc Psychiatry*. 2015;54(6):445-453 e442.

Section 2

Scientific Literature Review on Potential Health Effects of Marijuana Use

Chapter 10

Marijuana Use During Pregnancy and Breastfeeding

Retail Marijuana Public Health Advisory Committee

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Introduction

The Retail Marijuana Public Health Advisory Committee identified many important public health topics related to marijuana and has reviewed the scientific evidence currently available regarding those topics. This chapter includes reviews of adverse birth outcomes, effects of prenatal marijuana use on exposed offspring later in childhood or adolescence and effects of marijuana use by breastfeeding mothers.

Fetal development is a complex process that is dependent on conditions in the mother's body. It is sensitive to disruptions in her circulation, oxygen level, stress, hormones and other conditions and to chemicals passed from her blood to the fetus through the placenta. Three percent of all babies born in the United States have a birth defect.[1] Eight percent of Colorado babies are born at a low birth weight,[2] which puts them at risk for immediate health problems as well as inhibited growth, impaired cognitive development and chronic diseases later in life.[3]

Adverse effects of alcohol and tobacco consumption during pregnancy are well-documented. Women who smoke during pregnancy are more likely to have miscarriage and their babies are more likely to be premature, have low birth weight, have birth defects, or die from sudden infant death syndrome.[4] Babies of mothers who use alcohol during pregnancy are more likely to have birth defects, poor growth, and problems later in childhood with learning, memory, language, attention and coordination.[5] These known adverse effects of alcohol and tobacco use raise significant concern about the possible effects of marijuana use during pregnancy or breastfeeding.

Analysis of 2014 Pregnancy Risk Assessment Monitoring System (PRAMS) survey data, completed for this report, estimated that 5.7 percent of Colorado women who gave birth used marijuana during pregnancy and 4.5 percent used marijuana after delivery despite also breastfeeding. Marijuana's anti-nausea properties are a prominent reason women report using it during pregnancy.[6] It is critically important to investigate the effects of marijuana use during pregnancy on maternal and fetal health and the effects of use during pregnancy or breastfeeding on growth and development of children months or years after birth.

Definitions

Anencephaly – a neural tube defect that results in underdevelopment or the absence of portions of the brain, skull, and scalp.

Cannabidiol (CBD) – a non-psychoactive cannabinoid that is a component of marijuana.

Gastroschisis – a birth defect where the abdominal (belly) wall has failed to close properly. The resulting hole allows the intestines to protrude outside the fetus.

Low birth weight – a baby who weighs less than birth 5.5 pounds at birth, regardless of the gestational age.

Miscarriage - a baby born before reaching 20 weeks of pregnancy and therefore unable to survive.

Neural tube defects (NTD) - birth defects of the brain, spinal cord or spine. The defects occur in the embryo during the first few weeks of pregnancy.

Newborn behavior issues – may include fussiness and sleep difficulties occurring during the first 28 days after birth.

Preterm delivery - a birth that occurs more than three weeks before the baby is due — in other words, after less than 37 weeks of pregnancy.

Psychotic symptoms - these include auditory or visual hallucinations, difficulty separating real from imagined, perception that self or others can read minds, perceived ability to predict the future, feeling that an outside force is controlling thoughts or actions, fear that someone intends to harm them, belief they have supernatural gifts, feeling emotionally unresponsive, occurrences of unclear speech or inability to speak, or difficulty organizing thoughts to complete activities.

Ventricular septal defects - a congenital heart defect also known as a "hole in the heart." The defect occurs when the wall (septum) that separates the right and left ventricles of the heart does not form properly.

Small for gestational age (SGA) – a baby that is born smaller than 90 percent of babies of the same gestational age (number of weeks of pregnancy).

Stillbirth - the birth of a baby that has died in the womb after having reached at least 20 weeks of pregnancy (earlier instances being regarded as abortion or miscarriage).

Sudden infant death syndrome (SIDS) - The sudden and unexplained death of a seemingly healthy baby less than a year old.

Tetrahydrocannabinol (THC) - the main psychoactive component of marijuana.

Vaporization of marijuana (vaping) - a method of marijuana use in which marijuana vapor, rather than smoke, is inhaled. Marijuana flower or concentrate is heated in a vaporizing device (vaporizer) to a temperature below the point of combustion, to produce vapor.

Key findings

The committee's findings about the effects of marijuana use during pregnancy fell primarily into two broad areas - effects seen at birth and effects seen months or years after birth. Biological evidence shows that THC, the main psychoactive component of marijuana, passes through the placenta to the fetus, so that the unborn child is exposed to THC if the mother uses marijuana. Marijuana use during pregnancy may be associated with an increased risk of heart defects or stillbirth. Stronger evidence was found for negative effects that are seen months or years after birth if a child's mother used marijuana while pregnant with the child. These include decreased growth and impaired cognitive function and attention. Decreased academic ability or increased depression symptoms may also occur. Finally, biological evidence shows that THC passes through breast milk to a breastfeeding child.

An important note for all key findings is that the available research evaluated the **association** between marijuana use and potential adverse health outcomes. This **association** does not prove that the marijuana use alone **caused** the effect. Despite the best efforts of researchers to account for confounding factors, there may be other important factors related to **causality** that were not identified. In addition, marijuana use was illegal everywhere in the United States prior to 1996. Research funding, when appropriated, was commonly sought to identify adverse effects from marijuana use. This legal fact introduces both funding bias and publication bias into the body of literature related to marijuana use. The Retail Marijuana Public Health Advisory Committee recognizes the limitations and biases inherent in the published literature and made efforts to ensure the information reviewed and synthesized is reflective of the current state of medical knowledge. Where information was lacking – for whatever reason – the committee identified this knowledge gap and recommended further research. This information will be updated as new research becomes available.

Recommendations

Health care providers' current collection of information on marijuana use by frequency, amount, potency and method is limited. Adequate assessment of the link between marijuana use during pregnancy and adverse health outcomes must begin with consistent, standardized data collection about marijuana use from pregnant women at each pregnancy-related medical appointment and followed by collection of accurate birth outcome data. The committee recommended public health monitoring to help clarify the possible contribution of marijuana use to key birth outcomes.

Educational programs for pregnant women, their families, and health care providers who care for pregnant women are needed to ensure that more information is shared about the known health effects, and also about what is unknown at present. Routinely asking about marijuana use during pregnancy would improve the ability of health care providers to identify and assist women who would benefit from education about the risks to exposed offspring and therapeutic alternatives to marijuana to treat symptoms during pregnancy. Educational materials about the potential risks of marijuana use during pregnancy and breastfeeding should be available and distributed at marijuana dispensaries.

The committee identified several research gaps. Most topics reviewed in this chapter need further research. Additionally, two important topics without identified research are miscarriage and placental health. Further research is needed on the presence of THC in breast milk, its absorption and metabolism by infants, and any resulting health effects. Additional research should be conducted regarding the effects of different forms of marijuana (e.g., smoked, edible, tinctures), increased marijuana potency, and cannabinoids such as cannabidiol (CBD) on the health of exposed offspring.

Table 1 Findings summary: Marijuana use during pregnancy and breastfeeding - effects on exposed offspring

For an explanation of the classifications "Substantial," "Moderate," etc., see Chapter 7. Systematic literature review process.

	Substantial	Moderate	Limited	Insufficient	Mixed
Effects on birth outcome			Stillbirth		Birth defects including NTD, gastroschisis
			Isolated simple ventricular septal defects		Preterm delivery
					Decreased birth weight
					Low birth weight
					Small for gestational age
Effects on exposed offspring		Attention problems	Decreased academic ability	Psychosis Symptoms at adolescence	Frequency of marijuana use during adolescence
		Decreased IQ scores in young children	Increased depression symptoms	Future initiation of marijuana use	Newborn behavior issues
		Decreased cognitive function	Delinquent behavior		
		Decreased growth	Failure to show association with SIDS (with use during pregnancy)		
Breastfeeding				Breastfeeding and SIDS	Breastfeeding and infant motor development

Evidence statements

Evidence statements are based on systematic scientific literature reviews performed by Colorado Department of Public Health and Environment staff with oversight and approval by the Retail Marijuana Public Health Advisory Committee. For an explanation of the classifications "Substantial," "Moderate," etc., see Chapter 7. Systematic literature review process. For details about the studies reviewed, see Appendix O.

Passage of THC through the placenta

1. Biological evidence shows that THC is passed through the placentas of women who use marijuana during pregnancy and that the fetus absorbs and metabolizes the THC and passes THC metabolites in the meconium.[7-10] (Added*)

Effects of marijuana use during pregnancy on outcomes seen at birth

Stillbirth

2. We found **LIMITED** evidence that maternal use of marijuana during pregnancy is associated with an increased risk of stillbirth.[11]

Birth defects

3. We found **MIXED** evidence for whether or not maternal use of marijuana during pregnancy is associated with birth defects.[12-14]
4. We found **MIXED** evidence for whether or not maternal use of marijuana during pregnancy is associated with neural tube defects such as anencephaly.[15-18]
5. We found **MIXED** evidence for whether or not maternal use of marijuana during pregnancy is associated with gastroschisis.[15,18,19]
6. We found **LIMITED** evidence that maternal use of marijuana during pregnancy is associated with isolated, simple ventricular septal defects (heart defects).[20]

Preterm delivery or abnormal birthweight

7. We found **MIXED** evidence for whether or not maternal use of marijuana during pregnancy is associated with preterm delivery.[12,21-27]
8. We found **MIXED** evidence for whether or not maternal use of marijuana during pregnancy is associated with decreased birth weight.[12,14,23,28-33]
9. We found **MIXED** evidence for whether or not maternal use of marijuana during pregnancy is associated with low-birth weight infants (birth weight <2,500g regardless of gestational age).[21,24,25,27,34,35]
10. We found **MIXED** evidence for whether or not maternal use of marijuana during pregnancy is associated with infants being born small for gestational age (birth weight less than 10th percentile for gestational age).[12,24,26]

* Revised = the statement has been adjusted since the 2014 edition of the report, due to new evidence. Added = the statement is new since the 2014 edition of the report. See Appendix O for dates of most recent literature review.

Effects of prenatal marijuana use on exposed offspring

Cognitive and academic

11. We found **MODERATE** evidence that maternal use of marijuana during pregnancy is associated with attention problems in exposed offspring.[36-39]
12. We found **MODERATE** evidence that maternal use of marijuana during pregnancy is associated with decreased IQ scores in exposed offspring.[40,41]
13. We found **MODERATE** evidence that maternal use of marijuana during pregnancy is associated with reduced cognitive function in exposed offspring.[42-44]
14. We found **LIMITED** evidence that maternal marijuana use during pregnancy is associated with decreased academic ability of exposed offspring.[45-47] (Revised*)

Mental health and substance use

15. We found **LIMITED** evidence that maternal use of marijuana during pregnancy is associated with increased depression symptoms in exposed offspring.[48]
16. We found **INSUFFICIENT** evidence to determine whether or not maternal marijuana use during pregnancy is associated with psychosis symptoms in exposed adolescent offspring.[49]
17. We found **INSUFFICIENT** evidence to determine whether or not maternal marijuana use during pregnancy is associated with initiation of marijuana use by the exposed offspring during adolescence.[50]
18. We found **MIXED** evidence for whether or not maternal marijuana use during pregnancy is associated with frequency of marijuana use by the exposed offspring during adolescence.[50,51]

Other

19. We found **MODERATE** evidence that maternal use of marijuana during pregnancy is associated with decreased growth in exposed offspring.[52,53]
20. We found **LIMITED** evidence that maternal marijuana use during pregnancy is associated with delinquent behaviors in exposed offspring.[54]
21. We found **MIXED** evidence for whether or not maternal use of marijuana during pregnancy is associated with newborn behavior issues.[55-59]
22. We found a **LIMITED** body of research that failed to show association between maternal use of cannabis during pregnancy and SIDS.[60,61]

Presence of THC in breast milk

23. Biological evidence shows that THC is present in the breast milk of women who use marijuana.[62]
24. Biological evidence shows that infants who drink breast milk containing THC absorb and metabolize the THC.[62]

Effects of marijuana use while breastfeeding

25. We found **MIXED** evidence for whether or not an association exists between maternal use of marijuana while breastfeeding and motor development in exposed infants.[63,64]
26. We found **INSUFFICIENT** evidence to determine whether or not infant exposure to marijuana (either from maternal marijuana use during breastfeeding or infant exposure to marijuana smoke) is associated with SIDS.[60]

* Revised = the statement has been adjusted since the 2014 edition of the report, due to new evidence. Added = the statement is new since the 2014 edition of the report. See Appendix O for dates of most recent literature review.

Public health statements

Public health statements are plain language translations of the major findings (Evidence Statements) from the systematic literature reviews. These statements have been officially approved by the Retail Marijuana Public Health Advisory Committee.

1. There is no known safe amount of marijuana use during pregnancy.
2. THC can pass from mother to the unborn child through the placenta.
3. The unborn child is exposed to THC used by the mother during pregnancy.
4. Marijuana use during pregnancy may be associated with an increased risk of stillbirth.
5. Marijuana use during pregnancy may be associated with an increased risk of heart defects (isolated simple ventricular septal defects) in exposed offspring.
6. Maternal use of marijuana during pregnancy is associated with negative effects on exposed offspring, including decreased cognitive function and attention. These effects may not appear until adolescence. (Revised*)
7. Maternal use of marijuana during pregnancy may be associated with decreased academic ability in exposed offspring. This effect may not appear until adolescence.(Revised*)
8. Maternal use of marijuana during pregnancy is associated with negative effects on exposed offspring, including decreased growth.
9. Marijuana use during pregnancy may be associated with increased depression symptoms and delinquent behaviors in exposed offspring.
10. There are negative effects of marijuana use during pregnancy regardless of when it is used during pregnancy.
11. THC can be passed from the mother's breast milk, potentially affecting the baby.

Public health recommendations

Public health recommendations have been suggested and approved by the Retail Marijuana Public Health Advisory Committee with the goals of: 1) Improving knowledge regarding population-based health effects of retail marijuana use and 2) Developing and targeting public health education and prevention strategies for high-risk sub populations.

Data quality issues

- Standardization of data collection on frequency, amount, potency, and method of marijuana use in medical records and other surveillance data sources.
- Specify marijuana use as separate from other drug use in medical records and other surveillance data sources.
- Add blood or urine testing in addition to self-report of marijuana use among pregnant women in Colorado.

* Revised = the statement has been adjusted since the 2014 edition of the report, due to new evidence. Added = the statement is new since the 2014 edition of the report. See Appendix O for dates of most recent literature review.

Surveillance

- Monitor prevalence of marijuana use by pregnant and breastfeeding women, reasons for use and perception of risks, including breakdowns by age and other demographics.
- Enhanced surveillance for birth outcomes of concern.
- Collection of reported marijuana use in electronic health records, including details of use.

Education

- Education for pregnant women on known risks of marijuana use during pregnancy and breastfeeding.
- Education for health care providers on known risks, prevalence of use among different patient populations, reported reasons for use, etc.
- Consider age of pregnant mother in risk reduction/educational programming.
- Public education via different media platforms, including those specific for pregnant women.
- Engage dispensaries as partners to post or make available educational materials about marijuana use during pregnancy or breastfeeding.

Informational resources

- Marijuana Pregnancy and Breastfeeding Guidance for Colorado Health Care Providers (CDPHE)[65]
- Marijuana and Your Baby (CDPHE)[66]

Guidelines and recommendations

The links provided below are for additional information purposes only. The RMPHAC has not formally reviewed these guidelines and recommendations.

- American College of Obstetrics and Gynecology (ACOG)[67]
- The Academy of Breastfeeding Medicine (ABM)[68]

Research gaps

The Retail Marijuana Public Health Advisory Committee identifies important gaps in the scientific literature that may impact public health policies and prevention strategies. Colorado should support unbiased research to help fill the following research gaps identified by the committee.

- Additional study on key birth outcomes and developmental outcomes months or years after birth, in relation to marijuana use during pregnancy.
- Study the effects of marijuana use during pregnancy on placental health
- Study possible association between marijuana use during pregnancy and miscarriage
- Additional research on the passage of THC into breast milk and metabolism by breastfeeding infants, including the length of time THC remains in breast milk.
- Study the effects of marijuana use while breastfeeding on growth and weight gain in infants.
- Study the effects of consuming marijuana edibles or vaping marijuana during pregnancy or breastfeeding.
- Impact of marijuana potency (THC content) on health effects of exposed offspring.
- Effect of cannabidiol (CBD) and other cannabinoid use during pregnancy and breastfeeding
- Include the reasons subjects use marijuana during pregnancy or breastfeeding in research.

References

1. Centers for Disease Control and Prevention. Birth Defects, Data & Statistics. 2016; https://www.cdc.gov/ncbddd/birthdefects/data.html. Accessed December 28, 2016,.
2. Colorado Department of Public Health and Environment. Low birth weight. 2016. https://www.colorado.gov/cdphe/low-birth-weight. Accessed December 28, 2016.
3. World Health Organization and UNICEF. *Low Birthweight: Country, Regional and Global Estimates*. 2004.
4. Centers for Disease Control and Prevention. Reproductive Health: Tobacco Use and Pregnancy. 2016; https://www.cdc.gov/reproductivehealth/maternalinfanthealth/tobaccousepregnancy/. Accessed December 28, 2016.
5. Centers for Disease Control and Prevention. Fetal Alcohol Spectrum Disorders (FASDs). 2016; https://www.cdc.gov/ncbddd/fasd/alcohol-use.html. Accessed December 28, 2016,
6. Roberson EK, Patrick WK, Hurwitz EL. Marijuana use and maternal experiences of severe nausea during pregnancy in Hawai'i. *Hawaii J Med Public Health*. 2014;73(9):283-287.
7. Joya X, Pujadas M, Falcon M, et al. Gas chromatography-mass spectrometry assay for the simultaneous quantification of drugs of abuse in human placenta at 12th week of gestation. *Forensic Sci Int*. 2010;196(1-3):38-42.
8. Marchei E, Pellegrini M, Pacifici R, et al. Quantification of Delta9-tetrahydrocannabinol and its major metabolites in meconium by gas chromatographic-mass spectrometric assay: assay validation and preliminary results of the "meconium project". *Ther Drug Monit*. 2006;28(5):700-706.
9. ElSohly MA, Stanford DF, Murphy TP, et al. Immunoassay and GC-MS procedures for the analysis of drugs of abuse in meconium. *J Anal Toxicol*. 1999;23(6):436-445.
10. ElSohly MA, Feng S. delta 9-THC metabolites in meconium: identification of 11-OH-delta 9-THC, 8 beta,11-diOH-delta 9-THC, and 11-nor-delta 9-THC-9-COOH as major metabolites of delta 9-THC. *J Anal Toxicol*. 1998;22(4):329-335.
11. Varner MW, Silver RM, Rowland Hogue CJ, et al. Association between stillbirth and illicit drug use and smoking during pregnancy. *Obstet Gynecol*. 2014;123(1):113-125.
12. Day N, Sambamoorthi U, Taylor P, et al. Prenatal marijuana use and neonatal outcome. *Neurotoxicol Teratol*. 1991;13(3):329-334.
13. Forrester MB, Merz RD. Risk of selected birth defects with prenatal illicit drug use, Hawaii, 1986-2002. *J Toxicol Environ Health A*. 2007;70(1):7-18.
14. Linn S, Schoenbaum SC, Monson RR, Rosner R, Stubblefield PC, Ryan KJ. The association of marijuana use with outcome of pregnancy. *Am J Public Health*. 1983;73(10):1161-1164.
15. David AL, Holloway A, Thomasson L, et al. A case-control study of maternal periconceptual and pregnancy recreational drug use and fetal malformation using hair analysis. *PLoS One*. 2014;9(10):e111038.
16. Shaw GM, Velie EM, Morland KB. Parental recreational drug use and risk for neural tube defects. *Am J Epidemiol*. 1996;144(12):1155-1160.
17. Suarez L, Brender JD, Langlois PH, Zhan FB, Moody K. Maternal exposures to hazardous waste sites and industrial facilities and risk of neural tube defects in offspring. *Ann Epidemiol*. 2007;17(10):772-777.
18. van Gelder MM, Reefhuis J, Caton AR, et al. Maternal periconceptional illicit drug use and the risk of congenital malformations. *Epidemiology*. 2009;20(1):60-66.

19. Forrester MB, Merz RD. Comparison of trends in gastroschisis and prenatal illicit drug use rates. *J Toxicol Environ Health A*. 2006;69(13):1253-1259.

20. Williams LJ, Correa A, Rasmussen S. Maternal lifestyle factors and risk for ventricular septal defects. *Birth Defects Res A Clin Mol Teratol*. 2004;70(2):59-64.

21. Bada HS, Das A, Bauer CR, et al. Low birth weight and preterm births: etiologic fraction attributable to prenatal drug exposure. *J Perinatol*. 2005;25(10):631-637.

22. Dekker GA, Lee SY, North RA, McCowan LM, Simpson NA, Roberts CT. Risk factors for preterm birth in an international prospective cohort of nulliparous women. *PLoS One*. 2012;7(7):e39154.

23. Fergusson DM, Horwood LJ, Northstone K, Childhood ASTALSoPa. Maternal use of cannabis and pregnancy outcome. *BJOG*. 2002;109(1):21-27.

24. Hayatbakhsh MR, Flenady VJ, Gibbons KS, et al. Birth outcomes associated with cannabis use before and during pregnancy. *Pediatr Res*. 2012;71(2):215-219.

25. Mark K, Desai A, Terplan M. Marijuana use and pregnancy: prevalence, associated characteristics, and birth outcomes. *Arch Womens Ment Health*. 2015;10.1007/s00737-015-0529-9.

26. Saurel-Cubizolles MJ, Prunet C, Blondel B. Cannabis use during pregnancy in France in 2010. *BJOG*. 2014;10.1111/1471-0528.12626.

27. Shiono PH, Klebanoff MA, Nugent RP, et al. The impact of cocaine and marijuana use on low birth weight and preterm birth: a multicenter study. *Am J Obstet Gynecol*. 1995;172(1 Pt 1):19-27.

28. El Marroun H, Tiemeier H, Steegers EA, et al. Intrauterine cannabis exposure affects fetal growth trajectories: the Generation R Study. *J Am Acad Child Adolesc Psychiatry*. 2009;48(12):1173-1181.

29. English DR, Hulse GK, Milne E, Holman CD, Bower CI. Maternal cannabis use and birth weight: a meta-analysis. *Addiction*. 1997;92(11):1553-1560.

30. Fried PA, O'Connell CM. A comparison of the effects of prenatal exposure to tobacco, alcohol, cannabis and caffeine on birth size and subsequent growth. *Neurotoxicol Teratol*. 1987;9(2):79-85.

31. Gray TR, Eiden RD, Leonard KE, Connors GJ, Shisler S, Huestis MA. Identifying prenatal cannabis exposure and effects of concurrent tobacco exposure on neonatal growth. *Clin Chem*. 2010;56(9):1442-1450.

32. Hingson R, Alpert JJ, Day N, et al. Effects of maternal drinking and marijuana use on fetal growth and development. *Pediatrics*. 1982;70(4):539-546.

33. Janisse JJ, Bailey BA, Ager J, Sokol RJ. Alcohol, tobacco, cocaine, and marijuana use: relative contributions to preterm delivery and fetal growth restriction. *Subst Abus*. 2014;35(1):60-67.

34. Conner SN, Carter EB, Tuuli MG, Macones GA, Cahill AG. Maternal marijuana use and neonatal morbidity. *Am J Obstet Gynecol*. 2015;10.1016/j.ajog.2015.05.050.

35. Schempf AH, Strobino DM. Illicit drug use and adverse birth outcomes: is it drugs or context? *J Urban Health*. 2008;85(6):858-873.

36. El Marroun H, Hudziak JJ, Tiemeier H, et al. Intrauterine cannabis exposure leads to more aggressive behavior and attention problems in 18-month-old girls. *Drug Alcohol Depend*. 2011;118(2-3):470-474.

37. Goldschmidt L, Day NL, Richardson GA. Effects of prenatal marijuana exposure on child behavior problems at age 10. *Neurotoxicol Teratol*. 2000;22(3):325-336.

38. Noland JS, Singer LT, Short EJ, et al. Prenatal drug exposure and selective attention in preschoolers. *Neurotoxicol Teratol*. 2005;27(3):429-438.

39. Fried PA, Smith AM. A literature review of the consequences of prenatal marihuana exposure. An emerging theme of a deficiency in aspects of executive function. *Neurotoxicol Teratol*. 2001;23(1):1-11.

40. Day NL, Richardson GA, Goldschmidt L, et al. Effect of prenatal marijuana exposure on the cognitive development of offspring at age three. *Neurotoxicol Teratol*. 1994;16(2):169-175.

41. Goldschmidt L, Richardson GA, Willford J, Day NL. Prenatal marijuana exposure and intelligence test performance at age 6. *J Am Acad Child Adolesc Psychiatry*. 2008;47(3):254-263.

42. Fried PA, Watkinson B, Gray R. Differential effects on cognitive functioning in 13- to 16-year-olds prenatally exposed to cigarettes and marihuana. *Neurotoxicol Teratol*. 2003;25(4):427-436.

43. Smith AM, Fried PA, Hogan MJ, Cameron I. Effects of prenatal marijuana on response inhibition: an fMRI study of young adults. *Neurotoxicol Teratol*. 2004;26(4):533-542.

44. Willford JA, Chandler LS, Goldschmidt L, Day NL. Effects of prenatal tobacco, alcohol and marijuana exposure on processing speed, visual-motor coordination, and interhemispheric transfer. *Neurotoxicol Teratol*. 2010;32(6):580-588.

45. Fried PA, Watkinson B, Siegel LS. Reading and language in 9- to 12-year olds prenatally exposed to cigarettes and marijuana. *Neurotoxicol Teratol*. 1997;19(3):171-183.

46. Goldschmidt L, Richardson GA, Cornelius MD, Day NL. Prenatal marijuana and alcohol exposure and academic achievement at age 10. *Neurotoxicol Teratol*. 2004;26(4):521-532.

47. Goldschmidt L, Richardson GA, Willford JA, Severtson SG, Day NL. School achievement in 14-year-old youths prenatally exposed to marijuana. *Neurotoxicol Teratol*. 2012;34(1):161-167.

48. Gray KA, Day NL, Leech S, Richardson GA. Prenatal marijuana exposure: effect on child depressive symptoms at ten years of age. *Neurotoxicol Teratol*. 2005;27(3):439-448.

49. Zammit S, Thomas K, Thompson A, et al. Maternal tobacco, cannabis and alcohol use during pregnancy and risk of adolescent psychotic symptoms in offspring. *Br J Psychiatry*. 2009;195(4):294-300.

50. Porath AJ, Fried PA. Effects of prenatal cigarette and marijuana exposure on drug use among offspring. *Neurotoxicol Teratol*. 2005;27(2):267-277.

51. Day NL, Goldschmidt L, Thomas CA. Prenatal marijuana exposure contributes to the prediction of marijuana use at age 14. *Addiction*. 2006;101(9):1313-1322.

52. Cornelius MD, Goldschmidt L, Day NL, Larkby C. Alcohol, tobacco and marijuana use among pregnant teenagers: 6-year follow-up of offspring growth effects. *Neurotoxicol Teratol*. 2002;24(6):703-710.

53. Fried PA, Watkinson B, Gray R. Growth from birth to early adolescence in offspring prenatally exposed to cigarettes and marijuana. *Neurotoxicol Teratol*. 1999;21(5):513-525.

54. Day NL, Leech SL, Goldschmidt L. The effects of prenatal marijuana exposure on delinquent behaviors are mediated by measures of neurocognitive functioning. *Neurotoxicol Teratol*. 2011;33(1):129-136.

55. de Moraes Barros MC, Guinsburg R, de Araújo Peres C, Mitsuhiro S, Chalem E, Laranjeira RR. Exposure to marijuana during pregnancy alters neurobehavior in the early neonatal period. *J Pediatr*. 2006;149(6):781-787.

56. Dreher MC, Nugent K, Hudgins R. Prenatal marijuana exposure and neonatal outcomes in Jamaica: an ethnographic study. *Pediatrics*. 1994;93(2):254-260.

57. Hayes JS, Lampart R, Dreher MC, Morgan L. Five-year follow-up of rural Jamaican children whose mothers used marijuana during pregnancy. *West Indian Med J*. 1991;40(3):120-123.

58. Lester BM, Dreher M. Effects of marijuana use during pregnancy on newborn cry. *Child Dev*. 1989;60(4):765-771.

59. Richardson GA, Day N, Taylor PM. The Effect of Prenatal Alcohol, Marijuana, and Tobacco Exposure on Neonatal Behavior. *Infant Behavior and Development*. 1989;12:199-209.

60. Klonoff-Cohen H, Lam-Kruglick P. Maternal and paternal recreational drug use and sudden infant death syndrome. *Arch Pediatr Adolesc Med*. 2001;155(7):765-770.

61. Scragg RK, Mitchell EA, Ford RP, Thompson JM, Taylor BJ, Stewart AW. Maternal cannabis use in the sudden death syndrome. *Acta Paediatr*. 2001;90(1):57-60.

62. Perez-Reyes M, Wall ME. Presence of delta9-tetrahydrocannabinol in human milk. *N Engl J Med*. 1982;307(13):819-820.

63. Astley SJ, Little RE. Maternal marijuana use during lactation and infant development at one year. *Neurotoxicol Teratol*. 1990;12(2):161-168.

64. Tennes K, Avitable N, Blackard C, et al. Marijuana: prenatal and postnatal exposure in the human. *NIDA Res Monogr*. 1985;59:48-60.

65. Colorado Department of Public Health and Environment. Marijuana Pregnancy and Breastfeeding Guidance For Colorado Health Care Providers. https://www.colorado.gov/pacific/sites/default/files/MJ_RMEP_Pregnancy-Breastfeeding-Clinical-Guidelines.pdf.

66. Colorado Department of Public Health and Environment. Marijuana and Your Baby. https://www.colorado.gov/pacific/sites/default/files/MJ_RMEP_Factsheet-Pregnancy-Breastfeeding.pdf.

67. The American College of Obstetricians and Gynecologists Committee Opinion. Marijuana Use During Pregnancy and Lactation. 2015, http://www.acog.org/Resources-And-Publications/Committee-Opinions/Committee-on-Obstetric-Practice/Marijuana-Use-During-Pregnancy-and-Lactation(637).

68. Reece-Stremtan S, Marinelli KA. ABM clinical protocol #21: guidelines for breastfeeding and substance use or substance use disorder, revised 2015. *Breastfeed Med*. 2015;10(3):135-141.

Section 2

Scientific Literature Review on Potential Health Effects of Marijuana Use

Chapter 11

Marijuana Use and Respiratory Effects

Retail Marijuana Public Health Advisory Committee

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Introduction

The Retail Marijuana Public Health Advisory Committee identified many important public health topics related to marijuana and has reviewed the scientific evidence currently available regarding those topics. This chapter includes reviews of respiratory diseases like chronic obstructive pulmonary disease (COPD), chronic bronchitis and asthma, respiratory infections and lung function relative to smoked marijuana, as well as potential health effects of vaporized marijuana.

Respiratory diseases and illnesses are a major burden in both health impact and financial cost in the United States. COPD, a progressive lung disease, is the third leading cause of death in the United States.[1] In Colorado, it is estimated that in 2010 there were more than 120,000 adults being treated for COPD with a total medical treatment cost over $735 million.[2] Asthma affects even more Colorado residents, estimated at more than 450,000 in 2012.[3] The financial cost of asthma in the United States in 2007 was estimated at $56 billion.[4]

Inhalation of combustion products, from tobacco smoking to wood-burning stoves, has consistently been associated with respiratory diseases.[5,6] For example, tobacco smoking is known to be the most common cause of COPD.[7] The U.S. National Health and Nutrition Examination Survey (NHANES) recently found that daily marijuana users have higher levels of toxic combustion by-products than non-users.[8] Furthermore, exposure to harmful products from smoking marijuana may be exacerbated by the way a marijuana joint is typically smoked, with deep and prolonged inhalation and no filter. Investigating the long-term respiratory effects of smoking marijuana is very important.

Marijuana vaporizing (vaping) is increasing in popularity as an alternative to smoking marijuana.[9] Marijuana users in two separate surveys believed vaporizing marijuana to be less harmful or "healthier" than smoking marijuana.[9,10] It is important to identify the potential harms from vaporized marijuana relative to not using marijuana and also to compare them with the potential harms from smoked marijuana.

Definitions

Levels of marijuana use

- Daily or near-daily use: 5-7 days/week.
- Weekly use: 1-4 days/week.
- Less-than-weekly use: less than 1 day/week.
- Acute use: marijuana used within the past few hours, such that the short-term effects or symptoms are still being experienced.

Bullous lung disease - destruction of lung tissue causing pockets of air to replace lung tissue, diagnosed by imaging.

Chronic bronchitis - a long term cough with sputum production that is diagnosed by symptoms.

Chronic obstructive pulmonary disease (COPD) - a severe form of small airway obstruction characterized by long-term poor airflow from the lungs, with common symptoms including of shortness of breath and cough with sputum production, diagnosed by pulmonary function tests.

Combustion by-products – chemicals produced when a material is burned. These chemicals including carbon monoxide and polycyclic aromatic hydrocarbons.

Dabbing - a method of marijuana use where a "dab" (small amount) of marijuana concentrate is placed on a pre-heated surface, creating concentrated marijuana vapor to be inhaled.

Emphysema - the breakdown of lung tissue, typically causing air trapping, poor airflow and shortness of breath, diagnosed by imaging.

Pneumothorax - the collapse of a lung caused by air or fluid filling up the space around the lung, an emergency condition diagnosed by physical exam and/or imaging.

Polycyclic aromatic hydrocarbons - a group of more than 100 different chemicals released from burning coal, oil, gasoline, trash, tobacco, wood, or other organic substances.

Pulmonary function (tests) - measurements that show how well the lungs move air in and out and how well they exchange oxygen and carbon dioxide with the blood.

Small airway obstruction - a condition causing air to be trapped in the lungs, making it difficult to breathe the air out to make room for the next breath, diagnosed by pulmonary function tests.

Tetrahydrocannabinol (THC) - the main psychoactive component of marijuana.

Vaporization of marijuana (vaping) - a method of marijuana use in which marijuana vapor, rather than smoke, is inhaled. Marijuana flower or concentrate is heated in a vaporizing device (vaporizer) to a temperature below the point of combustion, to produce vapor.

Key findings

The committee found strong evidence for an association between daily or near-daily marijuana use and chronic bronchitis with cough, wheezing and sputum production. Additionally, daily or near-daily marijuana use may be associated with bullous lung disease and pneumothorax in individuals younger than 40 years of age. Research is lacking on other aspects of lung health related to marijuana use. There is conflicting research regarding small airway obstruction and research is lacking concerning any possible association between marijuana use and COPD, emphysema or respiratory infections. A notable effect of acute use is a short-term improvement in lung airflow; however, evidence for long term benefits is lacking. Finally, smoked marijuana may deposit more particulate matter in the lungs per puff than tobacco smoking, and smokers who switch from marijuana smoking to marijuana vaporizing may have fewer respiratory symptoms and improved pulmonary function.

An important note for all key findings is that the available research evaluated the **association** between marijuana use and potential adverse health outcomes. This **association** does not prove that the marijuana use alone **caused** the effect. Despite the best efforts of researchers to account for confounding factors, there may be other important factors related to **causality** that were not identified. In addition, marijuana use was illegal everywhere in the United States prior to 1996. Research funding, when appropriated, was commonly sought to identify adverse effects from marijuana use. This legal fact introduces both funding bias and publication bias into the body of literature related to marijuana use. The Retail Marijuana Public Health Advisory Committee recognizes the limitations and biases inherent in the published literature and made efforts to ensure the information reviewed and synthesized is reflective of the current state of medical knowledge. Where information was lacking – for whatever reason – the committee identified this knowledge gap and recommended further research. This information will be updated as new research becomes available.

Recommendations

Recommendations from the committee reflect the need for improvement and standardization of data collection. Information on frequency, amount, potency and method of marijuana use should be collected consistently in both clinical settings and public health surveillance tools. Determinations of cumulative marijuana exposure also need improvement. Better quality measures of recent marijuana use should be used, such as blood THC levels or urinary metabolites instead of self-reported marijuana use. Public health should use data available in the Colorado Central Cancer Registry to monitor new cases of lung cancer. Additionally, monitoring for the prevalence of more chronic conditions such as COPD and asthma should be conducted in collaboration with the Colorado Hospital Association (CHA) and the All-Payer Claims Database available through the Center for Improving Value in Health Care (CIVHC). Educational opportunities exist with both primary and specialized health care providers regarding the potential adverse health effects related to marijuana use and respiratory disease, including the importance of understanding the possible additive risks to lung health related to smoking both tobacco and marijuana.

Research gaps identified include the need for studies of COPD and lung function, including improved methods to assess cumulative marijuana exposure, older age groups, and adequate numbers of non-tobacco smokers to eliminate the confounding introduced by tobacco smoking. Prospective studies of groups of marijuana users, monitoring lung function and symptoms over long time periods, are needed to clarify relationships between long-term marijuana use and respiratory diseases. Additional research on the potential respiratory effects of different methods of marijuana use (including vaporizing and dabbing) is needed to assess the long-term safety of these methods.

Table 1 Findings summary: Marijuana use and respiratory effects

For an explanation of the classifications "Substantial," "Moderate," etc., see Chapter 7. Systematic literature review process.

	Substantial	Moderate	Limited	Insufficient	Mixed
Smoked marijuana	Chronic bronchitis with cough/wheeze/ sputum		More particulate matter deposits compared to tobacco	COPD	Long-term daily or near-daily marijuana use associated with airway obstruction
	Acute use improves airflow		Failure to show association between less-than-weekly marijuana use and airway obstruction	Emphysema	
			Bullous lung disease and pneumothorax under 40 years of age	Respiratory infections	
Vaporized marijuana			Fewer symptoms and improved lung function after switching to vaporizing	Health effects of vaporized marijuana	
				Effects of vaporized marijuana on asthma	

Evidence statements

Evidence statements are based on systematic scientific literature reviews performed by Colorado Department of Public Health and Environment staff with oversight and approval by the Retail Marijuana Public Health Advisory Committee. For an explanation of the classifications "Substantial," "Moderate," etc., see Chapter 7. Systematic literature review process. For details about the studies reviewed, see Appendix P.

Smoked marijuana

1. We found **LIMITED** evidence that smoking marijuana deposits more particulate matter per puff in the lungs compared to tobacco smoke.[11]
2. We found **SUBSTANTIAL** evidence that daily or near-daily marijuana smoking is associated with chronic bronchitis, including chronic cough, sputum production, and wheezing.[12-20]
3. We found **INSUFFICIENT** evidence to determine whether or not smoking marijuana is associated with chronic obstructive pulmonary disease (COPD).[20,23] (Revised*)
4. We found **INSUFFICIENT** evidence to determine whether or not smoking marijuana is associated with emphysema.[16]
5. We found a **LIMITED** body of research that failed to show an association between less-than-weekly marijuana smoking and small airway obstruction.[19,22-25] (Added*)
6. We found **MIXED** evidence for whether or not long-term, daily or near-daily marijuana smoking is associated with small airway obstruction.[12,14-16,18-20,26] (Revised*)
7. We found **LIMITED** evidence that daily or near-daily marijuana smoking is associated with bullous lung disease leading to pneumothorax in individuals younger than 40 years of age.[27-30] (Revised*)
8. We found **INSUFFICIENT** evidence to determine whether or not smoking marijuana is associated with increased risk of respiratory infections.[17,31]
9. We found **SUBSTANTIAL** evidence that marijuana use (inhaled or oral) results in an immediate short-term improvement of lung airflow.[32-34]

Vaporized marijuana

10. We found **INSUFFICIENT** evidence to determine whether or not vaporizing marijuana is associated with long-term respiratory health effects[35].
11. We found **LIMITED** evidence that after one month, weekly or daily marijuana smokers who switched to vaporizing had fewer respiratory symptoms and improved pulmonary function.[36,37] (Added*)
12. We found **INSUFFICIENT** evidence to determine whether or not marijuana vaporization affects asthma symptoms. (Added*)

* Revised = the statement has been adjusted since the 2014 edition of the report, due to new evidence. Added = the statement is new since the 2014 edition of the report. See Appendix P for dates of most recent literature review.

Public health statements

Public health statements are plain language translations of the major findings (Evidence Statements) from the systematic literature reviews. These statements have been officially approved by the Retail Marijuana Public Health Advisory Committee.

1. Marijuana smoke may deposit more particulate matter in the lungs per puff compared to tobacco smoke.
2. Daily or near-daily marijuana smoking is strongly associated with chronic bronchitis, including chronic cough, sputum production and wheezing.
3. There is conflicting research on whether or not long-term daily or near-daily marijuana smoking is associated with decreased airflow from the lungs. (Revised*)
4. Daily or near-daily marijuana smoking may be associated with a specific type of lung damage called bullous lung disease, resulting in a collapsed lung, in individuals younger than 40 years of age.
5. One-time marijuana use (edible or smoked) is strongly associated with immediate, short-term (1 to 6 hours) improved airflow in the lungs.
6. Compared with weekly or daily marijuana smoking, short-term marijuana vaporizing (vaping) may be associated with fewer respiratory symptoms and improved pulmonary function. (Added*)

* Revised = the statement has been adjusted since the 2014 edition of the report, due to new evidence. Added = the statement is new since the 2014 edition of the report. See Appendix P for dates of most recent literature review.

Public health recommendations

Public health recommendations have been suggested and approved by the Retail Marijuana Public Health Advisory Committee with the goals of: 1) Improving knowledge regarding population-based health effects of retail marijuana use and 2) Developing and targeting public health education and prevention strategies for high-risk sub populations.

Data quality issues

- Include marijuana use on questionnaires completed during spirometry and pulmonary function testing, including method of use, frequency, amount and potency.
- Improved measures to determine cumulative marijuana exposure.
- Better quality measures of recent marijuana use, such as blood THC levels or urinary metabolites instead of self-reported cannabis use.

Surveillance

- Monitor statewide prevalence of COPD, asthma and other respiratory diseases through existing population-based surveys.
- Monitor health care utilization related to respiratory disorders using Colorado Hospital Association and/or All-Payer Claims databases.

Education

- Public education on marijuana use and chronic respiratory diseases.
- Public education on the potential for additive risks to lung health related to smoking both tobacco and marijuana.
- Public education that smoking marijuana is not a long-term treatment for asthma.

Research gaps

The Retail Marijuana Public Health Advisory Committee identifies important gaps in the scientific literature that may impact public health policies and prevention strategies. Colorado should support unbiased research to help fill the following research gaps identified by the committee.

- Improved studies of COPD and lung function related to marijuana use, especially including adequate numbers of non-tobacco smokers, assessment of cumulative marijuana exposure, and older age groups.
- Prospective studies of groups of marijuana users' lung function and symptoms over time.
- Improved studies of bullous lung disease to better define its relationship to marijuana use.
- Research on the potential respiratory effects of different methods of marijuana use, including vaporizing and dabbing.

References

1. American Lung Association. Lung Health & Diseases, COPD. 2016; http://www.lung.org/lung-health-and-diseases/lung-disease-lookup/copd/?referrer=https://www.google.com/. Accessed December 19, 2016,.
2. Ford ES, Murphy LB, Khavjou O, Giles WH, Holt JB, Croft JB. Total and state-specific medical and absenteeism costs of COPD among adults aged >/= 18 years in the United States for 2010 and projections through 2020. *Chest*. 2015;147(1):31-45.
3. American Lung Association EaSU. *Estimated Prevalence and Incidence of Lung Disease*. May 2014 2014.
4. Barnett SB, Nurmagambetov TA. Costs of asthma in the United States: 2002-2007. *J Allergy Clin Immunol*. 2011;127(1):145-152.
5. Centers for Disease Control and Prevention. Smoking & Tobacco Use, Health Effects of Cigarette Smoking. 2016; https://www.cdc.gov/tobacco/data_statistics/fact_sheets/health_effects/effects_cig_smoking/. Accessed December 21, 2016, 2016.
6. Naeher LP, Brauer M, Lipsett M, et al. Woodsmoke health effects: a review. *Inhal Toxicol*. 2007;19(1):67-106.
7. Decramer M, Janssens W, Miravitlles M. Chronic obstructive pulmonary disease. *Lancet*. 2012;379(9823):1341-1351.
8. Wei B, Alwis KU, Li Z, et al. Urinary concentrations of PAH and VOC metabolites in marijuana users. *Environ Int*. 2016;88:1-8.
9. Lee DC, Crosier BS, Borodovsky JT, Sargent JD, Budney AJ. Online survey characterizing vaporizer use among cannabis users. *Drug Alcohol Depend*. 2016;159:227-233.
10. Malouff JM, Rooke SE, Copeland J. Experiences of marijuana-vaporizer users. *Subst Abus*. 2014;35(2):127-128.
11. Wu TC, Tashkin DP, Djahed B, Rose JE. Pulmonary hazards of smoking marijuana as compared with tobacco. *N Engl J Med*. 1988;318(6):347-351.
12. Bloom JW, Kaltenborn WT, Paoletti P, Camilli A, Lebowitz MD. Respiratory effects of non-tobacco cigarettes. *Br Med J (Clin Res Ed)*. 1987;295(6612):1516-1518.
13. Roth MD, Arora A, Barsky SH, Kleerup EC, Simmons M, Tashkin DP. Airway inflammation in young marijuana and tobacco smokers. *Am J Respir Crit Care Med*. 1998;157(3 Pt 1):928-937.
14. Sherrill DL, Krzyzanowski M, Bloom JW, Lebowitz MD. Respiratory effects of non-tobacco cigarettes: a longitudinal study in general population. *Int J Epidemiol*. 1991;20(1):132-137.
15. Tashkin DP, Coulson AH, Clark VA, et al. Respiratory symptoms and lung function in habitual heavy smokers of marijuana alone, smokers of marijuana and tobacco, smokers of tobacco alone, and nonsmokers. *Am Rev Respir Dis*. 1987;135(1):209-216.
16. Aldington S, Williams M, Nowitz M, et al. Effects of cannabis on pulmonary structure, function and symptoms. *Thorax*. 2007;62(12):1058-1063.
17. Moore BA, Augustson EM, Moser RP, Budney AJ. Respiratory effects of marijuana and tobacco use in a U.S. sample. *J Gen Intern Med*. 2005;20(1):33-37.
18. Taylor DR, Poulton R, Moffitt TE, Ramankutty P, Sears MR. The respiratory effects of cannabis dependence in young adults. *Addiction*. 2000;95(11):1669-1677.

19. Kempker JA, Honig EG, Martin GS. The effects of marijuana exposure on expiratory airflow. A study of adults who participated in the U.S. National Health and Nutrition Examination Study. *Ann Am Thorac Soc*. 2015;12(2):135-141.

20. Macleod J, Robertson R, Copeland L, McKenzie J, Elton R, Reid P. Cannabis, tobacco smoking, and lung function: a cross-sectional observational study in a general practice population. *Br J Gen Pract*. 2015;65(631):e89-95.

21. Tashkin DP, Shapiro BJ, Lee YE, Harper CE. Subacute effects of heavy marihuana smoking on pulmonary function in healthy men. *N Engl J Med*. 1976;294(3):125-129.

22. Hancox RJ, Poulton R, Ely M, et al. Effects of cannabis on lung function: a population-based cohort study. *Eur Respir J*. 2010;35(1):42-47.

23. Tan WC, Lo C, Jong A, et al. Marijuana and chronic obstructive lung disease: a population-based study. *CMAJ*. 2009;180(8):814-820.

24. Pletcher MJ, Vittinghoff E, Kalhan R, et al. Association between marijuana exposure and pulmonary function over 20 years. *JAMA*. 2012;307(2):173-181.

25. Taylor DR, Fergusson DM, Milne BJ, et al. A longitudinal study of the effects of tobacco and cannabis exposure on lung function in young adults. *Addiction*. 2002;97(8):1055-1061.

26. Tashkin DP, Simmons MS, Sherrill DL, Coulson AH. Heavy habitual marijuana smoking does not cause an accelerated decline in FEV1 with age. *Am J Respir Crit Care Med*. 1997;155(1):141-148.

27. Beshay M, Kaiser H, Niedhart D, Reymond MA, Schmid RA. Emphysema and secondary pneumothorax in young adults smoking cannabis. *Eur J Cardiothorac Surg*. 2007;32(6):834-838.

28. Hii SW, Tam JD, Thompson BR, Naughton MT. Bullous lung disease due to marijuana. *Respirology*. 2008;13(1):122-127.

29. Johnson MK, Smith RP, Morrison D, Laszlo G, White RJ. Large lung bullae in marijuana smokers. *Thorax*. 2000;55(4):340-342.

30. Fiorelli A, Accardo M, Vicidomini G, Messina G, Laperuta P, Santini M. Does cannabis smoking predispose to lung bulla formation? *Asian Cardiovasc Thorac Ann*. 2014;22(1):65-71.

31. Polen MR, Sidney S, Tekawa IS, Sadler M, Friedman GD. Health care use by frequent marijuana smokers who do not smoke tobacco. *West J Med*. 1993;158(6):596-601.

32. Tashkin DP, Shapiro BJ, Frank IM. Acute pulmonary physiologic effects of smoked marijuana and oral 9 -tetrahydrocannabinol in healthy young men. *N Engl J Med*. 1973;289(7):336-341.

33. Tashkin DP, Shapiro BJ, Frank IM. Acute effects of smoked marijuana and oral delta9-tetrahydrocannabinol on specific airway conductance in asthmatic subjects. *Am Rev Respir Dis*. 1974;109(4):420-428.

34. Tashkin DP, Shapiro BJ, Lee YE, Harper CE. Effects of smoked marijuana in experimentally induced asthma. *Am Rev Respir Dis*. 1975;112(3):377-386.

35. Gieringer D. Waterpipe Study. *Multidisciplinary Assocation for Psycheldelic Studies (MAPS)*. 1996;6(3).

36. Earleywine M, Barnwell SS. Decreased respiratory symptoms in cannabis users who vaporize. *Harm Reduct J*. 2007;4:11.

37. Van Dam NT, Earleywine M. Pulmonary function in cannabis users: Support for a clinical trial of the vaporizer. *Int J Drug Policy*. 2010;21(6):511-513.

Section 2

Scientific Literature Review on Potential Health Effects of Marijuana Use

Chapter 12

Unintentional Marijuana Exposures in Children

Retail Marijuana Public Health Advisory Committee

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Introduction

The Retail Marijuana Public Health Advisory Committee identified many important public health topics related to marijuana use and has reviewed the scientific evidence currently available regarding those topics. This chapter includes reviews of unintentional marijuana exposure relative to marijuana legalization and child-resistant packaging.

In 2014, the Rocky Mountain Poison and Drug Center [*] (RMPDC) received nearly 25,000 calls about children under age five who had accidentally eaten or been exposed to medications or chemicals.[1] About one-third of RMPDC calls are referred to receive medical care. Parents and caregivers know that very young children naturally put things in their mouths, and, as they get older, eat things they mistake for candy or food they like. Many edible marijuana products are made by adding concentrated THC to existing foods that look exactly like foods or candies a child might normally eat. Medical providers report that children who ingest marijuana can experience loss of coordination, trouble breathing, difficulty waking up, or even coma.[2] Analysis of 2014 and 2015 Colorado Child Health Survey data, completed for this report, estimated that approximately 14,000 homes in Colorado had children 1-14 years old and marijuana in the home with potentially unsafe storage. It is important to investigate the extent and impact of unintentional marijuana exposures, especially in children.

Definitions

Tetrahydrocannabinol (THC) – the main psychoactive component of marijuana.

Unintentional marijuana exposures – ingesting a substance without knowing that it contains THC or other cannabinoids, more commonly observed with edible marijuana products.

Key findings

Findings from this review have important implications. The committee found strong evidence that more unintentional marijuana exposures of children occur in states with increased legal access to marijuana, and that the exposures can lead to significant clinical effects requiring hospitalization. Additionally, evidence shows that child resistant packaging prevents exposure to children from potentially harmful substances.

An important note for all key findings is that the available research evaluated the **association** between marijuana use and potential adverse health outcomes. This **association** does not prove that the marijuana use alone **caused** the effect. Despite the best efforts of researchers to account for confounding factors, there may be other important factors related to **causality** that were not identified. In addition, marijuana use was illegal everywhere in the United States prior to 1996. Research funding, when appropriated, was commonly sought to identify adverse effects from marijuana use. This legal fact introduces both funding bias and publication bias into the body of literature related to marijuana use. The Retail Marijuana Public Health Advisory Committee recognizes the limitations and biases inherent in the published literature and made efforts to ensure the information reviewed and synthesized is reflective of the current state of medical knowledge. Where information was lacking – for whatever reason – the committee identified this knowledge gap and recommended further research. This information will be updated as new research becomes available.

[*] See Section 3, Chapter 1 Rocky Mountain Poison and Drug Center data for analyses of calls related to marijuana.

Recommendations

As in many other medical specialties, there is a critical need to collect complete data on amount, type and potency of marijuana product ingested. For pediatric exposures, this data is critical for clinical management if emergency medical services or hospitalization is needed. It is also valuable for future research. Continued monitoring of data on poison center calls, emergency room visits and hospitalizations will provide prevalence data on unintentional exposures in the pediatric population. The committee identified multiple opportunities to educate parents and caregivers about safe adult use and safe storage. Further research is needed on unintentional marijuana exposures in children, including the impact of various environmental factors, beliefs, laws and regulations. Examples of possible research topics include the effects of child-resistant packaging requirements, point-of-sale education, marijuana marketing and perception of harm.

Table 1 Findings summary: Unintentional marijuana exposures in children
For an explanation of the classifications "Substantial," "Moderate," etc., see Chapter 7. Systematic literature review process.

Substantial	Moderate	Limited	Insufficient	Mixed
Legal marijuana access increases unintentional marijuana exposures in children	Child-resistant packaging reduces unintentional pediatric poisonings			

Evidence statements

Evidence statements are based on systematic scientific literature reviews performed by Colorado Department of Public Health and Environment staff with oversight and approval by the Retail Marijuana Public Health Advisory Committee. For an explanation of the classifications "Substantial," "Moderate," etc., see Chapter 7. Systematic literature review process. For details about the studies reviewed, see Appendix Q.

1. We found **SUBSTANTIAL** evidence that more unintentional marijuana exposures among children occur in states with increased legal access to marijuana; and that the exposures can lead to significant clinical effects requiring medical attention.[3-5] (Revised*)
2. We found **MODERATE** evidence that the use of child-resistant packaging reduces unintentional pediatric poisonings from a wide range of hazardous household products including pharmaceutical products.[6-8]

Public health statements

Public health statements are plain language translations of the major findings (Evidence Statements) from the systematic literature reviews. These statements have been officially approved by the Retail Marijuana Public Health Advisory Committee.

1. Legal marijuana access is strongly associated with increased numbers of unintentional exposures in children which can lead to hospitalizations. (Revised*)
2. While little data are available for marijuana, evidence indicates that child resistant packaging prevents exposure to children from potentially harmful substances.

* Revised = the statement has been adjusted since the 2014 edition of the report, due to new evidence. Added = the statement is new since the 2014 edition of the report. See Appendix Q for dates of most recent literature review.

Public health recommendations

Public health recommendations have been suggested and approved by the Retail Marijuana Public Health Advisory Committee with the goals of: 1) Improving knowledge regarding population-based health effects of retail marijuana use and 2) Developing and targeting public health education and prevention strategies for high-risk sub populations.

Data quality issues

- Data collection in cases of unintentional marijuana exposure should include amount, type and potency of the marijuana when possible.

Surveillance

- Monitor pediatric emergency department visits, hospitalizations and poison center calls resulting from unintentional marijuana exposure.

Education

- Educate parents and caregivers about keeping marijuana and marijuana products away from children and using child resistant packaging.

Research gaps

The Retail Marijuana Public Health Advisory Committee identifies important gaps in the scientific literature that may impact public health policies and prevention strategies. Colorado should support unbiased research to help fill the following research gaps identified by the committee.

- Studies are needed to evaluate the impact of various environmental factors, beliefs, laws and regulations on unintentional marijuana exposure. These studies should include specific factors such as perception of harm, marijuana marketing, point-of-sale education and marijuana packaging requirements.

References

1. Rocky Mountain Poison & Drug Center (RMPDC). *Colorado 2014 Annual Report*. 2015.
2. Children's Hospital Colorado. Acute Marijuana Intoxication. 2016; https://www.childrenscolorado.org/conditions-and-advice/conditions-and-symptoms/conditions/acute-marijuana-intoxication/. Accessed December 23, 2016,
3. Wang GS, Roosevelt G, Le Lait MC, et al. Association of unintentional pediatric exposures with decriminalization of marijuana in the United States. *Ann Emerg Med*. 2014;63(6):684-689.
4. Onders B, Casavant MJ, Spiller HA, Chounthirath T, Smith GA. Marijuana Exposure Among Children Younger Than Six Years in the United States. *Clin Pediatr (Phila)*. 2015;10.1177/0009922815589912.
5. Wang GS, Roosevelt G, Heard K. Pediatric marijuana exposures in a medical marijuana state. *JAMA Pediatr*. 2013;167(7):630-633.
6. Breault HJ. Five years with 5 million child-resistant containers. *Clin Toxicol*. 1974;7(1):91-95.
7. Clarke A, Walton WW. Effect of safety packaging on aspirin ingestion by children. *Pediatrics*. 1979;63(5):687-693.
8. Rodgers GB. The effectiveness of child-resistant packaging for aspirin. *Arch Pediatr Adolesc Med*. 2002;156(9):929-933.

Section 3

Monitoring Possible Marijuana-Related Health Effects in Colorado

Retail Marijuana Public Health Advisory Committee

COLORADO
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Background

This chapter presents efforts of the Colorado Department of Public Health and Environment (CDPHE) to monitor the potential population-based health effects of legalized marijuana. Through 25-1.5-110, C.R.S., CDPHE was given statutory authority to:

- "...collect Colorado-specific data that reports adverse health events involving marijuana use from the all-payer claims database, hospital discharge data, and behavioral risk factors."

The purpose of this data collection and analysis was stated in 25-1.5-110 C.R.S. to "...monitor the emerging science and medical information relevant to the health effects associated with marijuana use." The data analyses reported in this chapter were reviewed by the Retail Marijuana Public Health Advisory Committee as outlined in 25-1.5-110 C.R.S. to help "...make recommendations as appropriate, for policies intended to protect consumers of marijuana or marijuana products and the general public."

This chapter focuses on the analysis of the two primary public health datasets used to monitor: 1) exposures to drugs and other toxic substances and 2) hospital and emergency department use.

We analyzed the data in this chapter using the following four time periods that reflect the status of marijuana legalization in Colorado:

- 2000 – prior to legalized medical marijuana
- 2001-2009 – medical marijuana legalized
- 2010-2013 – medical marijuana commercialized
- 2014-2016 – retail (recreational) marijuana legalized

Data sources

Rocky Mountain Poison and Drug Center data

The Rocky Mountain Poison and Drug Center (RMPDC) provides medical information to health care providers and the public to reduce toxicity, injury, and disease related to exposures of all kinds. RMPDC has been providing information and assistance to Colorado and the surrounding region for more than 50 years. RMPDC participates in the American Association of Poison Control Centers' National Poison Data System (NPDS). RMPDC and NPDS information is used by public health, pharmaceutical and medical institutions for research, education and prevention initiatives in Colorado and throughout the nation. Poison center call volume data are typically used as a surrogate data source to determine the potential for adverse health effects from exposure to chemicals, environmental agents, biotoxins and drugs. RMPDC data is one of the few near "real-time" data sources available to public health professionals. In this report marijuana exposure calls to RMPDC were examined from 2000 to 2016 to examine potential trends in relation to marijuana legalization periods.

Colorado Hospital Association data

The Colorado Hospital Association (CHA) collects data on hospitalizations and emergency department (ED) visits from participating hospitals in Colorado. The data include patient demographics, admit and discharge dates, and discharge diagnoses/billing codes and procedure codes. CHA has about 100 member hospitals, the vast majority of hospitals in Colorado. However, the database does not include inpatient mental health facilities, ambulatory surgical centers, long-term care facilities, military hospitals, and other outpatient treatment settings. The CHA dataset was used to investigate rates of hospitalizations and ED visits with marijuana-related billing codes.

Summary of key findings

The most prominent findings from Rocky Mountain Poison and Drug Center and Colorado Hospital Association data are described below. For additional results and details, see the individual chapters for RMPDC (page 239) and CHA (page 251).

RMPDC data

From 2000 to 2009, RMPDC marijuana exposure call volume remained fairly constant. In 2010, total annual marijuana exposure calls doubled, from 44 to 93. From 2010 to 2013, there was a slight additional increase in counts of marijuana exposure calls. Another large increase was seen in 2014, from 127 to 222. There were 229 marijuana exposure calls in 2015 and 201 in 2016. Most of these changes were due to calls involving marijuana only, with only a small increase in calls involving marijuana and other substances together.

For children ages 0-8 years, marijuana exposure calls averaged 5 per year from 2000 to 2009. They peaked in 2015 at 48 calls and dropped to 40 in 2016. Ages 9-17 years averaged 17 calls per year from 2000-2009, peaked at 63 in 2015 and dropped to 42 in 2016. Ages 18-24 years averaged 17 calls per year from 2000-2009, and increased to 35 in 2016. Adults age 25 years and older had the largest increase in the number of marijuana exposure calls, averaging 15 calls per year from 2000 to 2009 and peaking at 90 calls in 2014. Calls in this age group decreased to 78 in 2015 and 73 in 2016.

Nearly all calls for children ages 0-8 years were unintentional exposure in all time periods. From 2014 to 2016, unintentional exposures comprised 17 percent of calls for ages 9-17 years, 9 percent of calls for ages 18-24 years, and 23 percent of calls for ages 25 years and older. Data on type of marijuana product was only available for July 2014 to December 2016. For children ages 0-8 years, twice as many exposure calls were about edible marijuana products compared to smokeable products. In all other age groups, smokeable products were most common.

CHA data

The rates of hospitalizations and emergency department (ED) visits with poisonings possibly due to marijuana in children under 9 years old have increased over time since medical marijuana legalization in 2000, with the largest increase following medical marijuana commercialization in 2010. For 2014 and 2015, this rate was 14 per 100,000 hospitalizations and 9 per 100,000 ED visits. The number of hospitalizations and ED visits with poisonings possibly due to marijuana among children under 9 years old was higher in urban areas compared to rural areas.

When examining the rates of hospitalizations and ED visits with marijuana-related billing codes for all ages, there was an increasing trend in hospitalizations from 2001 to 2015, reaching 3,025 per 100,000. There was an increasing trend in ED visits from 2012 to 2014, reaching 1,039 per 100,000. ED visits declined in 2015 to 754 per 100,000. Rates of hospitalizations with marijuana-related billing codes were highest among males, adolescents and young adults, and blacks. Rates of ED visits were highest among males, young adults, and black and unknown races.

Rates of hospitalizations and ED visits with marijuana-related billing codes have increased throughout most counties in Colorado. In 2014, hospitalization rates tended to be highest in urban, mountain and southern counties and ED visit rates tended to be highest in mountain and southern counties.

Examination of primary diagnosis categories revealed that hospitalizations with marijuana-related billing codes were nine times more likely to have a primary diagnosis of a mental illness than those without marijuana-related billing codes. ED visits with marijuana-related billing codes were five times more likely to have a primary diagnosis of a mental illness than those without. Other primary diagnosis categories that were more likely among hospitalizations with marijuana-related billing codes were injuries and poisonings, diseases of the skin and subcutaneous tissue, diseases of the nervous system and sense organs, endocrine, nutritional, and metabolic diseases and immunity, and infectious and parasitic diseases. Among ED visits, unclassified codes and E codes were also more likely when a marijuana-related billing code was present.

Discussion

The data presented here provide important insights into 1) the yearly volume, trends over time and nature of marijuana exposure calls to the poison center among different age groups and 2) the rates of hospitalizations and emergency department visits for which a marijuana-related billing code was used, including patterns by age and other demographics. These data do have limitations. Changes in poison center calls, hospitalizations and emergency department visits might occur as a result of changes in the amount or type of marijuana use or an increased honesty in reporting marijuana use to health care providers. Changes in physician screening or reporting related to marijuana or changes in coding practices could affect the rates of hospitalizations and emergency department visits with marijuana-related billing codes. Some hospitalizations and ED visits with marijuana-related billing codes may not have been caused or contributed to by marijuana use. Finally, the poison center is not called in all cases of someone experiencing a marijuana-related adverse health symptoms or requiring medical attention following marijuana exposure. Nonetheless, these data reveal important trends.

Encouraging trends

- Marijuana exposure calls to the poison center appear to be decreasing since 2015, including unintentional exposures in children ages 0-8 years.
- The overall rate of emergency department visits with marijuana-related billing codes dropped 27 percent from 2014 to 2015 (2016 data is not available yet).

Trends to continue monitoring

- Marijuana exposure calls to the poison center continue to be higher in years after medical marijuana commercialization (2010-2016) than in previous years (2000-2009), including calls about children 0-8 years old with unintentional marijuana exposure.
- Edible marijuana products were involved in about 40 percent of marijuana exposure calls to the poison center. For children 0-8 years old, calls about edible marijuana were twice as common as calls about smokeable marijuana.
- The overall rate of hospitalizations with marijuana-related billing codes has increased each year since 2008.

- Among young adults (ages 18-25 years) in 2014 and 2015, about 8 percent of all hospitalizations and 2 percent of all emergency department visits had a marijuana-related billing code. This was higher than the rate among other age groups, and likely reflects the higher rate of marijuana use in this age group.
- Disparities in hospitalizations and emergency department visits also existed by sex and race, with higher rates among males and blacks across all time periods.
- Hospitalizations with marijuana-related billing codes are nine times more likely to have a primary mental health diagnosis compared to those without marijuana-related billing codes.

Recommendations and future directions

1. Continue using RMPDC and CHA data to monitor trends in potential marijuana health effects and assess the impact over time, especially among groups with higher rates of marijuana use.
2. Continue to monitor marijuana exposure calls, including intentionality and type of marijuana. CDPHE and RMPDC are working together to develop a surveillance protocol including additional information such as product name, source and potency.
3. Perform more detailed analyses on unintentional exposures to marijuana in children under age 9. This includes collecting additional primary data from medical records to assess the severity of the outcome, the source of the exposure and possible public health intervention strategies.
4. CDPHE is in the process of analyzing hospitalization and emergency department visit data to assess primary diagnoses in relation to marijuana-related billing codes, in particular for further clarification concerning mental health diagnoses.
5. Use the recent changes in hospitalization and emergency department visit coding (ICD-9 to ICD-10) to explore relationships between different marijuana-related billing codes and primary diagnoses.
6. CDPHE is evaluating death certificate and coroner's report data to determine how it can best be used in monitoring for potential-marijuana-related deaths.
7. CDPHE is working with a hospital in a Colorado ski town to collect new data regarding marijuana use associated with ski-related injuries.

Section 3

Monitoring Possible Marijuana-Related Health Effects in Colorado

Chapter 1

Rocky Mountain Poison and Drug Center (RMPDC) Data, 2000-2016

Retail Marijuana Public Health Advisory Committee

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Introduction

The Rocky Mountain Poison and Drug Center (RMPDC) provides medical information to health care providers and the public to reduce toxicity, injury, and disease related to exposures of all kinds. RMPDC has been providing information and assistance to Colorado and the surrounding region for more than 50 years. RMPDC participates in the American Association of Poison Control Centers' National Poison Data System (NPDS). RMPDC and NPDS information is used by public health, pharmaceutical and medical institutions for research, education and prevention initiatives in Colorado and throughout the nation. Poison Center call volume data are typically used as a surrogate data source to determine the potential for adverse health effects from exposure to chemicals, environmental agents, biotoxins, and drugs. RMPDC data are one of the few near "real-time" data sources available to public health professionals. These data have become an integral component of monitoring marijuana-related adverse health events[1-3]. In this report marijuana exposure calls to RMPDC were examined from 2000-2016 to examine potential trends in relation to marijuana legalization periods.

Methods

Human marijuana exposure calls to RMPDC were queried from NPDS using the marijuana generic category "cannabinoids and analogs" to assess counts of calls received regarding marijuana exposures (Appendix R). Calls with missing exposure information, exposures unrelated to marijuana, or exposures indicating *Medical Review Officer* were validated through a review of the call case notes by a pharmacist and physician. Exposures indicating synthetic marijuana analogs and THC medications like marinol, dronabinol, and cannabidiol were excluded from this analysis.

Counts of marijuana exposure calls were quantified by calendar year (2000-2016) for calls with marijuana exposures only and calls with marijuana in combination with other drug exposures. Counts of marijuana exposure calls were stratified into four age categories, intentionality (unintentional & intentional exposures), intentionality and age categories, and marijuana type (edibles, smokeables, & other) (Appendix R).

Results

There were 1,688 human marijuana exposure calls to RMPDC from 2000 to 2016 (See details about analytic population in Appendix Figure R.1). From 2000 to 2009, RMPDC marijuana exposure call volume remained fairly constant. However, in 2010 marijuana exposure calls significantly increased twofold compared to 2009 from 44 to 93. From 2010 to 2013 counts of marijuana exposure calls increased from 93 to 127 but the change was not significant. In 2014 marijuana exposure calls significantly increased compared to 2013 by 74.8% from 127 to 222. The number of marijuana exposures calls remained constant from 2014 (n=222) to 2015 (n=229).In 2016 the number of marijuana exposure calls decreased (n=201) but the change was not significant.

Beginning in 2012 larger proportions of the marijuana exposures calls were of marijuana only exposures (Figure 1). Ages 0-17 years and 25 years and older showed increased numbers of marijuana exposure calls in the *Medical Marijuana Commercialized* era (2010-2013) compared to the *Medical Marijuana Legalized* era (2001-2009), while ages 18-24 years remain fairly constant since the *Prior to Legalization of Medical Marijuana* era(2000) (Figure 2). In 2014 with the beginning of the *Retail Marijuana Legalized* era, all ages showed increased numbers of marijuana exposure calls compared to the *Medical Marijuana Commercialized* era (2010-2013) (Figure 2). This increase continued for ages 0-17 years in 2015. In 2016, only ages 18-24 years showed an increase in marijuana exposure calls (25 to 35 calls) after decreasing from 2014 to 2015 (31 to 25 calls)(Figure 2). All other ages showed a decrease in marijuana exposure calls in 2016 (Figure 2).

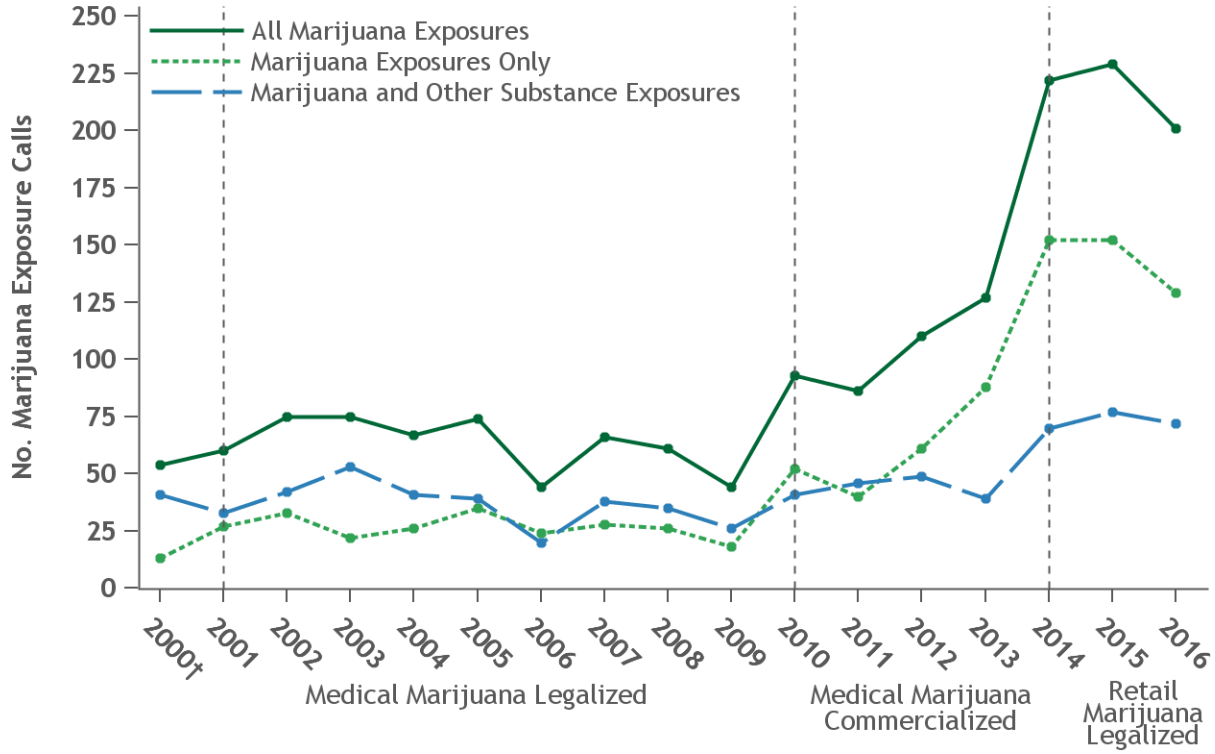
The numbers of intentional and unintentional marijuana exposure calls remained constant when examined from the *Prior to Legalization of Medical Marijuana* era (2000) through the *Medical Marijuana Legalized* era (2001-2009). However, both types of exposures began to increase in 2010 with the commercialization of medical marijuana and continued to increase through the legalization of retail marijuana and in 2015 (Figure 3). In 2016, both intentional and unintentional marijuana exposure calls decreased, from 139 to 113 and 80 to 73, respectively (Figure 3). Stratifying the calls into age groups by intentionality showed similar results where the number of marijuana exposure calls remained constant from 2000 to 2009 for both intentional and unintentional exposures (Figure 4). In 2010, numbers of intentional and unintentional marijuana exposure calls in all age groups began to increase; however, the highest numbers of unintentional marijuana exposures were among children 0-8 years old. The highest numbers of intentional marijuana exposures were in adults 25 years or older (Figure 4).

RMPDC began collecting information regarding the type of marijuana involved in the exposure call on July 1, 2014. Therefore the data were limited to July 1, 2014 to December 31, 2016 to examine the type of marijuana involved in the marijuana exposure calls. There were 529 marijuana exposure calls during this time period. Among these 38.3% (n=203) were edibles, 37.6% (n=199) were smokeables, and 24.0% (n=127) were other marijuana products (Figure 5). Among calls for children ages 0-8, edible marijuana products constitute 54.5% (n=60) of marijuana exposures, followed by smokeables (25.4%, n=28, typically eaten in this age group) and other marijuana products (22.7%, n=22) (Figure 6). Among ages 25 years and older, the proportion of edible (35.6%, n=69) and smokeable (37.6%, n=73) marijuana products were similar (Figure 6). Smokeable marijuana products represented the most prevalent type of exposures among those 9 to 24 years, followed by edibles and other marijuana products (Figure 6).

Limitations

Limitations of poison center data include self-selection bias: calls are self-reported; neither all individuals with symptoms, nor all health care providers managing patients with marijuana exposures call the poison center. Therefore, the number of cases reported is likely an underestimation and not necessarily a full representation of the population that needs the services of either RMPDC or urgent/emergency medical services for a toxic exposure.

Figure 1. Number of marijuana exposure calls to poison center by marijuana only and marijuana with other substances in Colorado



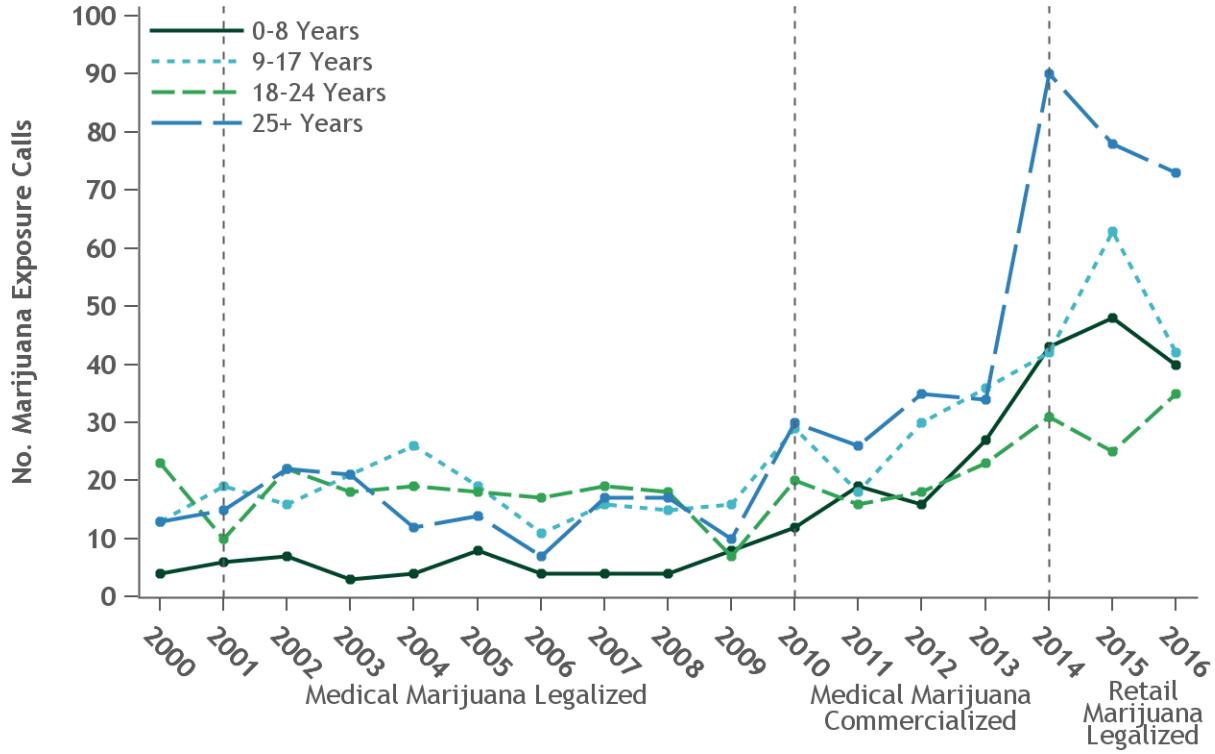
Produced by: EEOHT, CDPHE 2016.
*Counts significantly increased from previous year with a p value <0.003.
†Prior to legalized medical marijuana.
‡Data Source: National Poison Data System (NPDS) closed, human, marijuana exposure calls in Colorado from 2000 to 2016, n=1,688.

Major Findings

- Counts of calls remain fairly constant from 2000 to 2009.
- In 2010, marijuana exposure calls significantly increased from 44 to 93[a] and in 2014 calls related to marijuana significantly increased by 74.8% from 127 to 222.[b]
- In 2016, marijuana exposure calls decreased from 229 calls in 2015 to 201 calls.[c]

[a] *p* value<0.0001
[b] *p* value<0.0001
[c] For an explanation of terms and statistical comparisons used see Appendix R Table R.1.

Figure 2. Number of marijuana exposure calls to poison center by age group in Colorado



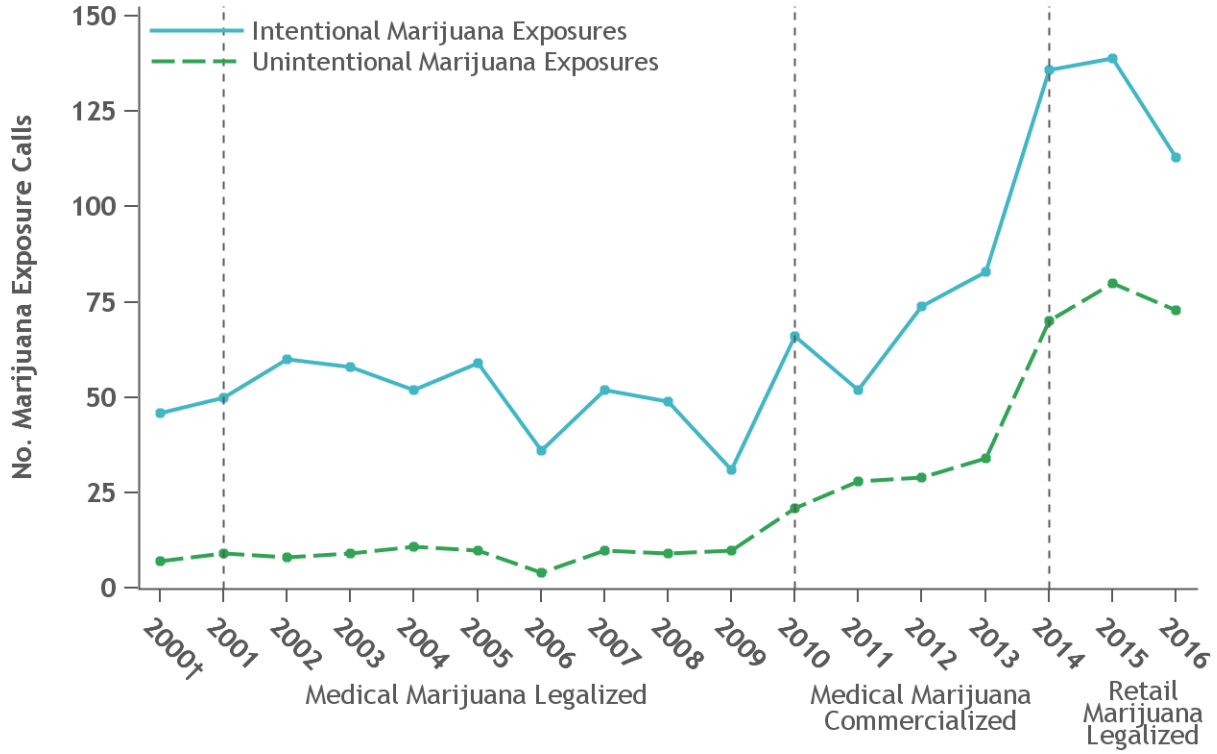
Produced by: EEOHT, CDPHE 2016.
†Data Source: National Poison Data System (NPDS) closed, human, marijuana exposure calls in Colorado from 2000 to 2016, n=1,542.

Major Findings

- Ages 0-17 years and 25 years and older showed increased numbers of marijuana exposure calls in the *Medical Marijuana Commercialized* era (2010-2013) compared to the *Medical Marijuana Legalized* era (2001-2009), while ages 18-24 years remain fairly constant since the *Prior to Legalization of Medical Marijuana* era (2000).
- In 2014, with the beginning of the *Retail Marijuana Legalized* era (2014-2016), all ages showed increased numbers of marijuana exposures calls compared to the *Medical Marijuana Commercialized* era (2010-2013).
- Marijuana exposure calls for 25 years and older increased from 34 in 2013 to peak at 90 in 2014, and then decreased in both 2015 (78) and 2016 (73).
- Marijuana exposure calls decreased from 2015 to 2016 in ages 0-8 years (48 to 40) and 9-17 years (63 to 42), and increased in ages 18-25 years (25 to 35).[d]

[d] For an explanation of terms and statistical comparisons used see Appendix R Table R.2.

Figure 3. Number of intentional and unintentional marijuana exposure calls to poison center in Colorado



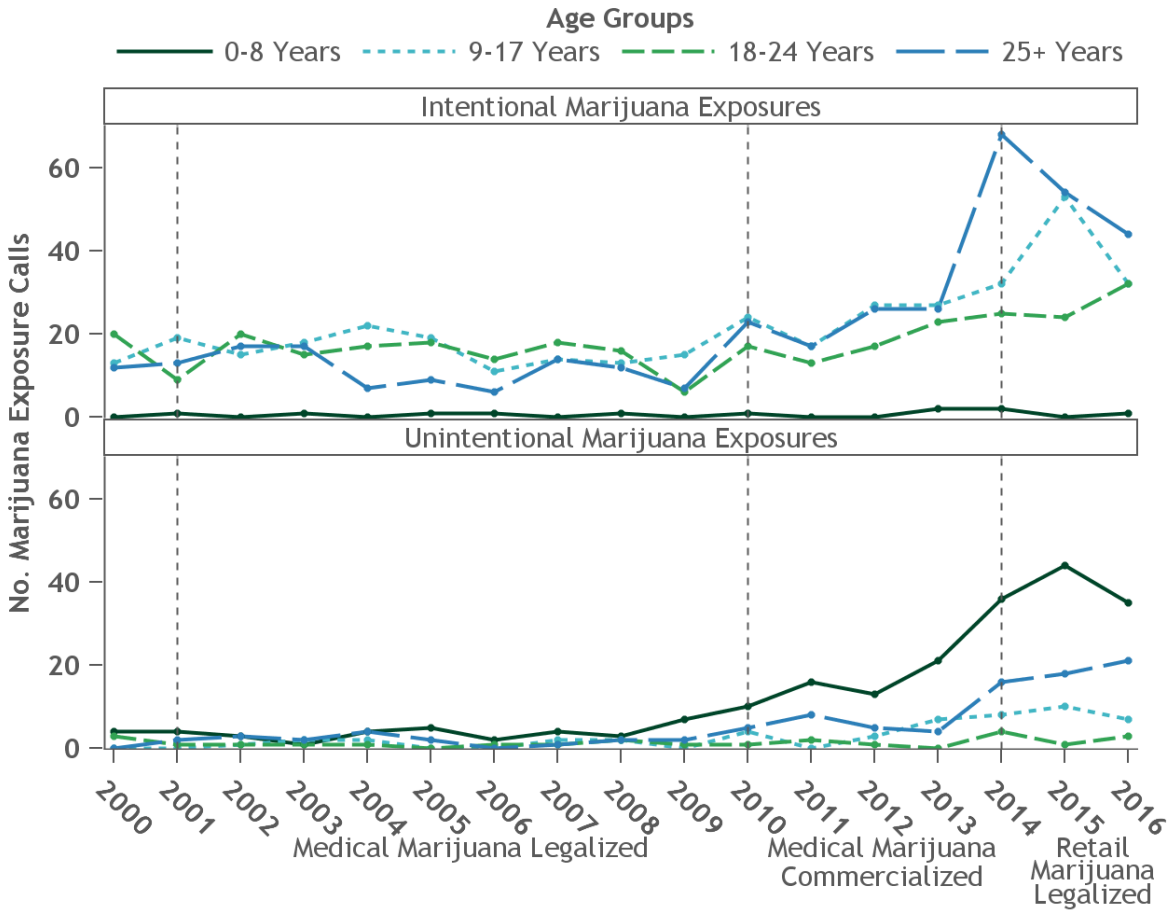
Produced by: EEOHT, CDPHE 2016.
†Prior to legalized medical marijuana.
‡Data Source: National Poison Data System (NPDS) closed, human, marijuana exposure calls in Colorado from 2000 to 2016, n=1,578.

Major Findings

- Numbers of both intentional and unintentional marijuana exposure calls remained constant from the *Prior to Legalization of Medical Marijuana* era (2000) through the *Medical Marijuana Legalized* era (2001-2009); however, they begin to increase in 2010 with the *Medical Marijuana Commercialized* era (2010-2013) and continued to increase through the *Retail Marijuana Legalized* era (2014-2016) until 2015.
- In 2016, both intentional and unintentional marijuana exposure calls decreased, from 139 and 80 in 2015 to 113 and 73, respectively; however, this trend was not significant.[e]

[e] For an explanation of terms and statistical comparisons used see Appendix R Table R.3.

Figure 4. Number of marijuana exposure calls to poison center by intention and age groups in Colorado



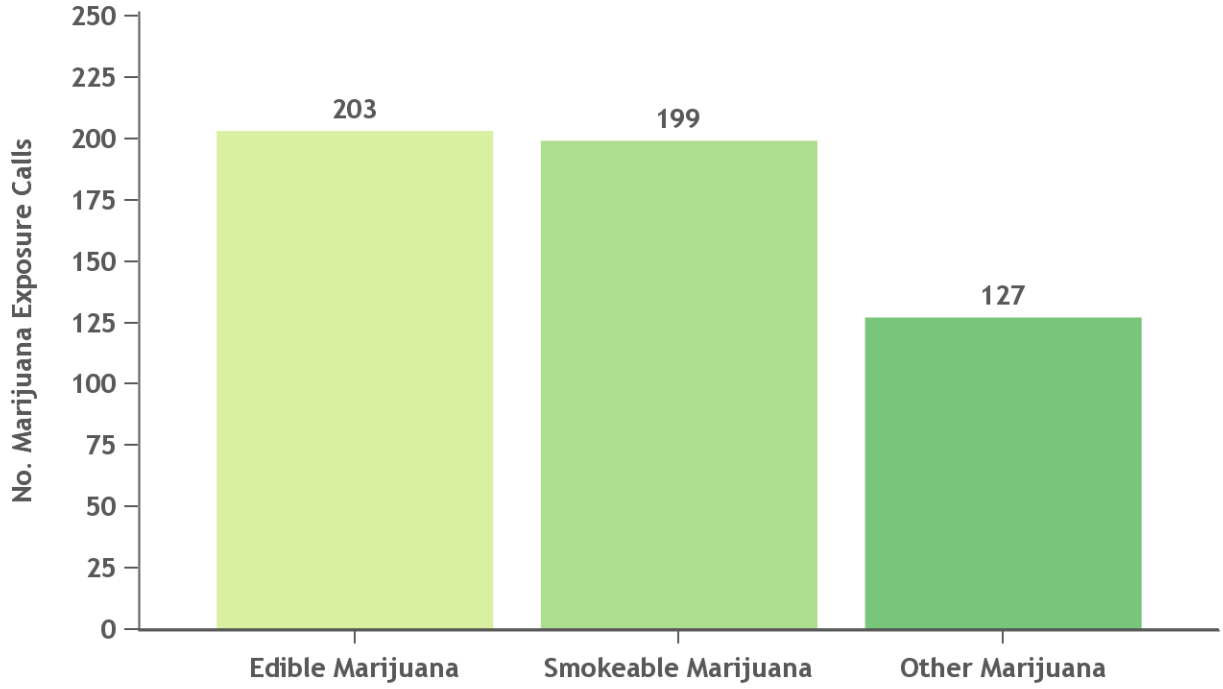
Produced by: EEOHT, CDPHE 2016.
†Data Source: National Poison Data System (NPDS) closed, human, marijuana exposure calls in Colorado from 2000 to 2016, n=1,437.

Major Findings

- Among all age groups, numbers of both intentional and unintentional marijuana exposures remained constant through the Medical Marijuana Legalized era (2000-2009).
- Numbers of intentional marijuana exposures began to increase among those aged 9 years and older in 2010 with those 25 years and older showing the largest increases.
- Numbers of unintentional marijuana exposures increased among all age groups beginning in 2010; however, those aged 0-8 years showed the largest increases.
- In 2016, intentional marijuana exposure among those 18-24 years increased (24 to 32) as well as unintentional marijuana exposure among those 25 years or older (18 to 21). Marijuana exposure calls, intentional and unintentional, among other age groups decreased or remained constant in 2016.[f]

[f] For an explanation of terms and statistical comparisons used see Appendix R Table R.4.

Figure 5. Number of marijuana exposure calls to poison center by marijuana type in Colorado, July 2014 to December 2016



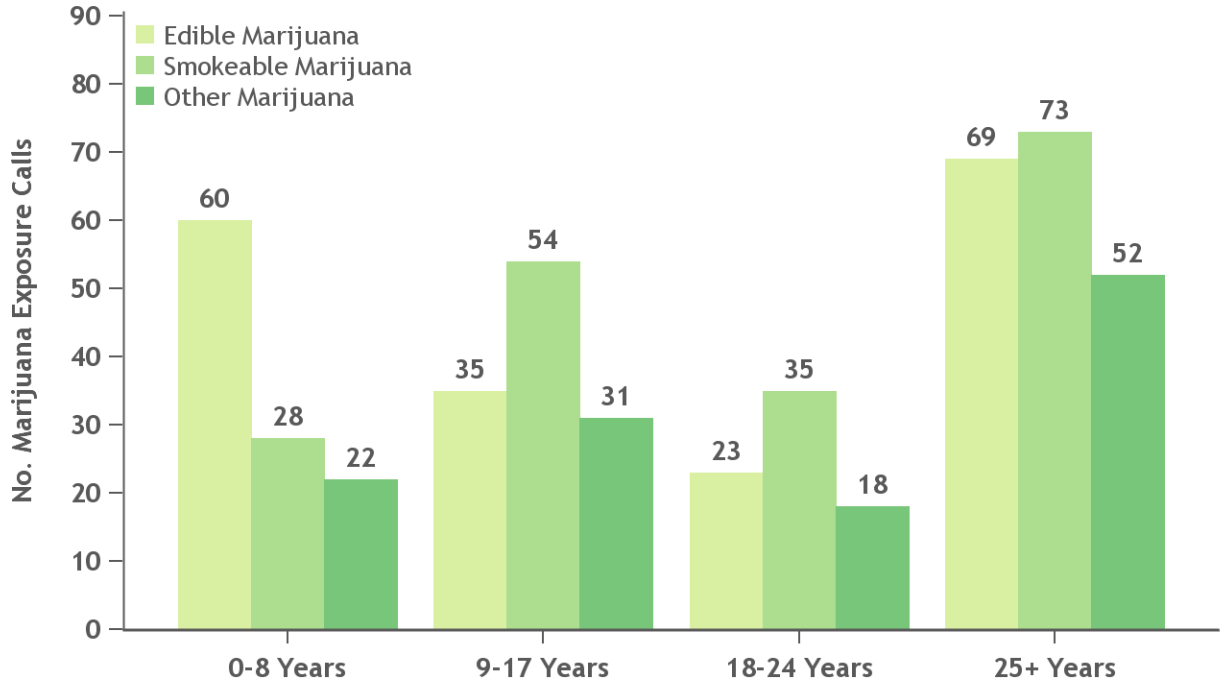
Produced by: EEOHT, CDPHE 2016.
*Data Source: National Poison Data System (NPDS) closed, human, marijuana exposure calls in Colorado from July 1, 2014 to December 31, 2016, n=529.

Major Findings

- There were 529 marijuana exposure calls from July 1, 2014 to December 31, 2016.
- Among marijuana exposure calls during this time period, 38.3% were edibles, 37.6% were smokeables, and 24.0% were other marijuana products.[g]

[g] For an explanation of terms and statistical comparisons used see Appendix R Table R.5.

Figure 6. Number of marijuana exposure calls to poison center by marijuana type and age groups in Colorado, July 2014 to December 2016



Produced by: EEOHT, CDPHE 2016.
†There were 29 calls not shown due to unknown age.
‡Data Source: National Poison Data System (NPDS) closed, human, marijuana exposure calls in Colorado from 2000 to 2016, n=529.

Major Findings

- Among children ages 0-8 years, edible marijuana products accounted for 54.5% (N=60) of marijuana exposures, followed by smokeables (25.4%, N=28) and other marijuana products (22.7%, N=22).
- Among those 9 to 24 years, the most prevalent type of marijuana exposures were smokeable marijuana products, followed by edibles and other marijuana products.
- Among ages 25 years and older, the number of marijuana exposure calls for edible and smokeable marijuana products were similar.[h]

[h] For an explanation of terms and statistical comparisons used see Appendix R Table R.5.

References

1. Davis JM, Mendelson B, Berkes JJ, Suleta K, Corsi KF, Booth RE. Public Health Effects of Medical Marijuana Legalization in Colorado. *Am J Prev Med*. 2015;10.1016/j.amepre.2015.06.034.
2. Onders B, Casavant MJ, Spiller HA, Chounthirath T, Smith GA. Marijuana Exposure Among Children Younger Than Six Years in the United States. *Clin Pediatr (Phila)*. 2015;10.1177/0009922815589912.
3. Wang GS, Roosevelt G, Le Lait MC, et al. Association of unintentional pediatric exposures with decriminalization of marijuana in the United States. *Ann Emerg Med*. 2014;63(6):684-689.

Section 3

Monitoring Possible Marijuana-Related Health Effects in Colorado

Chapter 2

Colorado Hospital Association (CHA) Data, 2000-September 2015

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Introduction

The Colorado Hospital Association (CHA) collects data on hospitalizations (HD) and emergency department (ED) discharges from participating hospitals in the state of Colorado. The data include patient demographics, admit and discharge dates, and discharge diagnoses/billing codes and procedure codes. There are roughly 100 member hospitals of CHA which includes the vast majority of hospitals in Colorado. However, the database does not include inpatient mental health facilities, ambulatory surgical centers, long term care facilities, military hospitals, and other outpatient treatment settings. The CHA dataset was used to investigate rates of HD and ED visits associated with possible marijuana exposures, diagnoses, and billing codes.

Methods

Marijuana-related billing codes

To determine HD and ED visits that were possibly associated with marijuana, four marijuana-related billing codes were used. The International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) is a U.S. Centers for Disease Control and Prevention modification of a set of codes established by the World Health Organization.[1,2] These billing codes are used to assign alphanumeric codes to patient diagnoses. On October 1, 2015 the nation updated its administrative coding from the ICD-9-CM system to ICD-10-CM. This analysis spans HD and ED visits from 2000 (2011 for ED visits) through September 2015. Analysis of the ICD-10-CM coded HD and ED visits will be completed once a full year of ICD-10-CM data is available. The four marijuana-related billing codes used were 305.20-305.23, 304.30-304.33, 969.6, and E854.1 and details about these codes can be found in Appendix S.

We examined HD and ED visit data in three different ways:

1. **Poisonings possibly due to marijuana in children under 9 years of age:** These data were chosen to represent unintentional use of marijuana by children and consisted of HD or ED visits that were coded with discharge codes related to poisoning by psychodysleptics.[3,4] Though psychodysleptic drugs include more than just marijuana, other drugs in this class have a low prevalence of use among children under 9 years of age. In addition, the age cut-off of 9 years was chosen to represent children who were unlikely to be intentionally using marijuana. This applies to Figure 1 and Map 1.
2. **Marijuana-related billing codes in listed diagnosis codes:** These data were chosen to represent the HD and ED visits where marijuana could be a causal, contributing, or coexisting factor noted by the physician during the HD or ED visit. HD and ED visits were included if they had a marijuana-related billing code in one or more of the up to 30 listed codes provided, but marijuana may not be a causal reason for the HD or ED visit. This applies to Figures 2-6 and Maps 2-6.
3. **Primary diagnoses:** Primary diagnoses were examined and compared for HD and ED visits with and without marijuana-related billing codes for all Colorado HD and ED visits from 2000 through September 2015 (2011 through September 2015 for ED visits). See Appendix S, Table S.7 for details. This applies to Figures 7 and 8.

Marijuana legalization eras

Rates of HD and ED visits were described over time by year. To evaluate the impact of changes in marijuana laws in Colorado, four marijuana legalization eras were chosen to display and compare these findings.

- 2000 – Prior to Legalized Medical Marijuana
- 2001-2009 – Medical Marijuana Legalized[5]
- 2010-2013 – Medical Marijuana Commercialized[6,7]
- 2014- September 2015 – Retail (Recreational) Marijuana Legalized[8]

Rates of HD and ED visits were calculated with the number of HD or ED visits with marijuana-related billing codes for a time period in the numerator and total number of HD or ED visits during that time period in the denominator. This proportion was multiplied by 100,000 (1,000 for county level data) to obtain a rate (Appendix S, Figure S.2). Rates of HD and ED visits were compared across years and marijuana legalization eras, and stratified by gender, age, race/ethnicity, and county (Appendix S). Prevalence of primary diagnosis categories were calculated for HD and ED visits with marijuana-related billing codes and for HD and ED visits without marijuana-related billing codes. Prevalence ratios and 95% confidence intervals were calculated comparing the prevalence of primary diagnosis categories by HD or ED visits with marijuana-related billing codes to HD or ED visits without marijuana-related billing codes for the top ten primary diagnosis categories (Appendix S, Figure S.3).

Results

The rates of HD and ED visits with poisonings possibly due to marijuana in children under 9 years old have increased over time since medical marijuana legalization in 2000 (Figure 1). However, this trend was only significant from medical marijuana legalization (2001-2009) to medical marijuana commercialization (2010-2013) (Figure 1). The number of HD and ED visits with poisonings possibly due to marijuana among children under 9 years was higher in urban areas compared to rural areas in Colorado (Map1).

When examining the rates of HD and ED visits with marijuana-related billing codes across years, there was an increasing trend in HD from 2001 to January through September 2015 with the highest rate of 1,260 per 100,000 in January through September 2015. There was also an increasing trend in ED visits from 2012 to 2014 with the highest rate of 1,039 per 100,000 in 2014. However, in January through September 2015 there was a decline in ED visits to 754 per 100,000 (Figure 2). When viewing the annual rates collapsed into marijuana legalization eras, the rate of HD with marijuana-related billing codes increased significantly from the legalization of medical marijuana (2001-2009) to the legalization of retail marijuana (2014-September 2015) (Figure 3). Furthermore, the decrease in ED visits observed in January through September of 2015 was no longer apparent when collapsed to marijuana legalization eras, and a significantly increasing trend was observed from the commercialization of medical marijuana (2011-2013) of 739 per 100,000 to the legalization of retail marijuana (2014-September 2015) of 913 per 100,000 (Figures 3).

The rates of HD with marijuana-related billing codes was highest in males (Figures 4.b), ages 9-24 years (Figures 5.b), and blacks (Figures 6.b). The rates of ED visits with marijuana-related billing codes was highest in males (Figures 4.a), ages 18-24 years (Figures 5.a), and black and unknown races (Figures 6.a).

Rates of HD marijuana-related billing codes have increased throughout most counties in Colorado since 2004, with the highest rates in Crowley county in 2014 (Maps 2, 3, & 4). Rates of ED visits marijuana-related billing codes have increased in throughout Colorado from 2011-2013 to 2014 (Maps 5 & 6). In 2014, the highest rates of ED visits with marijuana-related billing codes were in Summit County, while the highest numbers of ED visits were in Pueblo County (Map 6).

Examination of the 18 broad primary diagnosis categories for HD and ED visits revealed a nine-fold and five-fold increased prevalence of *mental illness* among HD and ED visits respectively with marijuana-related billing codes compared to HD and ED visits without marijuana-related billing codes (Figures 7 & 8). Also, there was a higher prevalence of *injuries and poisonings*, *diseases of the skin and subcutaneous tissue*, *diseases of the nervous system and sense organs, endocrine, nutritional, and metabolic diseases and immunity*, and *infectious and parasitic diseases* among HD with marijuana-related billing codes compared to HD without marijuana-related billing codes (Figure 8). The prevalence of *unclassified codes and E codes* was higher among ED visits with marijuana-related billing codes (Figure 7).

A summary of the results can be found with the following figures and detailed results can be found in Appendix S.

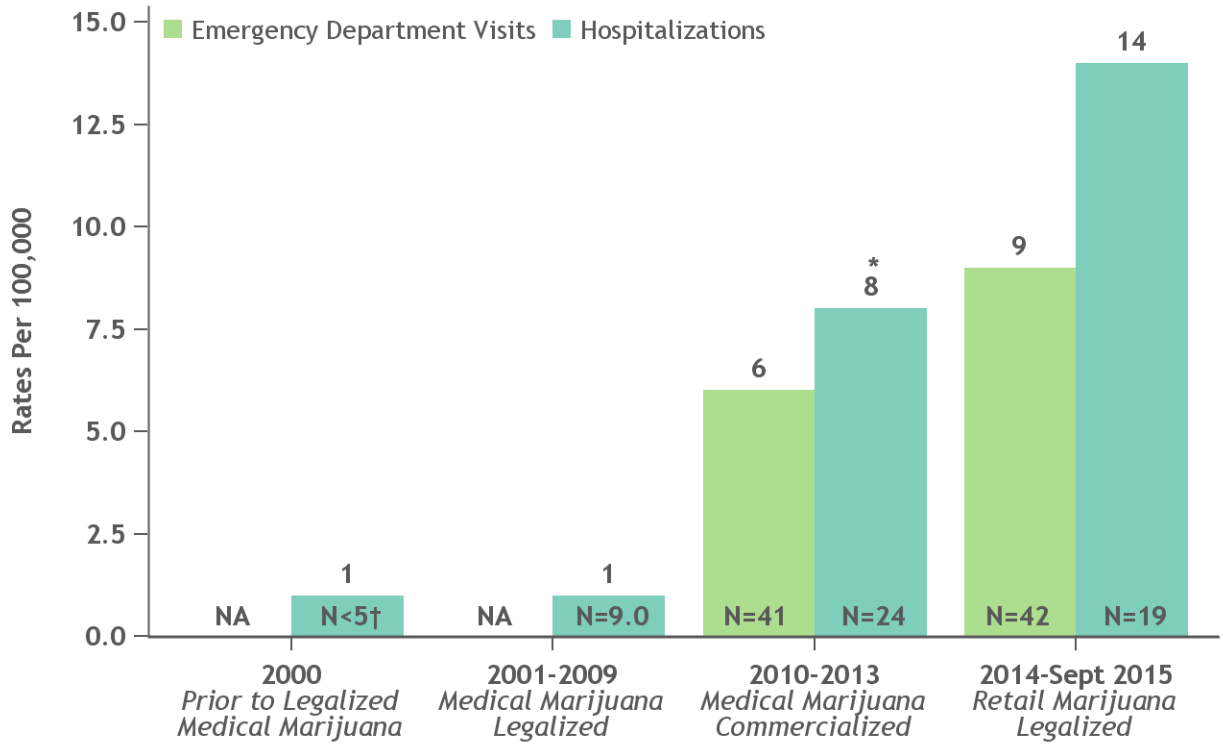
Limitations

The use of marijuana-related ICD-9-CM billing codes is not fully standardized and there may be differences in coding from hospital to hospital. This summary does not account for confounders like increases or changes in marijuana-related discharge coding by the hospitals. Changes in coding could have occurred due to an overall increased awareness regarding marijuana, changes in physician care or reporting related to marijuana, an increased honesty in patients reporting marijuana use to health care providers, or changes in coding practices by hospitals and emergency departments. Changes in marijuana coding could result in an over or underestimate HD and ED visit rates depending on the marijuana legalization era.

A major limitation is the inability to determine whether a discharge code is an exposure or diagnosis or if it is merely for billing. Furthermore, use of these billing codes does not necessarily indicate marijuana was the primary (or even secondary) reason for the HD or ED visit, rather the presence of a marijuana-related code reflects that marijuana use was noted by the treating physician. Therefore, this summary quantifies HD and ED visits with marijuana-related billing codes and does not quantify HD and ED visits due to marijuana. We hypothesize that this summary reflects marijuana use despite the limitations; however, it does not necessarily show the health care burden of marijuana use. Transition to ICD-10 coding may help clarify this issue.

In examining the 18 broad primary diagnosis categories in HD and ED visits with any mention of marijuana, causal associations between marijuana use and the diagnosis categories cannot be made. Furthermore, temporality between the associations found cannot be assessed; meaning it is unclear whether marijuana use preceded the primary diagnosis or the primary diagnosis preceded marijuana use. The associations found between HD and ED visits with marijuana coding and primary diagnosis categories point to specific health outcomes to direct future investigation and resources.

Figure 1. Children under 9 years of age; Rates of hospitalizations (HD) and emergency department (ED) visits with poisoning possibly due to marijuana in Colorado



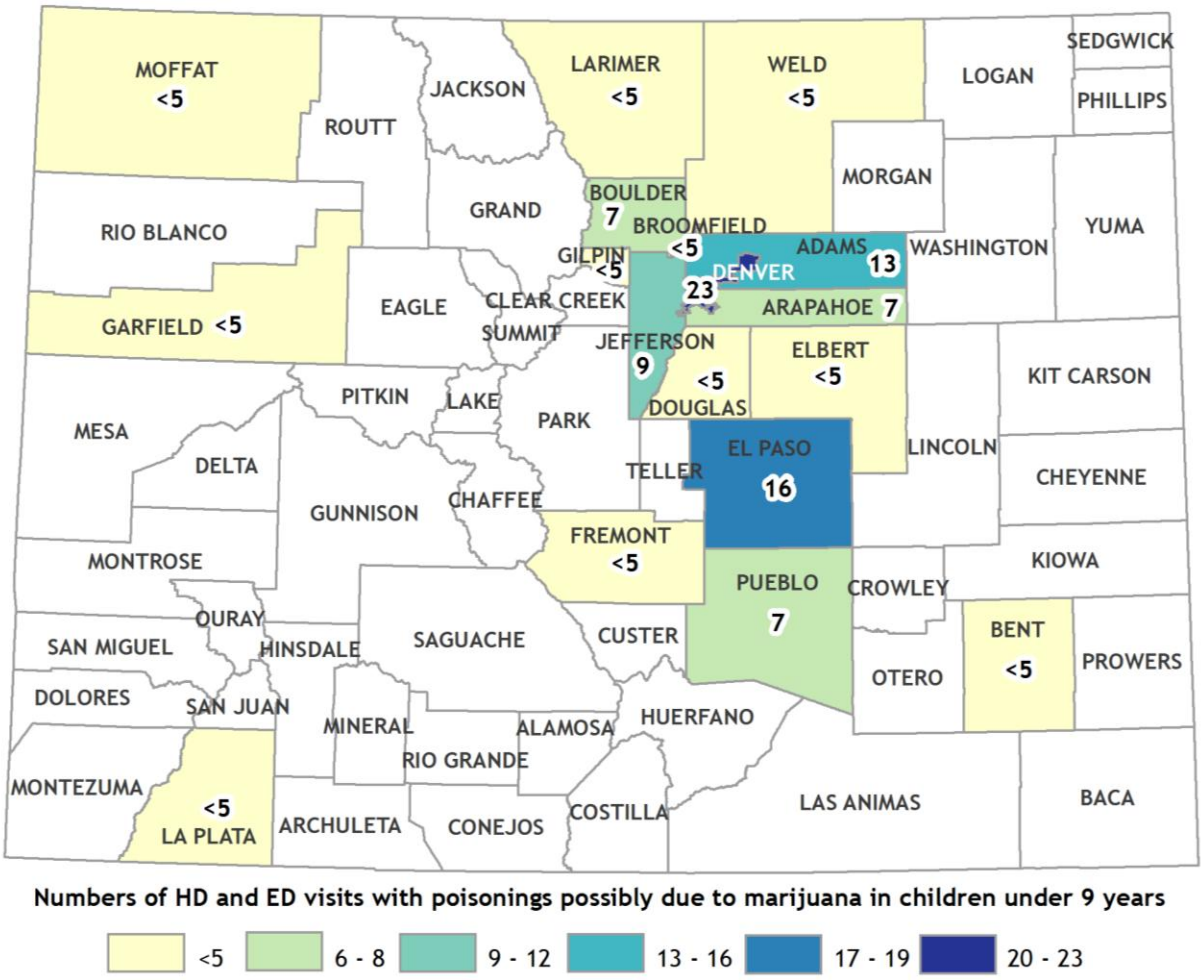
Produced by: EEOHT, CDPHE 2016
*Rate significantly increased from previous time period with a p-value <0.001.
†ICD-9-CM codes 969.6 and E854.1, poisoning and accidental poisoning by psychodysleptics, were used to determine HD and ED visits with poisonings possibly due to marijuana.
‡The Ns are the total number of HD or ED visits with poisoning possibly due to marijuana in the specified time period.
§Data Source: Colorado Hospital Association 2000-Sept 2015 (2011-Sept 2015 for ED visits).

Major findings:

- For children under 9 years old, rates of HD and ED visits had an increasing trend across legalization eras.
- Rates of HD with poisonings possibly due to marijuana in children under 9 years old increased eight-fold from 2001-2009 to 2010-2013.[a]
- The highest rates for both HD and ED visits in children under 9 years old were in 2014 through September 2015, though these rates were not significantly different from the previous time period.[b]

[a] HD rate per 100,000 2001-2009: 1 2010-2013: 8: X^2= 30.0, p<0.001
[b] 2014 to Sept 2015: HD rate per 100,000 (14), ED rate per 100,000 (9)
For an explanation of statistical comparisons used, see Appendix S. For data, see Appendix S Table S.1.

Map 1. Numbers of hospitalizations (HD) and emergency department (ED) Visits with poisonings possibly due to marijuana in children Under 9 Years of age in Colorado, 2004-2014 by county.

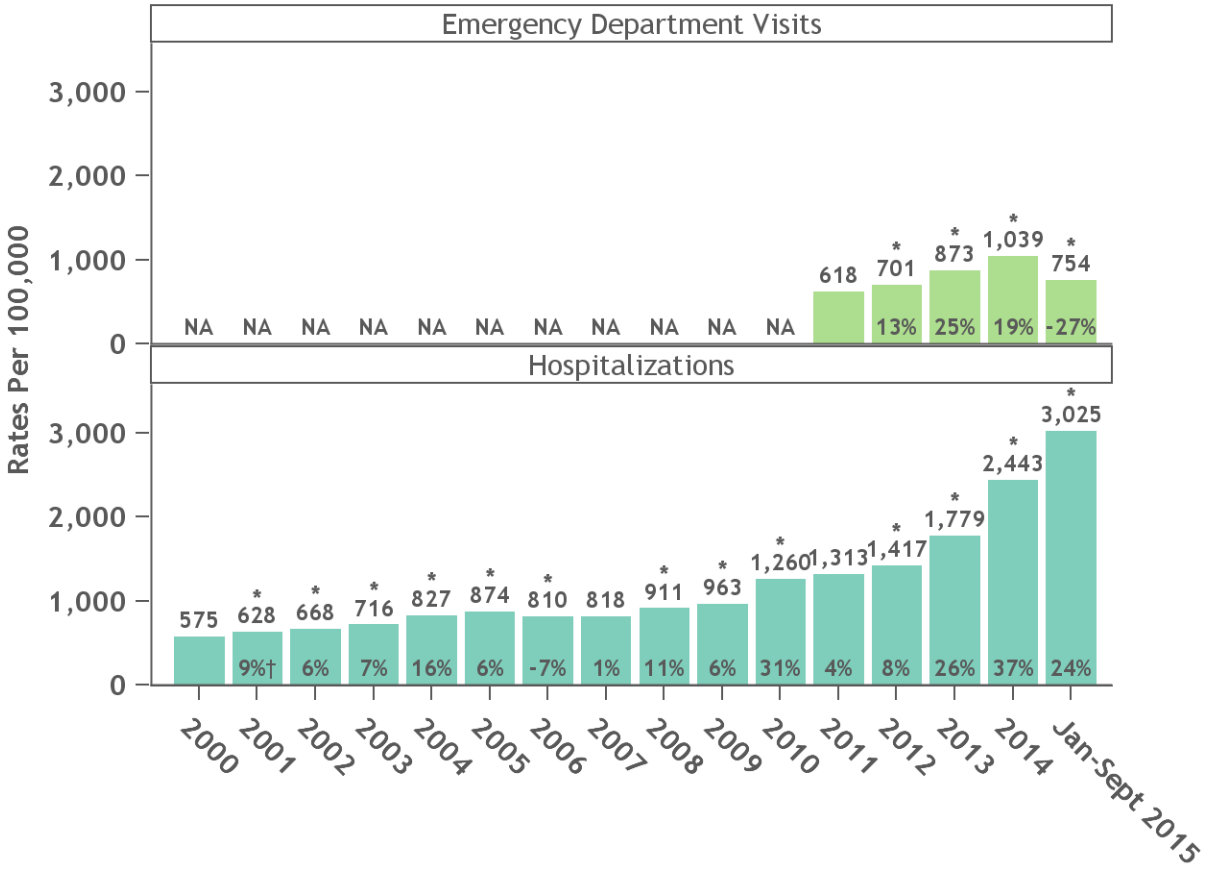


Produced by: EEOHT, CDPHE 2016
*Counties shown in white have no reported HD or ED visits with poisonings possibly due to marijuana in children under 9 years.
†ICD-9-CM codes 969.6 and E854.1 were used to determine HD and ED visits with poisonings possibly due to marijuana.
‡Data source: Colorado Hospital Association (CHA).

Major findings:

- Numbers of HD and ED visits were highest in Denver, El Paso, and Adams counties.
- Higher numbers of HD and ED visits were in urban areas compared to rural.

Figure 2. Rates of hospitalizations (HD) and emergency department (ED) visits with marijuana-related billing codes in Colorado.



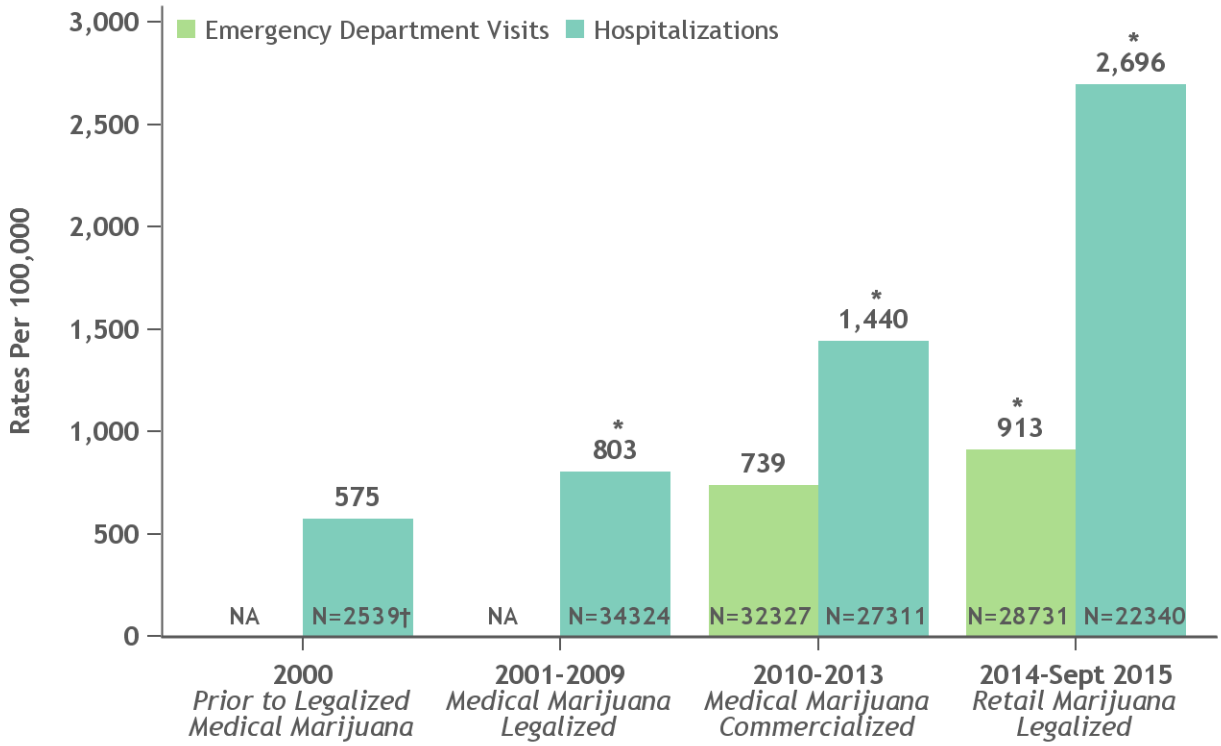
Produced by: EEOHT, CDPHE 2016
*Rate significantly increased from previous time period with a p-value <0.001.
†The percent change in rates of HD and ED visits compared to the previous year.
‡ICD-9-CM codes 305.20-305.23, 304.30-304.33, 969.6, and E854.1 were used to determine HD and ED visits with marijuana-related billing codes.
§Data Source: Colorado Hospital Association 2000-Sept 2015 (2011-Sept 2015 for ED visits).

Major findings:

- Rates of ED visits with marijuana-related billing codes showed an increasing trend from 2012 to 2014 and then decreased from 2014 to January through September of 2015 by 27%.[c]
- Rates of HD with marijuana-related billing codes showed an increasing trend beginning in 2001 with the highest rate of HD in January through September 2015.[d]
- The largest increases in rates were from 2013 to 2014 of 37% for HD[e] and 2012 to 2013 of 25% for ED visits.[f]

[c] Rate of ED visits per 100,000 : 2012 (701), 2013 (873), 2014 (1039), Jan- Sept 2015 (754) increase 27%
[d] Rate of HD per 100,000: Jan- Sept 2015 (3025)
[e] Rate of HD per 100,000: 2013 (1779), 2014 (2443) Increase 37%
[f] Rate of ED per 100,000: 2012 (701), 2013 (873) Increase 25%
For an explanation of statistical comparisons used, see Appendix S. For data, see Appendix S Table S.2.

Figure 3. Rates of hospitalizations (HD) and emergency department (ED) visits with marijuana-related billing codes in Colorado.



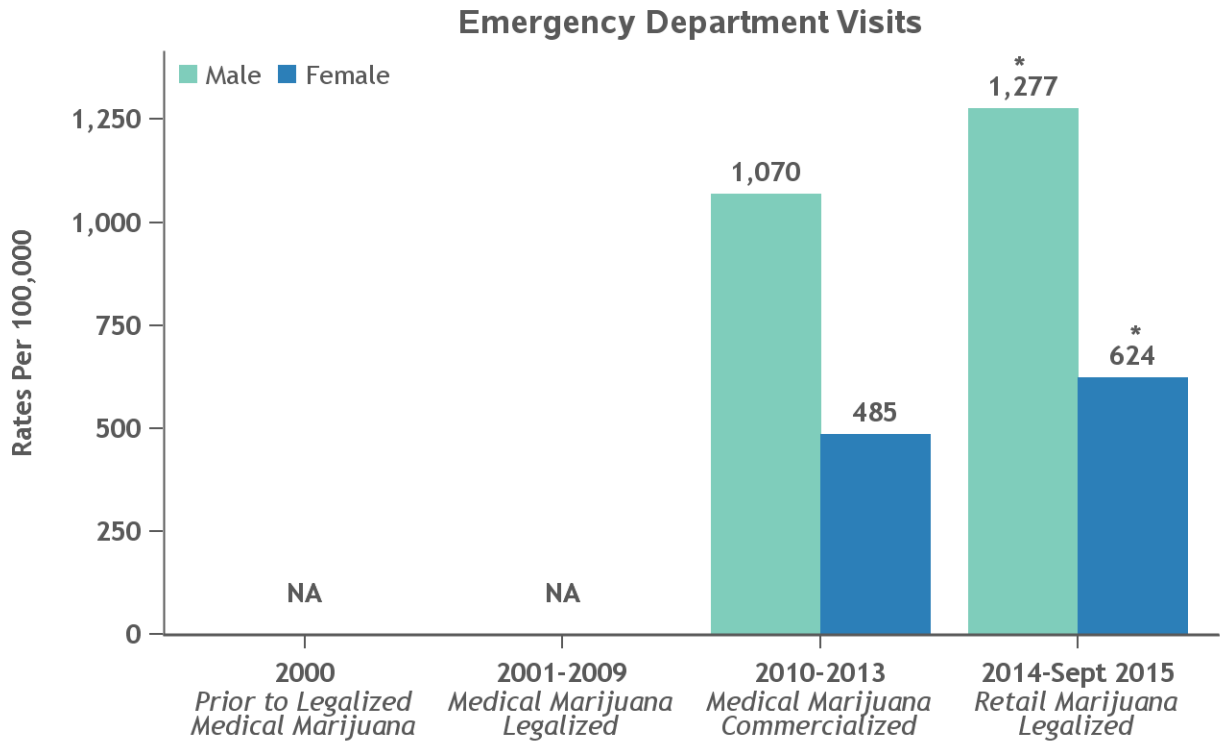
Produced by: EEOHT, CDPHE 2016
*Rate significantly increased from previous time period with a p-value <0.001.
†The Ns are the total number of HD or ED visits with marijuana-related billing codes in the specified time period.
‡ICD-9-CM codes 305.20-305.23, 304.30-304.33, 969.6, and E854.1 were used to determine HD and ED visits with marijuana-related billing codes.
§Data Source: Colorado Hospital Association 2000-Sept 2015 (2011-Sept 2015 for ED visits).

Major findings:

- Rates of HD with marijuana-related billing codes significantly increased by each time period from 2000 to 2014 through September 2015 with the largest increase of 87.2% from 2010-2013 to 2014 through September 2015.[g]
- Rates of ED visits significantly increased by 23.5% from 2010-2013 to 2014 through September 2015.[h]
- The highest rates for both HD and ED visits with marijuana-related billing codes were in 2014 through September 2015.[i]

[g] Rates of HD per 100,000: 2000 (575) vs 2001-2009 (803) X^2= 686.5, p<0.001; 2001-2009 (803) vs 2010-2013 (1440) X^2= 5384.4, p<0.001; 2010-2013 (1440) vs 2014-Sept 2015 (2696) X^2= 5084.9, p<0.001
[h] Rates of ED per 100,000: 2010-2013 (739) vs 2014-Sept 2015 (913) : X^2= 686.5, p<0.001
[i] Highest rates per 100,000: HD 2014-Sept 2015 (2696), ED: 2014-Sept 2015 (913)
For an explanation of statistical comparisons used, see Appendix S. For data, see Appendix S table S.3.

Figure 4.a Rates of emergency department (ED) visits with marijuana-related billing codes by gender.



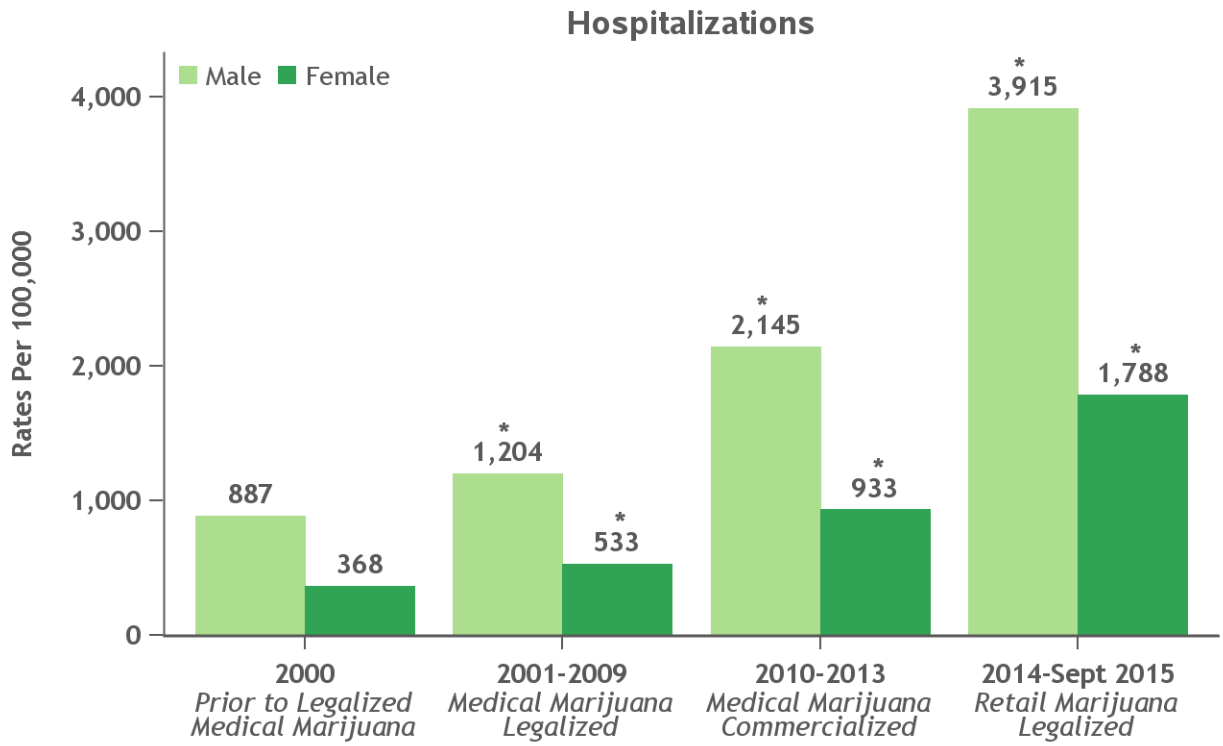
Produced by: EEOHT, CDPHE 2016
*Rate significantly increased from previous time period with a p-value <0.001.
†ICD-9-CM codes 969.6 and E854.1 were used to determine ED visits with marijuana-related billing codes.
‡Data Source: Colorado Hospital Association 2011-Sept 2015.

Major findings:

- Rates of ED visits significantly increased from 2011-2013 to 2014 through September 2015 for both males and females.[j]
- Males had consistently higher rates of ED visits with marijuana-related billing codes across time periods.

[j] Rate ED visits per 100,000: male 2011-2013 (1070) vs 2014-Sept 2015 (1277), X^2= 303.2, p<0.001;
female 2011-2013 (485) vs 2014-Sept 2015 (624), X^2= 364.7, p<0.001
For an explanation of statistical comparisons used, see Appendix S. data, see Appendix S table S.4.

Figure 4.b Rates of hospitalizations (HD) with marijuana-related billing codes by gender.



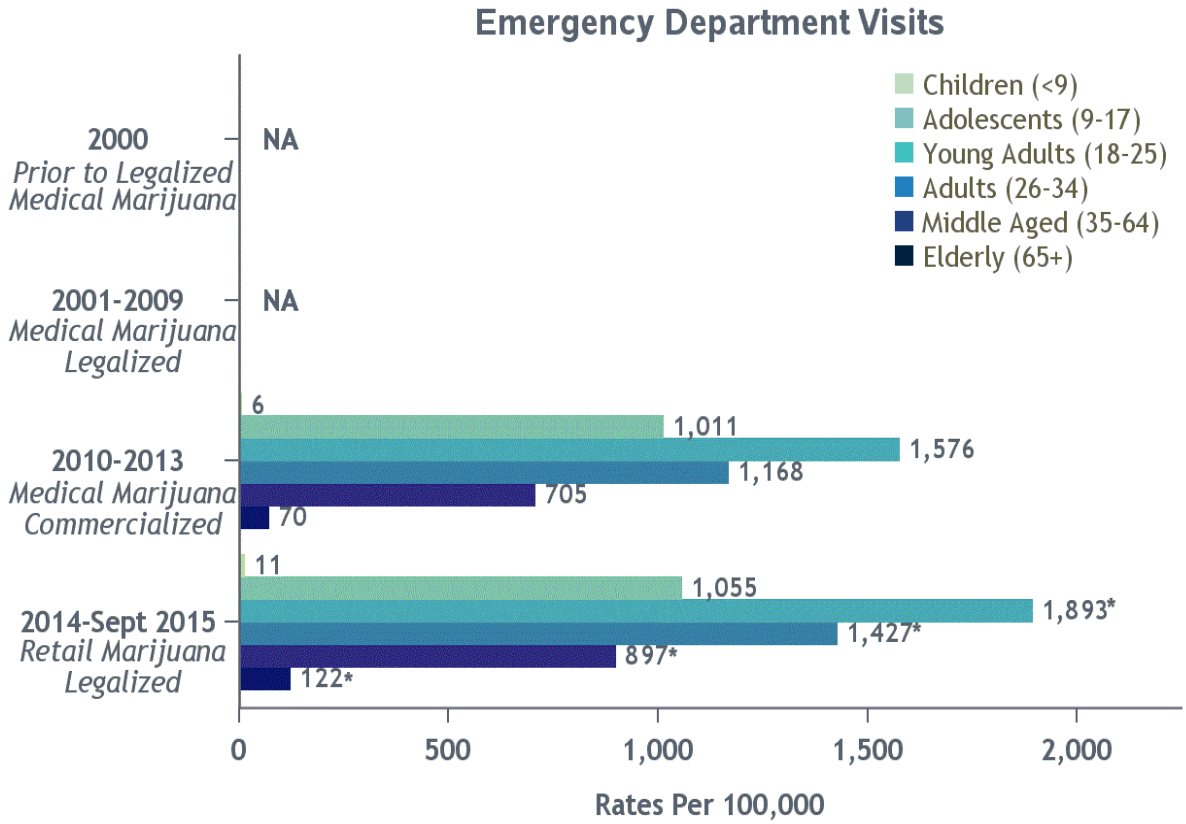
Produced by: EEOHT, CDPHE 2016
*Rate significantly increased from previous time period with a p-value <0.001.
†ICD-9-CM codes 969.6 and E854.1 were used to determine HD with marijuana-related billing codes.
‡Data Source: Colorado Hospital Association 2000-Sept 2015.

Major findings:

- Rates of HD with marijuana-related billing codes significantly increased each time period from year 2000 to 2014 through September 2015 for both males[k] and females.[l]
- Males had consistently higher rates of HD with possible marijuana exposures, diagnoses, or billing codes across time periods.

[k] Rate of male HD visits per 100,000: 2000 (887) vs 2001-2009 (1204), X^2= 138.7, p<0.001; 2001-2009 (1204) vs 2010-2013 (2145), X^2= 3252.5, p<0.001; 2010-2013 (2145) vs 2014-Sept 2015 (1277), X^2= 2926.8, p<0.001
[l] Rate of female HD visits per 100,000: 2000 (368) vs 2001-2009 (533), X^2= 128.0, p<0.001; 2001-2009 (533) vs 2010-2013 (933), X^2= 1895.8, p<0.001; 2010-2013 (933) vs 2014-Sept 2015 (1788), X^2= 2065.0, p<0.001
For an explanation of statistical comparisons used, see Appendix S. For data, see Appendix S table S.4.

Figure 5.a Rates of emergency department (ED) visits with marijuana-related billing codes by age categories.



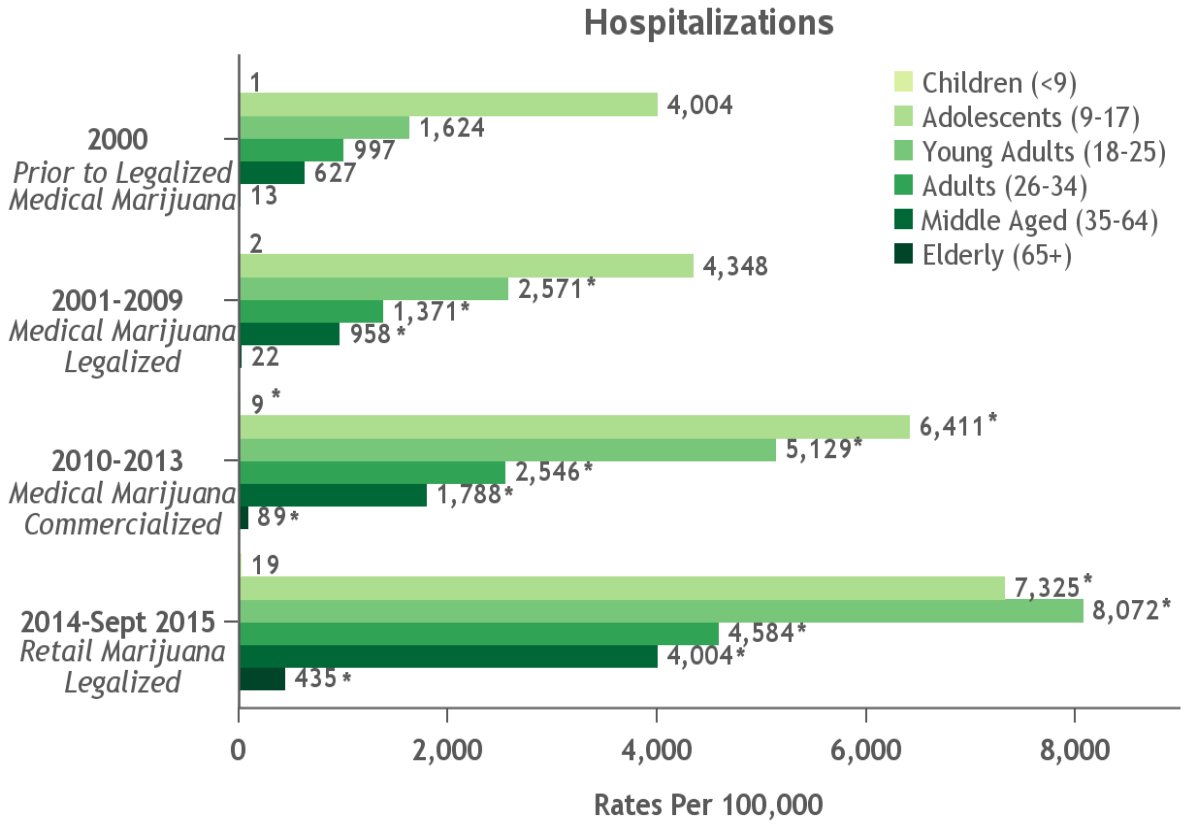
Produced by: EEOHT, CDPHE 2016
*Rate significantly increased from previous time period with a p-value <0.001.
†ICD-9-CM codes 969.6 and E854.1 were used to determine ED visits with marijuana-related billing codes.
‡Data Source: Colorado Hospital Association 2011-Sept 2015.

Major findings:

- Rates of ED visits with marijuana-related billing codes significantly increased for all age groups except children and adolescents from 2011-2013 to 2014 through September 2015.[m]

[m] Rate of ED visits per 100,000: YA 2010-2013 (1576) vs 2014-Sept 2015 (1893), X^2= 154.3, p<0.001; adult 2010-2013 (1168) vs 2014-Sept 2015 (1427), X^2= 153.1, p<0.001; middle aged 2010-2013 (705) vs 2014-Sept 2015 (897), X^2= 289.5, p<0.001; elderly 2010-2013 (70) vs 2014-Sept 2015 (122), X^2= 64.4, p<0.001
For an explanation of statistical comparisons used, see Appendix S. For data, see Appendix S table S.5.

Figure 5.b Rates of hospitalizations (HD) with marijuana-related billing codes by age categories.



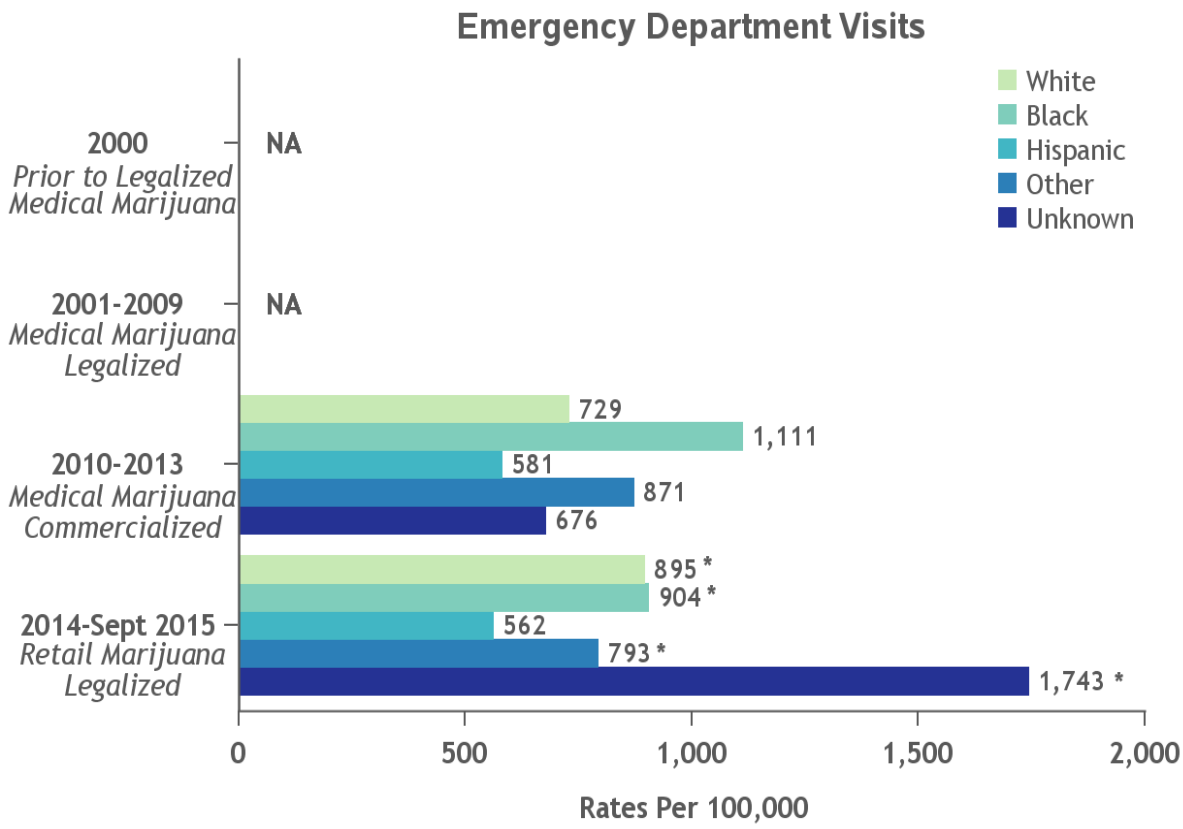
Produced by: EEOHT, CDPHE 2016
*Rate significantly increased from previous time period with a p-value <0.001.
†ICD-9-CM codes 969.6 and E854.1 were used to determine HD with marijuana-related billing codes.
‡Data Source: Colorado Hospital Association 2000-Sept 2015.

Major findings:

- Rates of HD with marijuana-related billing codes significantly increased for all age groups from 2001-2009 to 2010-2013 and for those 9 and older for 2010-2013 to 2014 through September 2015.[n]

[n] Rate of HD visits per 100,000: Child 2001-2009 (2) vs 2010-2013 (2), X^2= 28.2, p<0.001; Adolescent 2001-2009 (4348) vs 2010-2013 (6411), X^2= 315.6, p<0.001; 2010-2013 (6411) vs 2014-Sept 2015 (7325), X^2= 19.6, p<0.001; YA 2000(1624) vs 2001-2009 (2571), X^2= 131.5, p<0.001; 2001-2009 (2571) vs 2010-2013 (5129), X^2= 2123.6, p<0.001; 2010-2013 (5129) vs 2014-Sept 2015 (8072), X^2= 634.9, p<0.001; Adult 2000(997) vs 2001-2009 (1371), X^2= 48.7, p<0.001; 2001-2009 (1371) vs 2010-2013 (2546), X^2= 1205.2, p<0.001; 2010-2013 (2546) vs 2014-Sept 2015 (4584), X^2= 904.0, p<0.001; middle aged 2000(627) vs 2001-2009 (958), X^2= 143.4, p<0.001; 2001-2009 (958) vs 2010-2013 (1788), X^2= 2384.5, p<0.001; 2010-2013 (1788) vs 2014-Sept 2015 (4004), X^2= 3754, p<0.001; Elderly 2001-2009 (22) vs 2010-2013 (89), X^2= 406.2, p<0.001; 2010-2013 (89) 2014-Sept 2015 (435), X^2= 1082.3, p<0.001
For an explanation of statistical comparisons used, see Appendix S. For data, see Appendix S table S.5.

Figure 6.a Rates of emergency department (ED) visits with marijuana-related billing codes by race/ethnicity.



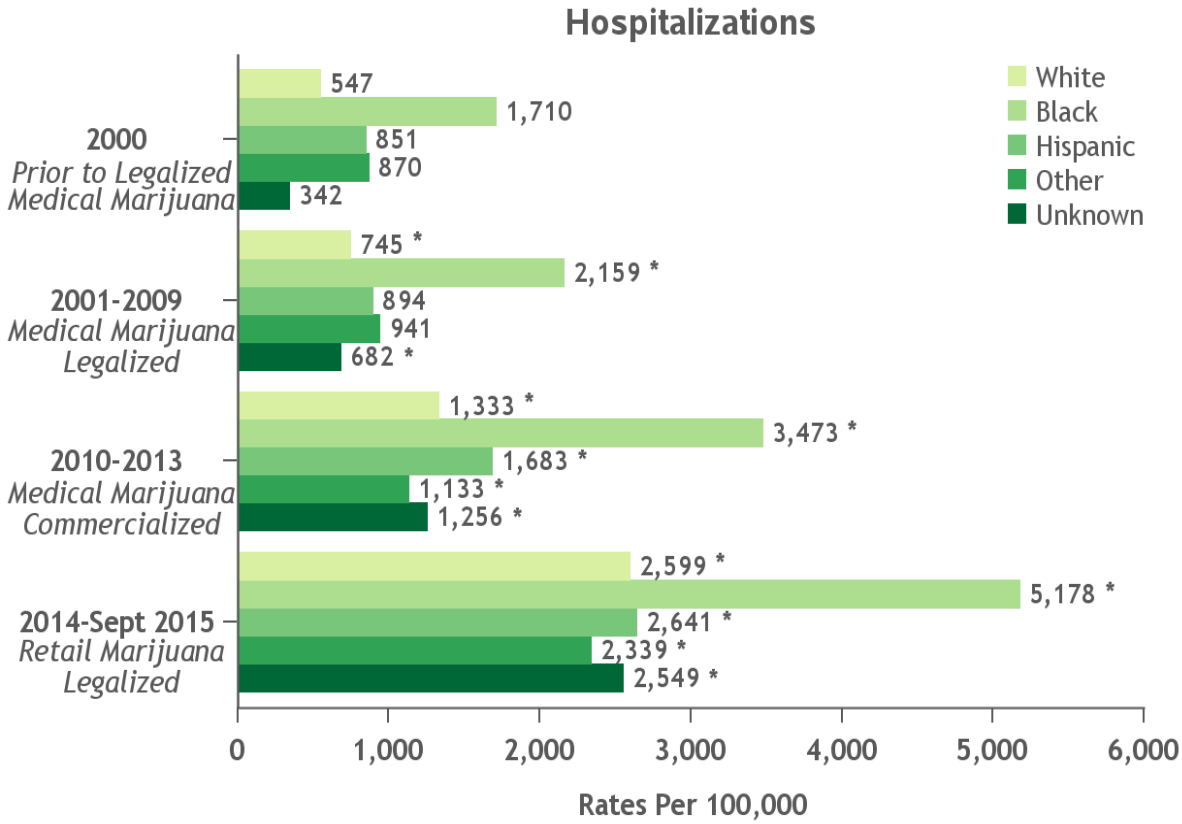
Produced by: EEOHT, CDPHE 2016
*Rate significantly increased from previous time period with a p-value <0.001.
†ICD-9-CM codes 969.6 and E854.1 were used to determine ED visits with marijuana-related billing codes.
‡Other race included Asian, Native American, and Other races. Unknown race was recorded as "unknown" not including missing data.
§Data Source: Colorado Hospital Association 2011-Sept 2015.

Major findings:

- Rates of ED visits with marijuana-related billing codes significantly increased from 2010-2013 to 2014 through September 2015 for White, Black, Other, and Unknown races.[o]

[o]Rate of ED visits per 100,000: White 2010-2013 (729) vs 2014-Sept 2015 (895), X^2= 409.0, p<0.001; Black 2010-2013 (1111) vs 2014-Sept 2015 (895), X^2= 50.7, p<0.001; Other 2010-2013 (581) vs 2014-Sept 2015 (562), X^2= 13.1, p<0.001; Unknown 2010-2013 (676) vs 2014-Sept 2015 (1743), X^2= 1509.3, p<0.001
For an explanation of statistical comparisons used, see Appendix S. For data, see Appendix S table S.6.

Figure 6.b Rates of hospitalizations (HD) with marijuana-related billing codes by race/ethnicity.



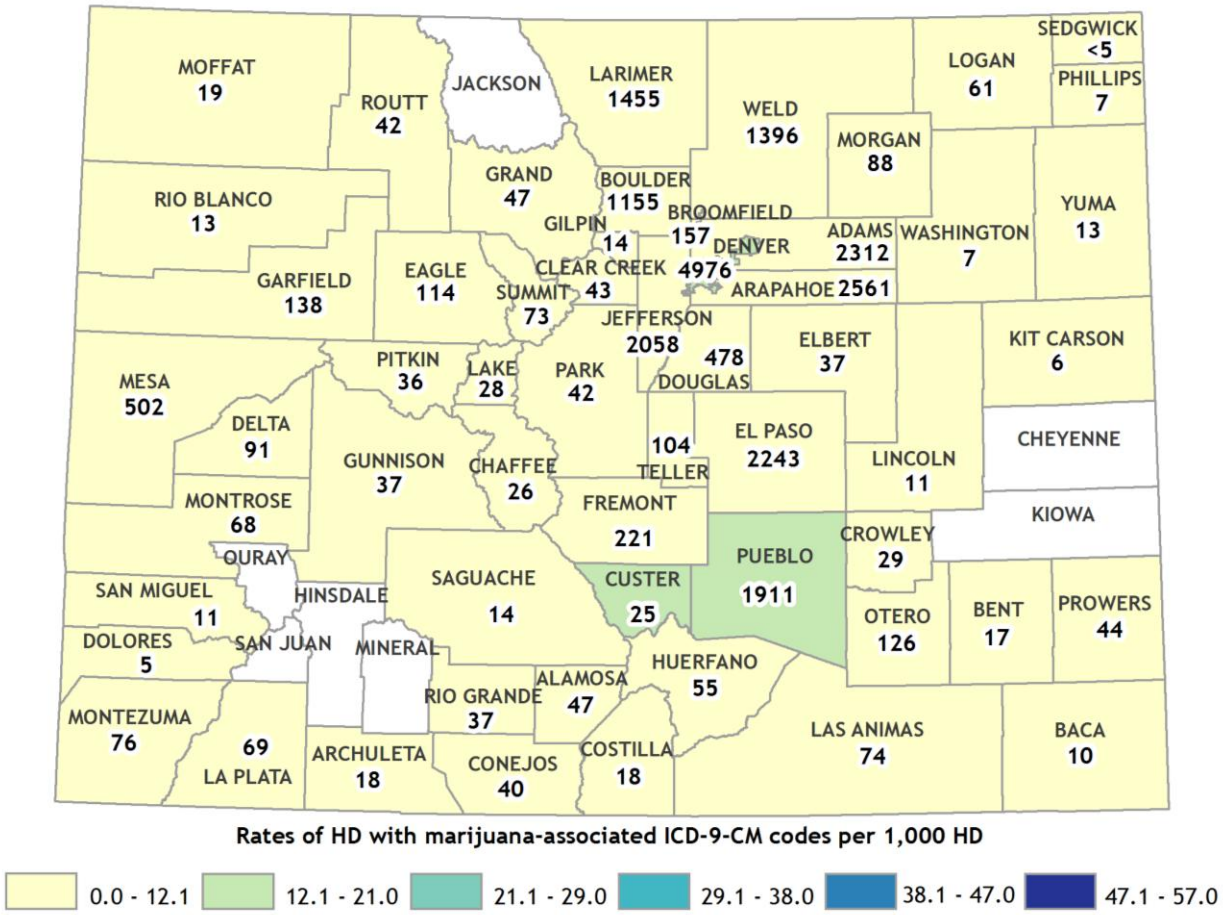
Produced by: EEOHT, CDPHE 2016
*Rate significantly increased from previous time period with a p-value <0.001.
†ICD-9-CM codes 969.6 and E854.1 were used to determine HD with marijuana-related billing codes.
‡Other race included Asian, Native American, and Other races. Unknown race was recorded as "unknown" not including missing data.
§Data Source: Colorado Hospital Association 2000-Sept 2015.

Major findings:

- Rates of HD with marijuana-related billing codes significantly increased each time period for White, Black, and Unknown races.[p]
- Rates of HD with marijuana-related billing codes for all races significantly increased each time period from 2001-2009 to 2014 through September 2015.[q]

[p] Rate of HD visits per 100,000: White 2000 (547) vs 2001-2009 (745), X^2= 122.0, p<0.001; 2001-2009 (745) vs 2010-2013 (1333), X^2= 3127.2, p<0.001; 2010-2013 (1333) vs 2014-Sept 2015 (2599), X^2= 3903.7, p<0.001; Black 2000 (1710) vs 2001-2009 (2159), X^2= 12.3, p<0.001; 2001-2009 (2159) vs 2010-2013 (3473), X^2= 362.5, p<0.001; 2010-2013 (3473) vs 2014-Sept 2015 (5178), X^2= 198.1, p<0.001; Unknown 2000 (342) vs 2001-2009 (682), X^2= 165.4, p<0.001; 2001-2009 (682) vs 2010-2013 (1256), X^2= 594.7, p<0.001; 2010-2013 (1256) vs 2014-Sept 2015 (2549), X^2= 431.2, p<0.001
[q] Rate of HD visits per 100,000: Hispanic 2001-2009 (894) vs 2010-2013 (1683), X^2= 793.8, p<0.001; 2010-2013 (1683) vs 2014-Sept 2015 (2641), X^2= 223.1, p<0.001; Other 2001-2009 (941) vs 2010-2013 (1133), X^2= 31.6, p<0.001; 2010-2013 (1133) vs 2014-Sept 2015 (2339), X^2= 455.1, p<0.001
For an explanation of statistical comparisons used, see Appendix S. For data, see Appendix S table S.6.

Map 2. Rates and numbers of hospitalizations (HD) with marijuana-related billing codes Per 1,000 HD in all ages in Colorado From 2004-2009.

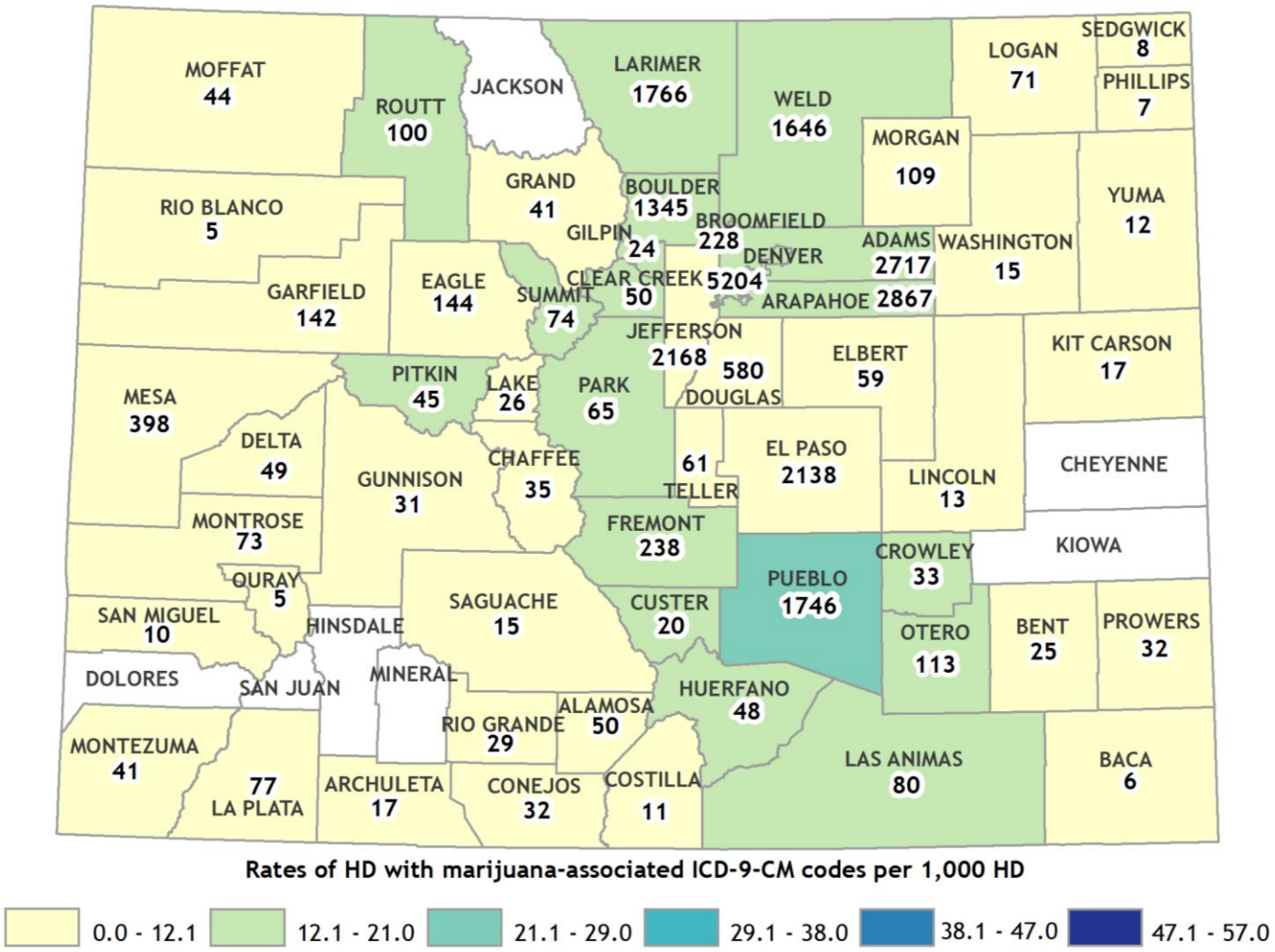


Produced by: EEOHT, CDPHE 2016
*Counties shown in white have no reported ED visits with marijuana-related billing codes.
†The number inside the counties was the total number of HD with marijuana-related billing codes in the specified county.
‡ICD-9-CM codes 305.20-305.23, 304.30-304.33, 969.6, and E854.1 were used to determine HD with marijuana-related billing codes.
§ Data Source: Colorado Hospital Association 2004-2009.

Major findings

- Rates and numbers of HD with marijuana-related billing codes were higher in urban areas compared to rural areas.
- The highest rates were in Pueblo (16 per 1,000 HD), Denver (13 per 1,000 HD), and Custer (12 per 1,000 HD) counties while the highest numbers of HD were in Denver (N=4,976 HD), Arapahoe (N=2,561 HD), and Adams (N=2,561 HD) counties.

Map 3. Rates and numbers of hospitalizations (HD) with marijuana-related billing codes per 1,000 hospitalizations in all ages in Colorado from 2010-2013.

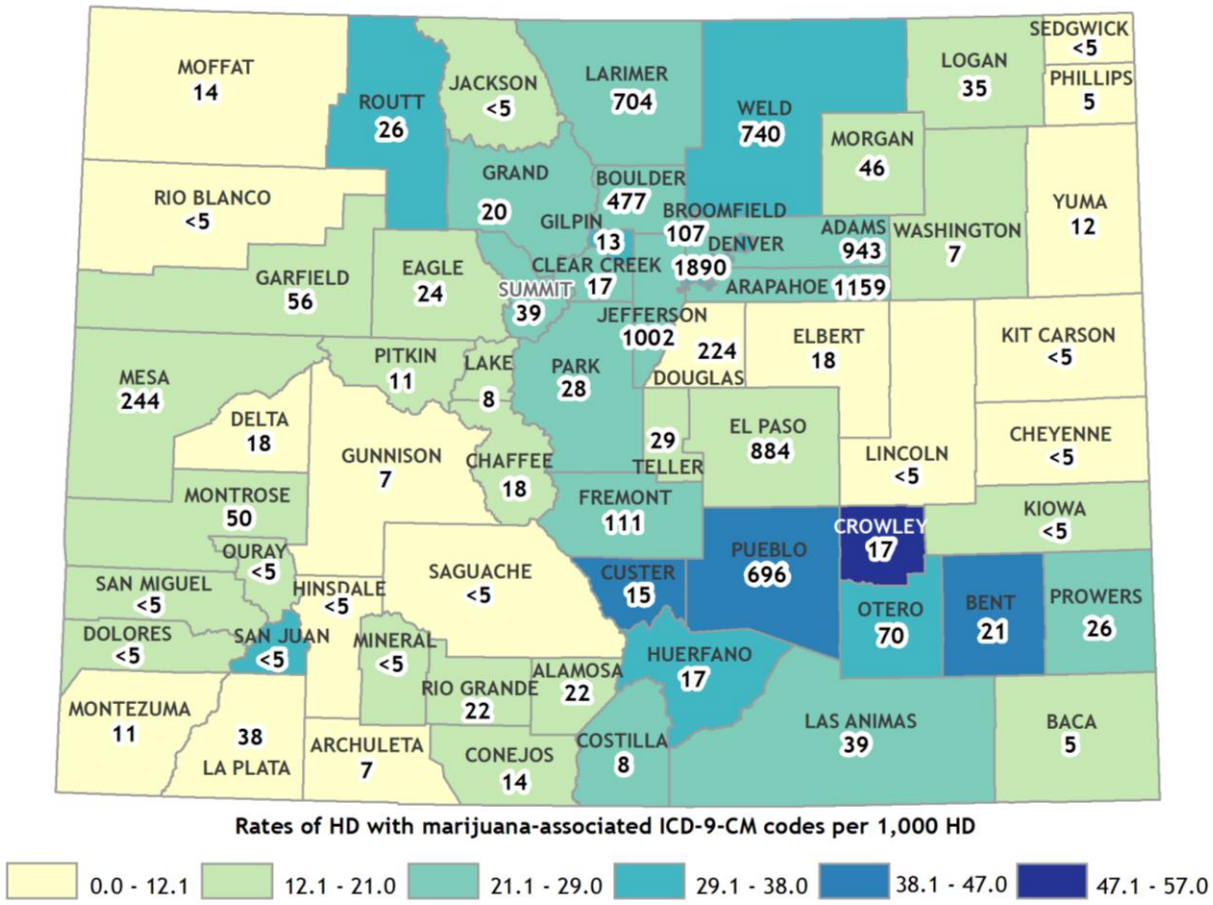


Produced by: EEOHT, CDPHE 2016
*Counties shown in white have no reported ED visits with marijuana-related billing codes.
†The number inside the county was the total number of HD with marijuana-related billing codes in the specified county.
‡ICD-9-CM codes 305.20-305.23, 304.30-304.33, 969.6, and E854.1 were used to determine HD with marijuana-related billing codes.
§ Data Source: Colorado Hospital Association 2010-2013.

Major findings

- Rates and numbers of HD with marijuana-related billing codes were higher in urban areas compared to rural areas.
- The highest rates were in Pueblo County (24 HD per 1,000 HD); however, the highest number of HD was in Denver County (N=5,204 HD).

Map 4. Rates and numbers of hospitalizations (HD) with marijuana-related billing codes per 1,000 hospitalizations in all ages in Colorado in 2014-September 2015.

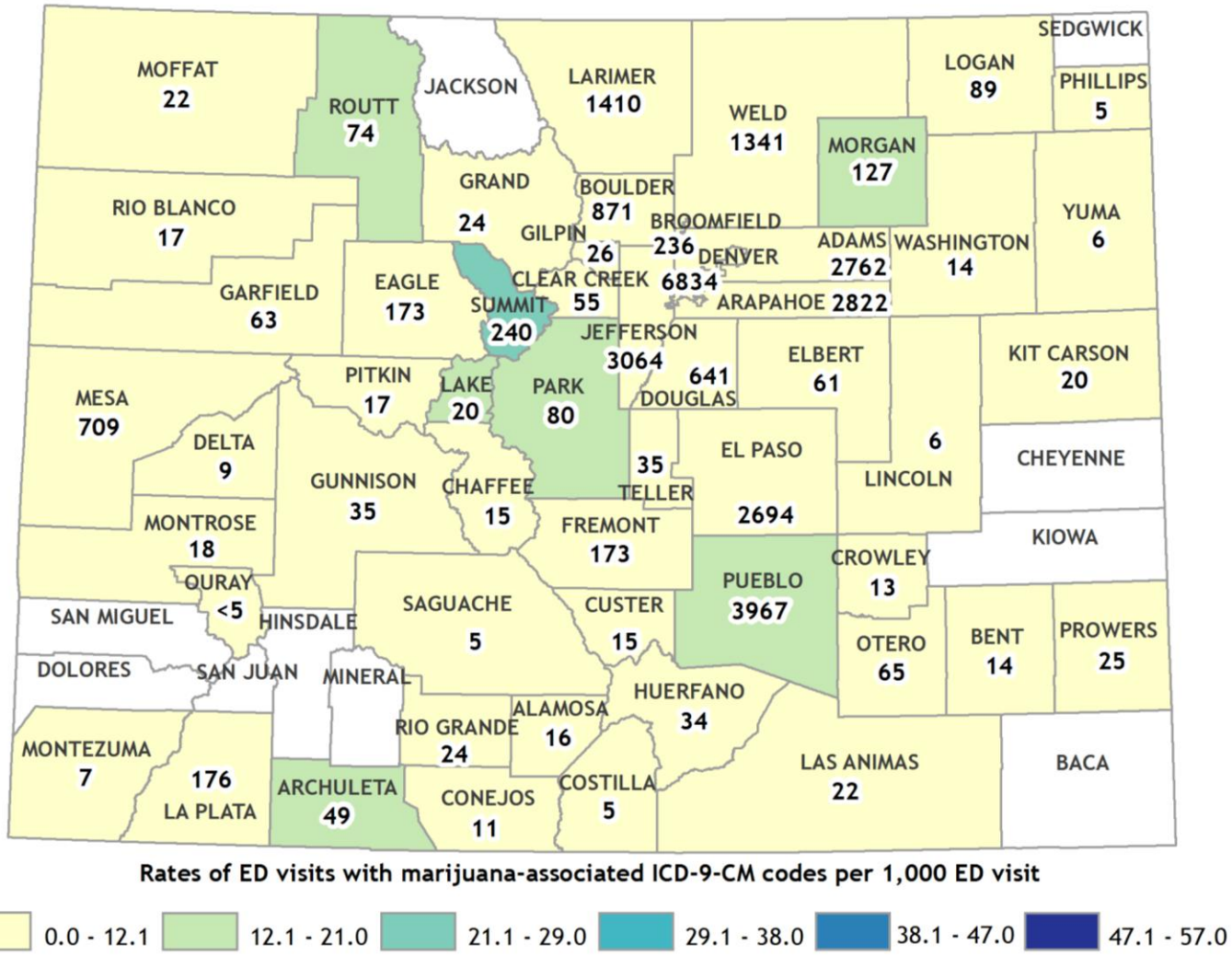


Produced by: EEOHT, CDPHE 2016
* Counties shown in white have no reported HD with marijuana-related billing codes.
†The number inside the county was the total number of HD marijuana-related billing codes in the specified county.
‡ICD-9-CM codes 305.20-305.23, 304.30-304.33, 969.6, and E854.1 were used to determine HD with marijuana-related billing codes.
§ Data Source: Colorado Hospital Association 2014-Sept 2015.

Major findings

- Numbers of HD with marijuana-related billing codes were higher in urban areas compared to rural areas.
- The highest rates of HD were in Crowley County (56 per 1,000 HD) while the highest numbers of HD were in Denver County (N=1,749 HD).

Map 5. Rates and numbers of emergency department (ED) Visits with marijuana-related billing codes per 1,000 ED visits in all ages in Colorado from 2011-2013.



Produced by: EEOHT, CDPHE 2016

* Counties shown in white have no reported ED visits with marijuana-related billing codes.

†The number inside the county was the total number of ED visits with possible marijuana-related billing codes in the specified county.

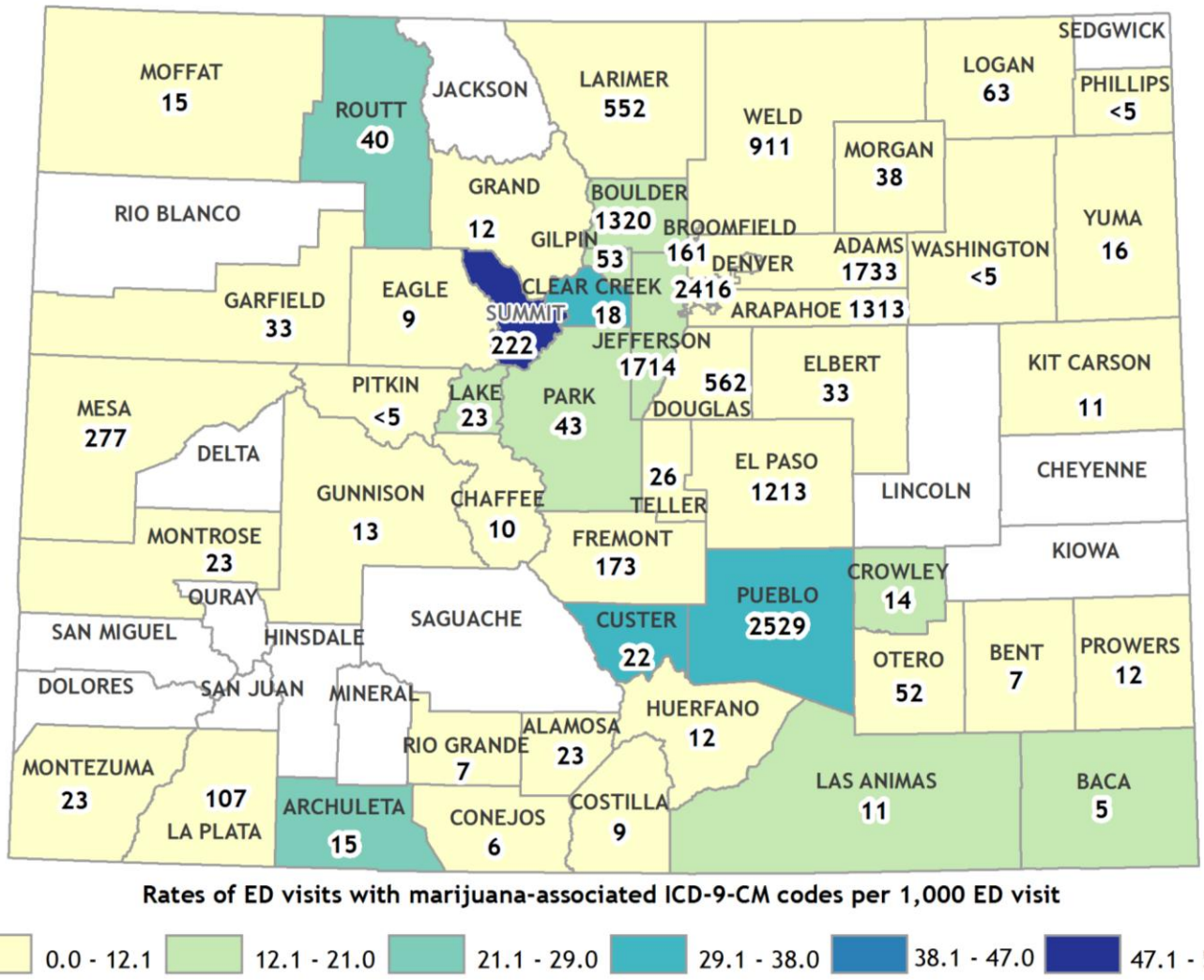
‡ICD-9-CM codes 305.20-305.23, 304.30-304.33, 969.6, and E854.1 were used to determine ED visits with marijuana-related billing codes.

§ Data Source: Colorado Hospital Association 2011-2013.

Major findings

- The rates of ED visits remained fairly constant from urban to rural counties; however, the numbers of ED visits were higher in urban counties compared to rural counties.
- The highest rates of ED visits were in Summit (21 per 1,000), Routt (17 per 1,000), Pueblo (17 per 1,000), Lake (13 per 1,000), Park (13 per 1,000) and Archuleta (13 per 1,000) counties, while the highest numbers of ED visits were in Denver (N=6,834) and Pueblo (N=3,967) counties.

Map 6. Rates and numbers of emergency department (ED) visits with marijuana-related billing codes[b] per 1,000 hospitalizations in all ages in Colorado in 2014-September 2015.

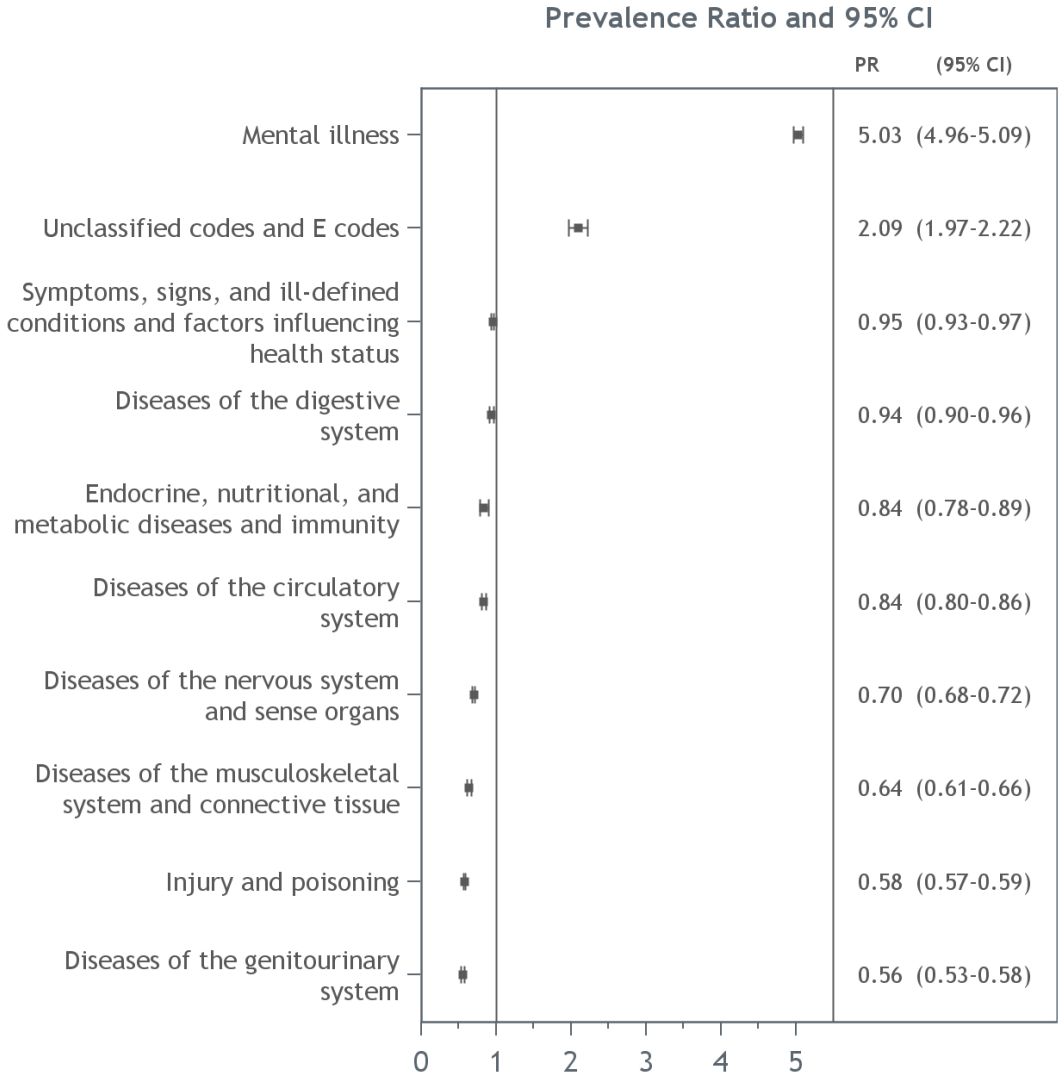


Produced by: EEOHT, CDPHE 2016
* Counties shown in white have no reported ED visits with marijuana-related billing codes.
†The number inside the county was the total number of ED visits with marijuana-related billing codes in the specified county.
‡ICD-9-CM codes 305.20-305.23, 304.30-304.33, 969.6, and E854.1 were used to determine ED visits with marijuana-related billing codes.
§ Data Source: Colorado Hospital Association 2014-Sept 2015.

Major findings

- The rate of ED visits increased in Adams, Alamosa, Arapahoe, Archuleta, Baca, Boulder, Broomfield, Chaffee, Clear Creek, Costilla, Crowley, Custer, Dolores, Douglas, El Paso, Elbert, Fremont, Garfield, Gilpin, Grand, Jefferson, Kit Carson, La Plata, Lake, Las Animas, Logan, Mesa, Moffat, Montezuma, Montrose, Morgan, Otero, Park, Phillips, Pueblo, Routt, Summit, Teller, Washington, Weld, and Yuma counties from 2011-2013.
- The highest rates of ED visits were in Summit County (56 per 1,000), while the highest numbers of ED visits were in Pueblo County (N=2,529).

Figure 7. Top ten primary diagnosis categories among emergency department (ED) visits with marijuana-related billing codes compared to those without in Colorado from 2011 through September 2015.

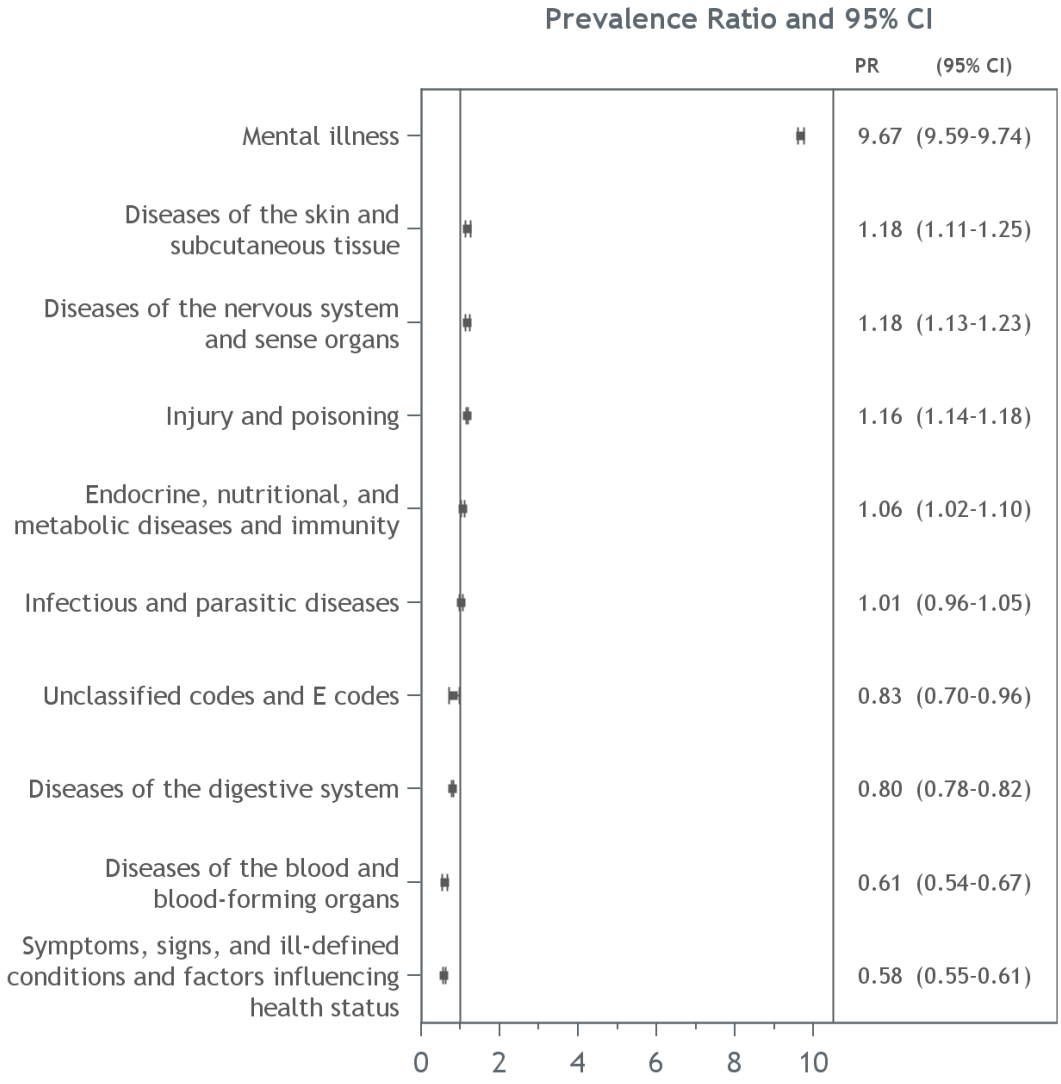


Produced by: EEOHT, CDPHE 2016
*ED visits with marijuana-related billing codes included 304.30-304.33, 305.20-305.23, 969.6, and E854.1 in any of the listed 30 diagnosis codes.
†PR=Prevalence Ratio, CI=Confidence Interval
‡Data Source: Colorado Hospital Association 2011-Sept 2015.

Major findings

- The prevalence of the primary diagnosis category *mental illness* was five-fold higher and the category of *unclassified codes and E codes* was two-fold higher among ED visits with marijuana-related billing codes compared to ED visits without marijuana-related billing codes.

Figure 8. Top ten primary diagnosis categories among hospitalizations (HD) with marijuana-related billing codes compared to those without in Colorado from 2000 through September 2015.



Produced by: EEOHT, CDPHE 2016
*Hospitalizations with marijuana-related billing codes included 304.30-304.33, 305.20-305.23, 969.6, and E854.1 in any of the listed 30 diagnosis codes.
†PR=Prevalence Ratio, CI=Confidence Interval
‡Data Source: Colorado Hospital Association 2000-Sept 2015

Major findings

- The prevalence of the primary diagnosis category *mental illness* among HD with marijuana-related billing codes was nine-fold higher compared to HD without marijuana-related billing codes.

References

1. Centers for Disease Control and Prevention. Scientific Data Documentation: International Classificaiton of Diseases-9-CM, (1979). 2014; http://wonder.cdc.gov/wonder/sci_data/codes/icd9/type_txt/icd9cm.asp. Accessed November 3, 2015.
2. Practice Management Information Corporation [PMIC]. *International Classification of Diseases 9th Revision Clinical Modification*. Vol 1, 2, & 3. Sixth ed. Los Angeles, California 2015.
3. Thomas K, Johnson R. *State Injury Indicators Report: Instruction for Preparing 2013 Data*. Atlanta (GA): Centers for Disease Control and Prevention, National Center for Injury Prevention and Control;2015.
4. Safe States. *Consensus Recommendations for National and State Poisoning Surveillance: Report from the Injury Surveillance Work-group (ISW7)*. Atlanta: Safe States; 2012 2012.
5. CO Const. amend. 20 art. XVIII §14 http://www.lexisnexis.com/hottopics/colorado/?app=00075&view=full&interface=1&docinfo=off&searchtype=lt&search=Colo.+Const.+Art.+XVIII%2C+Section+14.
6. H.B. 10-1284 (CO 2010).
7. Ogden DW. "Memorandum to All United States Attorneys on Investigations and Prosecutions in States Authorizing the Medical Use of Marijuana" 19, October 2009. In: U.S. Department of Justice, ed, https://www.justice.gov/opa/blog/memorandum-selected-united-state-attorneys-investigations-and-prosecutions-states. Washington, DC.
8. CO Const. amend. 64 art. XVIII §16.

Retail Marijuana Public Health Advisory Committee

Membership Roster
2015-2016

Mike Van Dyke, PhD, CIH

CDPHE Marijuana Health Monitoring & Research Program Representative,
Chairman

Dr. Van Dyke is the Chief of the Environmental Epidemiology, Occupational Health, and Toxicology Branch at the Colorado Department of Public Health and Environment. Dr. Van Dyke is trained in the evaluation and control of occupational and environmental chemical exposures. He has spent the last 20 years working in public and occupational health focusing on chemical exposures, environmental and occupational epidemiology, and risk communication.

Shireen Banerji, PharmD, DABAT

Poison Center Representative

Dr. Banerji is the Clinical Manager of the Rocky Mountain Poison Center (RMPC). RMPC, a division of Denver Health, serves as the poison center for 5 states. She holds faculty appointments in four schools of pharmacy including University of Colorado School of Pharmacy. She is responsible for managing the clinical operations of RMPC which includes training, teaching, research, quality control, and continuing education of the poison center hotline staff. She has select administrative roles and also serves as clinical toxicologist and resource to staff. She works in conjunction with EPA, CDC and local and state health departments when toxicological emergencies with potential threat to public health arise, to provide clinical management and real-time and historical surveillance. Areas of interest include pediatric toxicology, medication safety, and poison prevention.

Laura Borgelt, PharmD

Pharmacologist/Clinical Pharmacy Specialist

Dr. Laura Borgelt is an Associate Dean and Professor at the University of Colorado Anschutz Medical Campus in the Departments of Clinical Pharmacy and Family Medicine. Dr. Borgelt's teaching, practice, and research focus on patient safety and women's health. Her initial interest in educating providers and patients about medical marijuana started about seven years ago when she was asked clinical questions about its use in pregnant and lactating women. Since that time, she has investigated the potential effectiveness and risks of marijuana in a comprehensive manner and has provided evidence-based presentations to various organizations at the state and national level. She has served on five different working groups regarding rulemaking in the state of Colorado involving consumer safety and social issues. Through her training, research, and experience, Dr. Borgelt has extensive knowledge of marijuana with regards to its pharmacology, pharmacokinetics, pharmacodynamics, therapeutic effectiveness, and potential risks.

Ashley Brooks-Russell, PhD, MPH

Colorado School of Public Health Representative

Dr. Brooks-Russell is an assistant professor at the Colorado School of Public Health and a member of the Injury Prevention, Education and Research Program. She completed her doctoral training in Health Behavior at the University of North Carolina at Chapel Hill and completed a postdoctoral fellowship at the Prevention Research Branch at the Eunice Kennedy Shriver National Institute of Child Health and Human Development. Her current research focuses on the areas of adolescent substance use and impaired driving.

Russell Bowler, MD, PhD

Pulmonologist

Dr. Bowler is Professor of Medicine at National Jewish Health in Denver and University of Colorado in Aurora, Colorado. He has multiple NIH and foundation grants to study the effects of tobacco and marijuana on lung health. There is a strong emphasis on generation and integration of genetics, genomics, proteomics and metabolomics data. Complementary animal and laboratory exposure models are used to demonstrate proof of concept using discoveries from human Omics work. He runs on of the country's largest clinical databases and biobanks of smokers with over 3000 well-characterized subjects.

Ken Gershman, MD, MPH

CDPHE, Medical Marijuana Representative

Dr. Gershman is Manager of the Marijuana Research Grants Program at the Colorado Department of Public Health and Environment (CDPHE). He has worked as a public health practitioner at CDPHE for 24 years in the areas of communicable disease control and chronic disease prevention, including managing the Cancer, Cardiovascular Disease and Chronic Pulmonary Disease (CCPD) Amendment 35 grant program.

Heath Harmon, MPH

Local Public Health Representative

Heath Harmon is the Director of Health Divisions at Boulder County Public Health (BCPH). He has more than 20 years of public health experience spanning communicable disease epidemiology, environmental health, emergency preparedness and response, adolescent health, maternal and child health, health communications, health planning, and health policy. Mr. Harmon completed his Master of Public Health from the University of South Florida in 2000 and currently devotes his time at BCPH to health policy, health equity, and organizational leadership initiatives.

Rebecca Helfand, PhD

Substance Abuse and Mental Health Epidemiologist

Dr. Helfand is the Director of Data and Evaluation at the Colorado Department of Human Services' Office of Behavioral Health. She completed her doctoral training at Baylor University and completed a postdoctoral fellowship at the Institute for Behavioral Genetics and the University of Colorado, Boulder. Dr. Helfand's current work focuses on analysis of mental health and substance abuse treatment data for the state of Colorado.

Sharon Langendoerfer, MD

Neonatology and Pregnancy

Dr. Langendoerfer is a retired Pediatrician and Neonatologist from Denver Health
Medical Center. For many years she has cared for high risk infants and children, including those exposed before birth to alcohol and other drugs.

Andrew Monte, MD

Medical Toxicologist

Dr. Monte is an emergency medicine physician and medical toxicologist at University of Colorado and the Rocky Mountain Poison and Drug Center. Dr. Monte is an active researcher studying human exposures to a variety of poisons, toxins, and drugs.

Kristina T. Phillips, PhD

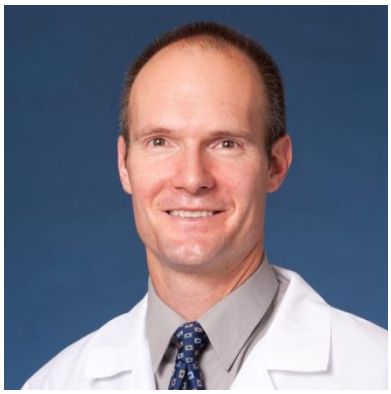
Psychologist

Dr. Phillips is a licensed Clinical Psychologist and Professor in the School of Psychological Sciences at the University of Northern Colorado (UNC). She completed her doctoral work at Bowling Green State University and her post-doctoral training at the Center for Alcohol and Addiction Studies at Brown University. Her primary research interests focus on consequences associated with illicit substance use (e.g., academic problems related to marijuana use, health consequences of injection drug use), treatment development and efficacy, and ecological momentary assessment. Dr. Phillips has been the principal investigator or co-investigator on several NIH grants, including projects testing the efficacy of a brief intervention for people who inject drugs and a new study that examines academic outcomes associated with heavy marijuana use in college students.

Judith Shlay, MD, MSPH

Surveillance Epidemiologist/Local Public Health Representative

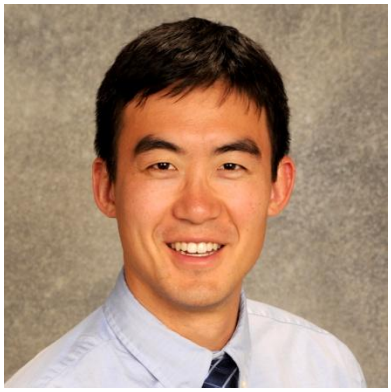
Dr. Shlay is the Interim Director of Denver Public Health (DPH) and a Professor of Family Medicine at the University of Colorado, School of Medicine. She has been working on various programs at DPH for the past 27 years. Dr. Shlay has been the principal investigator for a number of projects focusing on health promotion and disease prevention, HIV-related metabolic and neurologic disorders, immunization delivery, reproductive health, sexually transmitted infections, substance abuse, teen pregnancy prevention, and tobacco prevention. In addition to her public health work, Dr. Shlay is a primary care provider through Denver Health's Community Health Services Department.



Christian Thurstone, MD

Addiction Psychiatrist

Dr. Thurstone is a child psychiatrist, general psychiatrist, and addiction psychiatrist. He is an Associate Professor of Psychiatry at the University of Colorado and the Medical Director of Addiction Services at Denver Health. His research focuses on clinical studies related to adolescent substance use disorders.



George Sam Wang, MD

Pediatrician

Dr. Wang is board certified in general pediatrics, pediatric emergency medicine and medical toxicology. He is an Assistant Professor of Pediatrics, Department of Pediatrics, Section of Emergency Medicine and Medical Toxicology at University of Colorado Anschutz Medical Campus and Children's Hospital Colorado and a volunteer faculty member with the Rocky Mountain Poison and Drug Center. Dr. Wang's focus or research is ingestions and exposures in the pediatric population, and a major has been prevention of unintentional marijuana exposures among children and also the use of cannabidiol in pediatric epilepsy.

Tista Ghosh, MD, MPH

CDPHE, Alternate Member

Dr. Ghosh is a physician trained in both internal medicine and preventive medicine, with a master's degree in public health from Yale University. She also has had specialized training in applied epidemiology and public health practice through the Centers for Disease Control and Prevention's Epidemic Intelligence Service Program. Dr. Ghosh has experience in both communicable and non-communicable disease epidemiology and public health research, as well as over a decade of experience in public health at the local, state, federal and international levels. She serves as both the deputy chief medical officer of the Colorado Department of Public Health and Environment and the director of Public Health Programs.

Glossary

Abnormal female reproductive function
Abnormal ovulation, implantation, placenta formation, or reproductive hormone levels.

Abnormal male reproductive function
Abnormal sperm count, concentration, motility or structure, or abnormal reproductive hormone levels.

Acute marijuana use
Marijuana used within the past few hours, such that the short-term effects or symptoms are still being experienced.

Adolescent
Individual 9 to 17 years of age.

Adult
Individual 25 years or older.

Analgesic
A medication used to relieve pain.

Anencephaly
A neural tube defect that results in underdevelopment or the absence of portions of the brain, skull, and scalp.

Bullous lung disease
Destruction of lung tissue causing pockets of air to replace lung tissue, diagnosed by imaging.

Cancer-causing chemicals
Chemicals known to cause cancer in humans, including polycyclic aromatic hydrocarbons.

Cannabidiol (CBD)
A non-psychoactive cannabinoid that is a component of marijuana.

Cannabinoid hyperemesis syndrome
A term currently used by some medical professionals to describe cyclic vomiting occurring in long-time marijuana users. A formal medical definition, including clinical diagnostic criteria, has not yet been established.

Cannabis use disorder
A formal diagnosis indicating two or more of these factors: hazardous use, social/interpersonal problems related to use, neglects major roles in order to use, legal problems, withdrawal, tolerance, uses more or longer than planned, repeated attempts to quit or reduce use, much time is spent using, physical or psychological problems related to use, and/or gives up activities in order to use; commonly called addiction.

Cardiovascular disease
A disease of the heart and/or blood vessels, including both heart disease and stroke.

Child
Individual up to 9 years of age.

Chronic bronchitis
A long term cough with sputum production that is diagnosed by symptoms.

Chronic obstructive pulmonary disease (COPD)
A severe form of small airway obstruction characterized by long-term poor airflow from the lungs, with common symptoms including of shortness of breath and cough with sputum production, diagnosed by pulmonary function tests.

Cognitive abilities
Brain-based skills we need to carry out any task from the simplest to the most complex, which include retrieving information from memory, using logic to solve problems, communicating through language, mentally visualizing a concept and focusing attention when distractions are present.

Combustion by-products
Chemicals produced when a material is burned. These chemicals including carbon monoxide and polycyclic aromatic hydrocarbons.

Cyclic vomiting
Eepisodes of severe, repeated vomiting.

Dabbing
A method of marijuana use where a "dab" (small amount) of marijuana concentrate is placed on a pre-heated surface, creating concentrated marijuana vapor to be inhaled.

Daily or near-daily use
Marijuana use on 5 to 7 days per week.

Driving impairment
A reduced ability to perform the various elements of driving.

Drug-drug interaction
A potentially dangerous interaction that occurs when the effects of one medication are changed by the use of another medication or drug. An example is when a person taking a blood thinner starts a new medication or drug that causes an increase in the blood thinner, leading to bleeding. Similar interactions can occur with many medications.

Electronic smoking device (vaporizer or e-cigarette)
A vaporizing device, with a rechargeable battery, that heats material such as marijuana flower (bud) or liquids containing THC or nicotine to produce vapor for inhalation. Used as an alternative to smoking marijuana or tobacco.

mphysema
The breakdown of lung tissue, typically causing air trapping, poor airflow and shortness of breath, diagnosed by imaging.

Executive function
an umbrella term for the management (regulation, control) of cognitive processes, including working memory, reasoning, task flexibility, organization, time and space management, and problem solving as well as planning and execution.

Gastroschisis
A birth defect where the abdominal (belly) wall has failed to close properly. The resulting hole allows the intestines to protrude outside the fetus.

Hash oil extraction
A technique that removes THC (the psychoactive component of marijuana) from the plant material in a concentrated form. This concentrate can then be smoked, vaporized, mixed into food or drink, or used on the skin. A very common method of extraction uses butane, which is highly flammable.

Heart disease
Encompasses several conditions that affect the heart, including coronary heart disease, myocardial infarction (heart attack), heart failure, arrhythmias and heart valve problems.

Injury
Physical damage to the body resulting from acute exposure to thermal, mechanical, electrical, or chemical energy.

Illicit drugs
Fall into two categories: 1) Those drugs that are illegal to process, sell, and consume; includes cocaine, methamphetamine, ecstasy and heroin. 2) Those drugs that are legal to process, sell, and consume when prescribed by a physician, but are then misused or used without a prescription; includes prescription pain medication and prescription sedatives.

Intelligence quotient (IQ)
a number used to express the apparent relative intelligence of a person, determined by one's performance on a standardized intelligence test relative to the average performance of others of the same age.

Ischemic stroke
Occurs as a result of an obstruction within a blood vessel supplying blood to the brain.

Joint
See **Marijuana cigarette**

Less-than-weekly use - marijuana use on less than 1 day/week.

Levels of marijuana use
- Daily or near daily use - 5-7 days/week.
- Weekly use - 1-4 days/week.
- Less-than-weekly use: less than 1 day/week.
- Acute use: Used within the last few hours, such that the short-term effects or symptoms are still being experienced.

Low birth weight
Baby who weighs less than 5.5 pounds at birth, regardless of the gestational age.

Mainstream smoke
Also known as firsthand smoke, it is the smoke that a smoker inhales from a lit cigarette, pipe, or joint and then exhales.

Marijuana addiction
An informal term which is more commonly used than cannabis use disorder, but the two are considered equivalent by the committee and many mental health professionals.

Marijuana cigarette
“Currently available” marijuana cigarette contains approximately 0.5 gm total weight and 12-23%% THC (potency); also called a “joint”.

Marijuana combustion
The heating of marijuana flower or concentrate by applying a direct heat source of 230 degrees Celsius or above in order to produce smoke for inhalation. Combustion methods include burning a joint, blunt, pipe, or bong bowl.

Miscarriage
A baby born before reaching 20 weeks of pregnancy and therefore unable to survive.

Myocardial infarction
The medical term for a 'heart attack,' which occurs when blood flow to the heart is blocked, causing injury to part of the heart muscle. This can cause a life-threatening change in heart rhythm (arrhythmia).

Neural tube defects (NTD)
Birth defects of the brain, spinal cord or spine. The defects occur in the embryo during the first few weeks of pregnancy.

Newborn behavior issues
May include fussiness and sleep difficulties occurring during the first 28 days after birth.

Nonseminoma
The more common type of testicular cancer which tends to grow more quickly than seminomas and are often made up of more than one type of cell.

Nulliparous
A woman who has never carried a pregnancy beyond 20 weeks.

Opioid
One of many medications or street drugs including heroin, opium and prescription pain medications such as morphine, hydrocodone (Vicodin, Norco, Lortab), oxycodone (Percocet, OxyContin), hydromorphone (Dilaudid), fentanyl and methadone.

Older adult
Individual 65 years of age or older

Pharmacokinetic / pharmacodynamic
The absorption, distribution, metabolism and excretion of a drug and the effect the drug has on the body.

Physical dating violence
Physically aggressive behavior among current or former romantic, sexual/intimate, or dating partners, including hitting, kicking, choking, slapping, etc. Psychological, emotional, verbal or sexual violence were not included, nor were threats of violence.

Physical dating violence perpetration (PDVP)
To commit physical violence against a partner.

Physical dating violence victimization (PDVV)
To be harmed by physical violence committed by a partner.

Pneumothorax
The collapse of a lung caused by air or fluid filling up the space around the lung, an emergency condition diagnosed by physical exam and/or imaging.

Polycyclic aromatic hydrocarbons
A group of more than 100 different chemicals released from burning coal, oil, gasoline, trash, tobacco, wood, or other organic substances.

Preterm delivery
A birth that occurs more than three weeks before the baby is due — in other words, after less than 37 weeks of pregnancy.

PRISMA
Evidence-based minimum set of items for reporting in systematic reviews and meta-analyses to help authors improve reporting.

Psychotic disorders
These include schizophrenia, schizoaffective, schizophreniform, schizotypal, and delusional disorders. These formal diagnoses are made when a combination of psychotic symptoms are present (possibly combined with other mental health symptoms), the symptoms cause significant problems with work, relationships or self-care, and they have been present for six months or longer.

Psychotic symptoms
These include auditory or visual hallucinations, difficulty separating real from imagined, perception that self or others can read minds, perceived ability to predict the future, feeling that an outside force is controlling thoughts or actions, fear that someone intends to harm them, belief they have supernatural gifts, apathy, social withdrawal, absent or blunted emotions, occurrences of unclear speech or inability to speak, or difficulty organizing thoughts to complete activities.

Pulmonary function (tests)
Measurements that show how well the lungs move air in and out and how well they exchange oxygen and carbon dioxide with the blood.

Recreational injury
Any injury outside the workplace and not classified as a motor vehicle (MV) crash.

Route of Exposure
The physical passageway which the marijuana product takes to enter the body; (for example) oral/ingested, smoked, or topical.

Secondhand marijuana smoke exposure
The smoke that is inhaled by non-smokers when near to a person smoking marijuana, also known as passive exposure.
• Typical conditions: exposure at or below the level of smoke present in a small ventilated room (such as with open windows or an exhaust fan) with multiple people smoking marijuana.
• Extreme conditions: exposure at or above the level of smoke present in an small room (or a vehicle) without ventilation and with multiple people smoking marijuana.

Sidestream smoke
The smoke that wafts off the end of a lit cigarette, pipe or joint into the surrounding air.

SIDS
See **Sudden infant death syndrome**

Small airway obstruction
A condition causing air to be trapped in the lungs, making it difficult to breathe the air out to make room for the next breath, diagnosed by pulmonary function tests.

Small for gestational age (SGA)
A baby that is born smaller than 90 percent of babies of the same gestational age (number of weeks of pregnancy).

Smoked dose
Dependent on the potency and dry weight of cannabis flower, a.k.a. marijuana bud. It is approximately equal to the product of potency (%THC) and weight (mg).

Smoking topography
How a person smokes a substance, including measures of the number of puffs and puff volume, duration, and velocity.

Stillbirth
The birth of an baby that has died in the womb after having reached at least 20 weeks of pregnancy (earlier instances being regarded as abortion or miscarriage).

Stroke
An event that blocks blood flow to part of the brain or causes bleeding into the brain, causing permanent damage.

Sudden infant death syndrome (SIDS)
The sudden and unexplained death of a seemingly healthy baby less than a year old.

Tetrahydrocannabinol (THC)
The main psychoactive component of marijuana.

Thirdhand marijuana smoke exposure
Residual contamination left in rooms and on clothes after marijuana smoking.

Unintentional marijuana exposures
Ingesting a substance without knowing that it contains THC or other cannabinoids, more commonly observed with edible marijuana products.

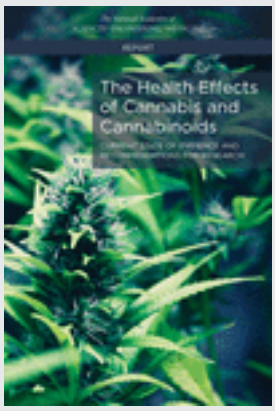
Vaporization of marijuana (vaping)
A method of marijuana use in which marijuana vapor, rather than smoke, is inhaled. Marijuana flower or concentrate is heated in a vaporizing device (vaporizer) to a temperature below the point of combustion, to produce vapor.

Ventricular septal defect
A congenital heart defect also known as a "hole in the heart." The defect occurs when the wall (septum) that separates the right and left ventricles of the heart does not form properly.

Water pipe
A pipe for smoking tobacco, marijuana, etc., that draws the smoke through water to cool it. Examples are a hookah and a bong.

Weekly use
Marijuana use on 1 to 4 days/week.

Young adult
Individual 18 to 24 years of age.



The Health Effects of Cannabis and Cannabinoids: The Current State of Evidence and Recommendations for Research

DETAILS

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Board on Population Health and Public Health Practice

Health and Medicine Division

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Proceedings chronicle the presentations and discussions at a workshop, symposium, or other convening event. The statements and opinions contained in proceedings are those of the participants and have not been endorsed by other participants, the planning committee, or the National Academies of Sciences, Engineering, and Medicine.

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COMMITTEE OF THE HEALTH EFFECTS OF MARIJUANA: AN EVIDENCE REVIEW AND RESEARCH AGENDA

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Reviewers

This report has been reviewed in draft form by individuals chosen for their diverse perspectives and technical expertise. The purpose of this independent review is to provide candid and critical comments that will assist the institution in making its published report as sound as possible and to ensure that the report meets institutional standards for objectivity, evidence, and responsiveness to the study charge. The review comments and draft manuscript remain confidential to protect the integrity of the deliberative process. We wish to thank the following individuals for their review of this report:

Eric Bass, Johns Hopkins University
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Mary D'Alton, Columbia University Medical Center
Raul Gonzalez, Florida International University
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Robin Mermelstein, University of Illinois at Chicago
Aron Lichtman, Virginia Commonwealth University
John H. Krystal, Yale University School of Medicine

Although the reviewers listed above have provided many constructive comments and suggestions, they were not asked to endorse the conclusions or recommendations nor did they see the final draft of the report before its release. The review of this report was overseen by **Eric B. Larson**, Group Health Research Institute, and **Bobbie A. Berkowitz**, Columbia University Medical Center. They were responsible for making certain that an independent examination of this report was carried out in accordance with institutional procedures and that all review comments were carefully considered. Responsibility for the final content of this report rests entirely with the authoring committee and the institution.

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This report reflects contributions from a number of individuals and groups. The committee takes this opportunity to recognize those who so generously gave their time and expertise to inform its deliberations.

To begin, the committee would like to thank the sponsors of this study for their guidance and support. Support for the committee's work was generously provided by the Alaska Mental Health Trust Authority; Arizona Department of Health Services; California Department of Public Health; CDC Foundation; Centers for Disease Control and Prevention; Mat-Su Health Foundation; National Highway Traffic Safety Administration; National Institutes of Health/National Cancer Institute; National Institutes of Health/National Institute on Drug Abuse; Oregon Health Authority; The Colorado Health Foundation; The Robert W. Woodruff Foundation; Truth Initiative; U.S. Food and Drug Administration; and Washington State Department of Health.

The committee greatly benefited from the opportunity for discussion with individuals who attended and presented at their open session meetings (see Appendix D). The committee is thankful for the many contributions of these individuals.

The committee could not have done its work without the support and guidance provided by the National Academies project staff: Leigh Miles Jackson, study director; Jennifer Cohen, program officer; Kelsey Geiser, research associate; R. Brian Woodbury, research associate; Sara Tharakan, research associate; Matthew Masiello, research assistant; and Marjorie Pichon, senior program assistant. The committee is also grateful to Hope R. Hare and Doris Romero for their administrative and financial assistance on this project, and gratefully acknowledges Kathleen Stratton and Rose Marie Martinez of the Board on Population Health and Public Health Practices for the guidance they provided throughout this important study.

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Contents

PREFACE

At the time of this report's release in January 2017, 28 states and the District of Columbia have legalized cannabis for the treatment of medical conditions. Eight of these states and the District of Columbia have also legalized cannabis for recreational use. In addition to the growing availability of legalized cannabis, there has also been a rapid expansion in the types of available cannabis products, including edibles, oils, and a variety of inhaled substances. The growing acceptance, accessibility, and use of cannabis raise important public health concerns and there is a clear need to establish what is known and what needs to be known about the health effects of cannabis use.

The committee was tasked with conducting a comprehensive review of the current evidence regarding the health effects of using cannabis and cannabis-derived products. The study was conducted in a limited time frame in order to respond to a quickly moving landscape, but as described in the report's methods section, the amount of work that this report entailed and the volume of literature reviewed clearly indicates the substantial effort involved and the importance of this issue to the committee.

In the current report, the committee presents a rigorous and thoughtful summary of the landscape of cannabis and health and puts forth recommendations to help advance the research field and better inform public health decisions. I wish to express my deepest gratitude to my fellow committee members who worked so hard and with good grace to accomplish this task. As with other National Academies of Sciences, Engineering, and Medicine reports, the work of the committee would have been far more difficult, if not impossible, without the support of a dedicated, knowledgeable and also very hardworking National Academies staff.

Marie McCormick, *Chair*
Committee on the Health Effects of Marijuana: An Evidence Review and Research Agenda

SUMMARY

Over the past 20 years there have been substantial changes to the cannabis policy landscape. To date, 28 states and the District of Columbia have legalized cannabis for the treatment of medical conditions (NCSL, 2016). Eight of these states and the District of Columbia have also legalized cannabis for recreational use. These landmark changes in policy have markedly changed cannabis use patterns and perceived levels of risk. Based on a recent nationwide survey, 22.2 million Americans (12 years of age and older) reported using cannabis in the past 30 days and between 2002 and 2015 the percentage of past month cannabis users in this age range have increased steadily from 6.2 to 8.3 percent (CBHSQ, 2016).

Despite the extensive changes in policy at the state level and the rapid rise in the use of cannabis both for medical purposes and for recreational use, conclusive evidence regarding the short- and long-term health effects (harms and benefits) of cannabis use remains elusive. A lack of scientific research has resulted in a lack of information on the health implications of cannabis use, which is a significant public health concern for vulnerable populations such as adolescents and pregnant women. Unlike other substances, such as alcohol or tobacco, whose use may confer risk, no accepted standards exist to help guide individuals as they make choices regarding the issues of if, when, where, and how to use cannabis safely and, in regard to therapeutic uses, effectively.

Within this context, in March of 2016, the Health and Medicine Division (formerly the Institute of Medicine [IOM] [1] of the National Academies of Sciences, Engineering, and Medicine (the National Academies) was asked to convene a committee of experts to conduct a comprehensive review of the literature regarding the health effects of using cannabis and/or its constituents that had appeared since the publication of the IOM 1999 report *Marijuana and Medicine*. The resulting Committee on the Health Effects of Marijuana consisted of 16 experts in the areas of marijuana, addiction, oncology, cardiology, neurodevelopment, respiratory disease, pediatric and adolescent health, immunology, toxicology, preclinical research, epidemiology, systematic review, and public health. The sponsors of this report include federal, state, philanthropic and nongovernmental organizations, including the Alaska Mental Health Trust Authority; Arizona Department of Health Services; California Department of Public Health; CDC Foundation; Centers for Disease Control and Prevention (CDC); Mat-Su Health Foundation; National Highway Traffic Safety Administration; National Institutes of Health/ National Cancer Institute; National Institutes of Health/National Institute on Drug Abuse; Oregon Health Authority; The Colorado Health Foundation; The Robert W. Woodruff Foundation; Truth Initiative; U.S. Food and Drug Administration; and Washington State Department of Health.

[1] As of March 2016, the Health and Medicine Division continues the consensus studies and convening activities previously carried out by the Institute of Medicine (IOM).

In its statement of task, the committee was asked to make recommendations for a research agenda that will identify the most critical research questions regarding the association of cannabis use with health outcomes (both harms and benefits) that can be answered in the short term (i.e., within a 3-year time frame), as well as steps that should be taken in the short term to ensure that sufficient data are being gathered to answer long-term questions. Of note, throughout the report the committee has attempted to highlight research conclusions that affect certain populations (e.g., pregnant women, adolescents) that may be more vulnerable to potential harmful effects of cannabis use. The committee's full statement of task is presented in Box S-1.

BOX S-1
Statement of Task

The National Academies of Sciences, Engineering, and Medicine (the National Academies) will appoint an ad hoc committee to develop a comprehensive, in-depth review of existing evidence regarding the health effects of using marijuana and/or its constituents.

The committee will develop a consensus report with two primary sections: (1) a section of the report will summarize what can be determined about the health effects of marijuana use and, (2) a section of the report will summarize potential therapeutic uses of marijuana. The report will also provide a background overview of the cannabinoid/endocannabinoid system, history of use in the United States and the regulation and policy landscape. In addition, the report will outline and make recommendations regarding a research agenda identifying the most critical research questions regarding the association of marijuana use with health outcomes (both risks and therapeutic) that can be answered in the short term (i.e., within a 3-year time frame) as well as any steps that should be taken in the short term to ensure that sufficient data are being gathered to answer long-term questions (e.g., appropriate questions on large population surveillance surveys, clinical data collection or other data capture, and resolution of barriers to linkage between survey data and death/morbidity registries to enable population-level morbidity and mortality effects estimates). The committee should focus on questions and consequences with the potential for the greatest public health impact, while shedding light on the characteristics of marijuana use that impact both short- and long-term health.

In conducting its work, the committee will conduct a comprehensive review of the evidence, using accepted approaches of literature search, evidence review, grading and synthesis. Studies reviewed regarding health risks should be as broad as possible, including but not limited to epidemiology and clinical studies, and toxicology and animal studies when determined appropriate by the committee. The committee will provide summary determinations regarding causality based on strength of evidence. Both U.S. and international studies may be reviewed based upon relevance and methodological rigor.

STUDY CONTEXT AND APPROACH

Over the past 20 years the IOM published several consensus reports that focused on the health effects of marijuana or addressed marijuana within the context of other drug or substance abuse topics.[2] The two IOM reports that most prominently informed the committee's work were *Marijuana and Health,* published in 1982, and the 1999 report *Marijuana and Medicine: Assessing the Science Base.* Although these reports differed in scope, they were useful in providing a comprehensive body of evidence upon which the current committee could build.

[2] See https://www.nap.edu/search/?year=1995&rpp=20&ft=1&term=marijuana (accessed January 5, 2017).

The scientific literature on cannabis use has grown substantially since the 1999 publication of *Marijuana and Medicine.* The committee conducted an extensive search of relevant databases, including Medline, Embase, the Cochrane Database of Systematic Reviews, and PsycINFO and initially retrieved more than 24,000 abstracts that could have potentially been relevant to this study. These abstracts were reduced by limiting articles to those published in English and removing case reports, editorials, studies by "anonymous" authors, conference abstracts, and commentaries. In the end, the committee considered more than 10,700 abstracts for their relevance to this report.

Given the large scientific literature on cannabis, the breadth of the statement of task, and the time constraints of the study, the committee developed an approach that resulted in giving primacy to recently published systematic reviews (since 2011) and high-quality primary research for eleven groups of health endpoints (see Box S-2). For each health endpoint, systematic reviews were identified and assessed for quality using published criteria; only fair- and good-quality reviews were considered by the committee. The committee's conclusions are based on the findings from the most recently published systematic review and all relevant fair- and good-quality primary research published after the systematic review. Where no systematic review existed, the committee reviewed all relevant primary research published between January 1, 1999 and August 1, 2016. Primary research was assessed using standard approaches (e.g., Cochrane Quality Assessment, Newcastle-Ontario scale) as a guide.

BOX S-2
Health Topics and Prioritized Health Endpoints
(listed in the order in which they appear in the report)

Therapeutic effects

- Chronic pain; cancer, chemotherapy-induced nausea/vomiting; appetite and weight loss; irritable bowel syndrome; epilepsy; spasticity related to multiple sclerosis; Tourette syndrome; amyotrophic lateral sclerosis; Huntington's disease; Parkinson's disease; dystonia; Alzheimer's disease/dementia; glaucoma; traumatic brain injury/spinal cord injury; addiction; anxiety; depression; sleep disorders; posttraumatic stress disorder; schizophrenia

Cancer

- Lung cancer; oral cancer; esophageal cancer; testicular cancer; other cancer

Cardiometabolic risk

- Acute myocardial infarction; stroke; metabolic dysregulation, metabolic syndrome, prediabetes, and diabetes

Respiratory disease

- Pulmonary function; respiratory symptoms (including chronic bronchitis); chronic obstructive pulmonary disorder; asthma

Immunity

- Immune Function; infectious disease

Injury and death

- All-cause mortality; occupational injury; motor vehicle crash; overdose injury and death

Prenatal, perinatal, and postnatal exposure to cannabis

- Pregnancy complications for the mother; fetal growth and development; neonatal conditions; later outcomes for the infant

Psychosocial

- Cognition (learning, memory, attention, intelligence); academic achievement and educational outcomes; employment/income; social relationships and other social roles

Mental health

- Schizophrenia other psychotic disorders; bipolar disorders, depression; suicide; anxiety; posttraumatic stress disorder

Problem cannabis use

- Cannabis use disorder

Cannabis Use and abuse of other substances

- Abuse of other substances

The search strategies and processes described above were developed and adopted by the committee in order to adequately address a broad statement of task in a limited timeframe, while adhering to the National Academies' high standards for the quality and rigor of committee reports. Readers of this report should recognize two important points. First, the committee was not tasked to conduct multiple systematic reviews, which would have required a lengthy and robust series of processes. The committee did, however, adopt key features of that process: a comprehensive literature search, assessments by more than one person of the quality (risk of bias) of key literature and the conclusions, pre-specification of the questions of interest before conclusions were formulated, standard language to allow comparisons between conclusions, and declarations of conflict of interest via the National Academies conflict-of-interest policies. Second, there is a possibility that some literature was missed because of the practical steps taken to narrow a very large literature to one that was manageable within the timeframe available to the committee. Furthermore, very good research may not be reflected in this report because it did not directly address the health endpoint research questions that were prioritized by the committee.

This report is organized into four parts and 16 chapters. Part I: Introduction and Background, Part II: Therapeutic Effects of Cannabis and Cannabinoid, Part III: Other Health Effects, and Part IV: Research Barriers and Recommendations. In Part II, most of the evidence reviewed in this chapter derives from clinical and basic science research conducted for the specific purpose of answering an a priori question of whether cannabis and/or cannabinoids are an effective treatment for a specific disease or health condition. The evidence reviewed in Part III derives from epidemiological research that primarily reviews the effects of smoked cannabis. It is of note that several of the prioritized health endpoints discussed in Part III are also reviewed in Part II, albeit from the perspective of effects associated with using cannabis for primarily recreational, as opposed to therapeutic, purposes.

Several health endpoints are discussed in multiple chapters of the report (e.g., cancer, schizophrenia); however, it is important to note that the research conclusions regarding potential harms and benefits discussed in these chapters may differ. This is, in part, due to differences in the study design of the reviewed evidence, differences in characteristics of cannabis or cannabinoid exposure (e.g., form, dose, frequency of use), and the populations studied. As such,

it is important that the reader is aware that this report was not designed to reconcile the proposed harms and benefits of cannabis or cannabinoid use across the report's chapters. In drafting the report's conclusions, the committee made an effort to be as specific as possible about the type and/or duration of cannabis or cannabinoid exposure and where relevant, cross-referenced findings from other report chapters.

REPORT CONCLUSIONS ON THE ASSOCIATION BETWEEN CANNABIS USE AND HEALTH

From their review, the committee arrived at nearly 100 different research conclusions related to cannabis or cannabinoid use and health. Informed by the reports of previous IOM committees,[3] the committee developed standard language to categorize the weight of evidence regarding whether cannabis or cannabinoids use (for therapeutic purposes) are an effective or ineffective treatment for the prioritized health endpoints of interest, or whether cannabis or cannabinoid use (primarily for recreational purposes) are statistically associated with the prioritized health endpoints of interest. Box S-3 below describes these categories and the general parameters for the types of evidence supporting each category. For a full listing of the committee's conclusions, please see the chapter's annex.

Box S-3
Weight-of-Evidence Categories

CONCLUSIVE EVIDENCE

For therapeutic effects: There is strong evidence from randomized controlled trials to support the conclusion that cannabis or cannabinoids are an effective or ineffective treatment for the health endpoint of interest.

For other health effects: There is strong evidence from randomized controlled trials to support or refute a statistical association between cannabis or cannabinoid use and the health endpoint of interest.

For this level of evidence, there are many supportive findings from good-quality studies with no credible opposing findings. A firm conclusion can be made, and the limitations to the evidence, including chance, bias, and confounding factors, can be ruled out with reasonable confidence.

SUBSTANTIAL EVIDENCE

For therapeutic effects: There is strong evidence to support the conclusion that cannabis or cannabinoids are an effective or ineffective treatment for the health endpoint of interest.

For other health effects: There is strong evidence to support or refute a statistical association between cannabis or cannabinoid use and the health endpoint of interest.

For this level of evidence, there are several supportive findings from good-quality studies with very few

[3] *Adverse Effects of Vaccines* (IOM, 2012); *Treatment of Posttraumatic Stress Disorder: An Assessment of the Evidence*, (IOM, 2008); *Veterans and Agent Orange: Update 2014* (NASEM, 2016).

or no credible opposing findings. A firm conclusion can be made, but minor limitations, including chance, bias, and confounding factors, cannot be ruled out with reasonable confidence.

MODERATE EVIDENCE

For therapeutic effects: There is some evidence to support the conclusion that cannabis or cannabinoids are an effective or ineffective treatment for the health endpoint of interest.

For other health effects: There is some evidence to support or refute a statistical association between cannabis or cannabinoid use and the health endpoint of interest.

For this level of evidence, there are several supportive findings from good- to fair-quality studies with very few or no credible opposing findings. A general conclusion can be made, but limitations, including chance, bias, and confounding factors, cannot be ruled out with reasonable confidence.

LIMITED EVIDENCE

For therapeutic effects: There is weak evidence to support the conclusion that cannabis or cannabinoids are an effective or ineffective treatment for the health endpoint of interest.

For other health effects: There is weak evidence to support or refute a statistical association between cannabis or cannabinoid use and the health endpoint of interest.

For this level of evidence, there are supportive findings from fair-quality studies or mixed findings with most favoring one conclusion. A conclusion can be made, but there is significant uncertainty due to chance, bias, and confounding factors.

NO OR INSUFFICIENT EVIDENCE TO SUPPORT THE ASSOCIATION

For therapeutic effects: There is no or insufficient evidence to support the conclusion that cannabis or cannabinoids are an effective or ineffective treatment for the health endpoint of interest.

For other health effects: There is no or insufficient evidence to support or refute a statistical association between cannabis or cannabinoid use and the health endpoint of interest.

For this level of evidence, there are mixed findings, a single poor study, or health endpoint has not been studied at all. No conclusion can be made because of substantial uncertainty due to chance, bias, and confounding factors.

REPORT RECOMMENDATIONS

This is a pivotal time in world of cannabis policy and research. Shifting public sentiment, conflicting and impeded scientific research, and legislative battles have fueled the debate about what, if any, harms or benefits can be attributed to the use of cannabis or its derivatives. The committee has put forth a substantial number of research conclusions on the health effects of cannabis and cannabinoids. Based on their research conclusions, the committee members formulated four recommendations to address research gaps, improve research quality, improve surveillance capacity, and address research barriers. The report's full recommendations are described below.

Address Research Gaps

Recommendation 1: To develop a comprehensive evidence base on the short- and long-term health effects of cannabis use (both beneficial and harmful effects), public agencies,[4] philanthropic and professional organizations, private companies, and clinical and public health research groups should provide funding and support for a national cannabis research agenda that addresses key gaps in the evidence base. Prioritized research streams and objectives should include, but need not be limited to:

Clinical and Observational Research

- Examine the health effects of cannabis use in at-risk or under-researched populations, such as children and youth (often described as less than 18 years of age) and older populations (generally over 50 years of age), pregnant and breastfeeding women, and heavy cannabis users.
- Investigate the pharmacokinetic and pharmacodynamic properties of cannabis, modes of delivery, different concentrations, in various populations, including the dose–response relationships of cannabis and THC or other cannabinoids.
- Determine the benefits and harms associated with understudied cannabis products, such as edibles, concentrates, and topicals.
- Conduct well-controlled trials on the potential beneficial and harmful health effects of using different forms of cannabis, such as inhaled (smoked or vaporized) whole cannabis plant and oral cannabis.
- Characterize the health effects of cannabis on unstudied and understudied health endpoints, such as epilepsy in pediatric populations; symptoms of posttraumatic stress disorder; childhood and adult cancers; cannabis-related overdoses and poisonings; and other high-priority health endpoints.

Health Policy and Health Economics Research

- Identify models, including existing state cannabis policy models, for sustainable funding of national, state, and local public health surveillance systems.
- Investigate the economic impact of recreational and medical cannabis use on national and state public health and health care systems, health insurance providers, and patients.

[4] Agencies may include the CDC, relevant agencies of the NIH, and the FDA.

Public Health and Public Safety Research

- Identify gaps in the cannabis-related knowledge and skills of health care and public health professionals, and assess the need for, and performance of, continuing education programs that address these gaps.
- Characterize public safety concerns related to recreational cannabis use and evaluate existing quality assurance, safety, and packaging standards for recreational cannabis products.

Improve Research Quality

Recommendation 2: To promote the development of conclusive evidence on the short- and long-term health effects of cannabis use (both beneficial and harmful effects), agencies of the United States Department of Health and Human Services, including the National Institutes of Health and the Centers for Disease Control and Prevention should jointly fund a workshop to develop a set of research standards and benchmarks to guide and ensure the production of high-quality cannabis research. Workshop objectives should include, but need not be limited to:

- The development of a minimum dataset for observational and clinical studies, standards for research methods and design, and guidelines for data collection methods.
- Adaptation of existing research-reporting standards to the needs of cannabis research.
- The development of uniform terminology for clinical and epidemiological cannabis research.
- The development of standardized and evidence-based question banks for clinical research and public health surveillance tools.

Improve Surveillance Capacity

Recommendation 3: To ensure that sufficient data are available to inform research on the short- and long-term health effects of cannabis use (both beneficial and harmful effects), the Centers for Disease Control and Prevention, the Substance Abuse and Mental Health Services Administration, the Association of State and Territorial Health Officials, National Association of County and City Health Officials, the Association of Public Health Laboratories, and state and local public health departments should fund and support improvements to federal public health surveillance systems and state-based public health surveillance efforts. Potential efforts should include, but need not be limited to:

- The development of question banks on the beneficial and harmful health effects of therapeutic and recreational cannabis use and their incorporation into major public health surveys, including the National Health and Nutrition Examination Survey, National Health Interview Survey, Behavioral Risk Factor Surveillance System, National Survey on Drug Use and Health, Youth Risk Behavior Surveillance System, National Vital Statistics System, Medical Expenditure Panel Survey, and the National Survey of Family Growth.
- Determining the capacity to collect and reliably interpret data from diagnostic classification codes in administrative data (e.g., *International Classification of Diseases-10*)

- The establishment and utilization of state-based testing facilities to analyze the chemical composition of cannabis and products containing cannabis, cannabinoids, or THC.
- The development of novel diagnostic technologies that allow for rapid, accurate, and non-invasive assessment of cannabis exposure and impairment.
- Strategies for surveillance of harmful effects of cannabis for therapeutic use.

Address Research Barriers

Recommendation 4: **The Centers for Disease Control and Prevention, National Institutes of Health, Food and Drug Administration, industry groups, and nongovernmental organizations should fund the convening of a committee of experts tasked to produce an objective and evidence-based report that fully characterizes the impacts of regulatory barriers to cannabis research and that proposes strategies for supporting development of the resources and infrastructure necessary to conduct a comprehensive cannabis research agenda. Committee objectives should include, but need not be limited to:**

- Proposing strategies for expanding access to research-grade marijuana, through the creation and approval of new facilities for growing and storing cannabis.
- Identifying nontraditional funding sources and mechanisms to support a comprehensive national cannabis research agenda.
- Investigating strategies for improving the quality, diversity, and external validity of research-grade cannabis products.

REFERENCES

CBHSQ (Center for Behavioral Health Statistics and Quality). 2016. Behavioral health trends in the United States: Results from the 2014 National Survey on Drug Use and Health (HHS Publication No. SMA 15-4927, NSDUH Series H-50). https://www.samhsa.gov/data/sites/default/files/NSDUH-FFR1-2015/NSDUH-FFR1-2015/NSDUH-FFR1-2015.pdf (accessed December 5, 2016).

IOM (Institute of Medicine). 2008. Treatment of postraumatic stress disorder: An assessment of the evidence. Washington, DC: The National Academies Press.

IOM. 2012. Adverse effects of vaccines: Evidence and causality. Washington, DC: The National Academies Press.

NASEM (National Academies of Sciences, Engineering, and Medicine). 2016. Veterans and Agent Orange: Update 2014. Washington, DC: The National Academies Press.

National Conference of State Legislatures. 2016. State medical marijuana laws. November 9. http://www.ncsl.org/research/health/state-medical-marijuana-laws.aspx (accessed November 21, 2016).

ANNEX

Report Conclusions[5]

Chapter 4 Conclusions—Therapeutic Effects

There is conclusive or substantial evidence that cannabis or cannabinoids are effective:

- For the treatment of chronic pain in adults (cannabis) (4-1)
- As anti-emetics in the treatment of chemotherapy-induced nausea and vomiting (oral cannabinoids) (4-3)
- For improving patient-reported multiple sclerosis spasticity symptoms (oral cannabinoids) (4-7a)

There is moderate evidence that cannabis or cannabinoids are effective for:

- Improving short-term sleep outcomes in individuals with sleep disturbance associated with obstructive sleep apnea syndrome, fibromyalgia, chronic pain, and multiple sclerosis (cannabinoids, primarily nabiximols) (4-19)

There is limited evidence that cannabis or cannabinoids are effective for:

- Increasing appetite and decreasing weight loss associated with HIV/AIDS (cannabis and oral cannabinoids) (4-4a)
- Improving clinician-measured multiple sclerosis spasticity symptoms (oral cannabinoids) (4-7a)
- Improving symptoms of Tourette syndrome (THC capsules) (4-8)
- Improving anxiety symptoms, as assessed by a public speaking test, in individuals with social anxiety disorders (cannabidiol) (4-17)
  Improving symptoms of posttraumatic stress disorder (nabilone; one single, small fair-quality trial) (4-20)

There is limited evidence of a statistical association between cannabinoids and:

- Better outcomes (i.e., mortality, disability) after a traumatic brain injury or intracranial hemorrhage (4-15)

There is limited evidence that cannabis or cannabinoids are *ineffective* for:

- Improving symptoms associated with dementia (cannabinoids) (4-13)
- Improving intraocular pressure associated with glaucoma (cannabinoids) (4-14)
  Reducing depressive symptoms in individuals with chronic pain or multiple sclerosis (nabiximols, dronabinol, and nabilone) (4-18)

There is no or insufficient evidence to support or refute the conclusion that cannabis or cannabinoids are an effective treatment for:

- Cancers, including glioma (cannabinoids) (4-2)
- Cancer-associated anorexia cachexia syndrome and anorexia nervosa (cannabinoids) (4-

[5] Numbers in parentheses correspond to chapter conclusion numbers.

4b)
- Symptoms of irritable bowel syndrome (dronabinol) (4-5)
- Epilepsy (cannabinoids) (4-6)
- Spasticity in patients with paralysis due to spinal cord injury (cannabinoids) (4-7b)
- Symptoms associated with amyotrophic lateral sclerosis (cannabinoids) (4-9)
- Chorea and certain neuropsychiatric symptoms associated with Huntington's disease (oral cannabinoids) (4-10)
- Motor system symptoms associated with Parkinson's disease or the levodopa-induced dyskinesia (cannabinoids) (4-11)
- Dystonia (nabilone and dronabinol) (4-12)
- Achieving abstinence in the use of addictive substances (cannabinoids) (4-16)
- Mental health outcomes in individuals with schizophrenia or schizophreniform psychosis (cannabidiol) (4-21)

Chapter 5 Conclusions—Cancer

There is moderate evidence of *no* statistical association between cannabis use and:
- Incidence of lung cancer (cannabis smoking) (5-1)
- Incidence of head and neck cancers (5-2)

There is limited evidence of a statistical association between cannabis smoking and:
- Non-seminoma-type testicular germ cell tumors (current, frequent, or chronic cannabis smoking) (5-3)

There is no or insufficient evidence to support or refute a statistical association between cannabis use and:
- Incidence of esophageal cancer (cannabis smoking) (5-4)
- Incidence of prostate cancer, cervical cancer, malignant gliomas, non-Hodgkin lymphoma, penile cancer, anal cancer, Kaposi's sarcoma, or bladder cancer (5-5)
- Subsequent risk of developing acute myeloid leukemia/acute non-lymphoblastic leukemia, acute lymphoblastic leukemia, rhabdomyosarcoma, astrocytoma, or neuroblastoma in offspring (parental cannabis use) (5-6)

Chapter 6 Conclusions—Cardiometabolic Risk

There is limited evidence of a statistical association between cannabis use and:
- The triggering of acute myocardial infarction (cannabis smoking) (6-1a)
- Ischemic stroke or subarachnoid hemorrhage (6-2)
- Decreased risk of metabolic syndrome and diabetes (6-3a)
- Increased risk of prediabetes (6-3b)

There is no evidence to support or refute a statistical association between *chronic effects* of cannabis use and:
- The increased risk of acute myocardial infarction (6-1b)

Chapter 7 Conclusions—Respiratory Disease

There is substantial evidence of a statistical association between cannabis smoking and:

- Worse respiratory symptoms and more frequent chronic bronchitis episodes (long-term cannabis smoking) (7-3a)

There is moderate evidence of a statistical association between cannabis smoking and:

- Improved airway dynamics with acute use, but not with chronic use (7-1a)
- Higher forced vital capacity (FVC) (7-1b)

There is moderate evidence of a statistical association between *the cessation* of cannabis smoking and:

- Improvements in respiratory symptoms (7-3b)

There is limited evidence of a statistical association between cannabis smoking and:

- An increased risk of developing chronic obstructive pulmonary disease (COPD) when controlled for tobacco use (occasional cannabis smoking) (7-2a)

There is no or insufficient evidence to support or refute a statistical association between cannabis smoking and:

- Hospital admissions for COPD (7-2b)
- Asthma development or asthma exacerbation (7-4)

Chapter 8 Conclusions—Immunity

There is limited evidence of a statistical association between cannabis smoking and:

- A decrease in the production of several inflammatory cytokines in healthy individuals (8-1a)

There is limited evidence of *no* statistical association between cannabis use and:

- The progression of liver fibrosis or hepatic disease in individuals with viral Hepatitis C (HCV) (daily cannabis use) (8-3)

There is no or insufficient evidence to support or refute a statistical association between cannabis use and:

- Other adverse immune cell responses in healthy individuals (cannabis smoking) (8-1b)
- Adverse effects on immune status in individuals with HIV (cannabis or dronabinol use) (8-2)
- Increased incidence of oral human papilloma virus (HPV) (regular cannabis use) (8-4)

Chapter 9 Conclusions—Injury and Death

There is substantial evidence of a statistical association between cannabis use and:

- Increased risk of motor vehicle crashes (9-3)

There is moderate evidence of a statistical association between cannabis use and:

- Increased risk of overdose injuries, including respiratory distress, among pediatric populations in U.S. states where cannabis is legal (9-4b)

There is no or insufficient evidence to support or refute a statistical association between cannabis use and:

- All-cause mortality (self-reported cannabis use) (9-1)
- Occupational accidents or injuries (general, non-medical cannabis use) (9-2)
- Death due to cannabis overdose (9-4a)

Chapter 10 Conclusions—Prenatal, Perinatal, and Neonatal Exposure

There is substantial evidence of a statistical association between maternal cannabis smoking and:

- Lower birth weight of the offspring (10-2)

There is limited evidence of a statistical association between maternal cannabis smoking and:

- Pregnancy complications for the mother (10-1)
- Admission of the infant to the neonatal intensive care unit (NICU) (10-3)

There is insufficient evidence to support or refute a statistical association between maternal cannabis smoking and:

- Later outcomes in the offspring (e.g., sudden infant death syndrome, cognition/academic achievement, and later substance use) (10-4)

Chapter 11 Conclusions—Psychosocial

There is moderate evidence of a statistical association between cannabis use and:

- The impairment in the cognitive domains of learning, memory, and attention (acute cannabis use) (11-1a)

There is limited evidence of a statistical association between cannabis use and:

- Impaired academic achievement and education outcomes (11-2)
- Increased rates of unemployment and/or low income (11-3)
- Impaired social functioning or engagement in developmentally appropriate social roles (11-4)

There is limited evidence of a statistical association between *sustained abstinence from* cannabis use and:

- Impairments in the cognitive domains of learning, memory, and attention (11-1b)

Chapter 12 Conclusions—Mental Health

There is substantial evidence of a statistical association between cannabis use and:

- The development of schizophrenia or other psychoses, with the highest risk among the most frequent users (12-1)

There is moderate evidence of a statistical association between cannabis use and:

- Better cognitive performance among individuals with psychotic disorders and a history of cannabis use (12-2a)
- Increased symptoms of mania and hypomania in individuals diagnosed with bipolar disorders (regular cannabis use) (12-4)
- A small increased risk for the development of depressive disorders (12-5)
- Increased incidence of suicidal ideation and suicide attempts with a higher incidence among heavier users (12-7a)
- Increased incidence of suicide completion (12-7b)
- Increased incidence of social anxiety disorder (regular cannabis use) (12-8b)

There is moderate evidence of *no* statistical association between cannabis use and:

- Worsening of negative symptoms of schizophrenia (e.g., blunted affect) among individuals with psychotic disorders (12-2c)

There is limited evidence of a statistical association between cannabis use and:

- An increase in positive symptoms of schizophrenia (e.g., hallucinations) among individuals with psychotic disorders (12-2b)
- The likelihood of developing bipolar disorder, particularly among regular or daily users (12-3)
- The development of any type of anxiety disorder, except social anxiety disorder (12-8a)
- Increased symptoms of anxiety (near daily cannabis use) (12-9)
- Increased severity of posttraumatic stress disorder symptoms among individuals with posttraumatic stress disorder (12-11)

There is no evidence to support or refute a statistical association between cannabis use and:

- Changes in the course or symptoms of depressive disorders (12-6)
- The development of posttraumatic stress disorder (12-10)

Chapter 13 Conclusions—Problem Cannabis Use

There is substantial evidence that:

- Stimulant treatment of attention deficit hyperactivity disorder (ADHD) during adolescence is *not* a risk factor for the development of problem cannabis use (13-2e)
- Being male and smoking cigarettes are risk factors for the progression of cannabis use to problem cannabis use (13-2i)
- Initiating cannabis use at an earlier age is a risk factor for the development of problem cannabis use (13-2j)

There is substantial evidence of a statistical association between:

- Increases in cannabis use frequency and the progression to developing problem cannabis use (13-1)
- Being male and the severity of problem cannabis use, but the recurrence of problem cannabis use does not differ between males and females (13-3b)

There is moderate evidence that:

- Anxiety, personality disorders, and bipolar disorders are *not* risk factors for the development of problem cannabis use (13-2b)
- Major depressive disorder is a risk factor for the development of problem cannabis use (13-2c)
- Adolescent ADHD is *not* a risk factor for the development of problem cannabis use (13-2d)
- Being male is a risk factor for the development of problem cannabis use (13-2f)
- Exposure to the combined use of abused drugs is a risk factor for the development of problem cannabis use (13-2g)
- Neither alcohol nor nicotine dependence alone are risk factors for the progression from cannabis use to problem cannabis use (13-2h)
- During adolescence the frequency of cannabis use, oppositional behaviors, a younger age of first alcohol use, nicotine use, parental substance use, poor school performance, antisocial behaviors, and childhood sexual abuse are risk factors for the development of problem cannabis use (13-2k)

There is moderate evidence of a statistical association between:

- A persistence of problem cannabis use and a history of psychiatric treatment (13-3a)
- Problem cannabis use and increased severity of posttraumatic stress disorder symptoms (13-3c)

There is limited evidence that:

- Childhood anxiety and childhood depression are risk factors for the development of problem cannabis use (13-2a)

Chapter 14 Conclusions—Abuse of Other Substances

There is moderate evidence of a statistical association between cannabis use and:

- The development of substance dependence and/or a substance abuse disorder for substances including, alcohol, tobacco, and other illicit drugs (14-3)

There is limited evidence of a statistical association between cannabis use and:

- The initiation of tobacco use (14-1)
- Changes in the rates and use patterns of other licit and illicit substances (14-2)

Chapter 15 Conclusions—Challenges and Barriers in Conducting Cannabis and Cannabinoid Research

There are several challenges and barriers in conducting cannabis and cannabinoid research, including:

- There are specific regulatory barriers, including the classification of cannabis as a Schedule I substance, that impede the advancement of cannabis and cannabinoid research (15-1)
- It is often difficult for researchers to gain access to the quantity, quality, and type of cannabis product necessary to address specific research questions on the health effects of cannabis use (15-2)
- A diverse network of funders is needed to support cannabis and cannabinoid research that explores the beneficial and harmful health effects of cannabis use (15-3)
- To develop conclusive evidence for the effects of cannabis use on short- and long-term health outcomes, improvements and standardization in research methodology (including those used in controlled trials and observational studies) are needed (15-4)

Part I
Introduction and Background

1

Introduction

Significant changes have taken place in the policy landscape surrounding cannabis legalization, production, and use. Over the past 20 years there have been substantial changes to the cannabis policy landscape. To date, 28 states and the District of Columbia have legalized cannabis for the treatment of medical conditions (NCSL, 2016). Eight of these states and the District of Columbia have also legalized cannabis for recreational use. These landmark changes in policy have markedly changed cannabis use patterns and perceived levels of risk. Based on a recent nationwide survey, 22.2 million Americans (12 years of age and older) reported using cannabis in the past 30 days and between 2002 and 2015 the percentage of past month cannabis users in this age range have increased steadily from 6.2 to 8.3 percent (CBHSQ, 2016).

Despite this reported rapid rise in the use of cannabis, both for medical purposes and for recreational use, conclusive evidence regarding the short- and long-term health effects of cannabis use remains elusive. While a myriad of studies have examined cannabis use in all its various forms (Calabria et al., 2010; Whiting et al., 2015, 2016; WHO, 2016), often these research conclusions are not appropriately synthesized, translated for, or communicated to policy makers, health care providers, state health officials, or other stakeholders who have been charged with influencing and enacting policies, procedures, and laws related to cannabis use. Unlike other substances whose use may confer risk, such as alcohol or tobacco, no accepted standards for the safe use or appropriate doses are available to help guide individuals as they make choices regarding the issues of if, when, where, and how to use cannabis safely and, in regard to therapeutic uses, effectively (Freeman et al., 2014; Marsot et al., 2016). Moreover, studying the potential health impacts of cannabis presents its own set of unique challenges. Current challenges include the existence of certain regulations and policies that restrict access to cannabis products suited for research purposes (e.g., Schedule 1 status; regulatory approvals), the limited availability of funding for comprehensive cannabis research, and cross-cutting methodological challenges. Additionally, researchers are often unable to obtain the necessary quantity, quality, or type of cannabis product to address cutting-edge public health research questions.

STUDY CHARGE

Shifting public sentiment, conflicting and impeded scientific research, and legislative battles have fueled the debate about what, if any, harms or benefits can be attributed to the use of cannabis or its derivatives. In March 2016 the Health and Medicine Division[1] of the National Academies of Sciences, Engineering, and Medicine (the National Academies) was asked to

[1] As of March 2016, the Health and Medicine Division continues the consensus studies and convening activities previously carried out by the Institute of Medicine (IOM).

convene a committee of experts to conduct a comprehensive review of literature regarding the health consequences of using cannabis or its constituents that had appeared since the publication of the 1999 Institute of Medicine (IOM) report *Marijuana and Medicine* (IOM, 1999). In addition, the committee was asked to make recommendations for a research agenda that will identify the most critical research questions regarding the association of cannabis use with health outcomes (both harms and benefits) that can be answered in the short term (i.e., within a 3-year time frame), as well as steps that should be taken in the short term to ensure that sufficient data are being gathered to answer long-term questions. Of note, throughout this report the committee has attempted to highlight research conclusions that affect certain populations (e.g., pregnant women, adolescents) that may be at greater risk for potential adverse effects of cannabis use. The committee's full statement of task is presented in Box 1-1.

The resulting Committee on the Health Effects of Marijuana included experts in the areas of marijuana, addiction, oncology, cardiology, neurodevelopment, pulmonary, pediatric and adolescent health, immunology, toxicology, preclinical research, epidemiology, systematic review, and public health. (See Appendix E for the biographical sketches of committee members.)

In conducting its work, the committee met six times from March 2016 through December 2016. In conjunction with two of those meetings, the committee held half-day public information-gathering sessions which allowed the committee to hear from study sponsors, experts, and other stakeholders. These discussions helped to inform the committee's deliberations.

Sponsors of this report include federal, state, philanthropic and nongovernmental organizations. These include the Alaska Mental Health Trust Authority; Arizona Department of Health Services; California Department of Public Health; CDC Foundation; Centers for Disease Control and Prevention (CDC); Mat-Su Health Foundation; National Highway Traffic Safety Administration; National Institutes of Health/National Cancer Institute; National Institutes of Health/National Institute on Drug Abuse; Oregon Health Authority; The Colorado Health Foundation; The Robert W. Woodruff Foundation; Truth Initiative; U.S. Food and Drug Administration; and the Washington State Department of Health.

BOX 1-1
Statement of Task

The National Academies of Sciences, Engineering, and Medicine (the National Academies) will appoint an ad hoc committee to develop a comprehensive, in-depth review of existing evidence regarding the health effects of using marijuana and/or its constituents.

The committee will develop a consensus report with two primary sections: (1) a section of the report will summarize what can be determined about the health effects of marijuana use and, (2) a section of the report will summarize potential therapeutic uses of marijuana. The report will also provide a background overview of the cannabinoid/endocannabinoid system, history of use in the United States and the regulation and policy landscape. In addition, the report will outline and make recommendations regarding a research agenda identifying the most critical research questions regarding the association of marijuana use with health outcomes (both risks and therapeutic) that can be answered in the short term (i.e., within a 3-year time frame) as well as any steps that should be taken in the short term to ensure that sufficient data are being gathered to answer long-term questions (e.g., appropriate questions on large population surveillance surveys, clinical data collection or other data capture, and resolution of barriers to linkage between survey data and death/morbidity registries to enable population-level morbidity and mortality effects estimates). The committee should focus on questions and consequences with the

potential for the greatest public health impact, while shedding light on the characteristics of marijuana use that impact both short- and long-term health.

In conducting its work, the committee will conduct a comprehensive review of the evidence, using accepted approaches of literature search, evidence review, grading and synthesis. Studies reviewed regarding health risks should be as broad as possible, including but not limited to epidemiology and clinical studies, and toxicology and animal studies when determined appropriate by the committee. The committee will provide summary determinations regarding causality based on strength of evidence. Both U.S. and international studies may be reviewed based upon relevance and methodological rigor.

STUDY CONTEXT AND APPROACH

Over the past 20 years the IOM has published several consensus reports that focused on the health effects of marijuana or addressed marijuana within the context of other drug or substance abuse topics.[2] Two IOM reports that most prominently informed the committee's work were *Marijuana and Health* (IOM, 1982), and the 1999 report *Marijuana and Medicine: Assessing the Science Base* (IOM, 1999). Although these reports differed in scope, they were useful in providing a comprehensive body of evidence upon which the current committee could build.

Marijuana and Health (IOM, 1982) was commissioned by the former Secretary of Health and Human Services and the former director of the National Institutes of Health, Joseph Califano Jr., and Donald S. Fredrickson, respectively. The study's committee was appointed to (1) analyze the potential hazards of marijuana use on user safety and health, (2) analyze data concerning the therapeutic value of marijuana, (3) assess the federal research programs, (4) identify new research directions, and (5) draw conclusions that would assist future policy decision making. The authoring committee concluded that there was evidence indicating that marijuana has a broad range of psychological and biological effects, some of which under certain conditions are harmful to human health, but there was a substantial lack of definitive evidence to characterize the seriousness of harm. The committee's major conclusion was that "what little we know for certain about the effects of marijuana on human health—and all that we have reason to suspect—justifies serious national concern" (IOM, 1982, p. 5). The committee's major recommendation called for an intensification and more comprehensive research effort into the effects of marijuana on the health of the American people.

In 1997 the White House Office of National Drug Control Policy contracted with the Institute of Medicine to conduct a scientific review of available literature to determine the potential health benefits and risks of marijuana and its constituent cannabinoids. The resulting report, *Marijuana and Medicine* (IOM, 1999), offered several conclusions and recommendations (see Box 1-2) on the effects of isolated cannabinoids, the efficacy of cannabinoid drugs, the influence of psychological effects on therapeutic effects, physiological risks, marijuana dependence and withdrawal, marijuana as a "gateway drug," and the use of smoked marijuana.

[2] See https://www.nap.edu/search/?year=1995&rpp=20&ft=1&term=marijuana (Accessed : July, 2016)

BOX 1-2
***Marijuana and Medicine: Assessing the Science Base* (1999)**
Conclusions and Recommendations

Conclusions:

- At this point, our knowledge about the biology of marijuana and cannabinoids allows us to make some general conclusions:
  - Cannabinoids likely have a natural role in pain modulation, control of movement, and memory.
  - The natural role of cannabinoids in immune systems is likely multi-faceted and remains unclear.
  - The brain develops tolerance to cannabinoids.
  - Animal research demonstrates the potential for dependence, but this potential is observed under a narrower range of conditions than with benzodiazepines, opiates, cocaine, or nicotine.
  - Withdrawal symptoms can be observed in animals but appear to be mild compared to opiates or benzodiazepines, such as diazepam (Valium).
- The different cannabinoid receptor types found in the body appear to play different roles in normal human physiology. In addition, some effects of cannabinoids appear to be independent of those receptors. The variety of mechanisms through which cannabinoids can influence human physiology underlies the variety of potential therapeutic uses for drugs that might act selectively on different cannabinoid systems.
- Scientific data indicate the potential therapeutic value of cannabinoid drugs, primarily tetrahydrocannabinol (THC), for pain relief, control of nausea and vomiting, and appetite stimulation; smoked marijuana, however, is a crude THC delivery system that also delivers harmful substances.
- The psychological effects of cannabinoids, such as anxiety reduction, sedation, and euphoria can influence their potential therapeutic value. Those effects are potentially undesirable for certain patients and situations and beneficial for others. In addition, psychological effects can complicate the interpretation of other aspects of the drug's effect.
- Numerous studies suggest that marijuana smoke is an important risk factor in the development of respiratory disease. A distinctive marijuana withdrawal syndrome has been identified, but it is mild and short lived. The syndrome includes restlessness, irritability, mild agitation, insomnia, sleep disturbance, nausea, and cramping.
- Present data on drug use progression neither support nor refute the suggestion that medical availability would increase drug abuse. However, this question is beyond the issues normally considered for medical uses of drugs and should not be a factor in evaluating the therapeutic potential of marijuana or cannabinoids.

Recommendations:

- Research should continue into the physiological effects of synthetic and plant-derived cannabinoids and the natural function of cannabinoids found in the body. Because different cannabinoids appear to have different effects, cannabinoid research should include, but not be restricted to, effects attributable to THC alone.
- Clinical trials of cannabinoid drugs for symptom management should be conducted with the goal of developing rapid-onset, reliable, and safe delivery systems.
- Psychological effects of cannabinoids such as anxiety reduction and sedation, which can influence medical benefits, should be evaluated in clinical trials.
- Studies to define the individual health risks of smoking marijuana should be conducted, particularly among populations in which marijuana use is prevalent.

- Clinical trials of marijuana use for medical purposes should be conducted under the following limited circumstances: trials should involve only short-term marijuana use (less than 6 months), should be conducted in patients with conditions for which there is reasonable expectation of efficacy, should be approved by institutional review boards, and should collect data about efficacy.
- Short-term use of smoked marijuana (less than six months) for patients with debilitating symptoms (such as intractable pain or vomiting) must meet the following conditions:
  - failure of all approved medications to provide relief has been documented,
  - the symptoms can reasonably be expected to be relieved by rapid-onset cannabinoid drugs,
  - such treatment is administered under medical supervision in a manner that allows for assessment of treatment effectiveness,
  - and involves an oversight strategy comparable to an institutional review board process that could provide guidance within 24 hours of a submission by a physician to provide marijuana to a patient for a specified use.

SOURCE: IOM, 1999.

The scientific literature on cannabis use has grown substantially since the publication of *Marijuana and Medicine* in 1999. The current committee conducted an extensive search of relevant databases, including Medline, Embase, the Cochrane Database of Systematic Reviews, and PsycINFO and initially retrieved more than 24,000 abstracts for articles published since the 1999 report that could potentially be relevant to this study. These abstracts were reduced by limiting articles to those published in English and removing case reports, editorials, studies by "anonymous" authors, conference abstracts, and commentaries. In the end, the committee considered more than 10,700 abstracts for their relevance to this report. (See Appendix B for details.)

The methodological approach taken by the committee to conduct this comprehensive literature review and meet the objectives outlined in the Statement of Task is detailed in Appendix B and briefly described here. Given the large scientific literature on cannabis, the breadth of the statement of task, and the time constraints of the study, the committee developed an approach that resulted in giving primacy to recently published systematic reviews (since 2011) and high-quality primary research that studied one or more of eleven groups of health endpoints (see Figure 1-1 and Box 1-3). For each health endpoint, systematic reviews were identified and assessed for quality using methods adapted from published criteria (Whiting et al., 2016); only reviews that were assessed by the committee as being of good or fair quality were considered in this comprehensive review. The committee's conclusions are based on the findings from the most recently published systematic review and all relevant primary literature that was determined to be fair- and good-quality that was published after the most recent systematic review. Where no systematic review existed, the committee reviewed all relevant primary research from January 1, 1999 through August 1, 2016. Primary research was evaluated using global assessments of the quality of available studies guided by standard approaches and methodologies (Cochrane Quality Assessment [Higgins et al., 2011], Newcastle-Ontario scale [Wells et al., 2014]). Any deviations from this approach are noted in the relevant chapters. For a comprehensive description of the committees approach to evaluating the available literature, please refer to Appendix B.

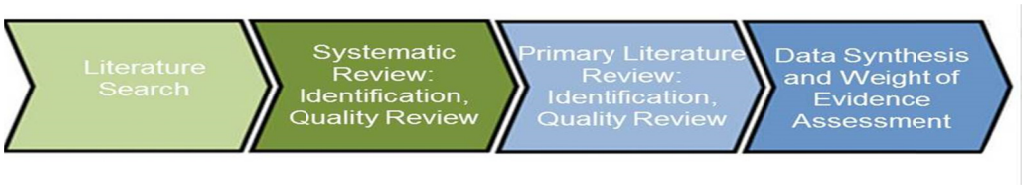

FIGURE 1-1 Summary of the committee's process.

BOX 1-3
Health Topics and Prioritized Health Endpoints
(listed in the order in which they appear in the report)

Therapeutic effects
- Chronic pain; cancer, chemotherapy-induced nausea/vomiting; appetite and weight loss; irritable bowel syndrome; epilepsy; spasticity related to multiple sclerosis; Tourette syndrome; amyotrophic lateral sclerosis; Huntington's disease; Parkinson's disease; dystonia; Alzheimer's disease/dementia; glaucoma; traumatic brain injury/spinal cord injury; addiction; anxiety; depression; sleep disorders; posttraumatic stress disorder; schizophrenia

Cancer
- Lung cancer; oral cancer; esophageal cancer; testicular cancer; other cancer

Cardiometabolic risk
- Acute myocardial infarction; stroke; metabolic dysregulation, metabolic syndrome, prediabetes, and diabetes

Respiratory disease
- Pulmonary function; respiratory symptoms (including chronic bronchitis); chronic obstructive pulmonary disorder; asthma

Immunity
- Immune Function; infectious disease

Injury and death
- All-cause mortality; occupational injury; motor vehicle crash; overdose injury and death

Prenatal, perinatal, and postnatal exposure to cannabis
- Pregnancy complications for the mother; fetal growth and development; neonatal conditions; later outcomes for the infant

Psychosocial
- Cognition (learning, memory, attention, intelligence); academic achievement and educational outcomes; employment/income; social relationships and other social roles

Mental health
- Schizophrenia other psychotic disorders; bipolar disorders, depression; suicide; anxiety; posttraumatic stress disorder

Problem cannabis use
- Cannabis use disorder

Cannabis Use and abuse of other substances
- Abuse of other substances

Informed by the reports of previous IOM committees,[3] the committee developed standard language to categorize the weight of evidence regarding whether cannabis or cannabinoids use (for therapeutic purposes) are an effective or ineffective treatment for the prioritized health endpoints of interest, or whether cannabis or cannabinoid use (primarily for recreational purposes) are statistically associated with the prioritized health endpoints of interest. Box 1-4 below describes these categories and the general parameters for the types of evidence supporting each category. The committee used these weight-of-evidence categories in their conclusions.

BOX 1-4
Weight-of-Evidence Categories

CONCLUSIVE EVIDENCE

For therapeutic effects: There is strong evidence from randomized controlled trials to support the conclusion that cannabis or cannabinoids are an effective or ineffective treatment for the health endpoint of interest.

For other health effects: There is strong evidence from randomized controlled trials to support or refute a statistical association between cannabis or cannabinoid use and the health endpoint of interest.

For this level of evidence, there are many supportive findings from good-quality studies with no credible opposing findings. A firm conclusion can be made, and the limitations to the evidence, including chance, bias, and confounding factors, can be ruled out with reasonable confidence.

SUBSTANTIAL EVIDENCE

For therapeutic effects: There is strong evidence to support the conclusion that cannabis or cannabinoids are an effective or ineffective treatment for the health endpoint of interest.

For other health effects: There is strong evidence to support or refute a statistical association between cannabis or cannabinoid use and the health endpoint of interest.

For this level of evidence, there are several supportive findings from good-quality studies with very few or no credible opposing findings. A firm conclusion can be made, but minor limitations, including chance, bias, and confounding factors, cannot be ruled out with reasonable confidence.

MODERATE EVIDENCE

For therapeutic effects: There is some evidence to support the conclusion that cannabis or cannabinoids are an effective or ineffective treatment for the health endpoint of interest.

For other health effects: There is some evidence to support or refute a statistical association between cannabis or cannabinoid use and the health endpoint of interest.

For this level of evidence, there are several supportive findings from good- to fair-quality studies with

[3] *Adverse Effects of Vaccines* (IOM, 2012); *Treatment of Posttraumatic Stress Disorder: An Assessment of the Evidence*, (IOM, 2008); *Veterans and Agent Orange: Update 2014* (NASEM, 2016).

very few or no credible opposing findings. A general conclusion can be made, but limitations, including chance, bias, and confounding factors, cannot be ruled out with reasonable confidence.

LIMITED EVIDENCE

For therapeutic effects: There is weak evidence to support the conclusion that cannabis or cannabinoids are an effective or ineffective treatment for the health endpoint of interest.

For other health effects: There is weak evidence to support or refute a statistical association between cannabis or cannabinoid use and the health endpoint of interest.

For this level of evidence, there are supportive findings from fair-quality studies or mixed findings with most favoring one conclusion. A conclusion can be made, but there is significant uncertainty due to chance, bias, and confounding factors.

NO OR INSUFFICIENT EVIDENCE TO SUPPORT THE ASSOCIATION

For therapeutic effects: There is no or insufficient evidence to support the conclusion that cannabis or cannabinoids are an effective or ineffective treatment for the health endpoint of interest.

For other health effects: There is no or insufficient evidence to support or refute a statistical association between cannabis or cannabinoid use and the health endpoint of interest.

For this level of evidence, there are mixed findings, a single poor study, or health endpoint has not been studied at all. No conclusion can be made because of substantial uncertainty due to chance, bias, and confounding factors.

The search strategies and processes described above were developed and adopted by the committee in order to adequately address a broad statement of task in a limited timeframe, while adhering to the National Academies high standards for the quality and rigor of committee reports.

First, the committee was not tasked with conducting multiple systematic reviews, which would have implied a lengthy and robust series of processes. The committee, however, adopted key features of that process: a comprehensive literature search, assessments by more than one person of the quality (risk of bias) of key literature and the conclusions, pre-specification of the questions of interest before conclusions were formulated, standard language to allow comparisons between conclusions, and declarations of conflict of interest via the National Academies' conflict-of-interest policies.

Second, there is a possibility that some literature was missed because of the practical steps taken to narrow a very large literature to one that was manageable within the timeframe available to the committee. Furthermore, some very good research may not have been reviewed in this report because it did not directly address the specific health endpoint questions formulated by the committee.

Special Considerations for the Report

Biological Plausibility

After careful consideration, the committee chose not to attempt to review basic, non-human research in order to attempt to bolster evidence for identified health outcomes from cannabis exposure. This policy was in part dictated by the time constraints available for crafting this report. Also, while basic research is in the end critical for understanding health outcome mechanisms and suggesting new and innovative interventions, it often can't explain the large number of null findings, the frequent variation among human study outcomes, the adverse clinical effects seen in some studies, nor the diversity in host susceptibility to cannabis exposure. Given the methodologic variation in the studies reviewed, as well as potential deficiencies in study design and execution, the committee focused its attention and energy on identifying high quality studies with the best information and lowest risk of bias as the way to ensure that report findings and conclusions were as informative and relevant as possible. In those instances where cannabis-disease associations seemed relatively secure and evidence-based, the committee believed that the findings would have clinical and public health importance even in the absence of supporting basic studies. Similarly, for those experimental studies where causation could be more explicitly determined, mostly in the area of therapeutics, these findings, if sufficiently robust and replicable, were deemed to stand on their own whether or not bolstered with mechanistic or biologically plausible underpinnings.

Considerations of Observational Studies

The vast majority of the systematic reviews, meta-analyses, and primary literature reviewed in Part II: Other Health Effects consists of observational studies. This is in contrast to the literature base in other fields such as therapeutics (discussed in Part I: Therapeutic Effects). As such, it was not possible to restrict the literature reviews to those that synthesized evidence from randomized clinical trials (RCTs). The methodology used for systematic reviews and meta-analysis originates in the synthesis of data from RCTs, where methodology is highly standardized and structured. The synthesis of observational studies presents some challenges that have not been fully met, arising, in part, out of the greater variety in study design.

Exposure measurement is always an additional concern when evaluating comprehensive reviews of observational studies. Assessment of cannabis exposure is particularly challenging because of its illegal status (in most settings) and the reliance on self-report. Inherent difficulties in accurately assessing the exposure in terms of dose, specific type of cannabis product used, mode of intake, duration, frequency, and other variables result in the variability in definitions used to operationalize cannabis exposure. Additionally, observational studies often have to contend with confounders related to polysubstance use, which obscures the ability to answer

questions about the effects of "cannabis only" on the health effects. Moreover, in some cases, samples included different populations (adolescents versus adults), cannabis use history (i.e., chronic vs. acute), and patterns of use (i.e., frequency, dose, quantity) all of which provide mixed or inconsistent evidence as to the effects of cannabis on a specific outcome. Additional limitations include a lack of longitudinal assessments and small study cohorts.

There is also a concern about the broad reporting standards across cannabis research fields. For example, several systematic reviews on cognition discussed in the report's Psychosocial chapter did not consistently describe the methods for scoring the evidence for each endpoint. That is, the reviews include scores of the strength and consistency of the evidence for each outcome, but provided less information about issues such as study design and statistical analyses. As a result, the committee found that the reviews did not include the conventional data generally found within quantitatively-based systematic examinations of a topic, or such as would be found in meta-analytic reviews. Reasons for this may include variations in study methodologies, instrumentation, populations, or research designs.

Despite these special considerations regarding the use of systematic reviews, meta-analyses, and primary literature of observational studies, the committee determined that using recent good- or fair-quality systematic reviews was the most appropriate approach to adequately address the committee's broad statement of task and comprehensive, prioritized research questions while maintaining a high standard for quality and rigor. For additional information on these considerations, please see Box 11-2 in Chapter 11: Psychosocial and Box 12-2 in Chapter 12: Mental Health.

Comparing Harms and Benefits of Cannabis Use

Several health endpoints are discussed in multiple chapters of the report (e.g., cancer, schizophrenia); however, it is important to note that the research conclusions regarding potential harms and benefits discussed in these chapters may differ. This is, in part, due to differences in the study design of the reviewed evidence, differences in characteristics of cannabis or cannabinoid exposure (e.g., form, dose, frequency of use), and the populations studied. As such, it is important that the reader is aware that this report was not designed to reconcile the proposed harms and benefits of cannabis or cannabinoid use across the report's chapters. In drafting the report's conclusions, the committee made an effort to be as specific as possible about the type and/or duration of cannabis or cannabinoid exposure and where relevant, cross-referenced findings from other report chapters.

Key Definitions

The terms "marijuana" and "cannabis" are often used interchangeably, particularly within the United States; however, these are two separate entities. Cannabis is a broad term that can be used to describe organic products (e.g., cannabinoids,[3] marijuana,[4] hemp[5]) derived from the

[3] Cannabinoids are a group of active chemical compounds found in cannabis. Among the more than 100 different types of cannabinoids are tetrahydrocannabinol (THC) and cannabidiol (CBD) (Small, 2015).

[4] In general, marijuana refers only to parts of the plant or derivative products that contain substantial levels of tetrahydrocannabinol (THC), the chemical compound that is found in the highest concentrations in the cannabis plant and which is primarily responsible for the plant's intoxicative qualities (Small, 2015).

[5] Under U.S. law, cannabis plants with very low levels of THC (not more than 0.3 percent) are not considered marijuana but instead "industrial hemp" (Small, 2015).

Cannabis sativa plant. These products exist in various forms and are used for a number of different purposes (e.g., medical, industrial, recreational). Given its broad potential, the all-encompassing word "cannabis" has been adopted as the standard terminology within scientific and scholarly communities. The committee uses the term "cannabis" rather than "marijuana" throughout this report.

The committee notes the existence of "cannabimimetic agents" (often referred to as "K2" or "spice") which are made up of dried plant matter sprayed with synthetic chemicals that mimic the effect of THC by interacting with cannabinoid receptors in the brain (King, 2014). At the request of the study sponsors, non-therapeutic synthetic cannabinoids are not considered in this study.

REPORT ORGANIZATION

This report is organized into four parts and 16 chapters. Part I: Introduction and Background (Chapters 1–3) provides an overview of the origin, purpose, and organization of the report, as well as essential information on cannabis and cannabis-derived medications and products, and the history and current state of federal and state cannabis policy. In addition to this Introduction (Chapter 1), Chapter 2 (Cannabis) reviews the biology of cannabis and its constituent compounds, exploring the biochemistry of the marijuana plant, its derivatives, and the different routes of administration. Additionally this chapter provides an overview of synthetic versions of cannabis, including Food and Drug Administration–approved medicinal synthetics and manufactured cannabis (street drugs such as K2, spice). Chapter 3 (Cannabis: Prevalence of Use, Regulation, and Current Policy Landscape) provides an overview of cannabis use in the United States and reviews policy related to cannabis legislation.

Part II: Therapeutic Effects of Cannabis and Cannabinoids (Chapter 4) discusses the health effects of cannabis and cannabinoids used for therapeutic purposes, in relation to the most commonly reported conditions for medical cannabis use (in states where usage is legal), as well as the current qualifying ailments recognized by state medical marijuana programs. Most of the evidence reviewed in this chapter derives from clinical and basic science research conducted for the specific purpose of answering an a priori question of whether cannabis and/or cannabinoids are an effective treatment for a specific disease or health condition. The vast majority of these studies examined the potential therapeutic effect of cannabinoids (e.g., FDA-approved synthetics), rather than smoked cannabis.

Part III: Other Health Effects (Chapters 5–14) discusses the health effects of cannabis and/or cannabis-derived products used for primarily recreational and other non-therapeutic purposes. Most of the evidence reviewed in Part III derives from epidemiological research primarily focusing on smoked cannabis. It is of note that several of the prioritized health conditions discussed in Part III are also reviewed in Part II, albeit from the perspective of effects associated with using cannabis for primarily recreational, as opposed to therapeutic, purposes. A bulleted list of chapter highlights are included in the introduction of the chapters in Part II and Part III of the report.

Within Part III, the effects of cannabis use on cancer incidence are discussed in Chapter 5. Chapter 6 addresses cardiometabolic risks of cannabis use, including effects on acute myocardial infarction, stroke, and metabolic effects—metabolic dysregulation, metabolic syndrome, prediabetes, and diabetes mellitus. Respiratory disease—pulmonary function, chronic

obstructive pulmonary disease, respiratory symptoms including chronic bronchitis, and asthma—are discussed in Chapter 7. Immunity and infection are discussed in Chapter 8. The effects of cannabis use on overall mortality, overdose death, employment injuries, and motor vehicle crashes are reviewed in Chapter 9, Injury and Death. Prenatal, neonatal, and perinatal effects are discussed in Chapter 10. Psychosocial effects, including the effects of cannabis on learning, memory, attention, academic achievement, employment and income, and social relationships and social roles are discussed in Chapter 11, and mental health conditions, including schizophrenia and other psychosis, bipolar disorder, depression, suicide, anxiety, and post-traumatic stress disorder are discussed in Chapter 12. Chapter 13 discusses problem cannabis use, including cannabis use disorder, and the abuse of other substances is discussed in Chapter 14.

Part IV: Research Barriers and Recommendations (Chapters 15–16) reviews the regulatory barriers and methodological challenges that hinder cannabis research, and recommends the actions necessary to successfully implement a comprehensive cannabis research agenda. Chapter 15 provides an overview of barriers to studying cannabis, including regulatory, policy, and financial, as well as of methodological challenges, and Chapter 16 outlines the committee's proposed research agenda, detailing both short-term and long term objectives.

Appendixes A–E contain the report glossary, details about the committee's search strategy, systematic reviews considered in this report, open session agendas, and biographical sketches of committee and staff members.

REFERENCES

Calabria, B., L. Degenhardt, W. Hall, and M. Lynskey. 2010. Does cannabis use increase the risk of death? Systematic review of epidemiological evidence on adverse effects of cannabis use. *Drug and Alcohol Review* 29(3):318–330.

CBHSQ (Center for Behavioral Health Statistics and Quality). 2016. *Behavioral health trends in the United States: Results from the 2014 National Survey on Drug Use and Health*. https://www.samhsa.gov/data/sites/default/files/NSDUH-FFR1-2015/NSDUH-FFR1-2015/NSDUH-FFR1-2015.pdf (accessed January 3, 2017).

Freeman, T. P. , C. J. Morgan, C. Hindocha, G. Schafer, R. K. Das, and H. V. Curran. 2014. Just say "know": How do cannabinoid concentrations influence users' estimates of cannabis potency and the amount they roll in joints? *Addiction* 109(10):1686–1694.

Higgins, J. P. T, D. G. Altman, P. C. Gøtzsche, P. Jüni, D. Moher, A. D. Oxman, J. Savović, K. F. Schulz, L. Weeks, J. A. C. Sterne, Cochrane Bias Methods Group, and Cochrane Statistical Methods Group. 2011. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 343:d5928.

IOM (Institute of Medicine). 1982. *Marijuana and health*. Washington, D.C. National Academy Press.

IOM. 1999. *Marijuana and medicine: Assessing the science base*. Washington, DC National Academy Press.

IOM. 2008. *Treatment of posttraumatic stress disorder: An assessment of the evidence*. Washington, DC: The National Academies Press.

IOM. 2012. *Adverse effects of vaccines: Evidence and causality*. Washington, DC: The National Academies Press.

IOM .2014. *Veterans and Agent Orange: Update 2014*. Washington, DC: The National Academies Press.

King, L.A. 2014. Legal controls on cannabimimetics: An international dilemma? *Drug Testing and Analysis* 6(1-2):80–87.

Marsot, A., C. Audebert, L. Attolini, B. Lacarelle, J. Micallef, and O. Blin. 2016. Comparison of cannabinoid concentrations in plasma, oral fluid and urine in occasional cannabis smokers after smoking cannabis cigarette. *Journal of Pharmacy and Pharmaceutical Sciences* 19(3):411–422.

National Conference of State Legislatures. 2016. *State medical marijuana laws.* November 9. http://www.ncsl.org/research/health/state-medical-marijuana-laws.aspx (accessed November 21, 2016).

Small, E. 2015. Evolution and classification of Cannabis sativa (marijuana, hemp) in relation to human utilization. *The Botanical Review* 81(3):189–294.

Wells, G. A., B. Shea, D. O'Connell, J. Peterson, V. Welch, M. Losos, and P. Tugwell, 2014. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp (accessed November 2, 2016).

Whiting, P. F., R. F. Wolff, S. Deshpande, M. Di Nisio, S. Duffy, A. V. Hernandez, J. C. Keurentjes, S. Lang, K. Misso, S. Ryder, S. Schmidlkofer, M. Westwood, and J. Kleijnen. 2015. Cannabinoids for medical use: A systematic review and meta-analysis. *JAMA* 313(24):2456–2473.

Whiting, P., J. Savovic, J. P. T. Higgings, D. M. Caldwell, B. C. Reeves, B. Shea, P. Davies, J. Kleijnen, R. Churchill, and the ROBIS Group. 2016. ROBIS: A new tool to assess risk of bias in systematic reviews was developed. *Journal of Clinical Epidemiology* 69:225–234.

WHO (World Health Organization). 2016. *The Health and Social Effects of Nnonmedical Cannabis Use.* Geneva, Switzerland: WHO Document Production Services.

2
Cannabis

HISTORY OF CANNABIS

Cannabis sativa is one of the world's oldest cultivated plants (Russo, 2007). Although the earliest written records of the human use of cannabis date from the sixth century B.C. (ca. 2,600 cal BP), existing evidence suggests that its use in Europe and East Asia started in the early Holocene (ca. 8,000 cal BP) (Long et al., 2016). Many 19th century practitioners ascribed medicinal properties to cannabis after the drug found its way to Europe during a period of colonial expansion into Africa and Asia. For example, in the 19th century William B. O'Shaughnessy, an Irish physician working at the Medical College and Hospital in Calcutta, first introduced cannabis (Indian hemp) to Western medicine as a treatment for tetanus and other convulsive diseases (O'Shaughnessy, 1840). At approximately the same time, French physician Jean-Jacques Moreau de Tours experimented with the use of cannabis preparations for the treatment of mental disorders (Moreau de Tours, 1845). Soon after, in 1851, cannabis was included in the third edition of the *Pharmacopoeia of the United States* (USP). Subsequent revisions of the USP described in detail how to prepare extracts and tinctures of dried cannabis flowers to be used as analgesic, hypnotic, and anticonvulsant (Russo, 2007; U.S. Pharmacopoeial Convention, 1916). Growing concerns about cannabis resulted in the outlawing of cannabis in several states in the early 1900s and federal prohibition of the drug in 1937 with the passage of the Marihuana Tax Act. In response to these concerns, in 1942 the American Medical Association removed cannabis from the 12th edition of *U.S. Pharmacopeia* (IOM, 1999).

THE CANNABIS PLANT

Cannabis cultivars are considered as part of one genus, *Cannabis*, family Cannabaceae, order Urticales (Kuddus et al., 2013). Two accepted genera of Cannabaceae are Cannabis and Humulus (hops). There is, however, an ongoing debate concerning the taxonomic differentiation within the *Cannabis* genus (Laursen, 2015). On the basis of genetic variations, a multitypic genus with at least two putative species, *Cannabis sativa* and *Cannabis indica*, has been proposed by some researchers (Clarke and Merlin, 2015; Hillig, 2005). Other researchers have suggested a unique species *Cannabis sativa* with the genetic differences explained by variations at the subspecies- and variety-levels or at a biotype-level of putative taxa (Small, 2015).

Chemical Constituents of Cannabis

To date, more than 104 different cannabinoids[1] have been identified in cannabis (ElSohly et al, 2014). Other compounds identified include terpenoids, flavonoids, nitrogenous compounds, and more common plant molecules (American Herbal Pharmacopoeia, 2013). Among these, Δ^9-THC has received the most attention for being responsible for the intoxicated state sought after by recreational cannabis users, owing to its ability to act as a partial agonist[2] for type-1 cannabinoid receptors (CB_1). Cannabinoids exist mainly in the plant as their carboxylic precursors (Δ^9-THCA and CBDA) and are decarboxylated by light or heat while in storage or when combusted (Grotenhermen, 2003). Δ^9-THC is synthesized within the glandular trichomes present in the flowers, leaves, and bracts of the female plant. It shares a common precursor, olivetoic acid, with another quantitatively important constituent of *Cannabis sativa*, cannabidiol (CBD), which is the most abundant cannabinoid in hemp. For this reason, the genetic profile and relative level of expression of the enzymes responsible for their synthesis (genotype), namely THCA synthase and CBDA synthase, determine the chemical composition of a particular cultivar (chemotype).

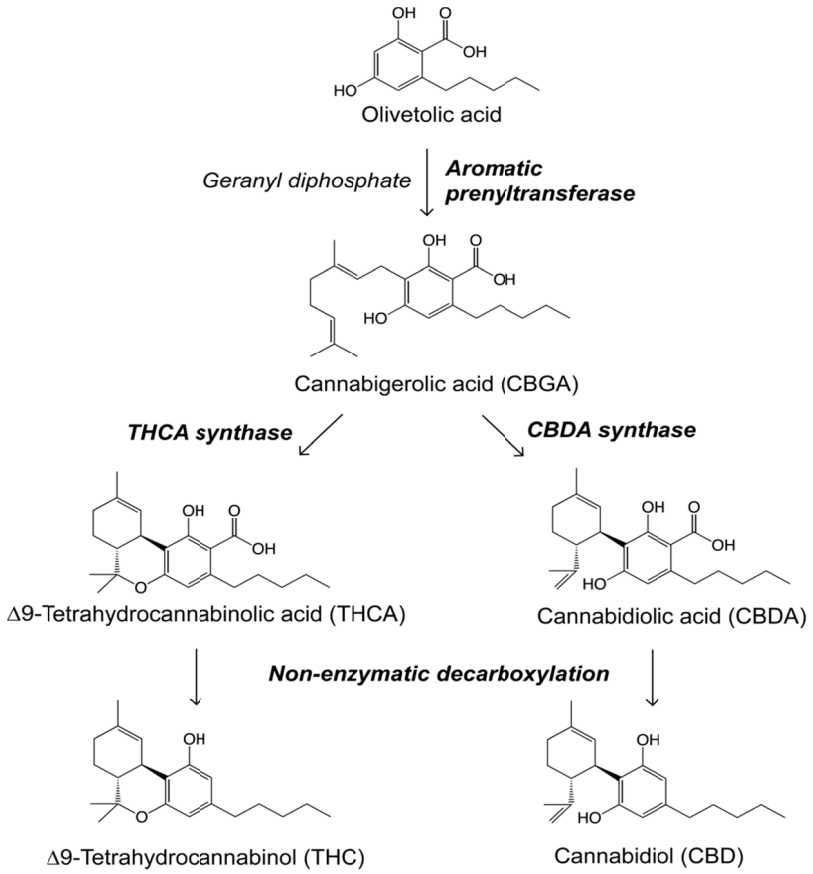

FIGURE 2-1 Synthetic pathway of the main cannabinoids, Δ^9-THC and CBD, from the common precursor, olivetol.

[1] Cannabinoids are a group of psychoactive chemical compounds found in the cannabis plant.

[2] *Partial agonists* are ligands that interact with their receptors to produce a level of response that is less than the response to full agonists.

Cannabis plants typically exhibit one of the three main different chemotypes based on the absolute and relative concentrations of Δ^9-THCA and CBDA (see Table 2-1), which makes it possible to distinguish among the Δ^9-THC-type, or drug-type; the intermediate type; and the CBD-type, cannabis plants grown for fiber (industrial hemp) or seed oil in which the content of Δ^9-THC does not exceed 0.3 percent on a dry-weight basis (Chandra et al., 2013). CBD is, however, pharmacologically active, and, therefore, classifying cannabis in terms of drug- and fiber-producing seems inaccurate. Both THC- and CBD-types are considered drug-types, and both cultivars could theoretically be exploited to produce fiber.

TABLE 2-1 Cannabis Phenotypes

Chemotype	Δ^9-THC	CBD	CBD: Δ^9-THC ratio
THC-type	0.5–15%	0.01–0.16%	<0.02
Hybrid	0.5–5%	0.9–7.3%	0.6–4
CBD-type	0.05–0.7%	1.0–13.6%	>5

SOURCE: Modified from Galal et al. (2009). THCA-predominant strains can yield more than 25 percent Δ^9-THC; specifically selected CBDA clones can yield up to 20 percent CBD.

Pharmacological Properties of Δ^9-THC

In a series of studies conducted in the late 1930s and early 1940s, Roger Adams and co-workers isolated cannabinol and CBD from hemp oil and then isomerized CBD into a mixture of two tetrahydrocannabinols with "marihuana-like" physiological activity in dogs, proving their structure except for the final placement of one double bond (Adams et al., 1940a,b). Two years later, tetrahydrocannabinol was first isolated from cannabis resin (Wollner et al., 1942). In 1964, thanks to the development of potent analytical techniques such as nuclear magnetic resonance imaging, Gaoni and Mechoulam were able to identify the position of this elusive double bond, thus resolving the final structure of Δ^9-THC (Gaoni and Mechoulam, 1964).

In the late 1980s William Devane and Allyn Howlett first postulated the existence of cannabinoid receptors by showing how synthetic molecules designed to mimic the actions of Δ^9-THC were able to bind a selective site in brain membranes, thus inhibiting the intracellular synthesis of cyclic adenosine monophosphate (cAMP) through a G protein–mediated mechanism (Devane et al., 1988). The mapping of cannabinoid-binding sites in the rat brain (Herkenham et al., 1990) and the molecular cloning of the first cannabinoid receptor gene (Matsuda et al., 1990) subsequently corroborated this hypothesis. Three years later, a second G protein–coupled cannabinoid receptor was cloned from a promyelocytic cell line and termed CB_2 (Munro et al., 1993).

Both CB_1 and CB_2 signal through the transducing G proteins, G_i and G_o, and their activation by Δ^9-THC or other agonists causes the inhibition of adenylyl cyclase activity, the closing of voltage-gated calcium channels, the opening of inwardly rectifying potassium channels, and the stimulation of mitogen-activated protein kinases such as ERK and focal adhesion kinases (FAKs) (Mackie, 2006).

The expression pattern of CB_1 receptors in brain structures correlates with the psychoactive effects of cannabis. In mammals, high concentrations of CB_1 are found in areas that regulate appetite, memory, fear extinction, motor responses, and posture such as the

hippocampus, basal ganglia, basolateral amygdala, hypothalamus, and cerebellum (Mackie, 2006). CB_1 is also found in a number of non-neural tissues, including the gastrointestinal tract, adipocytes, liver, and skeletal muscle. In addition to CB_1, the brain also contains a small number of CB_2 receptors, although this subtype is mainly expressed in macrophages and macrophage-derived cells such as microglia, osteoclasts, and osteoblasts (Mackie, 2006).

Pharmacological Properties of Cannabidiol (CBD)

Cannabidiol was first isolated from hemp oil in 1940 (Adams et al., 1940a) and its structure predicted by chemical methods (Adams et al., 1940b); its fine structure was determined in later studies (Mechoulam and Shvo, 1963). CBD lacks the cannabis-like intoxicating properties of Δ^9-THC and, for this reason, has been traditionally considered non-psychoactive. CBD displays very low affinity for CB_1 and CB_2 cannabinoid receptors (Thomas et al., 2007), but might be able to negatively modulate CB_1 via an allosteric mechanism (Laprairie et al., 2015)[3]; however, CBD can interfere with the deactivation of the endocannabinoid molecule anandamide, either by targeting its uptake or its enzymatic degradation, catalyzed by fatty-acid amide hydrolase (FAAH) which could indirectly activate CB_1 (De Petrocellis et al., 2011; Elmes et al., 2015).

CBD is also a known agonist of serotonin 5-HT1A receptors (Russo et al., 2005) and transient receptor potential vanilloid type 1 (TRPV1) receptors (Bisogno et al., 2001). It can also enhance adenosine receptor signaling by inhibiting adenosine inactivation, suggesting a potential therapeutic role in pain and inflammation (Carrier et al. 2006). The antioxidant and anti-inflammatory properties of this compound may explain its potential neuroprotective actions (Scuderi et al., 2009). Irrespective of the mechanism of action, there is evidence that CBD could potentially be exploited in the treatment and symptom relief of various neurological disorders such as epilepsy and seizures (Hofmann and Frazier, 2013; Jones et al., 2010), psychosis (Leweke et al., 2016), anxiety (Bergamaschi et al., 2011), movement disorders (e.g. Huntington's disease and amyotrophic lateral sclerosis) (DeLago and Fernandez-Ruiz, 2007; Iuvone et al., 2009) and multiple sclerosis (Lakhan and Rowland, 2009).

BOX 2-1
Endocannabinoids and Their Signaling Systems

There are two endocannabinoids, 2-archidonoylglycerol (2-AG) and anandamide.

2-AG

2-AG is generated by the enzymatic activity of a membrane-associated diacylglycerol lipase (DGL), which converts Sn2-arachidonic acid containing diacylglycerols into 2-AG (see Figure 2-2). Two isoforms of DGL, alpha and beta, have been identified. The alpha isoform generates 2-AG utilized during neuronal development and for synaptic communication between neurons, while the beta isoform may contribute to both brain development and inflammation. The activity of DGL-alpha is regulated by intracellular calcium, glutathione, and cellular localization, and via posttranslational modification. Once produced, 2-AG can act via both CB_1 and CB_2 receptors to exert a range of biological effects in central and peripheral cells.

[3] Allosteric modulators are ligands that indirectly influence the effects of an agonist or inverse agonist at a target receptor. Allosteric modulators bind to a site distinct from that of the orthosteric agonist binding site.

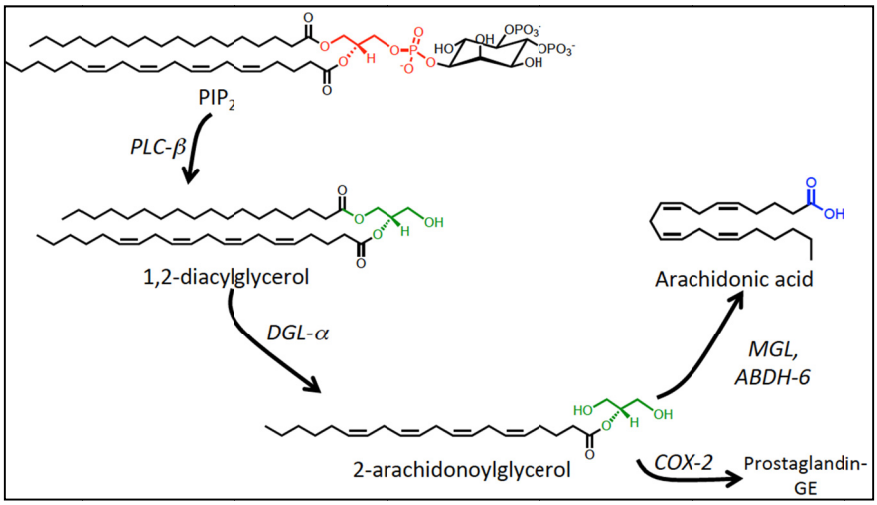

FIGURE 2-2 Pathways of 2-AG formation and deactivation.

2-AG is primarily degraded by monoacylglycerol lipase (MGL) into free arachidonic acid and glycerol. In the central nervous system (CNS), the free arachidonic acid generated by MGL-mediated hydrolysis of 2-AG may serve as a precursor for the generation of prostaglandins by cyclooxygenases. The activity of MGL can be regulated by posttranslational modification (e.g., sulfenylation). There is also evidence that 2-AG can be oxygenated by cyclooxygenase-2 to generate prostaglandin glycerols.

Anandamide

The formation of anandamide involves two steps (see Figure. 2-3). The first consists of the transfer of arachidonic acid from phosphatidylcholine (PC) to phosphatidylethanolamine (PE). This reaction is catalyzed by the *N*-acyltransferase PLA2G4E and yields a diverse group of *N*-arachidonoyl-substituted PE species (NAPEs). The second step is the cleavage of NAPEs to produce anandamide and may be mediated by either NAPE-specific phospholipase D (NAPE-PLD) or alpha/beta-hydrolase domain-4 (ABHD-4). PLA2G4E may represent the rate-limiting step for anandamide formation, though additional work is needed to confirm this possibility. After release into the extracellular milieu, anandamide is captured by neurons and glia through carrier-mediated transport and is subsequently hydrolyzed to arachidonic acid by fatty acid amide hydrolase (FAAH), a postsynaptic serine hydrolase expressed throughout the CNS. In microglia, anandamide might be also degraded by the lysosomal cysteine hydrolase, N-acylethanolamine acid amidase (NAAA).

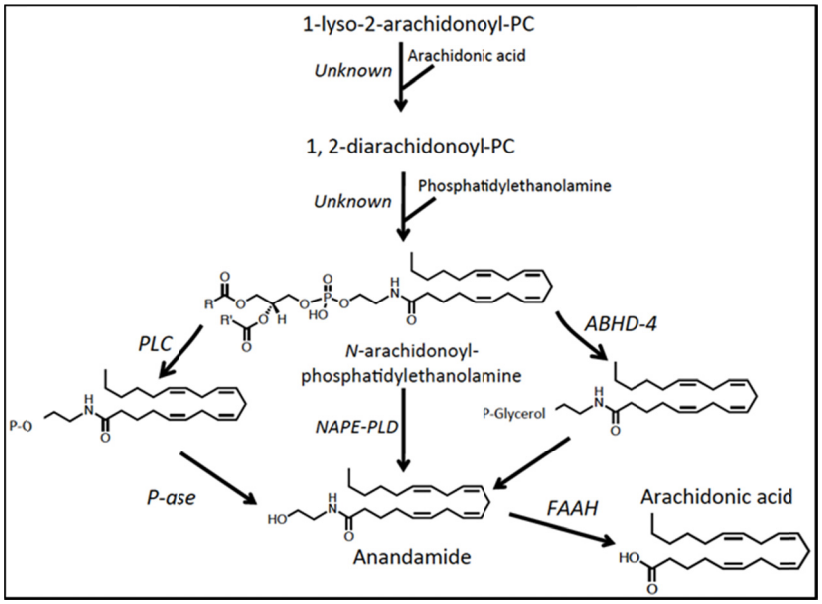

FIGURE 2-3 Pathways of anandamide formation and deactivation.

Endocannabinoid Synaptic Signaling (CB_1) (A Central Example)

One of the best-studied forms of endocannabinoid signaling occurs at CNS synapses. There are several unique features of endocannabinoid signaling relative to amino acid and peptide-based neurotransmitters. First, endocannabinoid signaling occurs in a retrograde direction, i.e., the signaling is initiated in postsynaptic neurons and acts upon presynaptic terminals. This is in stark contrast to traditional anterograde chemical neurotransmission, which is initiated at the axon terminal and conveys signals to postsynaptic neurons within a connected neuronal circuit or system. A second unique feature of this system is that, in contrast to classical neurotransmitters, endocannabinoids are not preformed and stored in vesicles pending release. In contrast, they are produced "on demand" upon stimulation of postsynaptic cells through a variety of signals.

The role of 2-AG in mediating endocannabinoid synaptic signaling has been well established during the past decade. Indeed, at excitatory synapses, all key components of 2-AG-mediated signaling (DGL-alpha, MGL, CB_1 receptor) are ideally localized to facilitate retrograde control of neurotransmitter release. Specifically, DGL-alpha is found in postsynaptic spines while MGL and CB_1 are located in axon terminals. The activity of DGL-alpha can be increased by stimulation of Gq-coupled-neurotransmitter receptors (e.g., metabotropic glutamate receptors) or by a calcium influx. Once active, DGL-alpha generates 2-AG at the cell membrane, which travels in a retrograde direction to the presynaptic terminal to interact with CB_1. The activation of CB_1 by 2-AG results in a reduction in presynaptic release probability predominantly via Gi/o-dependent signal transduction cascades. This synaptic depression can last for seconds to minutes or longer, depending on the duration of receptor stimulation and the specific types of downstream signaling cascades initiated. After interacting with the receptor, 2-AG is hydrolyzed primarily by MGL located in the cytosol of the presynaptic axon terminal. MGL in astrocytes may also contribute to the termination of 2-AG-mediated synaptic signaling.

There is also evidence that anandamide can act as a retrograde modulator of neurotransmitter release in a manner similar to 2-AG, but with some distinct differences that are suggestive of a broader paracrine mode of action.

SOURCE: Piomelli, 2015.

CANNABIS-DERIVED PRODUCTS

In the United States, cannabis-derived products are consumed for both medical and recreational purposes in a variety of ways. These include smoking or inhaling from cigarettes (joints), pipes (bowls), water pipes (bongs, hookahs), and blunts (cigars filled with cannabis); eating or drinking food products and beverages; or vaporizing the product. These different modes are used to consume different cannabis products, including cannabis "buds" (dried cannabis flowers); cannabis resin (hashish, bubble hash); and cannabis oil (butane honey oil, shatter, wax, crumble). The oil, which may contain up to 75 percent Δ^9-THC—versus 5 to 20 percent in the herb or resin (Raber et al., 2015)—is extracted from plant material using organic solvents, such as ethanol, hexane, butane, or supercritical (or subcritical) CO_2, and can be either smoked or vaporized by pressing the extracted oil against the heated surface of an oil rig pipe (dabbing). Cannabinoids can also be absorbed through the skin and mucosal tissues, so topical creams, patches, vaginal sprays and rectal suppositories are sometimes employed and used as a form of administering Δ^9-THC (Brenneisen et al., 1996). A broad selection of cannabis-derived products are also available in the form of food and snack items, beverages, clothing, and health and beauty aid products.

Potency of Cannabis

In the 1990s and early 2000s, the bulk of cannabis consumed in the United States was grown abroad and illicitly imported. The past decade has seen an influx of high-potency cannabis produced within the United States—for example,, "sinsemilla"—which is grown from clones rather than from seeds. Data from the Drug Enforcement Administration (DEA) seizures record a substantial increase in average potency, from 4 percent in 1995 to roughly 12 percent in 2014, both because high-quality U.S.-grown cannabis has taken market share from Mexican imports and because cannabis from both sources has grown in potency (ElSohly et al., 2016; Kilmer, 2014).

Route of Administration

The route of administration of cannabis can affect the onset, intensity, and duration of the psychotropic effects, the effects on organ systems, and the addictive potential and negative consequences associated with its use (Ehrler et al., 2015). The consumption of cannabis causes a particular combination of relaxation and euphoria, commonly referred to as a "high." When cannabis is smoked, Δ^9-THC quickly diffuses to the brain, eliciting a perceived high within seconds to minutes. Blood levels of Δ^9-THC reach a maximum after about 30 minutes and then rapidly subside within 1 to 3.5 hours (Fabritius et al., 2013; Huestis et al., 1992). Vaping has a onset, peak, and duration that are similar to those of smoking and produces a similar high (Abrams et al., 2007). "Dabbing," a term for flash-vaporizing butane hash oil-based concentrates, has been reported to offer a different and stronger intoxicating effect than smoking/vaping (Loflin, 2014). By contrast, eating does not produce effects for 30 minutes to 2 hours, and the perceived high is relatively prolonged, lasting 5 to 8 hours or even longer. The slow action of orally ingested cannabis is due to Δ^9-THC being absorbed by the intestine and transported to the liver (hepatic first pass) where it is converted into 11-OH-THC, an equipotent and longer-lasting metabolite (Huestis et al., 1992). Edibles make it harder to titrate the

intoxicating effects due to the delayed and variable onset. Consequently, edibles have been tied to the ingestion of excessive amounts of cannabis under the misperception that the initial dose had not produced the desired effect (Ghosh and Basu, 2015; MacCoun and Mello, 2015). The availability of edibles has also been associated with increased rates of accidental pediatric ingestion of cannabis (Wang et al., 2014).

Trends in Routes of Administration

There are no high-quality nationally representative data on the prevalence of the non-herbal forms of cannabis (e.g., edibles, oils, and other concentrates), but evidence suggests that they are more commonly used by medical cannabis patients in states with recreational or lenient medical cannabis policies (Daniulaityte et al., 2015; Pacula et al., 2016). Forty percent of 12th-grade past-year users reported using cannabis in edible form in medical cannabis states, versus 26 percent in states without medical cannabis laws (NIDA, 2014). In Washington State, an online survey from 2013 found that, among daily and near-daily cannabis users, 27.5 percent had used edibles, 22.8 percent had used hash resin, and 20.4 percent had "dabbed" in the past week (Kilmer et al., 2013).

Data from recreational cannabis sales in Washington and Colorado provide a glimpse of trends that are specific to markets that have legalized cannabis. In Washington State, herbal cannabis remains dominant, having accounted for two-thirds of all sales revenues in June 2016, but it is losing market share as "cannabis extracts for inhalation" become more popular, at 21 percent in June 2016 as compared with 12 percent one year prior. The sales of liquid and solid edibles (9 percent) combined account for most of the remaining sales.[4] Non-herbal varieties are even more popular on Colorado's recreational market, where herbal cannabis accounts for a narrow majority (56 percent) and sales of solid concentrates (24 percent) and edibles (13 percent) are on the rise (Castle, 2016).

Partly to provide a guide for the responsible use of non-herbal varieties of cannabis, states that have legalized the recreational cannabis have defined a standard "dose" of THC. Washington State and Colorado have set the standard "dose" of THC as 10 mg, while Oregon chose a lower limit of 5 mg. For perspective, the typical joint size in the United States is .66 g (Mariani et al., 2011) and the average potency is 8 percent THC (Fabritius et al., 2013), resulting in an average dose of 8.25 mg THC per joint; higher THC levels ranging from 15–20 percent or higher would yield a THC dose between 9.9–13.2 mg. Occasional users report feeling "high" after consuming only 2–3 mg of THC (Hall and Pacula, 2010); however, users who have developed tolerance to the effects of THC via frequent use may prefer much larger quantities.

CLINICAL FEATURES OF CANNABIS INTOXICATION

During acute cannabis intoxication, the user's sociability and sensitivity to certain stimuli (e.g., colors, music) may be enhanced, the perception of time is altered, and the appetite for sweet and fatty foods is heightened. Some users report feeling relaxed or experiencing a pleasurable "rush" or buzz" after smoking cannabis (Agrawal et al., 2014). These subjective

[4] Author's calculations from Washington State Liquor and Cannabis Board's publicly available August 2016 "traceability" dataset ("biotrackthc_dispensing.csv"). Data requests available at: http://lcb.wa.gov/records/public-records (accessed January 5, 2017).

effects are often associated with decreased short-term memory, dry mouth, and impaired perception and motor skills. When very high blood levels of Δ^9-THC are attained, the person may experience panic attacks, paranoid thoughts, and hallucinations (Li et al., 2014). Furthermore, as legalized medical and recreational cannabis availability increase nationwide, the impairment of driving abilities during acute intoxication has become a public safety issue.

In addition to Δ^9-THC dosage, two main factors influence the intensity and duration of acute intoxication: individual differences in the rate of absorption and metabolism of Δ^9-THC, and the loss of sensitivity to its pharmacological actions. Prolonged CB_1 receptor occupation as a consequence of the sustained use of cannabis can trigger a process of desensitization, rendering subjects tolerant to the central and peripheral effects of Δ^9-THC and other cannabinoid agonists (Gonzalez et al., 2005). Animals exposed repeatedly to Δ^9-THC display decreased CB_1 receptor levels as well as impaired coupling between CB_1 and its transducing G-proteins (Gonzalez et al., 2005). Similarly, in humans, imaging studies have shown that chronic cannabis use leads to a down-regulation of CB_1 receptors in the cortical regions of the brain and that this effect can be reversed by abstinence (Hirvonen et al., 2012).

CANNABINOID-BASED MEDICATIONS

The U.S. Food and Drug Administration (FDA) has licensed three drugs based on cannabinoids (see Table 2-2). Dronabinol, the generic name for synthetic Δ^9-THC, is marketed under the trade name of Marinol® and is clinically indicated to counteract the nausea and vomiting associated with chemotherapy and to stimulate appetite in AIDS patients affected by wasting syndrome. A synthetic analog of Δ^9-THC, nabilone (Cesamet®), is prescribed for similar indications. Both dronabinol and nabilone are given orally and have a slow onset of action. In July 2016 the FDA approved Syndros®, a liquid formulation of dronabinol, for the treatment of patients experiencing chemotherapy-induced nausea and vomiting who have not responded to conventional antiemetic therapies. The agent is also indicated for treating anorexia associated with weight loss in patients with AIDS. Two additional cannabinoid-based medications have been examined by the FDA. Nabiximols (Sativex®) is an ethanol cannabis extract composed of Δ^9-THC and CBD in a one-to-one ratio. Nabiximols is administered as an oromucosal spray and is indicated in the symptomatic relief of multiple sclerosis and as an adjunctive analgesic treatment in cancer patients (Pertwee, 2012). As of September 2016, nabiximols has been launched in 15 countries including Canada, Germany, Italy, Spain, the United Kingdom and has been approved in a further 12, but not in the United States.[5] In response to the urgent need expressed by parents of children with intractable epilepsy, in 2013 the FDA allowed investigational new drug studies of Epidiolex®, a concentrated CBD oil (>98 percent CBD), also developed by GW Pharmaceuticals, as an anti-seizure medication for Dravet and Lennox-Gastaut syndromes.

[5] For additional information see: http://www.gwpharm.com (accessed January 5, 2017)

TABLE 2-2 Cannabinoid-Based Medications

	CANNABINOID-BASED MEDICATIONS		
	Substance	**Route of Administration**	**Description**
Natural Product Derived Compounds	**Cannabidiol (CBD)**	Oral capsule Oromucosal spray	Cannabinoid extracted from *Cannabis* plant
	Cannabis	Multiple	Multiple active cannabinoids
	Cannador	Oral capsule	THC and CBD from *Cannabis* extract
	Epidiolex® **(FDA Fast Track)**	Oil	Concentrated CBD from *Cannabis* extract
	Nabiximol (Sativex®) **(FDA Fast Track)**	Oromucosal spray	THC and CBD extract from two *Cannabis* plant varieties
	Tetrahydrocannabinol (THC)	Oral capsule Smoked Oromucosal spray	Active cannabinoid of *Cannabis* plant
	THC/CBD	Oral capsule	Combination of cannabinoids
Synthetic Compounds			
	Ajulemic acid (AjA) (FDA PHASE II Active)	Oral capsule	Synthetic nonpsychoactive cannabinoid
	Dronabinol (Marinol®; Syndros®) (FDA approved)	Oral capsule	Synthetic THC
	Nabilone (Cesamet®) (FDA approved)	Oral capsule	Synthetic cannabinoid—THC analogue

SYNTHETIC CANNABINOIDS AS RECREATIONAL DRUGS

In addition to nabilone, many other synthetic cannabinoids agonists have been described and widely tested on experimental animals to investigate the consequences of cannabinoid receptor activation[6] (e.g., CP-55940, WIN-55212-2, JWH-018) (Iversen, 2001; Pertwee, 2012). The therapeutic application of these highly potent molecules is limited by their CB_1-mediated psychotropic side effects, which presumably provide the rationale for the illicit use of some of them as an alternative to cannabis (Wells and Ott, 2011). Preclinical and clinical data in support of this claim remain, however, very limited. Internet-marketed products such as Spice, K2, and Eclipse are a blend of various types of plant material (typically herbs and spices) that have been sprayed with one of these synthetic cannabinoids (as well as other non-cannabinoid psychoactive drugs). Since 2009 more than 140 different synthetic cannabinoids have been identified in herbal

[6] Due to the determined scope of this report, non-therapeutic synthetic cannabinoids will not be discussed in the forthcoming chapters of the report.

mixtures consumed as recreational drugs. The synthetic cannabinoids used in "herbal mixtures" are chemically heterogeneous, most of them being aminoalkylindole derivatives such as naphthoylindoles (e.g., JWH-018 and JWH-210), cyclopropylindoles (e.g., UR-144, XLR-11), or quinoline esters (e.g., PB-22). They seem to appeal especially to young cannabis and polydrug users because they are relatively inexpensive, easily available through the Internet, and difficult to identify with standard immunoassay drug screenings. In contrast to Δ^9-THC, which is a partial agonist of the CB_1 receptor, many of the synthetic cannabinoids bind to CB_1 receptors with high affinity and efficacy, which may be also associated with higher potential of toxicity (Hermanns-Clausen et al. 2016). According to the National Institute on Drug Abuse (NIDA, 2012, p.2), people using these various blends have been admitted to Poison Control Centers reporting "rapid heart rate, vomiting, agitation, confusion, and hallucinations". Synthetic cannabinoids can also raise blood pressure and cause a reduced blood supply to the heart (myocardial ischemia), and in a few cases they have been associated with heart attacks. Regular users may experience withdrawal and symptoms of dependence (Tait et al., 2016).

CANNABIS CONTAMINANTS AND ADULTERANTS

The large economic potential and illicit aspect of cannabis has given rise to numerous potentially hazardous natural contaminants or artificial adulterants being reported in crude cannabis and cannabis preparations. Most frequent natural contaminants consist of degradation products, microbial contamination (e.g., fungi and bacteria), and heavy metals. These contaminants are usually introduced during cultivation and storage (McLaren et al., 2008; McPartland 2002). Growth enhancers and pest control chemicals are the most common risks to both the producer and the consumer. Cannabis can also be contaminated for marketing purposes. This usually entails adding substances (e.g., tiny glass beads, lead) to increase the weight of the cannabis product (Busse et al., 2008; Randerson, 2007) or adding psychotropic substances (e.g., tobacco, calamus) and cholinergic compounds to either enhance the efficacy of low-quality cannabis or to alleviate its side effects (McPartland, 2008). Additionally, some extraction and inhalation methods used for certain dosing formulations (tinctures, butane hash oil, "dabs") can result in substantial pesticide and solvent contamination (Thomas and Pollard, 2016).

REFERENCES

Abrams, D. I., H. P. Vizoso, S. B. Shade, C. Jay, M. E. Kelly, and N. L. Benowitz. 2007. Vaporization as a smokeless cannabis delivery system: A pilot study. *Clinical Pharmacology and Therapeutics* 82(5):572–578.

Adams, R., M. Hunt, and J. H. Clark. 1940a. Structure of cannabidiol, a product isolated from the marihuana extract of Minnesota wild hemp. I. *Journal of the American Chemical Society* 62(1):196–200.

Adams, R., D. C. Pease, C. K. Cain, B. R. Baker, J. H. Clark, H. Wolff, and R. B. Wearn. 1940b. Conversion of cannabidiol to a product with marihuana activity. *Journal of the American Chemical Society* 62(8):2245–2246.

Agrawal, A., P. A. Madden, K. K. Bucholz, A. C. Heath, and M. T. Lynskey. 2014. Initial reactions to tobacco and cannabis smoking: A twin study. *Addiction* 109(4):663–671.

American Herbal Pharmacopoeia. 2013. *Cannabis inflorescence: Cannabis spp.: Standards of identity, analysis, and quality control*. Scott's Valley, CA: American Herbal Pharmacopoeia.

Bergamaschi, M. M., R. H. Queiroz, M. H. Chagas, D. C. de Oliveira, B. S. De Martinis, F. Kapczinski, J. Quevedo, R. Roesler, N. Schröder, A. E. Nardi, R. Martín-Santos, J. E. Hallak, A. W. Zuardi, and J. A. Crippa. 2011. Cannabidiol reduces the anxiety induced by simulated public speaking in treatment-naive social phobia patients. *Neuropsychopharmacology* 36(6):1219–1226.

Bisogno, T., L. Hanus, L. De Petrocellis, S. Tchilibon, D. E. Ponde, I. Brandi, A. S. Moriello, J. B. Davis, R. Mechoulam, and V. Di Marzo. 2001. Molecular targets for cannabidiol and its synthetic analogues: Effect on vanilloid VR1 receptors and on the cellular uptake and enzymatic hydrolysis of anandamide. *British Journal of Pharmacology* 134(4):845–852.

Brenneisen, R., A. Egli, M. A. Elsohly, V. Henn, and Y. Spiess. 1996. The effect of orally and rectally administered delta 9-tetrahydrocannabinol on spasticity: A pilot study with 2 patients. *International Journal of Clinical Pharmacology and Therapeutics* 34(10):446–452.

Busse F., L. Omidi, K. Timper, A. Leichtle, M. Windgassen, E. Kluge, and M. Stumvoll. 2008. Lead poisoning due to adulterated marijuana. *New England Journal of Medicine* 358(15):1641–1642.

Carrier, E. J., J. A. Auchampach, and C. J. Hillard. 2006. Inhibition of an equilibrative nucleoside transporter by cannabidiol: A mechanism of cannabinoid immunosuppression. *Proceedings of the National Academy of Sciences* 103(20):7895–7900.

Castle, S. 2016. More growers brings surge in weed supplies, plunge in Boulder County pot prices. *Daily Camera*, August 26. http://www.dailycamera.com/boulder-business/ci_30295353/bumper-crop-growers-leads-surge-weed-supplies-plunge (accessed November 8, 2016).

Chandra, S., L. H., Khan IA, ElSohly M. 2012. The role of biotechnology in *Cannabis sativa* propagation for the production of phytocannabinoid. In S Chandra, H Lata, IA Khan, MA ElSohly (eds.), *Biotechnology for medicinal plants*. Berlin: Springer-Verlag. Pp. 123–148.

Clarke, R. C., and M. D. Merlin. 2015. *Cannabis: Evolution and ethnobotany.* Berkeley: University of California Press.

Daniulaityte, R., R. W. Nahhas, S. Wijeratne, R. G. Carlson, F. R. Lamy, S. S. Martins, E. W. Boyer, G. A. Smith, and A. Sheth. 2015. Time for dabs: Analyzing Twitter data on marijuana concentrates across the U.S. *Drug and Alcohol Dependence* 155:307–311.

de Lago, E. and J. Fernandez-Ruiz. 2007. Cannabinoids and neuroprotection in motor-related disorders. *CNS and Neurological Disorders in Drug Targets* 6(6):377–387.

De Petrocellis, L., A. Ligresti, A. S. Moriello, M. Allarà, T. Bisogno, S. Petrosino, C. G. Stott, and V. Di Marzo. 2011. Effects of cannabinoids and cannabinoid-enriched cannabis extracts on TRP channels and endocannabinoid metabolic enzymes. *British Journal of Pharmacology* 163(7):1479–1494.

Devane, W. A., F. A. Dysarz, 3rd, M. R. Johnson, L. S. Melvin, and A. C. Howlett. 1988. Determination and characterization of a cannabinoid receptor in rat brain. *Molecular Pharmacology* 34(5):605–613.

Ehrler, M. R., E. C. Deborah, D. A. Yurgelun-Todd. 2015. Subjective and cognitive effects of cannabinoids in marijuana smokers. In P. Campolongo and L. Fattore (eds.), *Cannabinoid modulation of emotion, memory, and motivation*. New York: Springer. Pp. 159–181.

Elmes, M. W., M. Kaczocha, W. T. Berger, K. Leung, B. P. Ralph, L. Wang, J. M. Sweeney, J. T. Miyauchi, S. E. Tsirka, I. Ojima, and D. G. Deutsch. 2015. Fatty acid-binding proteins (FABPs) are intracellular carriers for Delta9-tetrahydrocannabinol (THC) and cannabidiol (CBD). *Journal of Biological Chemistry* 290(14):8711–8721.

ElSohly, M. A. and W. Gul. 2014. *Handbook of cannabis (Chapter 2)*. Oxford, UK: Oxford University Press: P.20.

ElSohly, M. A., Z. Mehmedic, S. Foster, C. Gon, S. Chandra, and J. C. Church. 2016. Changes in cannabis potency over the last 2 decades (1995–2014): Analysis of current data in the United States. *Biological Psychiatry* 79(7):613–619.

Fabritius, M., H. Chtioui, G. Battistella, J. M. Annoni, K. Dao, B. Favrat, E. Fornari, E. Lauer, P. Maeder, and C. Giroud. 2013. Comparison of cannabinoid concentrations in oral fluid and whole blood

between occasional and regular cannabis smokers prior to and after smoking a cannabis joint. *Analytical and Bioanalytical Chemistry* 405(30):9791–9803.

Galal, A. M., D. Slade, W. Gul, A. T. El-Alfy, D. Ferreira, and M. A. Elsohly. 2009. Naturally occurring and related synthetic cannabinoids and their potential therapeutic applications. *Recent Patents on CNS Drug Discovery* 4:112–136.

Gaoni, Y., and R. Mechoulam. 1964. Isolation, structure, and partial synthesis of an active constituent of hashish. *Journal of the American Chemical Society* 86(8):1646–1647.

Ghosh, A., and D. Basu 2015. Cannabis and psychopathology: The meandering journey of the last decade. *Indian Journal of Psychiatry* 57(2):140–149.

Gonzalez, S., M. Cebeira, and J. Fernández-Ruiz. 2005. Cannabinoid tolerance and dependence: A review of studies in laboratory animals. *Pharmacology Biochemistry and Behavior* 81(2):300–318.

Grotenhermen, F. 2003. Pharmacokinetics and pharmacodynamics of cannabinoids. *Clinical Pharmacokinetics* 42(4):327–360.

Hall, W. D., and R. L. Pacula. 2010. *Cannabis use and dependence: Public health and public policy*. (reissue of 2003 first edition). Cambridge, UK: Cambridge University Press.

Herkenham, M., A. B. Lynn, M. D. Little, M. R. Johnson, L. S. Melvin, B. R. de Costa, and K. C. Rice. 1990. Cannabinoid receptor localization in brain. *Proceedings of the National Academy of Sciences* 87(5):1932–1936.

Hermanns-Clausen, M., J. Kithinji, M. Spehl, V. Angerer, F. Franz, F. Eyer, and V. Auwärter. 2016. Adverse effects after the use of JWH-210—A case series from the EU Spice II plus project. *Drug Testing and Analysis* 8(10):1030–1038.

Hillig, K. W. 2005. Genetic evidence for speciation in Cannabis (Cannabaceae). *Genetic Resources and Crop Evolution* 52(2):161–180.

Hirvonen, J., R. S. Goodwin, C. T. Li, G. E. Terry, S. S. Zoghbi, C. Morse, V. W. Pike, N. D. Volkow, M. A. Huestis, and R. B. Innis. 2012. Reversible and regionally selective downregulation of brain cannabinoid CB1 receptors in chronic daily cannabis smokers. *Molecular Psychiatry* 17(6):642–649.

Hofmann, M. E. and C. J. Frazier. 2013. Marijuana, endocannabinoids, and epilepsy: potential and challenges for improved therapeutic intervention. *Experimental Neurology* 244:43–50.

Huestis, M. A., J. E. Henningfield, and E. J. Cone. 1992. Blood cannabinoids. I. Absorption of THC and formation of 11-OH-THC and THCCOOH during and after smoking marijuana. *Journal of Analytical Toxicology* 16(5):276–282.

IOM (Institute of Medicine). 1999. *Marijuana and medicine: Assessing the science base*. Washington, DC:National Academy Press.

Iuvone, T., G. Esposito, D. De Filippis, C. Scuderi, and L. Steardo. 2009. Cannabidiol: A promising drug for neurodegenerative disorders? *CNS Neuroscience and Therapeutics* 15(1):65–75.

Iversen, L. 2000. *The science of marijuana*. New York: Oxford University Press.

Jones, N. A., A. J. Hill, I. Smith, S. A. Bevan, C. M. Williams, B. J. Whalley, and G. J. Stephens. 2010. Cannabidiol displays antiepileptiform and antiseizure properties in vitro and in vivo. *Journal of Pharmacology and Experimental Therapeutics* 332(2):569–577.

Kilmer, B. 2014. Policy designs for cannabis legalization: Starting with the eight Ps. *The American Journal of Drug and Alcohol Abuse* 40(4):259–261.

Kilmer, B., J. P. Caulkins, G. Midgette, L. Dahlkemper, R. J. MacCoun, and R. L. Pacula. 2013. *Before the grand opening: Measuring Washington State's marijuana market in the last year before legalized commercial sales.* Santa Monica, CA: RAND Corporation.

Kuddus, M., I. A. M. Ginawi, and A. Al-Hazimi. 2013. Cannabis sativa: An ancient wild edible plant of India. *Emirates Journal of Food and Agriculture* 25(10):736–745.

Lakhan, S. E. and M. Rowland. 2009. Whole plant cannabis extracts in the treatment of spasticity in multiple sclerosis: A systematic review. *BMC Neurology* 9:59.

Laprairie, R. B., A. M. Bagher, M. E. Kelly, and E. M. Denovan-Wright. 2015. Cannabidiol is a negative allosteric modulator of the cannabinoid CB1 receptor. *British Journal of Pharmacology* 172(20):4790–4805.

Laursen, L. 2015. Botany: The cultivation of weed. *Nature* 525(7570):S4–S5.

Leweke, F. M., J. K. Mueller, B. Lange, and C. Rohleder. 2016. Therapeutic Potential of Cannabinoids in Psychosis. *Biological Psychiatry* 79(7):604–612.

Li, R. F., G. T. Lu, L. Li, H. Z. Su, G. F. Feng, Y. Chen, Y. Q. He, B. L. Jiang, D. J. Tang, and J. L. Tang. 2014. Identification of a putative cognate sensor kinase for the two-component response regulator HrpG, a key regulator controlling the expression of the *hrp* genes in *Xanthomonas campestris* pv. *Campestris*. *Environmental Microbiology* 16(7):2053–2071.

Loflin, M., and M. Earleywine. 2014. A new method of cannabis ingestion: The dangers of dabs? *Addictive Behaviors* 39(10):1430–1433.

Long, T., M. Wagner, D. Demske, C. Leipe, and P. E. Tarasov. 2016. Cannabis in Eurasia: Origin of human use and Bronze Age trans-continental connections. *Vegetation History and Achaeobotany* 25:1–14.

MacCoun, R. J., and M. M. Mello. 2015. Half-baked—The retail promotion of marijuana edibles. *New England Journal of Medicine* 372(11):989–991.

Mackie, K. 2006. Cannabinoid receptors as therapeutic targets. *Annual Review of Pharmacology and Toxicology* 46:101–122.

Mariani J.J., D. Brooks, M. Haney, and F. R. Levin. 2011. Quantification and comparison of marijuana smoking practices: blunts, joints, and pipes. *Drug and Alcohol Dependence* 113(2-3):249–251.

Matsuda, L. A., S. J. Lolait, M. J. Brownstein, A. C. Young, and T. I. Bonner. 1990. Structure of a cannabinoid receptor and functional expression of the cloned cDNA. *Nature* 346(6284):561–564.

McLaren, J., W. Swift, P. Dillon, and S. Allsop. 2008. Cannabis potency and contamination: A review of the literature. *Addiction* 103(7):1100–1109.

McPartland, J. M., D. J. Blanchon, and R. E. Musty. 2008. Cannabimimetic effects modulated by cholinergic compounds. *Addiction Biology* 13(3–4):411–415.

Mechoulam, R., and Y. Shvo. 1963. Hashish. I. The structure of cannabidiol. *Tetrahedron* 19(12):2073–2078.

Moreau de Tours, J. J. 1845. *Du Hachisch et de L'alienation mentale*. Paris: Librairie de Fortin, Masson et Ca.

Munro, S., K. L. Thomas, and M. Abu-Shaar. 1993. Molecular characterization of a peripheral receptor for cannabinoids. *Nature* 365(6441):61–65.

NIDA (National Institute on Drug Abuse). 2012. *DrugFacts: Spice (Synthetic Marijuana)*. Rockville, MD: U.S. Department of Health and Human Services, National Institutes of Health.

NIDA. 2014. *Monitoring the Future Survey, Overview of Findings 2014*. https://www.drugabuse.gov/related-topics/trends-statistics/monitoring-future/monitoring-future-survey-overview-findings-2014 (accessed November 14, 2016).

O'Shaughnessy, W. B. 1840. New remedy for tetanus and other convulsive disorders. *The Boston Medical and Surgical Journal* 23:153–155.

Pacula, R. L., M. Jacobson, and E. J. Maksabedian. 2016. In the weeds: A baseline view of cannabis use among legalizing states and their neighbours. *Addiction* 111(6):973–980.

Pertwee, R. G. 2012. Targeting the endocannabinoid system with cannabinoid receptor agonists: Pharmacological strategies and therapeutic possibilities. *Philosophical Transactions of the Royal Society of London B: Biological Sciences* 367(1607):3353–3363.

Piomelli, D. 2015. *Neurobiology of marijuana*. In Textbook of Substance Abuse Treatment, Galanter M, Kleber HD, Brady KT, eds. American Psychiatric Publishing, Arlington VA. PP. 335–350.

Raber, J. C., S. Elzinga, and C. Kaplan. 2015. Understanding dabs: Contamination concerns of cannabis concentrates and cannabinoid transfer during the act of dabbing. *Journal of Toxicological Science* 40(6):797–803.

Randerson, J. 2007. Warning issued over cannabis adulterated with glass beads. *The Guardian*, January 12. https://www.theguardian.com/society/2007/jan/12/drugsandalcohol.drugs (accessed November 8, 2016).

Russo, E. B. 2007. History of cannabis and its preparations in saga, science, and sobriquet. *Chemistry and Biodiversity* 4(8):1614–1648.

Russo, E. B., A. Burnett, B. Hall, K. K. Parker. 2005. Agonistic properties of cannabidiol at 5-HT1a receptors. *Neurochemical Research* 30(8):1037–1043.

Scuderi, C., D. D. Filippis, T. Iuvone, A. Blasio, A. Steardo, and G. Esposito. 2009. Cannabidiol in medicine: A review of its therapeutic potential in CNS disorders. *Phytotherapy Research* 23(5):597–602.

Small, E. 2015. Evolution and classification of *Cannabis sativa* (marijuana, hemp) in relation to human utilization. *The Botanical Review* 81(3):189–294.

Tait, R. J., D. Caldicott, D. Mountain, S. L. Hill, and S. Lenton. 2016. A systematic review of adverse events arising from the use of synthetic cannabinoids and their associated treatment. *Clinical Toxicology* 54(1):1–13.

Thomas, A., G. L. Baillie, A. M. Phillips, R. K. Razdan, R. A. Ross, and R. G. Pertwee. 2007. Cannabidiol displays unexpectedly high potency as an antagonist of CB1 and CB2 receptor agonists in vitro. British Journal of Pharmacology 150(5):613–623.

Thomas, B. F., and G. T. Pollard. 2016. Preparation and distribution of cannabis and cannabis-derived dosage formulations for investigational and therapeutic use in the United States. *Frontiers in Pharmacology* 7:285.

U.S. Pharmacopoeial Convention. 1916. *Pharmacopoeia of the United States*. Philadelphia, PA: P. Blakiston's Son & Company.

Wang, G. S., G. Roosevelt, M. C. Le Lait, E. M. Martinez, B. Bucher-Bartelson, A. C. Bronstein, and K. Heard. 2014. Association of unintentional pediatric exposures with decriminalization of marijuana in the United States. *Annals of Emerging Medicine* 63(6):684–689.

Wells, D. L. and C. A. Ott. 2011. The new marijuana. *Annals of Pharmacotherapy* 45(3):414–417.

Wollner, H. J., J. R. Matchett, J. Levine, and S. Loewe. 1942. Isolation of a physiologically active tetrahydrocannabinol from Cannabis sativa resin. *Journal of the American Chemical Society* 64(1):26–29.

3
Cannabis: Prevalence of Use, Regulation, and Current Policy Landscape

PREVALENCE OF CANNABIS USE IN THE UNITED STATES (1975–2014)

The popularity of cannabis has ebbed and flowed over the past century. Despite being outlawed in several states in the early 1900's and being federally prohibition in 1937, cannabis remained relatively obscure until the 1960s, when an upsurge in use among adolescents and young adults brought the drug into the mainstream. Since the early 1970s, two surveys, the National Survey on Drug Use and Health (NSDUH) and Monitoring the Future, have provided nationally representative data on self-reported use of cannabis. The NSDUH (called the National Household Survey on Drug Abuse until 2002) has polled Americans 12 years of age and older since 1971, and Monitoring the Future has polled high school seniors since 1976, adding 8th- and 10th-graders in 1991 (ICPSR, 2016; CBHSQ, 2014). Both national surveys include questions that ask respondents whether they have ever used cannabis and if they have used cannabis within the past year or within the past 30 days. These data have been used to categorize users, with those reporting use within the past month often considered to be "active" or "current" users. Monitoring the Future also asks youth about how easily they could access cannabis, whether they approve of its use, and how risky they perceive it to be. Other national surveys of interest include the Centers for Disease Control and Prevention's (CDC's) Youth Risk Behavior Survey, which surveys the health-risk behaviors of 9th- through 12th-grade students on a biannual basis,[1] and the CDC's Behavioral Risk Factor Surveillance System,[2] which collects state and local data regarding health-related risk behaviors, chronic health conditions, and the use of preventive services. It is of note that many surveillance surveys differ in their design and methodology, which often limits the ability to compare and compile data across studies.

The prevalence of cannabis use peaked in the late 1970s, when over one-third of high school seniors (37 percent in 1976) and one in eight Americans over 12 years old (12.8 percent in 1979) reported past-month use (Johnston et al., 2015). Self-reported past-month use declined throughout the 1980s and by 1992 was just one-third of the 1970s peak, both among high school seniors (12.1 percent) and the general population (4.4 percent). The recorded decline in use did not last long. The mid 1990s saw rapid increases, with use by high school seniors nearly doubling within just the 5 years from 1992 (11.9 percent) to 1997 (23.7 percent). Throughout the late 1990s and early 2000s, the rates of use largely stagnated, with trends among youth and the general population moving roughly in parallel (Johnston et al., 2015).

The years since 2007 have seen steady year-over-year increases in general population past-month use, rising from 5.8 percent to 8.4 percent in 2014 (a 45 percent increase). There is

[1] For additional information: http://www.cdc.gov/healthyyouth/data/yrbs/results.htm (accessed January 6, 2016).

[2] For additional information: http://www.cdc.gov/brfss/about/index.htm (accessed January 6, 2016).

no single clear explanation for the post-2007 increases in use. Hypothesized causes include declining potency-adjusted prices on the illicit market; the proliferation of medical cannabis laws, especially those that allow for sale at brick-and-mortar dispensaries; and changing public perceptions about the harms of cannabis use (Sevigny, 2014).

Today, cannabis is the most popular illicit drug in the United States (in terms of past-month users), trailed by prescription-type drugs used for non-medical purposes, such as pain relievers (3.8 million), tranquilizers (1.9m) and stimulants (1.7m), and by prohibited drugs such as cocaine (1.9m), hallucinogens (1.2m), and heroin (0.3m) (CBHSQ, 2016a). A recent survey showed that the primary use of cannabis in the United States remains recreational (89.5 percent of adult cannabis users), with only 10.5 percent reporting use solely for medical purposes, and 36.1 percent reporting a mixed medical/recreational use (Schauer et al., 2016).

In 2015, an estimated 22.2 million of more than 265 million Americans aged 12 years or age or older, reported having used cannabis in the past month (8.3 percent) (CBHSQ, 2016a). Cannabis use is most prevalent among young people aged 18 to 25 (19.8 percent using in the past month) (CBHSQ, 2016a). Interestingly, since 2002 the use of cannabis has decreased among 12- to 17-years-olds, while markedly increasing in the senior population, i.e., those over 55 years (Azofeifa et al., 2016).

Males are nearly twice as likely (10.6 percent) to use cannabis as females (6.2 percent) (see Table 3-1). Black Americans use cannabis at the highest rate among major ethnic groups (10.7 percent), followed by whites (8.4 percent) and Hispanics (7.2 percent) (CBHSQ, 2016b). Use is also more common among lower-income Americans and those without college degrees (Davenport and Caulkins, 2016).

TABLE 3-1 Past-Month Use Rates by Demographic

	Past-Month Use Rate (%)
Ethnicity	
White, Non-Hispanic	8.4
African American, Non-Hispanic	10.7
Hispanic	7.2
Asian Non-Hispanic	3.0
Gender	
Male	10.6
Female	6.2
Education	
Less Than High School	8.2
High School Graduate	9.1
Some College	10.5
College Grad	5.9
Family Income[a]	
Less than $10k	13.6
$20k–$29.9k	9.7
$50k–$74.9k	7.8
$75k +	6.6

Age[a]	
12–17	7.1
18–25	20.1
26-34	13.0
35-49	7.1
50+	3.9

NOTE: [a] Calculated with the Substance Abuse and Mental Health Services Administration (SAMHSA)'s public online data analysis system (PDAS). Crosstab: IRMJRC x CATAG3 (CBHSQ, 2016b).
SOURCE: Derived from CBHSQ, 2016b.

Different demographics have different rates of cannabis use. For example, dividing the population by age yields stark differences. Data from the Monitoring the Future survey show that more than one-fifth (21.3 percent) of high school seniors reported past-month use in 2015 (Johnston et al., 2016). According to NSDUH data, past-month use is highest among 18- to 25-year-olds (19.8 percent) and lower in older groups. All age groups have shown increases in past month cannabis use since 2002, with the sole exception of adolescents between 12 and 17, whose use in 2015 (7.0 percent) was lower than that reported in 2002 (8.2 percent) (CBHSQ, 2016a).

Volume and Intensity of Cannabis Use Today

A different and often overlooked picture of cannabis use is painted when it is measured in terms of volume or intensity of use rather than the prevalence of current users. The NSDUH survey asks past-month cannabis users how many days in the past 30 they have used "marijuana or hashish," allowing researchers to measure the volume of use by aggregating reported use-days or by tracking the number of users who report use on more than 20 days in the past 30, termed heavy or "daily/near-daily" users.

Today, 22.2 million Americans 12 years of age and older report current cannabis use (defined as "users in the past 30 days") (CBHSQ, 2016a). As a proportion of past-month users, heavy users have grown from roughly one in nine in 1992 to more than one in three (35.4 percent) in 2014, indicating an increased intensity of use among current users.[3] Furthermore, the population of heavy users has not only become larger, it has also become older. Burns et al. note an inversion of the ratio of youth (ages 12–17) to older adults (age 50 and over): in 2002, more than three times as many youths as older adults were using cannabis on a daily or near-daily basis; by 2011, 2.5 times as adults as youth were daily or near-daily cannabis users (Burns et al., 2013).

Generally, the intensity of use correlates with use prevalence: groups with high prevalence tend to be the same as those with high intensity. But some groups are noticeable exceptions. For example, Americans with less than a high school education are less likely to report past-month use than Americans with a high school diploma or with a partial college education, but in terms of past-month use, those with less than a high school education are most

[3] Computed by NSDUH cross-tabs for 1992 and 2014. For 1992: https://www.icpsr.umich.edu/icpsrweb/ICPSR/series/64/studies/6887?archive=ICPSR&sortBy=7 (accessed January 6, 2017). Compute "MRJMON" against "MJDAY30A", recoded as "MJDAY30A(r: 0-20;21-30)." For 2014: http://www.icpsr.umich.edu/cgi-bin/SDA/NAHDAP/hsda?nahdap+36361-0001 (accessed January 6, 2017). Compute "IRMJRC" against "MJDAY30A," recoded as "MJDAY30A(r: 0-20;21-30)."

likely to report daily/near-daily use (44.8 percent). Likewise, among age demographics, 26- to 34-year-olds report less past-month use than 18-to-25 year olds but report substantially more heavy use among current users (42.2 percent). Heavy use among past-month users is lowest among 12-to-17 year olds (7.4 percent). Younger users tend to have lighter habits. According to Monitoring the Future data, in 2015, 6 percent of high school seniors who used cannabis in the past month reported use on a *daily* basis, as did 3 percent of 10th-graders and 1.1 percent of 8th-graders (Johnston et al., 2015).

One result of the increased intensity of use among past-month users is that the bulk of cannabis consumption is increasingly concentrated among a small number of heavy users. By one estimate, the one-third of current cannabis users that use daily or near daily accounted for two-thirds of the reported days of past-month use and three-quarters of expenditures (Davenport and Caulkins, 2016).

CANNABIS REGULATION IN THE UNITED STATES

In the United States at the turn of the 20th century, cannabis was generally used for medical rather than recreational purposes. As such, the production and use of cannabis was regulated by consumer safety laws such as the Pure Food and Drug Act of 1906, which required producers to disclose and label the quantity of cannabis present in any product sold as food or medicine. Although several U.S. states enacted banns on cannabis between 1911 and 1930, it escaped early federal prohibitions, such as the Harrison Act of 1914, which regulated opium and derivatives of the coca plant (Musto, 1999).

Fear of "marihuana," as cannabis was beginning to be called, grew during the 1920s and 1930s as immigration from Mexico steadily increased in southwestern states. In the mid-1930s, the federal government, through the Federal Bureau of Narcotics, endorsed state-level actions and encouraged states to adopt the Marihuana Tax Act as a means to criminalize the unregistered and untaxed production and use of cannabis. National prohibition did not take shape, however, until Congress passed the Marijuana Tax Act of 1937, which regulated the production, distribution, and use of cannabis via Congress's power to tax commerce. The act required those dealing with cannabis to register with federal authorities and pay a tax (Booth, 2015; Musto, 1999). The supply and use of the drug was not criminalized, but non-medical supply or use was a violation and subject to a fine and imprisonment.

Today, cannabis is regulated by local, state, federal, and international law. State laws often mirror federal law, enshrined in the Comprehensive Drug Abuse Prevention and Control Act of 1970, which includes the Controlled Substances Act (CSA). The CSA modernized and consolidated earlier federal drug laws, making them consistent with international drug control conventions, specifically the United Nations Single Convention on Narcotic Drugs of 1961, which the United States ratified (Caulkins et al., 2016). The CSA placed cannabis in Schedule I, the most restrictive category reserved for substances that have no currently accepted medical use, alongside heroin and lysergic acid diethylamide (LSD). The federal government does not recognize the medical use of cannabis, citing no evidence of the accepted medical use of herbal cannabis. It bears mentioning that pharmaceutical-grade cannabinoids have been isolated and are scheduled apart from cannabis. For example, tetrahydrocannabinol (THC) is sold as Marinol, available with prescription (a Schedule III drug). That THC, which is the principal active ingredient in cannabis, in its pure form is listed in Schedule III indicates that the placement of

botanical or whole cannabis in Schedule 1 may be driven by the lack of recognition of medical use for the whole plant.

Federal criminal law prohibits the supply and use of cannabis with exceptions for medical and scientific purposes. The enforcement of cannabis prohibition by federal authorities has focused on international smuggling and domestic crop eradication as well as violations on federal lands. The federal government has relied on state and local authorities to enforce criminal prohibitions on cannabis retail and use. In 2014 there were more than 1.5 million arrests for drug law violations,[4] approximately 30,000 of which were made by the Drug Enforcement Administration (DEA).[5] However, federal law remains an important factor in regulating cannabis. While the National Institutes of Health (NIH) have funded cannabis research—$111 million on 281 cannabinoid research projects in 2015 alone (NIH, 2016)—the federal government has restricted research on cannabis by licensing a single producer under contract with the National Institute on Drug Abuse (NIDA) and requiring multiple administrative reviews on research proposals (Caulkins et al., 2016) (see Chapter 15—Challenges and Barriers to Cannabis Research for additional information).[6] Federal law also prohibits the importation of and intra- and interstate trade in cannabis. Tangentially, federal banking and commercial laws impede the development of commercial cannabis businesses. Though legal at the state level, the federal prohibition on cannabis prevents businesses from accessing the banking sector, precluding entrepreneurs from accessing lines of credit, electronic funds transfer, checking accounts, and other financial goods and services available to contemporary businesses. Federal tax code also prohibits cannabis businesses from deducting typical costs of business (Caulkins et al., 2015; Oglesby, 2015). In summary, the legal changes in cannabis policy during the past 50 years have been characterized primarily by three types of policies, each implemented by various states, beginning with (1) decriminalization throughout the 1970s, which preceded (2) medical cannabis laws and (3) regulated and licensed recreational cannabis.

Decriminalization of Possession and Use

States and localities perform most of the legwork involved in enforcing the criminal prohibition on cannabis, as they arrest and convict the vast majority of offenders. Each state maintains its own set of laws that regulate the supply and use of the drug. In most cases, acts involving cannabis are subject to criminal prohibition, but sanctions vary considerably by state, which are constitutionally entitled to establish their own criminal codes and penalties.

The reduction of statutory penalties for use-related acts, including personal possession, is referred to as *decriminalization* or *depenalization*. About a dozen U.S. states are often described as having decriminalized possession in the 1970s (Pecula et al., 2005), beginning with Oregon in 1973. This move to reduce penalties on cannabis use halted until 2001 when Nevada decriminalized possession of small amounts of cannabis. Today, 21 states, covering

[4] As a noteworthy caveat, within the United States there is evidence of racial-, social- and economic status-based disparities in the enforcement and issued penalties related to cannabis sale and use (Austin and Ressler, 2016). Within this context, it is important to acknowledge the potential impact of these laws on the health outcomes of disenfranchised communities.

[5] See https://ucr.fbi.gov/crime-in-the-u.s/2014/crime-in-the-u.s.-2014/tables/table-29 (accessed January 6, 2017) and https://www.dea.gov/resource-center/statistics.shtml#arrests (accessed January 6, 2017).

[6] In August 2016, NIDA announced a policy change intended to support an increase in the number of DEA-registered marijuana manufacturers. This change was designed to ensure a larger and more diverse supply of marijuana for FDA-authorized research purposes (DEA, 2016).

approximately 40 percent of the national population, have decriminalized possession of small amounts of cannabis (Caulkins et al., 2016).

During the 1970s, the federal government briefly considered abolishing criminal sanctions for use-related acts. The 1972 National Commission on Marihuana and Drug Abuse, appointed by President Nixon, recommended that federal law be amended to decriminalize cannabis possession, use, and low-level retail (Shafer Commission, 1972). Those recommendations were rejected by the Nixon Administration. President Carter raised the issue again in a 1977 speech to Congress, calling for federal decriminalization of cannabis possession, but his Administration did not succeed in changing policies (Musto, 1999).

Medical Cannabis Laws

The next major shift in state cannabis policy in the United States was the enactment of medical cannabis laws. Starting in 1996 California passed a popular referendum (Proposition 215) to allow individuals suffering from various illnesses to use herbal, whole plant cannabis, making California the first jurisdiction in the Western Hemisphere to legalize medical cannabis in some form. The law generally provides an affirmative defense for individuals using cannabis for medical purposes. Reforms at the state level continued in the waning years of the 20th century with a handful of states passing laws to allow doctors to prescribe medical cannabis or allow for a legal defense for use of medical cannabis. The permission of use of the flower or products derived from the cannabis flower has now spread to 28 states and the District of Columbia. Another 16 states allow limited access to low-tetrahydrocannabinol (THC)/high-cannabidiol (CBD) products (NCSL, 2016). Figure 3-2 demonstrates that low-THC/high-CBD laws are a recent phenomenon.

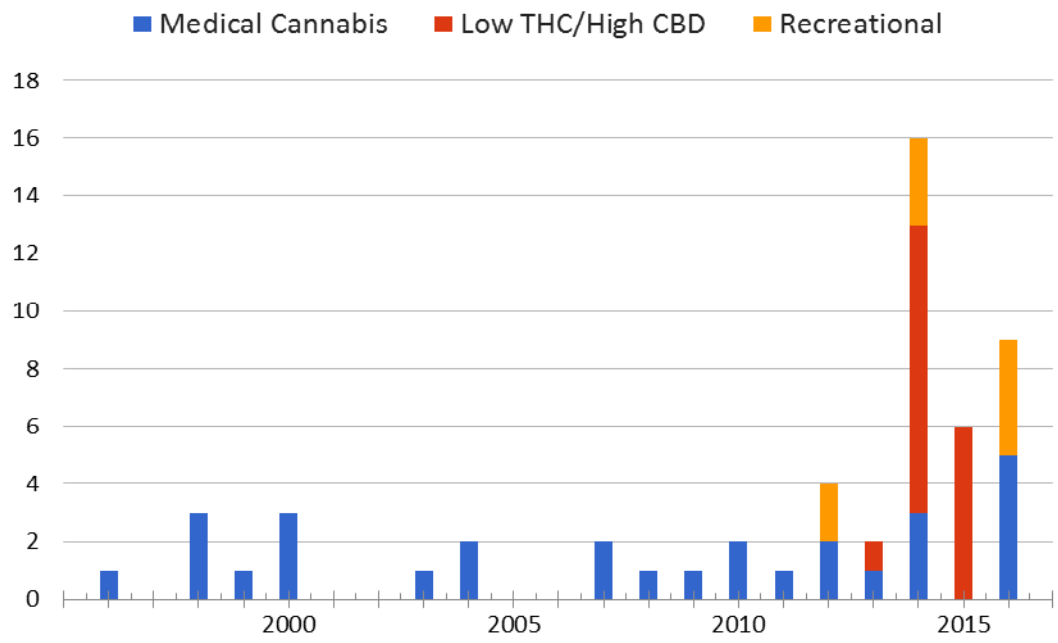

FIGURE 3-2 Passage of state cannabis laws (figure includes Washington DC).
SOURCE: Adapted from NCSL, 2016.

Medical cannabis laws and policies vary greatly in terms of the regulations governing supply and use. Some are more restrictive than others, limiting the access of the drug to a certain class of individuals who suffer from certain illnesses or conditions, or establishing stricter limits on the production and distribution of the substance to at-home cultivation by patients and caregivers. Some states legally protect and regulate the operation of storefronts known as dispensaries. In these states, patients with a recommendation can enter stores and obtain a wide array of cannabis and cannabis products. Some dispensaries openly advertise their wares and services to patients at point of sale, with others aggressively promoting their business to the general public.

When it comes to the distribution of medical cannabis, some states, such as New York, restrict the sale of medical cannabis to non-smokable forms of the drug. Others require that patients register with the state and identify their source of cannabis. Even within states regulations may vary. Some states allow for local bans and municipal ordinances to help regulate additional aspects of the supply of cannabis.

Non-Medical, Adult Recreational Use

In 2010 California voted on legalizing recreational cannabis—in effect, permitting and regulating the supply and distribution of cannabis for adults to use non-medically. Proposition 19 sought to repeal the state's criminal prohibitions on cannabis, regulating it for recreational purposes for those over 21 years of age. The initiative failed, with 54 percent voting against. Two years later residents of Colorado, Oregon, and Washington went to the polls to vote on legalizing the adult recreational use of cannabis. Oregon's initiative failed, with 53 percent of

voters rejecting the measure;[7] however, Colorado and Washington State, after passing ballot initiatives in November 2012, became the first jurisdictions to legalize the large-scale commercial production of cannabis for recreational use for adults over 21, with Colorado also permitting home cultivation. In November 2014 similar initiatives were approved by voters in Alaska[8] and Oregon. Washington, DC took a narrower approach by legalizing only possession and home cultivation. The D.C. City Council subsequently attempted to permit and regulate a commercial market but was blocked by the U.S. Congress.

The liberalization of cannabis laws has been a gradual process. Early steps included medical cannabis, including the allowance and, sometimes, legal protection of dispensaries. Later, Alaska, Colorado, Oregon, and Washington regulated the production and distribution of recreational cannabis by private, for-profit commercial actors along similar lines. Besides the general commercial design of these initiatives, the details of the regulations vary. Table 3-2 describes a few of the regulatory differences between Alaska, Colorado, Oregon, Washington, and the District of Columbia. With the exception of Washington State, all permit at-home cultivation. The District of Columbia follows a "grow and give" non-commercial model. None impose potency limits or require users to register.

In November 2016 California, Maine, Massachusetts, and Nevada voted to legalize adult measures related to recreational cannabis use and possession (NORML, 2016). Arkansas, Florida, Montana, and North Dakota voted in favor of medical marijuana initiatives.

[7] Oregon temporarily allowed sales of recreational cannabis through existing medical dispensaries beginning in October 2015, though licensed recreational stores are not expected to open until late 2016.

[8] Alaska is expected to allow recreational cannabis sales in licensed stores by late 2016.

TABLE 3-2 Regulatory Differences Across Four States (and the District of Columbia) That Have Legalized Recreational Cannabis

	Alaska	**Colorado**	**Oregon**	**Washington**	**Washington, DC**
Legal Process	Voter initiative, state statute	Voter initiative, amendment to state constitution	Voter initiative, state statute	Voter initiative, state statute	Voter initiative
When Passed	November 2014	November 2012	November 2014	November 2012	November 2014
When Implemented	February 2015: Personal possession, consumption, cultivation Late 2016 (expected): Retail sales	December 2012: Personal possession, consumption, cultivation January 2014: Retail sales	July 2015: Personal possession, consumption, cultivation October 1, 2015: Retail sales via medical dispensaries Late-2016 (expected): retail sales through licensed retailers	December 2012: Personal possession, consumption July 2014: Retail sales	February 2015: Personal possession, consumption, cultivation
Regulatory Authority	Marijuana Control Board (Alcoholic Beverage Control Board)	Marijuana Enforcement Division (Department of Revenue)	Oregon Liquor Control Commission	Liquor and Cannabis Board (formerly the Liquor Control Board)	Not applicable
Minimum Age	21	21	21	21	21
Residency Requirement	None	None	None	None	None
Personal Possession Quantity	28.5 g	28.5 g	In public: 28.5 g At home: 228 g	28.5 g	57 g
Home Cultivation	6 plants, 3 of which can be flowering	6 plants, 3 of which can be flowering	4 plants in flower	Not allowed	6 plants per person 12 plants per household, 3 of which can be flowering
Interpersonal Sharing	28.5 g	28.5 g	28.5 g	Not allowed	28.5 g
Retail Transaction Limit	28.5 g	Residents: 28.5 g Non-residents: 7 g	7 g	28.5 g	Not applicable

Retail Pricing Structure	Market	Market	Market	Market	Not applicable
Average Retail Price per Gram After Tax	No retail stores currently	$11.50	$10.00	$10.00	Not applicable
Maximum THC Content	None	None	None	None	None
Registration Requirements	None	None	None	None	None
Advertising	Final advertising regulations to be determined by the Alaska Department of Health and Social Services Division of Public Health	Restricted to media with no more than 30 percent of the audience under the age of 21	Entry sign required on exterior of dispensaries; Oregon Liquor Control Commission has authority to further regulate or prohibit advertising	Limited to one sign for retailers at business location	Not applicable, no commercial market
Taxation	$50 excise tax per ounce on sales or transfers from cultivation facility to retail store or product manufacturer	15 percent excise tax on cultivation; 10 percent retail marijuana sales tax; 2.9 percent state sales tax; local sales taxes	No tax on retail sales from October–December 2015; 25 percent sales tax after Jan. 5, 2016	July–June 2014: 25 percent tax at each stage (production, processing, retail) July 2015: 37 percent sales tax	Not applicable, no commercial market
Cannabis Clubs	Not explicitly allowed or prohibited; ban on in-store consumption repealed in November 2015	Not allowed	Not allowed	Not allowed	Not allowed; currently under investigation by city task force.
Medical Cannabis	2000: patient registry, possession, home cultivation	2000: patient registry, possession, consumption 2010: commercial production and sales	1999: patient registry, possession, home cultivation	1999: possession 2012: home cultivation, no patient registry	2011: patient registry

SOURCE: Adapted from UNODC World Drug Report 2016 (UNODC, 2016).

In order to develop and enforce regulations for a recreational cannabis industry, each state has appointed a regulatory agency. Washington State, Oregon, and Alaska delegated this responsibility to existing alcohol authorities, while Colorado expanded the responsibilities of the Medical Marijuana Enforcement Division under the Department of Revenue. To aid in drafting rules following the passage of their initiatives, state agencies held public hearings and working groups to solicit public input (Pardo, 2014).

The federal government has not challenged these state laws by invoking the supremacy clause of the U.S. Constitution. However, under the 10th Amendment, as reaffirmed by U.S. jurisprudence, the federal government cannot force a state to criminalize an act under state law (Garvey and Yeh, 2014). When the voters of these states passed initiatives to legalize, regulate, and tax recreational cannabis, they simultaneously repealed the penal provisions and sanctions prohibiting and criminalizing unauthorized cultivation, trafficking, and possession of cannabis. Under the Obama administration, the federal government seems to have opted for a more pragmatic solution which allows for a rules-based cannabis industry, as dictated by state regulations, while maintaining the future option to preempt.

POLICY LANDSCAPE

Most researchers recognize that a growing general public acceptance of the drug for medical and recreational purposes has been encouraging the changes at the state level. It remains to be seen if cannabis will be legalized at the national level or if such public opinion will continue. In 2015, according to a Gallup tracker poll, 58 percent of Americans favored legalizing cannabis, marking the third straight year that cannabis legalization found majority support (Gallop, 2015). Given that a large percentage of the U.S. population lives in states that permit some degree of access to THC-containing compounds via either the medical or recreational market, it is important to examine the current policy landscape, which may shape future state and federal regulations of cannabis.

State-Level Changes

State Regulated Use

Cannabis policy change has occurred at the state level in large part due to changing public sentiment. Many states have reformed their cannabis laws not from a deliberative legislative process, but through popular referendums. As discussed earlier, states have passed laws to allow qualifying individual's access to medical cannabis. These laws can be broadly divided into three distinct categories: loose medical, restricted access, and non-THC.

*S*ome of the earliest laws passed—and the laws generally found in most states west of the Mississippi River—are referred to as *loose medical*. In states with these policies, access to medical cannabis is not strictly limited to provable qualifying ailments, such as terminal cancer, HIV/AIDS, or glaucoma. A patient may access medical cannabis when his or her physician deems it necessary, and in some jurisdictions this amounts to little more than de facto legalization of recreational use. One study that surveyed more than 4,000 individuals seeking access to medical cannabis in California concluded that the typical patient was a white male in his early 30s who started using cannabis in his teens with fewer reported disabilities than the national average (O'Connell and Bou-Matar, 2007). Under *restricted access*, patients must meet

certain qualifying criteria (such as a qualifying medical condition) or are restricted to what types of medical products are available, or both. For example, New York prohibits the use of smokable herbal cannabis, allowing only tinctures, oils, concentrates, and other forms of products. *Non-THC* laws permit the use of no-THC or low-THC/high-CBD products, such as CBD oil, to treat a short list of qualifying conditions, such as refractory epilepsy. This category is by far the most restrictive, and states that adopt these non-THC policies generally prohibit the supply and distribution of such products, granting only a legal defense for their use.

That said, 28 states and the District of Columbia fall in one or the other of the first two categories and allow for loose or restricted medical use, where patients may access some form of THC-containing compound. Sixteen states fall in the non-THC category. A total of 44 states and the District of Columbia have amended their laws to allow for some form of medical cannabis (see Figure 3-3) (NCSL, 2016).

Of all the jurisdictions that allow for some sort of access to THC-containing compounds, cancer, HIV/AIDS, multiple sclerosis, and glaucoma are among the most recognized qualifying ailments (NCSL, 2016). And examination of all jurisdictions shows that most list seizures and epileptic seizures within their statutes (NCSL, 2016). However, several states are open in their interpretation, allowing for medical cannabis to be used to treat any illness for which the drug provides relief. Since few states maintain medical cannabis patient registries, the committee relied on data on the percentage of patients reporting certain qualifying illness in Oregon and Colorado (see Figure 3-4). As can be seen in the figure, the overwhelming majority obtained a recommendation on the basis of a claimed need to treat pain.

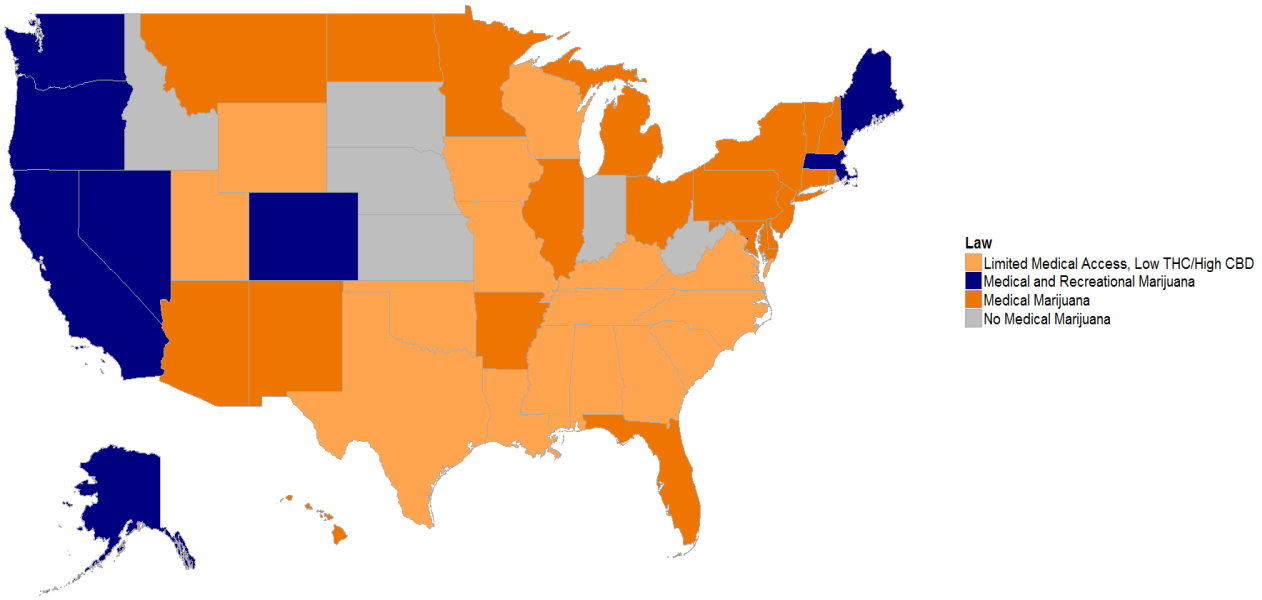

FIGURE 3-3 Cannabis laws by state, November 2016.
SOURCE: Adapted from NCSL, 2016.

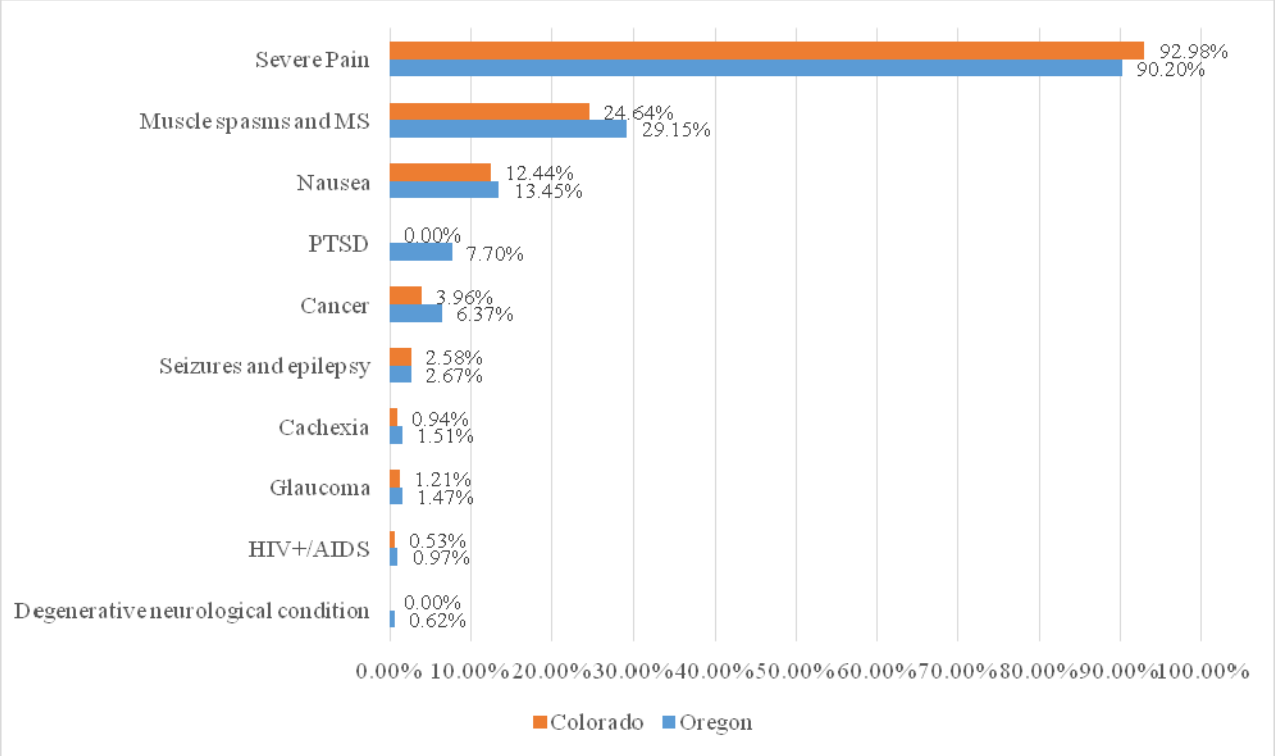

FIGURE 3-4 Number of medical cannabis patients in Colorado and Oregon in July 2016.
NOTE: Patients may report multiple qualifying ailments
SOURCES: Adapted from CDPHE, 2016; OHA, 2016.

State Research on Therapeutic Effects

In addition to state-level legal changes that regulate cannabis for either medical or recreational purposes, a few states have sought to expand research into cannabis's therapeutic effects. The Center for Medicinal Cannabis Research (CMCR) at the University of California was created in 2000 to conduct clinical and pre-clinical studies of cannabinoids, including smoked cannabis, for conditions for which cannabis may be beneficial. With state funding, the CMCR approved 21 federally approved studies: 13 have been completed, and six have been discontinued (CMCR, 2016).

Departing from this, Colorado has started to conduct research into the medicinal value of cannabis that is neither federally funded nor federally approved. In 2014 Colorado passed legislation to promote research into cannabis's medical benefits, creating the Medical Marijuana Scientific Advisory Council and appropriating $9 million in research grants. The advisory council approves research grants and evaluates research. As of early 2015, nine research grants have been approved with six studies currently under way.[9] Also in 2015, NIH provided $111 million in funding for 281 cannabinoid related research efforts nationwide (NIH, 2015).

[9] See the Colorado Department of Public Health and Environment's Medical Marijuana Scientific Advisory Council: https://www.colorado.gov/pacific/cdphe/approved-medical-marijuana-research-grants (accessed January 6, 2017).

EXECUTIVE BRANCH POLICIES

Federal Regulated Use

As discussed earlier, the executive branch of the federal government has extensive influence and impact when it comes to regulating cannabis. Despite the complex domestic arrangements established by the U.S. Constitution and the current political climate, the executive branch has not challenged state-level laws that are in violation with federal drug laws. The Obama Administration has issued a series of federal guidelines for states that are reforming cannabis laws, granting limited space for such policies.

In 2009 the U.S. Department of Justice issued a policy memo declaring that it was not the federal government's intent to prosecute individuals who abide by state medical cannabis laws (Ogden, 2009). That policy was later updated in August 2013 following the legalization of non-medical cannabis in Colorado and Washington. The current policy guidelines outline eight enforcement criteria whereby the federal government may intervene and prosecute an individual or group for violating the Controlled Substances Act (Cole, 2013). Furthermore, the Department of Justice stated that it expects states that have legalized cannabis to implement robust systems of enforcement and regulation to protect public health and safety; however, recent evaluations of the policy guidelines suggest that the Department of Justice has done little to evaluate how states comply with federal priorities (GAO, 2016).

Because cannabis is still federally prohibited, laws that govern other aspects of commerce, namely banking and finance, have prevented businesses that deal in cannabis from accessing lines of credit or banking (McErlean, 2015). Money laundering laws and the CSA prevent many banks from interacting with cannabis businesses. In order to ease this conflict the Department of the Treasury, through the Financial Crimes Enforcement Network (FinCEN), has issued a directive to financial establishments, allowing them to deal with cannabis businesses that comply with state laws (FinCEN, 2014).

Federal Research

Despite ongoing federal funding for cannabinoid research ($111 million in 2015 alone), cannabis researchers have found federal research funds to be restricted and limited. Research proposals were required to undergo a thorough and rigorous assessment by the DEA, NIDA, the U.S. Food and Drug Administration, and U.S. Department of Health and Human Services (HHS). If they were federally approved, researchers were limited in the type and quantity of cannabis available from the University of Mississippi, which was contracted by NIDA to act as the only licit supply of the drug for research (see Chapter 15—Challenges and Barriers to Cannabis Research for additional information). In 2015 the Obama administration, via HHS and the DEA, relaxed some regulatory restrictions, eliminating duplicative reviews of research proposals by the HHS as well as increasing the amount of cannabis available for research by raising the aggregate production quota of cannabis cultivated at University of Mississippi (DEA, 2016).

In August 2016 the DEA denied a petition to reschedule cannabis to Schedule II, citing that cannabis has no currently accepted medical use in treatment in the United States (DEA, 2016). The administration did, however, adopt a new policy to end the NIDA-contracted monopoly of research-grade cannabis by the University of Mississippi. Under new rules, the

DEA will facilitate cannabis research by increasing the number of private entities allowed to cultivate and distribute research-grade cannabis (DEA, 2016).

CONGRESSIONAL BRANCH POLICIES

Recently the 113th Congress used its regulatory powers to shape cannabis policy at both the state and subnational levels. In the Consolidated and Further Continuing Appropriations Act of 2015 (Public Law No. 113-235), lawmakers precluded the U.S. Department of Justice from using fiscal year 2015 appropriated funds to enforce the Controlled Substances Act to prevent states from implementing their own laws that authorize the use, distribution, possession, or cultivation of medical cannabis (Sec 538). In the same piece of legislation, Congress precluded the District of Columbia from using appropriated funds to regulate, legalize, or otherwise reduce penalties for the possession, distribution, or use of any schedule I substance, effectively blocking any citywide effort to regulate the trade in cannabis (Sec 908b) During the same session, Congress authorized the Secretary of Agriculture to promulgate rules to ensure that medical cannabis costs are not treated as a deduction in Supplemental Nutrition Assistance Program (SNAP) benefits as well as allowing universities and state departments of agriculture to cultivate industrial hemp for research purposes (Garvey et al., 2015).

Members of the current 114th Congress have proposed several pieces of legislation on cannabis. Some would remove cannabis from the Controlled Substances Act and treat the drug like alcohol. Others would end the civil asset forfeiture of real property of businesses that comply with state medical cannabis laws or authorize the U.S. Department of Veterans Affairs to offer recommendations regarding veterans' use of cannabis in compliance with state regimes. One bill in particular, the Medical Marijuana Research Act, has gained bipartisan support from proponents and opponents of cannabis reform in Congress. The bill would increase cannabis research by making the drug and plant more accessible to researchers.

PUBLIC OPINION

Public opinion toward cannabis seems to be driving many of the policy changes that have taken place to date. Cannabis found mainstream market appeal in the late 1960s and early 1970s, and, as a result, polling agencies started surveying the public opinion about the drug. In 1969 the Gallup Poll began asking Americans if they thought that the "use of cannabis should be made legal" and the company has continued to ask Americans the same question for nearly 50 years.[10]

Gallop poll responses showed that support for legal cannabis use increased to 28 percent in 1977 (the same year President Carter called for national decriminalization). For about 20 years, support declined and then plateaued at around 24 percent, only to inch upward 4 years after California passed legislation in favor of medical cannabis. By 2000, 31 percent of respondents favored legal use. Over the past 6 years, support has vacillated, but averaged 48 percent from 2010 through 2012 and has averaged 56 percent since 2013. In 2015, 58 percent of respondents favored legal use.

[10] It should be noted that the question is somewhat vague, implying "legalization" but referring to "use" of cannabis, not the legal production and distribution of the drug. This ambiguity may cloud respondents' answers.

Polling shows that the public is overwhelmingly in favor of the use of cannabis for medical purposes if prescribed by a doctor. No other company has tracked public opinion concerning medical cannabis over time in the same way as the Gallup Poll, but a collection of national surveys from ProCon indicate that since 1998, 60 to 85 percent of Americans have been supportive of the use of medical cannabis (ProCon, 2016). In a recent poll by Quinnipiac, 89 percent of respondents supported medical cannabis (Quinnipiac, 2016). However, it is of note that states attribute different medicinal value to different forms of the drug, restricting who can access what part of the plant. National surveys may not capture these distinctions that are made in state-level law or policy. Yet, the general shift over time suggests that the public is welcoming some changes in cannabis policy and law. There appears to be greater agreement that cannabis should be available as a medicine to those with certain qualifying conditions, but it is harder to find similar political agreement on recreational cannabis. It's unclear whether the wording of the Gallup Poll's public opinion question paints an accurate picture of the current and ongoing sentiment with respect to states that are legalizing recreational cannabis.

POLICY AND RESEARCH

The political landscape for the commercialization, decriminalization, and use of cannabis is constantly evolving. As federal and state agencies continue to grapple with these important public policy issues, it is important to consider that each political decision may have significant public health implications.

As laws and policies continue to change, research must also. Unfortunately, research on the health effects and potential therapeutic potential of cannabis use has been limited in this country, despite enormous changes at the state level. As such, there is currently limited research evidence to guide policy. This lack of aggregated knowledge is a significant impediment to not only scientific understanding of cannabis, but also the advancement of public policy and the nation's overall public health.

REFERENCES

Austin, W., and R. W. Ressler. 2016. Who gets arrested for marijuana use? The perils of being poor and black. *Applied Economics Letters* [Epub May 4, 2016], 1–3.

Azofeifa, A., M. E. Mattson, G. Schauer, T. McAfee, A. Grant, and R. Lyerla. 2016. National estimates of marijuana use and related indicators—National Survey on Drug Use and Health, United States, 2002–2014. *Morbidity and Mortality Weekly Report* 65(SS-11):1–25.

Booth, M. 2005. *Cannabis: A history*. New York: St. Martin's Press (Macmillan Publishers).

Burns, R. M., J. P. Caulkins, S. S. Everingham, and B. Kilmer. 2013. Statistics on cannabis users skew perceptions of cannabis use. *Front Psychiatry* 4:138.

Caulkins, J. P., B. Kilmer, M. Kleiman, R. J. MacCoun, G. Midgette, P. Oglesby, R. L. Pacula, and P. H. Reuter. 2015. *Considering marijuana legalization.* http://www.rand.org/content/dam/rand/pubs/research_reports/RR800/RR864/RAND_RR864.pdf (accessed November 22, 2016).

Caulkins, J. P., B. Kilmer, A. Hawken, and M. Kleiman. 2016. *Marijuana legalization: What everyone needs to know*. New York: Oxford University Press.

CBHSQ (Center for Behavioral Health Statistics and Quality). 2014. *National Survey on Drug Use and Health (NSDUH): Summary of Methodological Studies, 1971–2014.* Rockville, MD: Substance Abuse and Mental Health Services Administration.

CBHSQ. 2016a. *Key substance use and mental health indicators in the United States: Results from the 2015 National Survey on Drug Use and Health*. Rockville, MD: Substance Abuse and Mental Health Services Administration. https://www.samhsa.gov/data/sites/default/files/NSDUH-FFR1-2015/NSDUH-FFR1-2015/NSDUH-FFR1-2015.pdf (accessed January 9, 2017).

CBHSQ. 2016b. 2015 *National Survey on Drug Use and Health: Detailed Tables.* Rockville, MD: Substance Abuse and Mental Health Services Administration. https://www.samhsa.gov/data/sites/default/files/NSDUH-DetTabs-2015/NSDUH-DetTabs-2015/NSDUH-DetTabs-2015.pdf (accessed December 27, 2016).

CDPHE (Colorado Department of Public Health and Environment). 2016. *Medical Marijuana Registry Program Statistics, July 31, 2016*. https://www.colorado.gov/pacific/sites/default/files/CHED_MMR_Monthly_Report_Statistics_July_2016.pdf (accessed October 12, 2016).

CMCR (Center for Medical Cannabis Research). 2016. *Research:* Active studies, pending studies, completed studies, discontinued studies. http://www.cmcr.ucsd.edu (accessed December 16, 2016).

Cole, J. M. 2013. *Memorandum for all United States attorneys.* August 29. https://www.justice.gov/iso/opa/resources/3052013829132756857467.pdf (accessed November 10, 2016).

Davenport, S., and J. P. Caulkins. 2016. Evolution of the United States marijuana market in the decade of liberalization before full legalization. *Journal of Drug Issues* 46(4):411–427.

DEA (Drug Enforcement Administration). 2016. *DEA announces actions related to marijuana and industrial hemp.* https://www.dea.gov/divisions/hq/2016/hq081116.shtml (accessed November 10, 2016).

FinCEN (Financial Crimes Enforcement Network). 2014. *BSA expectations regarding marijuana-related businesses.* February 14. https://www.fincen.gov/sites/default/files/shared/FIN-2014-G001.pdf (accessed November 10, 2016).

Gallop (Gallop Tracking Poll). 2015. *In U.S., 58% back legal marijuana use*. http://www.gallup.com/poll/186260/back-legal-marijuana.aspx (accessed December 17, 2016).

GAO (U.S. Government Accountability Office). 2016. *State marijuana legalization: DOJ should document its approach to monitoring the effects of legalization*. February 1. GAO-16-1. http://www.gao.gov/products/GAO-16-1 (accessed November 10, 2016).

Garvey, T., and B. T. Yeh. 2014. *State legalization of recreational marijuana: Selected legal issues.* Congressional Research Service, January 13. https://fas.org/sgp/crs/misc/R43034.pdf (accessed November 10, 2016).

Garvey, T., C. Doyle, and D. H. Carpenter. 2015. *Marijuana: Medical and retail—Selected legal issues.* Congressional Research Service, April 8. https://fas.org/sgp/crs/misc/R43435.pdf (accessed November 10, 2016).

ICPSR. 2016. *Monitoring the Future (MTF) Series.* https://www.icpsr.umich.edu/icpsrweb/ICPSR/series/35 (accessed January 9, 2017).

Johnston, L. D., P. M. O'Malley, R. A. Miech, J. G. Bachman, and J. E. Schulenberg. 2016. *Monitoring the Future: National survey results on drug use, 1975–2015: Overview: key findings on adolescent drug use.* Ann Arbor, MI: Institute for Social Research, University of Michigan.

McErlean, E. D. 2015. The real green issue regarding recreational marijuana: Federal tax and banking laws in need of reform. *DePaul Law Review* 64(4):1079–1118.

Musto, David F. 1999. *The American disease: Origins of narcotic control*. New York: Oxford University Press.

NCSL (National Conference of State Legislatures). 2016. State medical marijuana laws. November 9. http://www.ncsl.org/research/health/state-medical-marijuana-laws.aspx (accessed November 10, 2016).

NIH (National Institutes of Health). 2016. NIH Research on Marijuana and Cannabinoids. https://www.drugabuse.gov/drugs-abuse/marijuana/nih-research-marijuana-cannabinoids (accessed December 16, 2016).

O'Connell, T. J., and C. B. Bou-Matar. 2007. Long term marijuana users seeking medical cannabis in California (2001–2007): Demographics, social characteristics, patterns of cannabis and other drug use of 4,117 applicants. *Harm Reduction Journal* 4(1):16.

Ogden, D. 2009. Memorandum for selected United States attorneys on investigations and prosecutions in states authorizing the medical use of marijuana. October 19. https://www.justice.gov/opa/blog/memorandum-selected-united-state-attorneys-investigations-and-prosecutions-states (accessed November 10, 2016).

Oglesby, P. 2015. *Supplemental thoughts about revenue from marijuana in Vermont* (January 16, 2015). https://ssrn.com/abstract=2551029 or http://dx.doi.org/10.2139/ssrn.2551029 (accessed December 16, 2016).

OHA (Oregon Health Authority). 2016. *Oregon Medical Marijuana Program Statistical Snapshot July, 2016*. https://public.health.oregon.gov/DiseasesConditions/ChronicDisease/MedicalMarijuanaProgram/Documents/OMMP-Statistical-Snapshot%20-07-2016.pdf (accessed October 12, 2016).

Pacula, R L, R. MacCoun, P. Reuter, J. Chriqui, B. Kilmer, K. Harris, L. Paoli, and C. Schäfer. 2005. What does it mean to decriminalize marijuana? A cross-national empirical examination. *Advances in Health Economics and Health Services Research* 16:347–369.

Pardo, B. 2014. Cannabis policy reforms in the Americas: A comparative analysis of Colorado, Washington, and Uruguay. *International Journal of Drug Policy* 25(4):727–735.

ProCon (ProCon.org). 2016. *Votes and polls, national*. http://medicalmarijuana.procon.org/view.additional-resource.php?resourceID=000151 (accessed December 10, 2016).

Quinnipiac (Quinnipiac University Poll. 2016. *Allow marijuana for vets with PTSD, U.S. voters say 10-1, Quinnipiac University national poll finds; slim majority says legalize marijuana in general.* https://poll.qu.edu/national/release-detail?ReleaseID=2354 (accessed December 16, 2016).

Schauer, G. L., B. A. King, R. E. Bunnell, G. Promoff, and T. A. McAfee. 2016. Toking, vaping, and eating for health or fun: Marijuana use patterns. *American Journal of Preventive Medicine* 50(1):1–8.

Sevigny, E. L., R. L. Pacula, R. L., and P. Heaton. 2014. The effects of medical marijuana laws on potency. *International Journal on Drug Policy* 25(2):308–319. http://doi.org/10.1016/j.drugpo.2014.01.003 (accessed November 10, 2016).

Shafer Commission. 1972. *Marijuana: Signal of misunderstanding*. First Report of the National Commission on Marijuana and Drug Abuse. Washington, DC: U.S. Government Printing Office.

UNODC (United Nations Office on Drugs and Crime). 2016. *World Drug Report 2016*. United Nations publication, Sales No. E.16.XI.7.

Part II
Therapeutic Effects

4
Therapeutic Effects of Cannabis and Cannabinoids

Chapter Highlights
• In adults with chemotherapy induced nausea and vomiting, oral cannabinoids are effective antiemetics. • In adults with chronic pain, patients who were treated with cannabis or cannabinoids are more likely to experience a clinically significant reduction in pain symptoms • In adults with multiple sclerosis (MS) related spasticity, short-term use of oral cannabinoids improves patient-reported spasticity symptoms. • For these conditions the effects of cannabinoids are modest; for all other conditions evaluated there is inadequate information to assess their effects.

Cannabis sativa has a long history as a medicinal plant dating back likely over two millennia (Russo et al., 2007). It was available as a licensed medicine in the United States for about a century before the American Medical Association removed it from the 12th edition of the U.S. Pharmacopeia (IOM, 1999). In 1985, pharmaceutical companies received approval to begin developing Δ-9-tetrahydrocannabinol preparations—dronabinol and nabilone—for therapeutic use, and as a result, cannabinoids were reintroduced into the armamentarium of willing healthcare providers (Grotenhermen and Müller-Vahl, 2012). Efforts are now being put into the trials of cannabidiol as a treatment for conditions such as epilepsy and schizophrenia,[1] although no such preparations have come to market at this time. Nabiximols, an oromucosal spray of a whole cannabis plant extract with a 1:1 ratio of tetrahydrocannabinol to cannabidiol, was initially licensed and approved in Europe, the United Kingdom, and Canada for the treatment of pain and spasticity associated with multiple sclerosis (GW Pharmaceuticals, 2016; Pertwee, 2012), but it continues to undergo evaluation in Phase III clinical trials in the United States.[2] Efforts are under way to develop targeted pharmaceuticals that are agonists or antagonists of the cannabinoid receptors or that modulate the production and degradation of the endocannabinoids, although such interventions have not yet demonstrated safety or effectiveness. Nonetheless, therapeutic agents targeting cannabinoid receptors and endocannabinoids are expected to become available in the future.

The renewed interest into the therapeutic effects of cannabis emanates from the movement that began 20 years ago to make cannabis available as a medicine to patients with a variety of conditions. It was in 1996 that Arizona and California first passed medicinal cannabis legislation, although Arizona later rescinded the approval, so it would be California that paved the way. At the time that this report was written, in 2016, 28 states and the District of Columbia

[1] Clinicaltrials.gov: NCT02447198, NCT02926859.
[2] Clinicaltrials.gov: NCT01361607.

had legalized the medical use of cannabis; eight states had legalized both medical and recreational use of cannabis; and another 16 states had allowed limited access to low-tetrahydrocannabinol (THC)/high-cannabidiol (CBD) products (i.e., products with low levels of THC and high levels of CBD) (NCSL, 2016). A recent national survey showed that among current adult users, 10.5 percent reported using cannabis solely for medical purposes, and 46.6 percent reported a mixed medical/recreational use (Schauer et al., 2016). Of the states that allow for some access to cannabis compounds, cancer, HIV/AIDS, multiple sclerosis, glaucoma, seizures/epilepsy, and pain are among the most recognized qualifying ailments (Belendiuk et al., 2015; NCSL, 2016) There are certain states that provide more flexibility than others and that allow the use of medical cannabis for the treatment of any illness for which the drug provides relief for the individual. Given the steady liberalization of cannabis laws, the numbers of these states are likely to increase and therefore support the efforts to clarify the potential therapeutic benefits of medical cannabis on various health outcomes.

For example, the most common conditions for which medical cannabis is used in Colorado and Oregon are pain, spasticity associated with multiple sclerosis, nausea, posttraumatic stress disorder, cancer, epilepsy, cachexia, glaucoma, HIV/AIDS, and degenerative neurological conditions (CDPHE, 2016; OHA, 2016). We added to these conditions of interest by examining lists of qualifying ailments in states where such use is legal under state law. The resulting therapeutic uses covered by this chapter are: chronic pain, chemotherapy-induced nausea and vomiting, anorexia and weight loss associated with HIV, cancer, irritable bowel syndrome, epilepsy, spasticity, Tourette syndrome, Alzheimer's disease, amyotrophic lateral sclerosis, Huntington's disease, Parkinson's disease, dementia, traumatic brain injury, glaucoma, addiction, anxiety, depression, sleep disorders, posttraumatic stress disorder, and schizophrenia and other psychoses. The committee is aware that there may be other conditions for which there is evidence of efficacy for cannabis or cannabinoids. In this chapter, the committee will discuss the findings from 16 of the most recent, good- to fair-quality systematic reviews and 21 primary literature articles that best address the committee's research questions of interest.

As a reminder to the reader, several of the prioritized health endpoints discussed here in Part III are also reviewed in chapters of Part II; however, the research conclusions within these chapters may differ. This is, in part, due to differences in the study design of the evidence reviewed (e.g., randomized controlled trials [RCTs] versus epidemiological studies), differences in the characteristics of cannabis or cannabinoid exposure (e.g., form, dose, frequency of use), and the populations studied. As such, it is important that the reader is aware that this report was not designed to reconcile the proposed harms and benefits of cannabis or cannabinoid use across chapters.

CHRONIC PAIN

Relief from chronic pain is by far the most common condition cited by patients for the medical use of cannabis. For example, Light et al. (2014) reported that 94 percent of Colorado medical marijuana ID cardholders indicated "severe pain" as a medical condition. Likewise, Ilgen et al. (2013) reported that 87 percent of participants in their study were seeking medical marijuana for pain relief. In addition, there is evidence that some individuals are replacing the use of conventional pain medications (e.g., opiates) with cannabis. For example, one recent study reported survey data from patrons of a Michigan medical marijuana dispensary suggesting

that medical cannabis use in pain patients was associated with a 64 percent reduction in opioid use (Boehnke et al., 2016). Similarly, recent analyses of prescription data from Medicare part D enrollees in states with medical access to cannabis suggest a significant reduction in the prescription of conventional pain medications (Bradford and Bradford, 2016). Combined with the survey data suggesting that pain is one of the primary reasons for the use of medical cannabis, these recent reports suggest that a number of pain patients are replacing the use of opioidswith cannabis, despite the fact that cannabis has not been approved by the U.S. Food and Drug Administration (FDA) for chronic pain.

Are Cannabis or Cannabinoids an Effective Treatment for the Reduction of Chronic Pain?

Systematic Reviews

Five good- to fair-quality systematic reviews were identified. Of those five reviews, Whiting et al. (2015) was the most comprehensive, both in terms of the target medical conditions and in terms of the cannabinoids tested. Snedecor et al. (2013) was narrowly focused on pain related to spinal cord injury, did not include any studies that used cannabis, and only identified one study investigating cannabinoids (dronabinol). Two reviews on pain related to rheumatoid arthritis did not contribute unique studies or findings (Fitzcharles et al., 2016; Richards et al., 2012). Finally, one review (Andreae et al., 2015) conducted a Bayesian analysis of five primary studies of peripheral neuropathy that had tested the efficacy of cannabis in flower form administered via inhalation. Two of the primary studies in that review were also included in the Whiting review, while the other three were not. It is worth noting that the conclusions across all of the reviews were largely consistent in suggesting that cannabinoids demonstrate a modest effect on pain. For the purposes of this discussion, the primary source of information for the effect on cannabinoids on chronic pain was the review by Whiting et al. (2015). Whiting et al included RCTs that compared cannabinoids to usual care, placebo or no treatment 10 conditions. Where RCTs were unavailable for a condition or outcome, nonrandomized studies including uncontrolled studies were considered. This information was supplemented by a search of the primary literature from April 2015 to August 2016 as well as by additional context from Andreae et al. (2015) that was specific to the effects of inhaled cannabinoids.

The rigorous screening approach used by Whiting et al. (2015) led to the identification of 28 randomized trials in patients with chronic pain (2,454 participants). Twenty-two of these trials evaluated plant-derived cannabinoids (nabiximols, 13 trials; plant flower that was smoked or vaporized, 5 trials; THC oramucosal spray, 3 trials; and oral THC, 1 trial) while five trials evaluated synthetic THC (i.e., nabilone). All but one of the selected primary trials used a placebo control, while the remaining trial used an active comparator (amitriptyline). The medical condition underlying the chronic pain was most often related to a neuropathy (17 trials); other conditions included cancer pain, multiple sclerosis, rheumatoid arthritis, musculoskeletal issues, and chemotherapy-induced pain. Analyses across seven trials that evaluated nabiximols and one that evaluated the effects of inhaled cannabis suggested that plant-derived cannabinoids increase the odds for improvement of pain by approximately 40 percent versus the control condition (odds ratio [OR] 1.41, 95% confidence interval [CI] = 0.99–2.00; 8 trials). The effects did not differ significantly across pain conditions, although it was not clear that there was adequate statistical power to test for such differences.

Only one trial (n = 50) that examined inhaled cannabis was included in the effect size estimates from Whiting et al. (2015). This study (Abrams et al., 2007) also indicated that cannabis reduced pain versus a placebo (OR 3.43, 95% CI = 1.03–11.48). It is worth noting that the effect size for inhaled cannabis is consistent with a separate recent review of five trials of the effect of inhaled cannabis on neuropathic pain (Andreae et al., 2015). The pooled odds ratios (ORs) from these trials contributed to the Bayesian pooled effect estimate of 3.22 for pain relief versus placebo (95% CI = 1.59–7.24) tested across 9 THC concentrations. There was also some evidence of a dose-dependent effect in these studies.

Primary Literature

In the addition to the reviews by Whiting et al. (2015) and Andreae et al. (2015), the committee identified two additional studies on the effect of cannabis flower on acute pain (Wallace et al., 2015; Wilsey et al., 2016). One of those studies found a dose-dependent effect of vaporized cannabis flower on spontaneous pain, with the high dose (7 percent THC) showing the strongest effect size (Wallace et al., 2015). The other study found that vaporized cannabis flower reduced pain but did not find a significant dose-dependent effect (Wilsey et al., 2016). These two studies are consistent with the previous reviews by Whiting et al. (2015) and Andreae et al. (2015), suggesting a reduction in pain after cannabis administration.

Discussion of Findings

The majority of studies on pain cited in Whiting et al. (2015) evaluated nabiximols outside the United States. In their review, the committee found that only a handful of studies have evaluated the use of cannabis in the United States and all of them evaluated cannabis in flower form provided by the National Institute on Drug Abuse that was either vaporized or smoked. In contrast, many of the cannabis products that are sold in state regulated markets bear little resemblance to the products that are available for research at the federal level in the United States. For example, in 2015 between 498,170 and 721,599 units of medical and recreational cannabis edibles were sold per month in Colorado (Colorado DOR, 2016, p. 12). Pain patients also use topical forms (e.g., transdermal patches and creams). Thus, while the use of cannabis for the treatment of pain is supported by well-controlled clinical trials as reviewed above, very little is known about the efficacy, dose, routes of administration, or side effects of commonly used and commercially available cannabis products in the United States. Given the ubiquitous availability of cannabis products in much of the nation, more research is needed on the various forms, routes of administration, and combination of cannabinoids.

CONCLUSION 4-1 There is substantial evidence that cannabis is an effective treatment for chronic pain in adults.

CANCER

Cancer is a broad term used to describe a wide-range of related diseases that are characterized by an abnormal, unregulated division of cells; it is a biological disorder that often results in tumor growth (NCI, 2015). Cancer is among the leading causes of mortality in the

United States, and by the close of 2016 there will be an estimated 1.7 million new cancer diagnoses (NCI, 2016). Relevant to the committee's interest, there is evidence to suggest that cannabinoids (and the endocannabinoid system more generally) may play a role in the cancer regulation processes (Rocha et al., 2014). Therefore, there is interest in determining the efficacy of cannabis or cannabinoids for the treatment of cancer.

Are Cannabis or Cannabinoids an Effective Treatment for Cancer?

Systematic Reviews

Using the committee's search strategy only one recent review was found to be of good- to fair-quality (Rocha et al., 2014).[3] The review focused exclusively on the anti-tumor effects of cannabinoids on gliomas.[4] Of the 2,260 studies identified through December 2012, 35 studies met the inclusion criteria. With the exception of a small clinical trial, these studies were all pre-clinical studies. All 16 of the in-vivo studies found an anti-tumor effect of cannabinoids.

Primary Literature

The committee did not identify any good-quality primary literature that reported on cannabis or cannabinoids for the treatment for cancer that were published subsequent to the data collection period of the most recently published good- or fair-quality systematic review addressing the research question.

Discussion of Findings

Clearly, there is insufficient evidence to make any statement about the efficacy of cannabinoids as a treatment for glioma. However, the signal from the pre-clinical literature suggests that clinical research with cannabinoids needs to be conducted.

CONCLUSION 4-2 There is insufficient evidence to support or refute the conclusion that cannabinoids are an effective treatment for cancers, including glioma.

CHEMOTHERAPY-INDUCED NAUSEA AND VOMITING

Nausea and vomiting are common side effects of many cytotoxic chemotherapy agents. A number of pharmaceutical interventions in various drug classes have been approved for the treatment of chemotherapy-induced nausea and vomiting. Among the cannabinoid medications, nabilone and dronabinol were initially approved in 1985 for nausea and vomiting associated with cancer chemotherapy in patients who failed to respond adequately to conventional antiemetic treatments (Todaro, 2012, pp. 488, 490).

[3] Due to the lack of recent, high-quality reviews, the committee has identified a research gap exists concerning the effectiveness of cannabis or cannabinoids in treating cancer in general.

[4] Glioma is a type of tumor that originates in the central nervous system (i.e., the brain or spine) and arises from glial cells.

Are Cannabis or Cannabinoids an Effective Treatment for the Reduction of Chemotherapy-Induced Nausea and Vomiting?

Systematic Reviews

Whiting et al. (2015) summarized 28 trials reporting on nausea and vomiting due to chemotherapy, most published before 1984, involving 1,772 participants. The cannabinoid therapies investigated in these trials included nabilone (14), tetrahydrocannabinol (6), levonantradol (4), dronabinol (3) and nabiximols (1). Eight studies were placebo controlled, and 20 included active comparators (prochlorperazine 15; chlorpromazine 2; dromperidone 2; and alizapride, hydroxyzine, metoclopramide, and ondansetron, 1 each). Two studies evaluated combinations of dronabinol with prochlorperazine or ondansetron. The average number of patients showing a complete nausea and vomiting response was greater with cannabinoids than placebo (OR 3.82, 95% CI = 1.55–9.42) in three trials of dronabinol and nabiximols that were considered low quality evidence. Whiting concluded that all trials suggested a greater benefit for cannabinoids than for both active agents and for placebo, although these did not reach statistical significance in all trials.

Of the 23 trials summarized in a Cochrane review (Smith et al., 2015), 19 were crossover design and 4 were parallel-group design. The cannabinoids investigated were nabilone (12) or dronabinol (11), with 9 placebo-controlled trials (819 participants) and 15 with active comparators (prochlorperazine, 11; metoclopramide, 2; chlorpromazine, 1; domperidone, 1). In two trials, a cannabinoid added to a standard anti-emetic was compared to the standard alone. While two of the placebo-controlled trials showed no significant difference in those reporting absence of nausea with cannabinoids (relative risk [RR] 2.0, 95% CI = 0.19–21), three showed a greater chance of having complete absence of vomiting with cannabinoids (RR 5.7, 95% CI = 2.16–13) and three showed a numerically higher chance of complete absence of both nausea and vomiting (RR 2.9, 95% CI = 1.8–4.7). There was no difference in outcome between patients who were cannabis-naïve and those that were not (P value = 0.4). Two trials found a patient preference for cannabinoids over the comparator. When compared to prochlorperazine, there was no significant difference in the control of nausea, vomiting, or both, although in seven of the trials there was a higher chance of patients reporting a preference for the cannabinoid therapy (RR 3.2, 95% CI = 2.2–4.7). In their review the investigators state that cannabinoids were highly effective, being more efficacious than placebo and similar to conventional antiemetics in treating chemotherapy-induced nausea and vomiting. Despite causing more adverse events such as dizziness, dysphoria, euphoria, "feeling high," and sedation, there was weak evidence for a preference for cannabinoids over placebo and stronger evidence for a preference over other anti-emetics. However despite these findings, the authors concluded that there was no evidence to support the use of cannabinoids over current first-line antiemetic therapies and that cannabinoids should be considered as useful adjunctive treatment "for people on moderately or highly emetogenic chemotherapy that are refractory to other anti-emetic treatments, when all other options have been tried" (Smith et al., 2015, p. 23).

Only 3 of the 28 trials in a systematic review of antiemetic therapies in children receiving chemotherapy involved cannabinoid therapies (nabilone 2; THC 1) (Phillips et al., 2016). The comparators were prochlorperazine in the first nabilone trial, domperidone in the second, and prochlorperazine and metoclopramide in two separate randomizations in the THC trial. In one trial with unclear risk of bias, THC dosed at 10 mg/m^2 five times on the day of chemotherapy

was superior to prochlorperazine in the complete control of acute nausea (RR, 20.7; 95% CI = 17.2–36.2) and vomiting (RR 19.0, 95% CI = 13.7–26.3). Another trial reported better nausea severity scores for nabilone compared to domperidone (1.5 versus 2.5 on a 0 to 3 [none to worst] scale) ($p = 0.01$). The largest and most recent trial in this review compared THC to proclorperzine and found no benefit over the control on emesis (RR 1.0, 95% CI = 0.85–1.17).

Primary Literature

An additional search of the primary literature since the review by Whiting et al. (2015) did not identify any additional studies. The primary literature was then searched in an effort to find studies of cannabinoids compared to the more widely used anti-emetics. One trial conducted in 2007 investigated a cannabinoid therapy compared to the current generation of serotonin antagonist anti-emetics, as opposed to the dopamine D2 receptor antagonists used in the earlier trials. This 64-patient study evaluated the frequently used anti-emetic ondansetron versus dronabinol versus the combination of the two in delayed chemotherapy-induced nausea and vomiting (Meiri et al., 2007). The two agents appeared similar in their effectiveness, with no added benefit from the combination. Hence, the cannabinoid again fared as well as the current standard anti-emetic in this more recent investigation.

Discussion of Findings

The oral THC preparations nabilone and dronabinol have been available for the treatment of chemotherapy-induced nausea and vomiting for more than 30 years (Grotenhermen and Müller-Vahl, 2012). They were both found to be superior to placebo and equivalent to the available antiemetics at the time that the original trials were conducted. A more recent investigation suggests that dronabinol is equivalent to ondansetron for delayed nausea and vomiting, although no comparison to the currently more widely used neurokinin-1 inhibitors has been conducted. In the earlier trials, patients reported a preference for the cannabinoids over available agents. Despite an abundance of anecdotal reports of the benefits of plant cannabis, either inhaled or ingested orally, as an effective treatment for chemotherapy-induced nausea and vomiting, there are no good-quality randomized trials investigating this option. This is in part due to the existing obstacles to investigating the potential therapeutic benefit of the cannabis plant. Nor have any of the reviewed trials investigated the effectiveness of cannabidiol or cannabidiol-enriched cannabis in chemotherapy-induced nausea and vomiting. Such information is frequently requested by patients seeking to control chemotherapy-induced nausea and vomiting without the psychoactive effects of the THC-based preparations. This is an identified gap in the research evidence, and would benefit as a future research priority.

CONCLUSION 4-3 There is conclusive evidence that oral cannabinoids are effective anti-emetics in the treatment of chemotherapy-induced nausea and vomiting.

ANOREXIA AND WEIGHT LOSS

Anorexia and weight loss are common side effects of many diseases, especially cancer. And prior to the availability of highly active antiretroviral therapy, a wasting syndrome was a

frequent clinical manifestation in patients with human immunodeficiency virus (HIV) infection and advanced acquired immune deficiency syndrome (AIDS). The labeled indications for dronabinol were expanded in 1992 to include treatment of anorexia associated with weight loss in patients with AIDS (IOM, 1999, p. 156).

Are Cannabis or Cannabinoids an Effective Treatment for Anorexia and Weight Loss Associated with HIV/AIDS, Cancer-Associated Anorexia-Cachexia Syndrome, and Anorexia Nervosa?

AIDS Wasting Syndrome

Systematic Reviews Two good-quality systematic reviews included trials investigating cannabinoid therapies in patients with HIV/AIDS. Four randomized controlled trials involving 255 patients were assessed by Whiting et al. (2015) who described all of the trials to be at high risk of bias (ROB) for reasons not elaborated.[5] All four studies included dronabinol, with one investigating inhaled cannabis as well. Three trials were placebo-controlled, and one used the progestational agent, megestrol acetate, as the comparator. The review authors concluded that there was some evidence suggesting that cannabinoids were effective in weight gain in HIV. A second systematic review focused on morbidity and mortality in HIV/AIDS as the primary outcomes, with changes in appetite and weight as secondary endpoints (Lutge et al., 2013). Seven RCTs conducted between 1993 and 2009 were included in the qualitative analysis. The trials compared dronabinol or inhaled cannabis with a placebo or with each other. In one study the individuals' weights increased significantly more ($p < 0.01$) on higher doses of cannabis (3.9 percent THC) and dronabinol (10 mg) than on lower doses. In a second trial, median weight was increased with inhaled cannabis (3.5 percent) by 3.0 kg ($p = 0.021$) and dronabinol (2.5 mg) by 3.2 kg ($p = 0.004$) when compared with a placebo (a 1.1-kg increase over a 21-day exposure). In a study with 88 evaluable patients, the dronabinol group gained an average of 0.1 kg, while the placebo recipients lost a mean of 0.4 kg ($p = 0.14$). The proportion of patients gaining at least 2 kg was the same in both groups. Most of the weight gain was in the body fat compartment when this was investigated. Changes in appetite, food, and caloric intake were not deemed to be evaluable in any of the studies. These investigators concluded that the evidence for the efficacy and safety of cannabis and cannabinoids is lacking to support utility in treating AIDS-associated anorexia.

Primary Literature The committee did not identify any good-quality primary literature that reported on cannabis or cannabinoids as effective treatments for AIDS wasting syndrome that were published subsequently to the data collection period of the most recently published good- or fair-quality systematic review addressing the research question. This is largely due to the virtual disappearance of the syndrome since effective antiretroviral therapies became available in the mid1990's.

[5] Key issues that led to high ROB ratings were: high (n = 1) or unclear (n = 3) ROB for allocation concealment; unclear ROB (n = 3) for blinded outcome assessments; high (n = 1) or unclear (n = 1) ROB for randomization.

Cancer-Associated Anorexia/Cachexia Syndrome

Systematic Reviews The committee did not identify a good- or fair-quality systematic review that reported on cannabis or cannabinoids as effective treatments for cancer-associated anorexia-cachexia syndrome.

Primary Literature A Phase III multi-center, randomized, double-blind, placebo-controlled trial was conducted by the Cannabis-In-Cachexia-Study-Group in patients with cancer-related anorexia/cachexia syndrome (Strasser et al., 2006). Patients with advanced cancer and weight loss of greater than 5 percent over 6 months were randomized 2:2:1 to receive treatment with a cannabis extract (standardized to THC 2.5 mg and cannabidiol 1.0 mg), THC 2.5 mg, or a placebo twice daily for 6 weeks. Appetite, mood, and nausea were monitored daily. Cancer-related quality of life and cannabinoid-related toxicity were also monitored. Only 164 of the 243 patients who were randomized completed the trial. An intent-to-treat analysis yielded no difference between the groups in appetite, quality of life, or toxicity. Increased appetite was reported by 73 percent of the cannabis-extract, 58 percent of the THC group, and 69 percent of the placebo recipients. Recruitment was terminated early by the data review board because it was believed to be unlikely that differences would emerge between the treatment arms. The findings in this study reinforce the results from an earlier trial investigating dronabinol, megestrol acetate or the combination in 469 advanced cancer patients with a loss of appetite and greater than 5 pounds weight loss over the prior 2 months (Jatoi et al., 2002). Megestrol acetate was superior to dronabinol for the improvement of both appetite and weight, with the combination therapy conferring no additional benefit. Seventy-five percent of the megestrol recipients reported an improvement in appetite compared to 49 percent of those receiving dronabinol ($p = 0.0001$). Of those in the combination arm, 66 percent reported improvement. A weight gain greater than or equal to 10 percent over their baseline at some point during the course of the trial was reported by 11 percent of those in the megestrol arm, compared with 3 percent of the dronabinol recipients ($p = 0.02$). The combination arm reported a weight gain in 8 percent. These findings confirm a similarly designed trial that was conducted in patients with AIDS wasting syndrome (Timpone et al., 1997).

Anorexia Nervosa

Systematic Reviews The committee did not identify a good- or fair-quality systematic review that reported on medical cannabis as an effective treatment for anorexia and nervosa.

Primary Literature Pharmacological interventions in the treatment of anorexia nervosa have not been promising to date. Andries et al. (2014) conducted a prospective, randomized, double-blind, controlled crossover trial in 24 women with anorexia nervosa of at least 5 years duration attending both psychiatric and somatic therapy as inpatients or outpatients. In addition to their standard psychotherapy and nutritional interventions, the participants received dronabinol 2.5 mg twice daily for 4 weeks and a matching placebo for 4 weeks, randomly assigned to two treatment sequences (dronabinol/placebo or placebo/dronabinol). The primary outcome was weight change assessed weekly. The secondary outcome was change in Eating Disorder Inventory-2 (EDI-2) scores. The participants had a significant weight gain of 1.00 kg (95% CI = 0.40–1.62) during dronabinol therapy and 0.34 kg (95% CI = −0.14–0.82) during placebo ($p = 0.03$). No

statistically different differences in EDI-2 score changes were seen during treatment with dronabinol or placebo, suggesting that there was no real effect on the participants' attitudinal and behavioral traits related to eating disorders. The authors acknowledged the small sample size and the short duration of exposure, as well as the potential psychogenic effects, but concluded that low-dose dronabinol is a safe adjuvant palliative therapy in a highly selected subgroup of chronically undernourished women with anorexia nervosa.

Discussion of Findings

There is some evidence for oral cannabinoids being able to increase weight in patients with the HIV-associated wasting syndrome and anorexia nervosa. No benefit has been demonstrated in cancer-related anorexia/cachexia syndrome. The studies have generally been small and of short duration and may not have investigated the optimal dose of the cannabinoid. In one study in HIV patients, both dronabinol and inhaled cannabis increased weight significantly compared to the placebo dronabinol. Cannabis has long been felt to have an orexigenic effect, increasing food intake (Abel, 1975). Small residential studies conducted in the 1980's found that inhaled cannabis increased caloric intake by 40 percent, with most of the increase occurring as snacks and not during meals (Foltin et al., 1988). Hence the results of the clinical trials in AIDS wasting and cancer-related anorexia-cachexia syndrome demonstrating little to no impact on appetite and weight were somewhat unexpected. One could postulate that perhaps other components of the plant in addition to THC may contribute to the effect of cannabis on appetite and food intake. There have not been any randomized controlled trials conducted studying the effect of plant-derived cannabis on appetite and weight with weight as the primary endpoint. This is in part due to existing obstacles to investigating the potential therapeutic benefit of the cannabis plant.

CONCLUSION 4-4

4-4(a) There is limited evidence that cannabis and oral cannabinoids are effective in increasing appetite and decreasing weight loss associated with HIV/AIDS.

4-4(b) There is insufficient evidence to support or refute the conclusion that cannabinoids are an effective treatment for cancer-associated anorexia cachexia syndrome and anorexia nervosa.

IRRITABLE BOWEL SYNDROME

Irritable bowel syndrome (IBS) is a common gastrointestinal disorder commonly associated with symptoms of abdominal cramping and changes in bowel movement patterns. Irritable bowel syndrome is classified into four types based on the types of bowel movements: IBS with diarrhea, IBS with constipation, IBS mixed, and IBS unclassified (NIDDK, 2015). Approximately 11 percent of the world's population suffers from at least one type of this disorder (Canavan et al., 2014).

Cannabinoid type 1 (CB1) receptors are present in the mucosa and neuromuscular layers of the colon and are also expressed in plasma cells and influence mucosal inflammation (Wright et al., 2005). In animal models, endocannabinoids acting on CB1 receptors inhibit gastric and small intestinal transit and colonic propulsion (Pinto et al., 2002). Studies in healthy volunteers have shown effects on gastric motility and colonic motility (Esfandyari et al., 2006). Thus, cannabinoids have the potential for therapeutic effect in patients with IBS (Wong et al., 2012).

Are Cannabis or Cannabinoids an Effective Treatment for the Symptoms of Irritable Bowel Syndrome?

Systematic Reviews

The committee did not identify a good- or fair-quality systematic review that reported on medical cannabis as an effective treatment for symptoms of irritable bowel syndrome.

Primary Literature

We identified a single relevant trial (Wong et al., 2012) evaluating dronabinol in patients with irritable bowel syndrome with diarrhea (IBS-D). This low-risk-of-bias trial enrolled 36 patients between the ages of 18 and 69 with IBS-D. Patients were randomized to dronabinol 2.5 mg BID[6] (n = 10), dronabinol 5 mg BID (n = 13), or placebo (n = 13) for 2 days. No overall treatment effects of dronabinol on gastric, small bowel, or colonic transit, as measured by radioscintigraphy, were detected.

Discussion of Findings

A single, small trial found no effect of two doses of dronabinol on gastrointestinal transit. The quality of evidence for the finding of no effect for irritable bowel syndrome is insufficient based on the short treatment duration, small sample size, short-term follow-up, and lack of patient-reported outcomes. Trials that evaluate the effects of cannabinoids on patient-reported outcomes are needed to further understand the clinical effects in patients with IBS.

CONCLUSION 4-5 There is insufficient evidence to support or refute the conclusion that dronabinol is an effective treatment for the symptoms of irritable bowel syndrome.

EPILEPSY

Epilepsy refers to a spectrum of chronic neurological disorders in which clusters of neurons in the brain sometimes signal abnormally and cause seizures (NINDS, 2016b). Epilepsy disorder affects an estimated 2.75 million Americans, across all age ranges and ethnicities (NINDS, 2016b). Although there are many anti-epileptic medications currently on the market, about one-third of persons with epilepsy will continue to have seizures even when treated

[6] BID is an abbreviation for the Latin phrase “bis in die” which means twice per day.

(Mohanraj and Brodie, 2006). Both THC and CBD can present seizures in animal models (Devinsky et al., 2014).

Are Cannabis or Cannabinoids an Effective Treatment for the Symptoms of Epilepsy?

Systematic Reviews

We identified two systematic reviews of randomized trials assessing the efficacy of cannabis or cannabinoids, used either as monotherapy or in addition to other therapies, in reducing seizure frequency in persons with epilepsy. Gloss and Vickrey (2014) published a systematic review of randomized controlled trials. They identified four reports (including one conference abstract and one letter to the editor) of cannabinoid trials, all of which they considered to be of low quality. Combined, the trials included a total of 48 patients. The systematic review's primary pre-specified outcome was freedom from seizures for either 12 months or three times the longest previous seizure-free interval. None of the four trials assessed this endpoint. Accordingly, Gloss and Vickrey asserted that no reliable conclusions could be drawn regarding the efficacy of cannabinoids for epilepsy.

Koppel et al. (2014) published a fair-quality systematic review. They identified no high-quality randomized trials, and concluded that the existing data were insufficient to support or refute the efficacy of cannabinoids for reducing seizure frequency.

Primary Literature

We identified two case series that reported on the experience of patients treated with cannabidiol for epilepsy that were published subsequent to the systematic reviews described above. The first of these was an open-label, expanded-access program of oral cannabidiol with no concurrent control group in patients with severe, intractable, childhood-onset epilepsy that was conducted at 11 U.S. epilepsy centers and reported by Devinsky et al. (2016) and by Rosenberg et al. (2015). Devinsky et al. reported on 162 patients age 1–30 years; Rosenberg et al. reported on 137 of these patients. The median monthly frequency of motor seizures was 30.0 (interquartile range [IQR] 11.0–96.0) at baseline and 15.8 (IQR 5.6–57.6) over the 12-week treatment period. The median reduction in motor seizures while receiving cannabidiol in this uncontrolled case series was 36.5 percent (IQR 0–64.7).

Tzadok et al. (2016) reported on the unblinded experience of Israeli pediatric epilepsy clinics treating 74 children and adolescents with intractable epilepsy with an oral formulation of cannabidiol and tetrahydrocannabinol at a 20:1 ratio for an average of 6 months. There was no concurrent control goup. Compared with baseline, 18 percent of children experienced a 75–100 percent reduction in seizure frequency, 34 percent experienced a 50–75 percent reduction, 12 percent reported a 25–50 percent reduction, 26 percent reported a reduction of less than 25 percent, and 7 percent reported aggravation of seizures that led to a discontinuation of the cannabinoid treatment.

The lack of a concurrent placebo control group and the resulting potential for regression to the mean and other sources of bias greatly reduce the strength of conclusions that can be drawn from the experiences reported by Devinsky et al. (2016), Rosenberg et al. (2015), and Tzadok et al. (2016) about the efficacy of cannabinoids for epilepsy. Randomized trials of the

efficacy of cannabidiol for different forms of epilepsy have been completed[7] but their results have not been published at the time of this report.

Discussion of Findings

Recent systematic reviews were unable to identify any randomized controlled trials evaluating the efficacy of cannabinoids for the treatment of epilepsy. Currently available clinical data therefore consist solely of uncontrolled case series, which do not provide high-quality evidence of efficacy. Randomized trials of the efficacy of cannabidiol for different forms of epilepsy have been completed and await publication.

CONCLUSION 4-6 There is insufficient evidence to support or refute the conclusion that cannabinoids are an effective treatment for epilepsy.

SPASTICITY ASSOCIATED WITH MULTIPLE SCLEROSIS OR SPINAL CORD INJURY

Spasticity is defined as disordered sensorimotor control resulting from an upper motor neuron lesion, presenting as intermittent or sustained involuntary activation of muscles (Pandyan et al., 2005). It occurs in some patients with chronic neurological conditions such as multiple sclerosis (MS) and paraplegia due to spinal cord injury. Recent studies have shown that some individuals with MS are seeking alternative therapies, including cannabis, to treat symptoms associated with MS (Zajicek et al., 2012).

Are Cannabis or Cannabinoids an Effective Treatment for Spasticity Associated with Multiple Sclerosis or Spinal Cord Injury?

Systematic Reviews

We identified two recent systematic reviews that assessed the efficacy of cannabis or cannabinoids in treating muscle spasticity in patients with MS or paraplegia due to spinal cord injury—the systematic review by Whiting et al. (2015) that examined evidence for a broad range of medical uses of cannabis or cannabinoids and the systematic review by Koppel et al. (2014) that focused more narrowly on neurologic conditions. Both systematic reviews examined only randomized, placebo-controlled trials. Whiting et al. excluded from their primary analysis trials that did not use a parallel group design (i.e., they excluded crossover trials) and performed a quantitative pooling of results. In contrast, Koppel et al. included crossover trials but did not perform a quantitative pooling of results.

Whiting et al. searched for studies examining the efficacy of cannabinoids for spasticity due to MS or paraplegia. They identified 11 studies that included patients with MS and 3 that included patients with paraplegia caused by spinal cord injury. None of the studies in patients with paraplegia caused by spinal cord injury were reported as full papers or included sufficient data to allow them to be included in pooled estimates. Whiting et al. reported that in their pooled

[7] Clinicaltrials.gov: NCT02224560, NCT02224690, NCT02091375, NCT02324673.

analysis of three trials in patients with MS, nabiximols and nabilone were associated with an average change (i.e., improvement) in spasticity rating assessed by a patient-reported numeric rating scale of −0.76 (95% CI = −1.38 to −0.14) on a 0 to 10 scale that was statistically greater than for placebo. They further reported finding no evidence for a difference according to type of cannabinoid (i.e., nabiximols versus nabilone). Whiting et al. also reported that the pooled odds of patient-reported improvement on a global impression-of-change score was greater with nabiximols than with placebo (OR 1.44, 95% CI = 1.07–1.94).

The review by Koppel et al. restricted its focus on spasticity to that due to MS. Their conclusions were broadly in agreement with corresponding conclusions from the review by Whiting et al. In particular, Koppel et al. concluded that in patients with MS, nabiximols and orally administered THC are "probably effective" for reducing patient-reported spasticity scores and that oral cannabis extract is "established as effective for reducing patient-reported scores" for spasticity (Koppel et al., 2014, p. 1558).

A commonly used scale for rating spasticity is the Ashworth scale (Ashworth, 1964). However, this scale has been criticized as unreliable, insensitive to therapeutic benefit, and reflective only of passive resistance to movement and not of other features of spasticity (Pandyan et al., 1999; Wade et al., 2010). Furthermore, no minimally important difference in the Ashworth scale has been established. Whiting et al. calculated a pooled measure of improvement on the Ashworth scale versus placebo based on five parallel-group-design trials. They reported that nabiximols, dronabinol, and oral THC/CBD were associated with a numerically greater average improvement on the Ashworth scale than placebo but that this difference was not statistically significant. This conclusion is in broad agreement with corresponding conclusions reached by Koppel et al. In particular, Koppel et al. concluded that nabiximols, oral cannabis extract and orally administered THC are "probably ineffective" for reducing objective measures of spasticity in the short term (6–15 weeks), although oral cannabis extract and orally administered THC are "possibly effective" for objective measures at 1 year.

Primary Literature

An additional placebo-controlled crossover trial of nabiximols for the treatment of spasticity in patients with MS was published after the period covered by the Whiting and Koppel systematic reviews (Leocani et al., 2015). This study randomized 44 patients but analyzed only 34 because of post-randomization exclusions and drop-outs. Such post-randomization exclusions and drop-outs reduce the strength of the evidence that is provided by this study. Patient-reported measures of spasticity were not assessed. After 4 weeks of treatment, response on the modified Ashworth scale (defined as improvement of at least 20 percent) was more common in the THC/CBD group (50 percent) than in the placebo group (23.5 percent), $p = 0.041$.

Discussion of Findings

Based on evidence from randomized controlled trials included in systematic reviews, an oral cannabis extract, nabiximols, and orally administered THC are probably effective for reducing patient-reported spasticity scores in patients with MS. The effect appears to be modest, as reflected by an average reduction of 0.76 units on a 0 to 10 scale. These agents have not consistently demonstrated a benefit on clinician-measured spasticity indices such as the modified Ashworth scale in patients with MS. Given the lack of published papers reporting the results of

trials conducted in patients with spasticity due to spinal cord injury, there is insufficient evidence to conclude that cannabinoids are effective for treating spasticity in this population.

CONCLUSION 4-7

4-7(a) There is substantial evidence that oral cannabinoids are an effective treatment for improving patient-reported multiple sclerosis spasticity symptoms, but limited evidence for an effect on clinician-measured spasticity.

4-7(b) There is insufficient evidence to support or refute the conclusion that cannabinoids are an effective treatment for spasticity in patients with paralysis due to spinal cord injury.

TOURETTE SYNDROME

Tourette syndrome is a neurological disorder characterized by sporadic movements or vocalizations commonly called "tics" (NINDS, 2014). While there is currently no cure for Tourette syndrome, recent efforts have explored whether cannabis may be effective in reducing symptoms commonly associated with the disorder (Koppel et al., 2014).

Are Cannabis or Cannabinoids an Effective Treatment for the Symptoms Associated with Tourette Syndrome?

Systematic Reviews

We identified two good-quality systematic reviews (Koppel et al., 2014; Whiting et al., 2015) that evaluated medical cannabis for Tourette syndrome. Both good-quality reviews identified the same trials, and we focus on the more recent review by Whiting et al. The two RCTs (4 reports), conducted by the same research group (Müller-Vahl et al., 2001, 2002, 2003a,b), compared THC capsules (maximum dose 10 mg daily) to placebo in 36 patients with Tourette syndrome. Tic severity, assessed by multiple measures, and global clinical outcomes were improved with THC capsules. On a 0–6 severity scale, symptoms were improved by less than 1 point. These outcomes were assessed at 2 days (unclear-risk-of-bias trial) and 6 weeks (high-risk-of-bias trial). Neither trial described randomization or allocation concealment adequately and the 6-week trial was rated high risk-of-bias for incomplete outcome data.

Primary Literature

The committee did not identify any good-quality primary literature that reported on medical cannabis as an effective treatment for Tourette syndrome, and that were published subsequent to the data collection period of the most recently published good- or fair-quality systematic review addressing the research question.

Discussion of Findings

No clear link has been established between symptoms of Tourette syndrome and cannabinoid sites or mechanism of action. However, case reports have suggested that cannabis can reduce tics and that the therapeutic effects of cannabis might be due to the anxiety-reducing properties of marijuana rather than to a specific anti-tic effect (Hemming and Yellowlees, 1993; Sandyk and Awerbuch, 1988). Two small trials (assessed as being of fair- to poor-quality) provide limited evidence for the therapeutic effects of THC capsules on tic severity and global clinical outcomes.

CONCLUSION 4-8 There is limited evidence that THC capsules are an effective treatment for improving symptoms of Tourette syndrome.

AMYOTROPHIC LATERAL SCLEROSIS

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease affecting the motor neurons in the spinal cord, brain stem, and motor cortex, ultimately leading to complete paralysis (Rossi et al., 2010). The pathogenesis of ALS remains unclear, but the disease is thought to result from the interplay of a number of mechanisms including neurofilament accumulation, excitotoxicity, oxidative stress, and neuroinflammation (Redler and Dokholyan, 2012), all of which may be amenable to manipulation of the endocannabinoid system and cannabinoid receptors.

Are Cannabis or Cannabinoids an Effective Treatment for the Symptoms Associated with Amyotrophic Lateral Sclerosis?

Systematic Reviews

The committee did not identify a good- or fair-quality systematic review that reported on medical cannabis as an effective treatment for symptoms associated with amyotrophic lateral sclerosis.

Primary Literature

On the basis of proposed pathogenesis and anecdotal reports of symptomatic benefit from the use of cannabis in patients with ALS, two small trials of dronabinol have been conducted. In a randomized, double-blind crossover study, 19 patients with ALS were treated with dronabinol doses of 2.5 to 10 mg daily for 4 weeks (Gelinas et al., 2002). Participants noted improvement in appetite and sleep but not in cramps or fasiculations (involuntary muscle twitches). The second study enrolled 27 patients with ALS who had moderate to severe cramps (greater than 4 on a 0–10 visual analogue scale) in a randomized, double-blind trial of dronabinol 5 mg twice daily or placebo, each given for 2 weeks with an intervening 2-week washout period (Weber et al., 2010). The primary endpoint was a change in cramp intensity with secondary endpoints of change in cramp number, intensity of fasciculations, quality of life, sleep, appetite, and depression. There was no difference between dronabinol and placebo seen in any of the endpoints. The

investigators reported that the dronabinol was very well tolerated and postulated that the dronabinol dose may have been too low as well as suggesting that a carryover effect in the crossover design may have obfuscated any differences in the treatment arms. The sample size was too small to discern anything but a large effect.

Discussion of Findings

Two small studies investigated the effect of dronabinol on symptoms associated with ALS. Although there were no differences from placebo in either trial, the sample sizes were small, the duration of the studies was short, and the dose of dronabinol may have been too small to ascertain any activity. The effect of cannabis was not investigated.

CONCLUSION 4-9 There is insufficient evidence that cannabinoids are an effective treatment for symptoms associated with amyotrophic lateral sclerosis.

HUNTINGTON'S DISEASE

Huntington's disease is characterized by chorea (abnormal, involuntary movement) along with cognitive decline and psychiatric impairment (Armstrong and Miyasaki, 2012). Worsening chorea significantly impacts patient quality of life. The pathophysiology and neurochemical basis of Huntington's disease are incompletely understood. Neuroprotective trials often investigate agents that may decrease oxidative stress or glutamatergic changes related to excitotoxic stress. There is some preclinical evidence and limited clinical evidence that suggest that changes in the endocannabinoid system may be linked to the pathophysiology of Huntington's disease (Pazos et al., 2008; van Laere et al., 2010).

Are Cannabis or Cannabinoids an Effective Treatment for the Motor Function and Cognitive Performance Associated with Huntington's Disease?

Systematic Reviews

The systematic review from the American Academy of Neurology includes two studies on Huntington's disease (Koppel et al., 2014). A randomized, double-blind, placebo-controlled crossover pilot trial investigated nabilone 1 or 2 mg daily for 5 weeks followed by placebo in 22 patients with symptomatic Huntington's disease (Curtis et al., 2009). An additional 22 patients were randomized to placebo followed by nabilone. The primary endpoint was the total motor score of the Unified Huntington's Disease Rating Scale (UHDRS). Secondary endpoints included the chorea, cognitive performance, and psychiatric changes measured with the same instrument. No significant difference in the total motor score was seen in the 37 evaluable patients (treatment difference 0.86, 95% CI = −1.8–3.52), with a 1-point change considered clinically significant. There was evidence of an improvement in the chorea subscore with nabilone (treatment difference 1.68, 95% CI = 0.44–2.92). There was no difference between treatments for cognition, but there was evidence of an improvement in the two neuropsychiatric outcome measures in the nabilone arm—UHDRS behavioral assessment (4.01, 95% CI = −0.11–8.13) and neuropsychiatric inventory (6.43, 95% CI = 0.2–12.66). The small estimated treatment effect with wide confidence intervals reduces the level of evidence for nabilone's effectiveness

from this pilot study. However, based on this trial, the American Academy of Neurology guideline concluded that "nabilone possibly modestly improves Huntington's disease chorea" (Armstrong and Miyasaki, 2012, p. 601). The second study included in the systematic review was a lower-quality, 15-patient randomized, double-blind, placebo-controlled trial investigating the effect of cannabidiol capsules at a dose of 10 mg/kg/day in two divided doses (Consroe et al., 1991). The endpoints in this study involving patients with Huntington's disease who were not on neuroleptics were chorea severity, functional limitations, and side effects. There were no statistically significant differences between cannabidiol and placebo in any outcomes, although the American Academy of Neurology considered the study to be underpowered.

Primary Literature

The committee did not identify any good-quality primary literature that reported on medical cannabis as an effective treatment for the declines in motor function and cognitive performance associated with Huntington's disease, that were published subsequent to the data collection period of the most recently published good- or fair-quality systematic review addressing the research question.

Discussion of Findings

Two small studies have investigated the potential benefit of cannabinoids in patients with Huntington's disease. Although nabilone appeared to have some potential benefit on chorea, cannabidiol appeared to be equal to placebo in ameliorating symptoms. Both studies were of short duration and likely underpowered because of their small sample sizes. Cannabis has not been investigated in Huntington's disease.

CONCLUSION 4-10 There is insufficient evidence to support or refute the conclusion that oral cannabinoids are an effective treatment for chorea and certain neuropsychiatric symptoms associated with Huntington's disease.

PARKINSON'S DISEASE

Parkinson's disease is a motor system disorder attributed to the loss of dopamine-producing brain cells. It is characterized clinically by tremor, rigidity, bradykinesia (slowness of movement), and impaired balance and coordination (PDF, 2016a). An estimated 60,000 Americans are diagnosed with this disorder each year (PDF, 2016b).

Although the disease is progressive and without cure, there are medications that can ameliorate some of the associated symptoms. Although levodopa has demonstrated efficacy for treating symptoms of Parkinson's disease, long-term use of levodopa is associated with the development of side effects, especially dyskinesias (involuntary movements) (NINDS, 2015). Evidence suggests that the endocannabinoid system plays a meaningful role in certain neurodegenerative processes (Krishnan et al., 2009), thus it may be useful to determine the efficacy of cannabinoids in treating the symptoms of neurodegenerative diseases.

Are Cannabis or Cannabinoids an Effective Treatment for the Motor System Symptoms Associated with Parkinson's Disease or the Levodopa-Induced Dyskinesia?

Systematic Reviews

The systematic review of cannabis in selected neurologic disorders (Koppel et al., 2014) identified two trials of cannabinoid therapies in patients with levodopa-induced dyskinesias. Nineteen patients with levodopa-induced dyskinesia greater than or equal to 2 as determined by questions 32–34 of the Unified Parkinson's Disease Rating Scale (UPDRS) were randomized in a double-blind, placebo-controlled crossover trial to receive Cannador capsules (containing THC 2.5 mg and CBD 1.25 mg) to a maximum dose of 0.25 mg/kg of THC daily or placebo (Carroll et al., 2004). The primary endpoint was the effect of treatment on the dyskinesia score of the UPDRS. Secondary endpoints included the impact of dyskinesia on function, pathophysiologic indicators of dyskinesia, duration of dyskinesia, quality of life, sleep, pain, and overall severity of Parkinson's disease. The overall treatment effect was +0.52, which indicated a worsening with Cannador, although this worsening was not statistically significant ($p = 0.09$). No effects were seen on the secondary outcomes. Although there were more adverse events on the drug than on the placebo, the investigators felt that the treatment was well tolerated. The study had limited statistical power to detect anything but a large treatment effect due to its small sample size. The second study included in the systematic review was an even smaller low-quality randomized, double-blind, placebo-controlled crossover trial involving seven patients with Parkinson's disease who had stable levodopa-induced dyskinesia present for 25–50 percent of the day (Sieradzan et al., 2001). Nabilone dosed at 0.03 mg/kg or a placebo was administered 12 hours and 1 hour before levodopa at a dose of 200 mg. The primary endpoint was total dyskinesia disability as measured using the Rush Dyskinesia Disability Scale.[8] The median total dyskinesia score after treatment with levodopa and nabilone was 17 (range 11–25) compared to 22 (range 16–26) after levodopa and placebo ($p < 0.05$). The anti-Parkinsonian actions of levodopa were not reduced by nabilone pretreatment. Although the authors stated that "nabilone significantly reduced total levodopa-induced dyskinesia compared with placebo" (Sieradzan et al., 2001, p. 2109) the fact that the results were generated by only seven patients receiving only two doses clearly reduces the ability to draw such an enthusiastic conclusion. Koppel concludes that oral cannabis extract "is probably ineffective for treating levodopa-induced dyskinesias" (Koppel et al., 2014, p. 1560).

Primary Literature

Cannabidiol capsules were evaluated in a randomized, double-blind, placebo-controlled trial conducted in 21 patients with Parkinson's disease (Chagas et al., 2014). The study was an exploratory trial to assess the effect of CBD in Parkinson's disease globally with the UPDRS and the Parkinson's Disease Questionnaire-39 (PDQ-39) used to assess overall functioning and well-being. Possible CBD adverse events were evaluated by a side effect rating scale. Baseline data were collected 1 week before commencing treatment with CBD at 75 mg/day or 300 mg/day or with a placebo, and the same assessments were repeated during the sixth and final week of the trial. No statistically significant differences were seen in the UPDRS between the three study

[8] The Dyskinesia Disability Scale is a 0–4 scale (absent to most severe) measuring the severity of dyskinesia (Goetz et al., 1994).

arms. There was a statistically significant difference in the variation between baseline and final assessment in the overall PDQ-39 score between placebo (6.50 ± 8.48) and CBD 300 mg/day (25.57 ± 16.30) ($p = 0.034$), which suggests that there might be a possible effect of CBD on improving quality of life.

An open-label observational study of 22 patients with Parkinson's disease attending a motor disorder clinic at a tertiary medical center collected data before and 30 minutes after patients smoked 0.5 grams of cannabis (Lotan et al., 2014). The instruments utilized included the UPDRS, the McGill Pain Scale, and a survey of subjective efficacy and adverse effects of cannabis. In addition, the effect of cannabis on motor symptoms was evaluated by two raters. The investigators found that the total motor symptoms score on the UPDRS improved from 33.1 (± 13.8) to 23.2 (± 10.5) ($p < 0.001$). Subcategories of the UPDRS that showed statistically significant improvement included tremor, rigidity, and bradykinesia. Pain and sleep were also reported to be improved after smoking cannabis. The results from this low-quality observational study prompted the investigators to propose that their findings should be confirmed in a larger, longer, randomized, double-blind, placebo-controlled trial.

Discussion of Findings

Small trials of oral cannabinoid preparations have demonstrated no benefit compared to a placebo in ameliorating the side effects of Parkinson's disease. A seven patient trial of nabilone suggested that it improved the dyskinesia associated with levodopa therapy, but the sample size limits the interpretation of the data. An observational study of inhaled cannabis demonstrated improved outcomes, but the lack of a control group and the small sample size are limitations.

CONCLUSION 4-11 There is insufficient evidence that cannabinoids are an effective treatment for the motor system symptoms associated with Parkinson's disease or the levodopa-induced dyskinesia.

DYSTONIA

Dystonia is a disorder characterized by sustained or repetitive muscle contractions which result in abnormal fixed postures or twisting, repetitive movements (NINDS, 2016a). Idiopathic cervical dystonia is the most common cause of focal dystonia. Oral pharmacological agents are generally ineffective, with repeated injections of botulinum toxin being the most effective current therapy. The pathophysiologic mechanisms of dystonia are poorly understood, but, as in other hyperkinetic movement disorders, underactivity of the output regions of the basal ganglia may be involved. Stimulation of the cannabinoid receptors has been postulated as a way to reduce dystonia (Zadikoff et al., 2011). Anecdotal reports have suggested that cannabis may alleviate symptoms associated with dystonia (Uribe Roca et al., 2005). In a 1986 preliminary open pilot study in which five patients with dystonic movement disorders received cannabidiol, dose-related improvements were observed in all five patients (Consroe et al., 1986).

Are Cannabis or Cannabinoids an Effective Treatment for Dystonia?

Systematic Reviews

The American Academy of Neurology systematic review (Koppel et al., 2014) identified one study that examined the effect of dronabinol on cervical dystonia. The review described the study as being underpowered to detect any differences between dronabinol and the placebo. Overall, nine patients with cervical dystonia were randomized to receive dronabinol 15 mg daily or a placebo in an 8-week crossover trial (Zadikoff et al., 2011). The primary outcome measure was the change in the Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) part A subscore at the beginning and end the of each 3-week treatment phase. There was no statistically significant effect of dronabinol on the dystonia compared with placebo as measured by the TWSTRS-A ($p = 0.24$).

Primary Literature

Fifteen patients with a clinical diagnosis of primary dystonia received a single dose of nabilone or placebo (0.03 mg/kg to the nearest whole milligram) on the study day (Fox et al., 2002). The primary outcome measure was the dystonia-movement scale portion of the Burke-Fahn-Marsden dystonia scale. Treatment with nabilone produced no significant reduction in the total dystonia movement scale score when compared with placebo ($p > 0.05$).

Discussion of Findings

Two small trials of dronabinol and nabilone failed to demonstrate a significant benefit of the cannabinoids in improving dystonia compared with placebo. Cannabis has not been studied in treatment of dystonia.

CONCLUSION 4-12 There is insufficient evidence to support or refute the conclusion that nabilone and dronabinol are an effective treatment for dystonia.

DEMENTIA

Dementia is characterized by a decline in cognition that typically affects multiple cognitive domains such as memory, language, executive function, and perceptual motor function (NIH, 2013). Alzheimer disease, vascular dementia, and Parkinson's disease with dementia are three prominent dementing disorders (NIA, n.d.). Behavioral and psychological symptoms, including agitation, aggression, and food refusal, are common in the more advanced stages of dementia. These symptoms cause distress to the patient and caregivers, and may precipitate the patient being placed in institutional care. Current treatments for dementia (e.g., cholinesterase inhibitors) have only modest effects, and treatments for behavioral disturbances such as antipsychotic medications, have both modest benefits and substantial adverse effects (Krishnan et al., 2009).

CB1 receptors are found throughout the central nervous system, and the endogenous cannabinoid system is thought to be important in the regulation of synaptic transmission (Baker

et al., 2003), a process that is disordered in patients with dementia. Accumulating evidence suggest that cannabinoids have the potential for neuroprotective effects (Grundy, 2002; Hampson et al., 1998; Shen and Thayer, 1998). This developing understanding of the endogenous cannabinoid system along with cannabinoids anxiolytic and appetite- stimulating effects provides a rationale for its study in patients with dementia.

Are Cannabis or Cannabinoids an Effective Treatment for the Symptoms Associated with Dementia?

Systematic Reviews

We identified two good-quality systematic reviews (Krishnan et al., 2009; van den Elsen et al., 2014) that evaluated cannabis for dementia. Both reviews identified the same two RCTs, which were synthesized qualitatively. A small randomized crossover trial (Volicer et al., 1997) evaluated dronabinol in 15 hospitalized patients with probable Alzheimer's disease who had behavior changes and were refusing food. Patients were randomized to dronabinol (2.5 mg twice daily) for 6 weeks and to placebo for 6 weeks. Data in this trial with a high risk of bias were presented in such a way that they could not be abstracted for analysis by systematic review authors. The primary study authors reported: increased weight during the 12 weeks regardless of order of treatment (dronabinol, 7.0 [SD 1.5] pounds, and placebo, 4.6 [SD 1.3] pounds, during the first 6 weeks); decreased disturbed behavior during dronabinol treatment, an effect that persisted in patients treated first with dronabinol, then placebo; decreased negative affect scores in both groups during the 12 weeks, more so when taking dronabinol than placebo; and no serious adverse events attributed to dronabinol, although one patient suffered a seizure following the first dose. One other open-label pilot study (Walther et al., 2006), which evaluated six patients with severe dementia for the effects of dronabinol on nighttime agitation did not meet eligibility criteria for the review by Krishnan et al.

Primary Literature

We identified one good-quality RCT that evaluated THC in 50 patients with Alzheimer disease, vascular or mixed dementia, and neuropsychiatric symptoms (van den Elsen et al., 2015). THC 1.5 mg given three times daily for 3 weeks did not improve overall neuropsychiatric symptoms, agitation, quality of life, or activities of daily living versus a placebo. Although the study recruited less than one-half of the planned sample, the authors estimated that there was only a 5 percent chance that enrolling more participants would have shown a clinically important effect on neuropsychiatric symptoms.

Discussion of Findings

The authors of the good-quality Cochrane systematic review, concluded that the "review finds no evidence that cannabinoids are effective in the improvement of disturbed behavior in dementia or treatment of other symptoms of dementia" (Krishnan et al., 2009, p. 8). Subsequently, a larger good-quality RCT found no benefit from low-dose THC. We agree that the evidence is limited due to the small number of patients enrolled, limits in the study design

and reporting, and inconsistent effects. The current limited evidence does not support a therapeutic effect of cannabinoids.

CONCLUSION 4-13 There is limited evidence that cannabinoids are ineffective treatments for improving the symptoms associated with dementia.

GLAUCOMA

Glaucoma is one of the leading causes of blindness within the United States (Mayo Clinic, 2015). This disorder is characterized as a group of eye conditions that can produce damage to the optic nerve and result in a loss of vision. This damage is often caused by abnormally high intraocular pressure (NEI, n.d.). Because high intraocular pressure is a known major risk factor that can be controlled (Prum et al., 2016, p. 52), most treatments have been designed to reduce it. Research suggests that cannabinoids may have potential as an effective treatment for reducing pressure in the eye (Tomida et al., 2007).

Are Cannabis or Cannabinoids an Effective Treatment for Glaucoma?

Systematic Reviews

We identified one good-quality systematic review (Whiting et al., 2015) that evaluated medical cannabis for the treatment of glaucoma. This review identified a single randomized crossover trial (six participants) in patients with glaucoma. The trial compared THC (5 mg oromucosal spray), cannabidiol (20 mg oromucosal spray), cannabidiol spray (40 mg oromucosal spray) and a placebo, examining intraocular pressure intermittently up until12 hours after treatment. Elevated intraocular pressure is one of the diagnostic criteria for glaucoma, and lowering intraocular pressure is a goal of glaucoma treatments (Prum et al., 2016). The trial was evaluated as "unclear" risk of bias. No differences in intraocular pressure were found between placebo and cannabinoids.

Primary Literature

The committee did not identify any good-quality primary literature that reported on the medical cannabis as an effective treatment for the symptoms of glaucoma and that were published subsequent to the data collection period of the most recently published good- or fair-quality systematic review addressing the research question.

Discussion of Findings

Lower intraocular pressure is a key target for glaucoma treatments. Non-randomized studies in healthy volunteers and glaucoma patients have shown short-term reductions in intraocular pressure with oral, topical eye drops, and intravenous cannabinoids, suggesting the potential for therapeutic benefit (IOM, 1999, pp. 174–175). A good-quality systemic review identified a single small trial that found no effect of two cannabinoids, given as an oromucosal spray, on intraocular pressure (Whiting et al., 2015). The quality of evidence for the finding of no effect is limited. However, to be effective, treatments targeting lower intraocular pressure

must provide continual, rather than transient, reductions in intraocular pressure. To date, those studies showing positive effects have shown only short-term benefit on intraocular pressure (hours) suggesting a limited potential for cannabinoids in the treatment of glaucoma.

CONCLUSION 4-14 There is limited evidence that cannabinoids are an ineffective treatment for improving intraocular pressure associated with glaucoma.

TRAUMATIC BRAIN INJURY/INTRACRANIAL HEMORRHAGE

Traumatic brain injury (TBI) is an acquired brain injury that can result from a sudden or violent hit to the head (NINDS, 2016c). TBI accounts for about 30 percent of all injury deaths in the United States (CDC, 2016). Intracranial hemorrhage (ICH), bleeding that occurs inside the skull, is a common complication of TBI which is associated with a worse prognosis of the injury (Bullock, 2000; CDC, 2015). There is small body of literature reporting the neuroprotective effects of cannabinoid analogs in pre-clinical studies of head injuries (Mechoulam et al., 2002) as well as in observational studies in humans (Di Napoli et al., 2016; Nguyen et al., 2014).

Are Cannabis or Cannabinoids an Effective Treatment or Prevention for Traumatic Brain Injury or Intracranial Hemorrhage?

Systematic Reviews

The committee did not identify a good- or fair-quality systematic review that evaluated the efficacy of cannabinoids as a treatment or prevention for traumatic brain injury or intracranial hemorrhage.

Primary Literature

There were two fair- to high-quality observational studies found in the literature. One study (n = 446) examined the TBI presentation and outcomes among patients with and without a positive THC blood test (Nguyen et al., 2014). Patients who were positive for THC were more likely to survive the TBI than those who were negative for THC (OR 0.224, 95% CI = 0.051–0.991). The authors used regression analysis to account for confounding variables (e.g., age, alcohol, Abbreviated Injury Score, Injury Severity Score, mechanism of injury, gender, and ethnicity). In the only other observational study that examined the association between cannabis use and brain outcomes, a study of intracranial hemorrhage patients (n = 725) found that individuals with a positive test of cannabis use demonstrated better primary outcome scores on the modified Rankin Scale[9] (adjusted common OR 0.544, 95% CI = 0.330–0.895) (Di Napoli et al., 2016). In their analysis, the authors adjusted for confounding variables that are known to be associated with worse ICH outcomes, including age, sex, Glasgow Coma Scale as continuous variables, and anticoagulant use.

[9] The modified Rankin Scale is a clinical assessment tool commonly used to measure the degree of disability following a stroke. Outcome scores from the scale range from 0 (no symptoms) to 6 (death) (Di Napoli et al., 2016, p. 249).

Discussion of Findings

The two studies discussed above (Di Napoli et al., 2016; Nguyen et al., 2014) provide very modest evidence that cannabis use may improve outcomes after TBI or ICH. However, more conclusive observational studies or randomized controlled trials will be necessary before any conclusions can be drawn about the neuroprotective effect of cannabinoids in clinical populations.

CONCLUSION 4-15 There is limited evidence of a statistical association between cannabinoids and better outcomes (i.e., mortality, disability) after a traumatic brain injury or intracranial hemorrhage.

ADDICTION

Drug addiction has been defined as a chronically relapsing disorder that is characterized by the compulsive desire to seek and use drugs with impaired control over substance use despite negative consequences (Prud'homme et al., 2015). The endocannabinoid system has been found to influence the acquisition and maintenance of drug-seeking behaviors, possibly through its role in reward and brain plasticity (Gardner, 2005; Heifets and Castillo, 2009). Furthermore, in laboratory settings orally administered dronabinol has been found to reduce cannabis withdrawal symptoms in cannabis users who were not seeking treatment to reduce cannabis use (Budney et al., 2007; Haney et al., 2004), and therefore may be expected to be useful as a substitute to assist to achieve and maintain abstinence of cannabis.

Are Cannabis or Cannabinoids an Effective Treatment for Achieving Abstinence from Addictive Substances?

Systematic Reviews

We identified two recent published reviews that examined randomized trials evaluating the effects of cannabis or cannabinoids on the use of addictive drugs including cannabis: one systematic review by Marshall et al. (2014) and one comprehensive review by Prud'homme et al. (2015).[10]

The review by Marshall et al. is a high-quality systematic review of randomized and quasi-randomized trials assessing the efficacy of drug therapies specifically for cannabis dependence. They identified two trials examining THC: one published by Levin et al. (2011) examining dronabinol and one published by Allsop et al. (2014) examining nabiximols.

The trial by Levin et al. (2011) was a randomized, placebo-controlled, double-blind trial, which assigned cannabis-dependent adults to receive dronabinol (n = 79) or placebo (n = 77) for

[10] Prud'homme (2015) is often categorized as a systematic review; however, the committee determined that the review lacks certain key elements of a systematic review, including a clearly stated research question, independent and duplicate data abstraction efforts, an assessment of the research quality and risk-of-bias, and a quantitative summary.

8 weeks, followed by a 2-week taper. Both groups received weekly individual therapy plus motivational enhancement therapy. Retention in the treatment program at the end of the maintenance phase was 77 percent in the dronabinol group and 61 percent in the placebo group (p-value for difference between groups = 0.02). Withdrawal symptoms declined more quickly in the dronabinol group than in the placebo group (p = 0.02). However, the primary outcome, the proportion of participants who achieved 2 consecutive weeks of abstinence at weeks 7–8, was 17.7 percent in the dronabinol group and 15.6 percent in the placebo group, which were not statistically significantly different from one another (p = 0.69).

The trial by Allsop et al. was randomized, placebo-controlled, and double-blind, and it enrolled adults seeking treatment for cannabis dependence. Subjects were patients who were hospitalized for 9 days and who received a 6-day regimen of nabiximols oromucosal spray (n = 27) or matching placebo (n = 24) together with standardized psychosocial interventions. The primary outcome was a change in the Cannabis Withdrawal Scale, which is a 19-item scale that measures withdrawal symptom severity on an 11-point Likert scale for the previous 24 hours. Over the 6-day treatment period, subjects in the nabiximols group reported a mean 66 percent reduction from baseline in the cannabis withdrawal scale, while patients in the placebo group reported a mean increase in the cannabis withdrawal scale of 52 percent (p-value for between-group difference = 0.01). The median time between hospital discharge and relapse to cannabis use was 15 days (95% CI = 3.55–26.45) in the nabiximols group and 6 days (95% CI = 0–27.12) in the placebo group. The difference between these times was not statistically significant (p-value for between-group difference = 0.81).

Based on the Levin et al. and Allsop et al. trials, Marshall et al. concluded that there was "moderate"-quality evidence that users of THC preparations were more likely to complete treatment than those given a placebo (RR 1.29, 95% CI = 1.08–1.55). However, the systematic review further concluded that, based on these two trials, the studied THC preparations were not associated with an increased likelihood of abstinence or a greater reduction in cannabis use than a placebo.

The review by Prud'homme et al. (2015) is a comprehensive review that broadly examined evidence on the effects of cannabidiol on addictive behaviors. The only randomized trial assessing the role of cannabis in reducing the use of an addictive substance was published by Morgan et al. (2013). That study was a pilot placebo-controlled trial that randomized cigarette smokers who wished to quit smoking to receive 400 µg inhaled cannabidiol (n = 12) or inhaled placebo (n = 12) for 1 week. Participants were instructed to use the inhaler when they felt the urge to smoke. The reduction in the number of cigarettes smoked per week was higher in the cannabidiol group than in the placebo group, although the difference was not statistically significant (p = 0.054). Rates of abstinence were not reported.

Primary Literature

The committee did not identify any good-quality primary literature that reported on medical cannabis as an effective treatment for the reduction in use ofaddictive substances and that were published subsequent to the data collection period of the most recently published good- or fair-quality systematic review addressing the research question.

Discussion of Findings

Based on the systematic reviews, neither of the two trials evaluating the efficacy of a cannabinoid in achieving or sustaining abstinence from cannabis showed a statistically significant effect. However, given the limited number of studies and their small size, their findings do not definitively rule out the existence of an effect. The only study examining the efficacy of a cannabinoid in cigarette smoking cessation was a pilot study that did not examine rates of abstinence. Thus, its efficacy for smoking cessation has not been thoroughly evaluated.

CONCLUSION 4-16 There is no evidence to support or refute the conclusion that cannabinoids are an effective treatment for achieving abstinence in the use of addictive substances.

ANXIETY

Anxiety disorders share features of excessive fear and anxiety which induce psychological and physical symptoms that can cause significant distress or interfere with social, occupational, and other areas of functioning (APA, 2013). In a given year, an estimated 18 percent of the United States adult population will suffer from symptoms associated with an anxiety disorder (NIMH, n.d.). Given the role of the endocannabinoid system in mood regulation, the committee decided to explore the relationship between anxiety and cannabis.

Are Cannabis or Cannabinoids an Effective Treatment for the Improvement of Anxiety Symptoms?

Systematic Reviews

The review by Whiting et al. (2015) was the most recent good quality review. This review identified one randomized trial with a high risk of bias that compared a single 600 mg dose of cannabidiol to a placebo in 24 participants with generalized social anxiety disorder. Cannabidiol was associated with a greater improvement on the anxiety factor of a 100-point visual analogue mood scale (mean difference from baseline −16.52, $p = 0.01$) compared with a placebo during a simulated public speaking test. Four other randomized controlled trials (232 participants) enrolled patients with chronic pain and reported on anxiety symptoms. The cannabinoids studied were: dronabinol, 10–20 mg daily; nabilone, maximum dose of 2 mg daily; and nabiximols, maximum dose of 4–48 sprays/day. Outcomes were assessed from 8 hours to 6 weeks after randomization; three of the four trials were judged to have a high risk of bias. These trials suggested greater short-term benefit with cannabinoids than placebo on self-reported anxiety symptoms.

Primary Literature

The committee did not identify any good-quality primary literature that reported on medical cannabis as an effective treatment for the improvement of anxiety symptoms and that

were published subsequent to the data collection period of the most recently published good- or fair-quality systematic review addressing the research question.

Discussion of Findings

There is limited evidence that cannabidiol improves anxiety symptoms, as assessed by a public speaking test, in patients with social anxiety disorder. These positive findings are limited by weaknesses in the study design (e.g., an inadequate description of randomization and allocation concealment), a single dose of CBD, and uncertain applicability to patients with other anxiety disorders. Limited evidence also suggests short-term benefits in patients with chronic pain and associated anxiety symptoms. In contrast, evidence from observational studies found moderate evidence that daily cannabis use is associated with increased anxiety symptoms and heavy cannabis use is associated with social phobia disorder (see Chapter 12).

CONCLUSION 4-17 There is limited evidence that cannabidiol is an effective treatment for the improvement of anxiety symptoms, as assessed by a public speaking test, in individuals with social anxiety disorders.

DEPRESSION

Depression is one of the nation's most common mental health disorders (ADAA, 2016). Across the many depressive disorders that exist (e.g., persistent depressive disorder, major depressive disorder, pre-menstrual dysphoric disorder) there are common symptomatic features of feelings of sadness, emptiness, or irritable mood, accompanied by somatic and cognitive changes that affect the individual's capacity to function (APA, 2013, p. 155). The endocannabinoid system is known to play a role in mood regulation (NIDA, 2015, p. 9); and therefore, the committee decided to explore the association between cannabis use and depressive disorders or symptoms.

Are Cannabis or Cannabinoids an Effective Treatment to Reduce Depressive Symptoms?

Systematic Reviews

The review by Whiting et al. (2015) was the most recent good-quality review. No RCTs were identified that specifically evaluated cannabis in patients with a depressive disorder. Five RCTs (634 participants) enrolled patients for other conditions (chronic pain or multiple sclerosis with spasticity) and reported on depressive symptoms. Only one study reported depressive symptoms at baseline; symptoms were mild. Nabiximols (n = 3; maximum dose ranged from 4 to 48 doses/day), dronabinol (10 mg and 20 mg daily) and nabilone capsules (maximum of eight mg) were compared to placebo; nabilone was also compared to dihydrocodeine. Outcomes were assessed from 8 hours to 9 weeks following randomization. Three of the five trials were judged to have a high risk of bias and the other two as unclear risk. Three studies (nabiximols, dronabinol) showed no effect using validated symptom scales. One study that evaluated three doses of nabiximols found increased depressive symptoms at the highest dose (11–14

sprays/day), but no difference compared to placebo at lower doses. The comparison of nabilone to dihydrocodone showed no difference in depressive symptoms.

Primary Literature

The committee did not identify any good-quality primary literature that reported on medical cannabis as an effective treatment to reduce depressive symptoms and that were published subsequent to the data collection period of the most recently published good- or fair-quality systematic review addressing the research question.

Discussion of Findings

Although patients report using cannabinoids for depression, our search and a good quality systematic review did not identify any RCTs evaluating the effects of medical cannabis in patients with depressive disorders. Trials in patients with chronic pain or multiple sclerosis with uncertain baseline depressive symptoms did not show an effect. There is no trial data addressing the effects of cannabinoids for major depressive disorder.

In Chapter 12: Mental Health, the committee reviews epidemiological evidence to examine the association between cannabis use and the development of depressive disorders, as well as the impact of cannabis use on the disorder's course or symptoms.

CONCLUSION 4-18 There is limited evidence that nabiximols, dronabinol, and nabilone are ineffective treatments for the reduction of depressive symptoms in individuals with chronic pain or multiple sclerosis.

SLEEP DISORDERS

Sleep disorders can be classified into major groups that include insomnia, sleep-related breathing disorders, parasomnias, sleep-related movement disorders, and circadian rhythm sleep–wake disorders (Sateia, 2014). Fifty million to 70 million adults in the United States report having some type of sleep disorder (ASA, 2016). In 2010, insomnia generated 5.5 million offices visits in the United States (Ford et al., 2014). There is some evidence to suggest that the endocannabinoid system may have a role in sleep. THC is associated in a dose-dependent manner with changes in slow-wave sleep, which is critical for learning and memory consolidation. Cannabis may also have effects on sleep latency, decreasing time to sleep onset at low doses and increasing time to sleep onset at higher doses (Garcia and Salloum, 2015). Thus, cannabinoids could have a role in treating sleep disorders.

Are Cannabis or Cannabinoids an Effective Treatment for Improving Sleep Outcomes?

Systematic Reviews

The review by Whiting et al. was the most recent good-quality review. Two RCTs (54 participants) evaluated cannabinoids (nabilone, dronabinol) for the treatment of sleep problems. A trial deemed to have a high risk of bias conducted in 22 patients with obstructive sleep apnea

showed a greater benefit of dronabinol (maximum dose of 10mg daily) than with a placebo on sleep apnea/hypopnea index (mean difference from baseline −19.64, p = 0.02) at 3 weeks follow-up. A crossover trial deemed to have a low risk of bias in 32 patients with fibromyalgia found improvements for nabilone 0.5 mg daily compared with 10 mg amitriptyline in insomnia (mean difference from baseline −3.25, 95% CI = −5.26 to −1.24) and greater sleep restfulness (mean difference from baseline 0.48, 95% CI = 0.01–0.95) at 2-week follow-up. Although the antidepressant amitriptyline is an established treatment for fibromyalgia, it is not FDA approved for insomnia and its use is limited by adverse effects.

Nineteen trials (3,231 participants) enrolled patients with other conditions (chronic pain or multiple sclerosis) and reported on sleep outcomes. Nabiximols (13 studies), THC/CBD capsules (2 studies), smoked THC (2 studies), and dronabinol or nabilone were compared to a placebo. Sleep outcomes were assessed at 2–15 weeks after randomization. Eleven of the 19 trials were judged to have a high risk of bias, 6 had an uncertain risk of bias and the other 2 were judged to have a low risk of bias. The meta-analysis found greater improvements with cannabinoids in sleep quality among 8 trials (weighted mean difference [WMD] −0.58, 95% CI = −0.87 to −0.29) and sleep disturbance among 3 trials (WMD −0.26, 95% CI = −0.52 to 0.00). These improvements in sleep quality and sleep disturbance were rated on a 10-point scale and would be considered small improvements. The summary estimate showing benefit was based primarily on studies of nabiximols.

Primary Literature

The committee did not identify any good-quality primary literature that reported on medical cannabis as an effective treatment to improve sleep outcomes and that were published subsequent to the data collection period of the most recently published good- or fair-quality systematic review addressing the research question.

Discussion of Findings

A high-quality systematic review found moderate evidence suggesting that cannabinoids (primarily nabiximols) improve short-term sleep outcomes in patients with sleep disturbance associated with obstructive sleep apnea, fibromyalgia, chronic pain, or multiple sclerosis. However, the single study using an active comparator used a drug (amitriptyline) that is considered second-line treatment due to the availability of newer, more effective treatments that have fewer adverse effects. The committee did not identify any clinical trials that evaluated the effects of cannabinoids in patients with primary chronic insomnia.

CONCLUSION 4-19 There is moderate evidence that cannabinoids, primarily nabiximols, are an effective treatment to improve short-term sleep outcomes in individuals with sleep disturbance associated with obstructive sleep apnea syndrome, fibromyalgia, chronic pain, and multiple sclerosis.

POSTTRAUMATIC STRESS DISORDER (PTSD)

Posttraumatic stress disorder (PTSD) falls within the broader trauma- and stressor-related disorders categorized by the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-V). The diagnostic criteria of PTSD include an exposure to a traumatic event (e.g., the threat of death, serious injury, or sexual violence) and exhibiting psychological distress symptoms that occur as a result of that exposure (e.g., intrusion symptoms, such as distressing memories; avoidance of stimuli that are associated with the traumatic event; negative alterations in mood and cognition; alterations in arousal and reactivity associated with the traumatic event; functional impairment) (APA, 2013, pp. 271–272). Given the known psychoactive effects of cannabis, the committee decided to explore the association between PTSD and cannabis use.

Are Cannabis or Cannabinoids an Effective Treatment for PTSD Symptoms?

Systematic Reviews

The committee did not identify a good- or fair-quality systematic review that reported on medical cannabis as an effective treatment for PTSD symptoms.

Primary Literature

We identified a fair-quality double-blind randomized crossover trial (Jetly et al., 2015) conducted in Canadian male military personnel with trauma-related nightmares despite standard treatments for PTSD. Ten participants were randomized to nabilone 0.5 mg that was titrated to a daily maximum of 3.0 mg or else to a placebo for 7 weeks. Following a 2-week washout period, subjects were then treated with the other study treatment and followed for an additional 7 weeks. Effects on sleep, nightmares, and global clinical state were assessed by the investigators; sleep time and general well-being were self-reported. Nightmares, global clinical state, and general well-being were improved more with nabilone treatment than placebo treatment ($p < 0.05$). There was no effect on sleep quality and quantity. Global clinical state was rated as very much improved or much improved for 7 of 10 subjects in the nabilone treatment period and 2 of 10 subjects in the placebo treatment periods.

Discussion of Findings

A single small crossover trial suggests potential benefit from the pharmaceutical cannabinoid nabilone. This limited evidence is most applicable to male veterans and contrasts with non-randomized studies showing limited evidence of a statistical association between cannabis use (*plant derived forms*) and *increased* severity of posttraumatic stress disorder symptoms among individuals with posttraumatic stress disorder (see Chapter 12). A search of the grey literature identified several recently initiated randomized controlled trials examining the benefits and harms of marijuana for PTSD.[11] One trial, examines the effects of four different types of cannabis with varying THC and CBD content on PTSD symptoms in 76 veterans (Bonn-Miller, 2016). Another trial is a Canadian study that evaluates different formulations of THC and CBD in 42 adults with PTSD (Eades, 2016). If these trials are successfully completely, they will

[11] Clinicaltrials.gov: NCT02102230, NCT02874898, NCT02517424, NCT02759185.

add substantially to the knowledge base, expanding the range of cannabinoids evaluated and the opportunity to examine the consistency of effects across studies.

CONCLUSION 4-20 There is limited evidence (one single, small fair-quality trial) that nabilone is effective for improving symptoms of posttraumatic stress disorder.

SCHIZOPHRENIA AND OTHER PSYCHOSES

Schizophrenia spectrum disorders and other psychotic disorders are mental health disorders characterized by three different classes of symptoms: positive symptoms (e.g., delusions, hallucinations, or disorganized or abnormal motor behavior), negative symptoms (e.g., diminished emotional expression, lack of interest or motivation to engage in social settings, speech disturbance, or anhedonia), and impaired cognition (e.g., disorganized thinking) (APA, 2013, p. 87; NIMH, 2015). Evidence suggests that the prevalence of cannabis use among people with schizophrenia is generally higher among the general population (McLoughlin et al., 2014). In most of the studies reviewed below, schizophrenia, schizophreniform disorder, schizoaffective disorder, and psychotic disorders are used as aggregate endpoints.

Are Cannabis or Cannabinoids an Effective Treatment for the Mental Health Outcomes of Patients with Schizophrenia or Other Psychoses?

Systematic Reviews

Two good-quality reviews (McLoughlin et al., 2014; Whiting et al., 2015) evaluated cannabinoids for the treatment of psychosis. We focus on the good-quality review by Whiting et al. as it is more current. Two RCTS with high-risks-of-bias (71 total participants with schizophrenia or schizophreniform psychosis) compared cannabidiol to the atypical antipsychotic amisulpride or a placebo. One trial reported no difference on mental health between CBD (maximum dose 800 mg/day) and amisulpride (maximum dose 800 mg/day) at 4 weeks (brief psychiatric rating scale mean difference −0.10, 95% CI = −9.20–8.90) or on mood (positive and negative syndrome scale mean difference 1.0; 95% CI = −12.6–14.6). A crossover trial showed no difference in effect on mood between CBD (maximum dose 600 mg/day) and placebo (positive and negative symptom scale mean difference 1, 95% CI = −12.60–14.60; Scale range 30–210).

Primary Literature

The committee did not identify any good-quality primary literature that reported on medical cannabis as an effective treatment for the mental health outcomes of patients with schizophrenia or other psychoses and that were published subsequent to the data collection period of the most recently published good- or fair-quality systematic review addressing the research question.

Discussion of Findings

Good-quality systematic reviews identified only two, small, unclear- to high-risk-of-bias trials evaluating cannabinoids for the treatment of schizophrenia. These studies provide only limited evidence due to the risk of bias, the short-term follow-up, and the evaluation of a single cannabinoid. Furthermore, the larger trial was designed to detect a moderate benefit of cannabidiol compared to the antipsychotic amisulpride, but it enrolled only 60 percent of the planned sample. Thus, it did not have the statistical power to detect small or moderate differences between CBD and amisulpride. Overall, the evidence is insufficient to determine if cannabidiol is an effective treatment for individuals with schizophrenia or schiophreniform psychosis.

In Chapter 12, the committee reviews epidemiological evidence to examine the association between cannabis use and the development of schizophrenia and other psychoses, as well as the impact of cannabis use on the disorder's course or symptoms.

CONCLUSION 4-21 There is insufficient evidence to support or refute the conclusion that cannabidiol is an effective treatment for the mental health outcomes in individuals with schizophrenia or schizophreniform psychosis.

RESESARCH GAPS

In reviewing the research evidence described above, the committee has identified the following research gaps exist concerning the effectiveness of cannabidiol or cannabidiol-enriched cannabis in treating:

- spasticity due to paraplegia from spinal cord injury
- cancer in general
- treating chemotherapy-induced nausea and vomiting
- symptoms of irritable bowel syndrome
- epilepsy
- symptoms associated with amyotrophic lateral sclerosis
- motor function and cognitive performance associated with Huntington's Disease
- motor system symptoms associated with Parkinson's disease or the levodopa-induced dyskinesia
- achieving abstinence or reduction in the use of addictive substances, including cannabis itself
- sleep outcomes in individuals with primary chronic insomnia
- posttraumatic stress disorder symptoms
- mental health outcomes in individuals with schizophrenia or schizophreniform psychosis
- cannabidiol short-term relief from anxiety symptoms

SUMMARY

This chapter outlines the committee's efforts to review the current evidence base for the potential efficacy of cannabis or cannabinoids on prioritized health conditions. The health conditions reviewed in this chapter include chronic pain, chemotherapy-induced nausea and vomiting; anorexia and weight loss associated with HIV; cancer; irritable bowel syndrome; epilepsy, spasticity, Tourette syndrome, Alzheimer's disease, amyotrophic lateral sclerosis, Huntington's disease, Parkinson's disease, dementia, traumatic brain injury, glaucoma, addiction, anxiety, depression, sleep disorders, posttraumatic stress disorder, and schizophrenia and other psychoses. The committee has formed a number of research conclusions related to these health endpoints; however, it is important that the chapter conclusions are interpreted within the context of the limitations discussed in the Discussion of Findings sections above. See Box 4-1 for a summary list of the chapter's conclusions.

We found conclusive or substantial evidence (ranging in modest to moderate effect) for benefit from cannabis or cannabinoids for chronic pain, chemotherapy-induced nausea and vomiting, and patient-reported symptoms of spasticity associated with multiple sclerosis. For chemotherapy-induced nausea and vomiting and spasticity associated with multiple sclerosis, the primary route of administration examined was the oral route. For chronic pain, most studies examined oral cannabis extract, although some examined smoked or vaporized cannabis. It is unknown whether and to what degree the results of these studies can be generalized to other products and routes of administration. For many of the other conditions discussed above, there is insufficient or no evidence upon which to base conclusions about therapeutic effects. The potential efficacy of cannabinoids for several of these conditions such as posttraumatic stress disorder and epilepsy should be prioritized given the substantial number of persons using cannabis for those conditions (Cougle et al., 2011; Massot-Tarrús and McLachlan, 2016). As identified in the chapter's Discussion of Findings sections, there are common themes in the type of study limitations found in this evidence base. The most common are limitations in the study design (e.g., a lack of appropriate control groups, a lack of long-term follow-ups), small sample sizes, and research gaps in examining the potential therapeutic benefits of different forms of cannabis (e.g., cannabis plant). These limitations highlight the need for substantial research to provide comprehensive and conclusive evidence on the therapeutic effects of cannabis and cannabinoids.

BOX 4-1
Summary of Chapter Conclusions*

There is conclusive or substantial evidence that cannabis or cannabinoids are effective:

- For the treatment of chronic pain in adults (cannabis) (4-1)
- As anti-emetics in the treatment of chemotherapy-induced nausea and vomiting (oral cannabinoids) (4-3)
- For improving patient-reported multiple sclerosis spasticity symptoms (oral cannabinoids) (4-7a)

There is moderate evidence that cannabis or cannabinoids are effective for:

- Improving short-term sleep outcomes in individuals with sleep disturbance associated with obstructive sleep apnea syndrome, fibromyalgia, chronic pain, and multiple sclerosis (cannabinoids, primarily nabiximols) (4-19)

There is limited evidence that cannabis or cannabinoids are effective for:

- Increasing appetite and decreasing weight loss associated with HIV/AIDS (cannabis and oral cannabinoids) (4-4a)
- Improving clinician-measured multiple sclerosis spasticity symptoms (oral cannabinoids) (4-7a)
- Improving symptoms of Tourette syndrome (THC capsules) (4-8)
- Improving anxiety symptoms, as assessed by a public speaking test, in individuals with social anxiety disorders (cannabidiol) (4-17)
  Improving symptoms of posttraumatic stress disorder (nabilone; one single, small fair-quality trial) (4-20)

There is limited evidence of a statistical association between cannabinoids and:

- Better outcomes (i.e., mortality, disability) after a traumatic brain injury or intracranial hemorrhage (4-15)

There is limited evidence that cannabis or cannabinoids are *ineffective* for:

- Improving symptoms associated with dementia (cannabinoids) (4-13)
- Improving intraocular pressure associated with glaucoma (cannabinoids) (4-14)
  Reducing depressive symptoms in individuals with chronic pain or multiple sclerosis (nabiximols, dronabinol, and nabilone) (4-18)

There is no or insufficient evidence to support or refute the conclusion that cannabis or cannabinoids are an effective treatment for:

- Cancers, including glioma (cannabinoids) (4-2)
- Cancer-associated anorexia cachexia syndrome and anorexia nervosa (cannabinoids) (4-4b)
- Symptoms of irritable bowel syndrome (dronabinol) (4-5)
- Epilepsy (cannabinoids) (4-6)
- Spasticity in patients with paralysis due to spinal cord injury (cannabinoids) (4-7b)
- Symptoms associated with amyotrophic lateral sclerosis (cannabinoids) (4-9)
- Chorea and certain neuropsychiatric symptoms associated with Huntington's disease (oral cannabinoids) (4-10)
- Motor system symptoms associated with Parkinson's disease or the levodopa-induced dyskinesia (cannabinoids) (4-11)
- Dystonia (nabilone and dronabinol) (4-12)
- Achieving abstinence in the use of addictive substances (cannabinoids) (4-16)
- Mental health outcomes in individuals with schizophrenia or schizophreniform psychosis (cannabidiol) (4-21)

*Numbers in parentheses corresponds with chapter conclusion number.

REFERENCES

Abel, E. L. 1975. Cannabis: Effects on hunger and thirst. *Behavioral Biology* 15(3):255-281.

Abrams, D. I., C. A. Jay, S. B. Shade, H. Vizoso, H. Reda, S. Press, M. E. Kelly, M. C. Rowbotham, and K. L. Petersen. 2007. Cannabis in painful HIV-associated sensory neuropathy: A randomized placebo-controlled trial. *Neurology* 68(7):515–521.

ADAA (Anxiety and Depression Association of America). 2016. Depression. https://www.adaa.org/understanding-anxiety/depression (accessed November 17, 2016).

Allsop, D. J., J. Copeland, N. Lintzeris, A. J. Dunlop, M. Montebello, C. Sadler, G. R. Rivas, R. M. Holland, P. Muhleisen, M. M. Norberg, J. Booth, and I. S. McGregor. 2014. Nabiximols as an agonist replacement therapy during cannabis withdrawal: A randomized clinical trial. *JAMA Psychiatry* 71(3):281–291.

Andreae, M. H., G. M. Carter, N. Shaparin, K. Suslov, R. J. Ellis, M. A. Ware, D. I. Abrams, H. Prasad, B. Wilsey, D. Indyk, M. Johnson, and H. S. Sacks. 2015. Inhaled cannabis for chronic neuropathic pain: A meta-analysis of individual patient data. *Journal of Pain* 16(12):1121–1232.

Andries, A., J. Frystyk, A. Flyvbjerg, and R. K. Støving. 2014. Dronabinol in severe, enduring anorexia nervosa: A randomized controlled trial. *International Journal of Eating Disorders* 47(1):18-23.

APA (American Psychiatric Association). 2013. *Diagnostic and statistical manual of mental disorders* (5th ed.). Arlington, VA: American Psychiatric Publishing.

Armstrong, M. J., and J. M. Miyasaki. 2012. Evidence-based guideline: Pharmacologic treatment of chorea in huntington disease: Report of the guideline development subcommittee of the american academy of neurology. *Neurology* 79(6):597–603.

ASA (American Sleep Association). Sleep and sleep disorder statistics. 2016. https://www.sleepassociation.org/sleep/sleep-statistics (accessed October 25, 2016).

Ashworth, B. 1964. Preliminary trial of carisoprodol in multiple sclerosis. *The Practitioner* 192:540–542.

Baker, D., G. Pryce, G. Giovannoni, and A. J. Thompson. 2003. The therapeutic potential of cannabis. *The Lancet Neurology* 2:291–298.

Belendiuk, K. A., L. L. Baldini, and M. O. Bonn-Miller. 2015. Narrative review of the safety and efficacy of marijuana for the treatment of commonly state-approved medical and psychiatric disorders. *Addiction Science & Clinical Practice* 10:10.

Boehnke, K. F., E. Litinas, and D. J. Clauw. 2016. Medical cannabis use is associated with decreased opiate medication use in a retrospective cross-sectional survey of patients with chronic pain. *Journal of Pain* 17(6):739–744.

Bonn-Miller, M. 2016. Study of four different potencies of smoked marijuana in 76 veterans with chronic, treatment-resistant PTSD. ClinicalTrials.gov. Bethesda, MA: National Library of Medicine. https://clinicaltrials.gov/ct2/show/NCT02759185 (accessed September 28, 2016)

Bradford, A. C., and W. D. Bradford. 2016. Medical marijuana laws reduce prescription medication use in Medicare part D. *Health Affairs* 35(7):1230–1236.

Budney, A. J., R. G. Vandrey, J. R. Hughes, B. A. Moore, and B. Bahrenburg. 2007. Oral delta-9-tetrahydrocannabinol suppresses cannabis withdrawal symptoms. *Drug and Alcohol Dependence* 86(1):22–29.

Bullock, R., R. Chesnut, G. L. Clifton, J. Ghajar, D. W. Marion, R. K. Narayan, D. W. Newell, L. H. Pitts, M. J. Rosner, B. C. Walters, and J. E. Wilberger. 2000. Management and prognosis of severe traumatic brain injury. *Journal of Neurotrauma* 17:451–627.

Canavan, C., J. West, and T. Card. 2014. The epidemiology of irritable bowel syndrome. *Clinical Epidemiology* 6:71–80.

Carroll, C. B., P. G. Bain, L. Teare, X. Liu, C. Joint, C. Wroath, S. G. Parkin, P. Fox, D. Wright, J. Hobart, and J. P. Zajicek. 2004. Cannabis for dyskinesia in Parkinson disease: A randomized double-blind crossover study. *Neurology* 63(7):1245–1250.

CDC (Centers for Disease Control and Prevention). 2015. Bleeding disorders glossary. https://www.cdc.gov/ncbddd/hemophilia/communitycounts/glossary.html (accessed November 17, 2016).

CDC. 2016. TBI: Get the facts. http://www.cdc.gov/traumaticbraininjury/get_the_facts.html (accessed November 17, 2016).

CDPHE (Colorado Department of Public Health and Environment). 2016. 2016 medical marijuana registry statistics. https://www.colorado.gov/pacific/cdphe/2016-medical-marijuana-registry-statistics (accessed October 28, 2016).

Chagas, M. H. N., A. W. Zuardi, V. Tumas, M. A. Pena-Pereira, E. T. Sobreira, M. M. Bergamaschi, A. C. Dos Santos, A. L. Teixeira, J. E. C. Hallak, and J. A. S. Crippa. 2014. Effects of cannabidiol in the treatment of patients with Parkinson's disease: An exploratory double-blind trial. *Journal of Psychopharmacology* 28(11):1088–1092.

Colorado DOR (Department of Revenue). 2016. MED 2015 Annual Update. Denver, CO: Colorado Department of Revenue. https://www.colorado.gov/pacific/sites/default/files/2015%20Annual%20Update%20FINAL%2009262016_1.pdf (accessed December 7, 2016).

Consroe, P., R. Sandyk, R., and S. Sinder. 1986. Open label evaluation of cannabidiol in dystonic movement disorders. *International Journal of Neuroscience* 30(4):277–282.

Consroe, P., J. Laguna, J. Allender, S. Snider, L. Stern, R. Sandyk, K. Kennedy, and K. Schram. 1991. Controlled clinical trial of cannabidiol in Huntington's disease. *Pharmacology, Biochemistry, and Behavior* 40(3):701–708.

Cougle, J. R., M. O. Bonn-Miller, A. A. Vujanovic, M. J. Zvolensky, and K. A. Hawkins. 2011. Posttraumatic stress disorder and cannabis use in a nationally representative sample. *Psychology of Addictive Behaviors* 25(3):554–558.

Curtis, A., I. Mitchell, S. Patel, N. Ives, and H. Rickards. 2009. A pilot study using nabilone for symptomatic treatment in Huntington's disease. *Movement Disorders* 24(15):2254–2259.

Devinsky, O., M. R. Cilio, H. Cross, J. Fernandez-Ruiz, J. French, C. Hill, R. Katz, V. Di Marzo, D. Jutras-Aswad, W. G. Notcutt, J. Martinez-Orgado, P. J. Robson, B. G. Rohrback, E. Thiele, B. Whalley, and D. Friedman. 2014. Cannabidiol: Pharmacology and potential therapeutic role in epilepsy and other neuropsychiatric disorders. *Epilepsia* 55(6):791–802.

Devinsky, O., E. Marsh, D. Friedman, E. Thiele, L. Laux, J. Sullivan, I. Miller, R. Flamini, A. Wilfong, F. Filloux, M. Wong, N. Tilton, P. Bruno, J. Bluvstein, J. Hedlund, R. Kamens, J. Maclean, S. Nangia, N. S. Singhal, C. A. Wilson, A. Patel, and M. R. Cilio. 2016. Cannabidiol in patients with treatment-resistant epilepsy: An open-label interventional trial. *The Lancet Neurology* 15(3):270–278.

Di Napoli, M., A. M. Zha, D. A. Godoy, L. Masotti, F. H. Schreuder, A. Popa-Wagner, and R. Behrouz. 2016. Prior cannabis use is associated with outcome after intracerebral hemorrhage. *Cerebrovascular Disease* 41(5–6):248–255.

Eades, J. 2016. Evaluating safety and efficacy of cannabis in participants with chronic posttraumatic stress disorder. ClinicalTrials.gov. Bethesda, MD: National Library of Medicine. https://clinicaltrials.gov/ct2/show/NCT02517424 (accessed September 28, 2016).

Esfandyari, T., M. Camilleri, I. Ferber, D. Burton, K. Baxter, and A. R. Zinsmeister. 2006. Effect of a cannabinoid agonist on gastrointestinal transit and postprandial satiation in healthy human subjects: A randomized, placebo-controlled study. *Neurogastroenterology & Motility* 18(9):831–838.

Fitzcharles, M. A., P. A. Ste-Marie, W. Hauser, D. J. Clauw, S. Jamal, J. Karsh, T. Landry, S. LeClercq, J. J. McDougall, Y. Shir, K. Shojania, and Z. Walsh. 2016. Efficacy, tolerability, and safety of cannabinoid treatments in the rheumatic diseases: A systematic review of randomized controlled trials. *Arthritis Care and Research* 68(5):681–688.

Foltin, R. W., M. W. Fischman, and M. F. Byrne. 1988. Effects of smoked marijuana on food intake and body weight of humans living in a residential laboratory. *Appetite* 11(1):1–14.

Ford, E.S., A. G. Wheaton, T. J. Cunningham, W. H. Giles, D. P. Chapman, J. B. Croft 2014. Trends in outpatient visits for insomnia, sleep apnea, and prescriptions for sleep medications among US adults: findings from the National Ambulatory Medical Care survey 1999–2010. *Sleep* 37(8):1283–1293.

Fox, S. H., M. Kellett, A. P. Moore, A. R. Crossman, and J. M. Brotchie. 2002. Randomised, double-blind, placebo-controlled trial to assess the potential of cannabinoid receptor stimulation in the treatment of dystonia. *Movement Disorders* 17(1):145–149.

Garcia, A. N., and I. M. Salloum. 2015. Polysomnograhic sleep disturbances in nicotine, caffeine, alcohol, cocaine, opioid, and cannabis use: A focused review. *American Journal of Addiction* 24(7):590–598.

Gardner, E. L. 2005. Endocannabinoid signaling system and brain reward: Emphasis on dopamine. *Pharmacology, Biochemistry & Behavior* 81(2):263–284.

Gelinas, D., R. G. Miller, and M. Abood. 2002. A pilot study of safety and tolerability of delta 9-THC (Marinol) treatment for ALS. *Amyotrophic Lateral Sclerosis and Other Motor Neuron Disorders* 3(Suppl 2):23–24.

Gloss, D. S., and B. Vickrey. 2014. Cannabinoids for epilepsy. *Cochrane Database of Systematic Reviews* 3:CD009270.

Goetz, C. G., G. T. Stebbins, H. M. Shale, A. E. Lang, D. A. Chernik, T. A. Chmura, J. E. Ahlskog, and E. E. Dorflinger. 1994. Utility of an objective dyskinesia rating scale for parkinson's disease: Inter- and intrarater reliability assessment. *Movement Disorders* 9(4):390–394.

Grotenhermen, F., and K. Müller-Vahl. 2012. The therapeutic potential of cannabis and cannabinoids. Deutsches Ärzteblatt International 109(29-30):495–501.

Grundy, R. I. 2002. The therapeutic potential of the cannabinoids in neuroprotection. *Expert Opinion on Investigational Drugs* 11:1365–1374.

GW Pharmaceuticals. 2016. Prescriber information. http://dev-gwpharma.pantheonsite.io/products-pipeline/sativex/prescriber-information-full (accessed November 15, 2016).

Hampson, A. J., M. Grimaldi, J. Axelrod, and D. Wink. 1998. Cannabidiol and delta-9-tetrahydrocannabinol are neuroprotective antioxidants. *Proceedings of the National Academy of Sciences* 95:8268–8273.

Haney, M., C. L. Hart, S. K. Vosburg, J. Nasser, A. Bennett, C. Zubaran, and R. W. Foltin. 2004. Marijuana withdrawal in humans: Effects of oral THC or divalproex. *Neuropsychopharmacology* 29(1):158–170.

Heifets, B. D., and P. E. Castillo. 2009. Endocannabinoid signaling and long-term synaptic plasticity. *Annual Review of Physiology* 71:283–306.

Hemming, M., and P. M. Yellowlees. 1993. Effective treatment of Tourette's syndrome with marijuana. *Journal of Psychopharmacology* 7:389–391.

Ilgen, M. A., K. Bohnert, F. Kleinberg, M. Jannausch, A. S. Bohnert, M. Walton, and F. C. Blow. 2013. Characteristics of adults seeking medical marijuana certification. *Drug and Alcohol Dependence* 132(3):654–659.

IOM (Institute of Medicine). 1999. *Marijuana and medicine: Assessing the science base*. Washington, DC: National Academy Press.

Jatoi, A., H. E. Windschitl, C. L. Loprinzi, J. A. Sloan, S. R. Dakhil, J. A. Mailliard, S. Pundaleeka, C. G. Kardinal, T. R. Fitch, J. E. Krook, P. J. Novotny, and B. Christensen. 2002. Dronabinol versus megestrol acetate versus combination therapy for cancer-associated anorexia: A North Central Cancer Treatment Group study. *Journal of Clinical Oncology* 20(2):567–573.

Jetly, R., A. Heber, G. Fraser, and D. Boisvert. 2015. The efficacy of nabilone, a synthetic cannabinoid, in the treatment of PTSD-associated nightmares: A preliminary randomized, double-blind, placebo-controlled cross-over design study. *Psychoneuroendocrinology* 51:585–588.

Koppel, B. S., J. C. Brust, T. Fife, J. Bronstein, S. Youssof, G. Gronseth, and D. Gloss. 2014. Systematic review: Efficacy and safety of medical marijuana in selected neurologic disorders: Report of the Guideline Development Subcommittee of the American Academy of Neurology. *Neurology* 82(17):1556–1563.

Krishnan, S., R. Cairns, and R. Howard. 2009. Cannabinoids for the treatment of dementia. *Cochrane Database of Systematic Reviews* (2):CD007204.

Leocani, L., A. Nuara, E. Houdayer, I. Schiavetti, U. Del Carro, S. Amadio, L. Straffi, P. Rossi, V. Martinelli, C. Vila, M. P. Sormani, and G. Comi. 2015. Sativex® and clinical-neurophysiological measures of spasticity in progressive multiple sclerosis. *Journal of Neurology* 262(11):2520–2527.

Levin, F. R., J. J. Mariani, D. J. Brooks, M. Pavlicova, W. Cheng, and E. V. Nunes. 2011. Dronabinol for the treatment of cannabis dependence: A randomized, double-blind, placebo-controlled trial. *Drug and Alcohol Dependence* 116(1–3):142–150.

Light, M. K., A. Orens, B. Lewandowski, and T. Pickton. 2014. Market size and demand for marijuana in Colorado. *The Marijuana Policy Group.* https://www.colorado.gov/pacific/sites/default/files/Market%20Size%20and%20Demand%20Study,%20July%209,%202014%5B1%5D.pdf (accessed November 17, 2016).

Lotan, I., T. A. Treves, Y. Roditi, and R. Djaldetti. 2014. Cannabis (medical marijuana) treatment for motor and non-motor symptoms of Parkinson disease: An open-label observational study. *Clinical Neuropharmacology* 37(2):41–44.

Lutge, E. E., A. Gray, and N. Siegfried. 2013. The medical use of cannabis for reducing morbidity and mortality in patients with HIV/AIDS. *Cochrane Database of Systematic Reviews* (4):CD005175.

Massot-Tarrús, A., and R. S. McLachlan. 2016. Marijuana use in adults admitted to a canadian epilepsy monitoring unit. Epilepsy & Behavior 63:73–78.

Marshall, K., L. Gowing, R. Ali, and B. Le Foll. 2014. Pharmacotherapies for cannabis dependence. *Cochrane Database of Systematic Reviews* 12:CD008940.

Mayo Clinic. 2015 Glaucoma. http://www.mayoclinic.org/diseases-conditions/glaucoma/basics/definition/con-20024042 (accessed December 1, 2016).

McLoughlin, B. C., J. A. PushpaRajah, D. Gillies, J. Rathbone, H. Variend, E. Kalakouti, and K. Kyprianou. 2014. Cannabis and schizophrenia. *Cochrane Database of Systematic Reviews* (10):CD004837.

Mechoulam, R., M. Spatz, and E. Shohami. 2002. Endocannabinoids and neuroprotection. *Science's STKE* (129):re5.

Meiri, E., H. Jhangiani, J. J. Vredenburgh, L. M. Barbato, F. J. Carter, H. M. Yang, and V. Baranowski. 2007. Efficacy of dronabinol alone and in combination with ondansetron versus ondansetron alone for delayed chemotherapy-induced nausea and vomiting. *Current Medical Research and Opinion* 23(3):533–543.

Mohanraj, R., and M. J. Brodie. 2006. Diagnosing refractory epilepsy: Response to sequential treatment schedules. *European Journal of Neurology* 13(3):277–282.

Morgan, C. J. A., R. K. Das, A. Joye, H. V. Curran, and S. K. Kamboj. 2013. Cannabidiol reduces cigarette consumption in tobacco smokers: Preliminary findings. *Addictive Behaviors* 38(9):2433–2436.

Müller-Vahl, K. R., A. Koblenz , M. Jöbges, H. Kolbe, H. M. Emrich, and U. Schneider. 2001. Influence of treatment of Tourette syndrome with Δ^9-tetrahydrocannabinol (Δ^9-THC) on neuropsychological performance. *Pharmacopsychiatry* 34(1):19–24.

Müller-Vahl, K. R., U. Schneider, A. Koblenz, M. Jöbges, H. Kolbe, T. Daldrup, and H. M. Emrich. 2002. Treatment of Tourette's syndrome with Δ^9-tetrahydrocannabinol (THC): A randomized crossover trial. *Pharmacopsychiatry* 35(2):57–61.

Müller-Vahl, K. R., H. Prevedel, K. Theloe, H. Kolbe, H. M. Emrich, and U. Schneider. 2003a. Treatment of Tourette syndrome with delta-9-tetrahydrocannabinol (Δ^9-THC): No influence on neuropsychological performance. *Neuropsychopharmacology* 28(2):384–388.

Müller-Vahl, K. R., U. Schneider, H. Prevedel, K. Theloe, H. Kolbe, T. Daldrup, and H. M. Emrich. 2003b. Delta 9-tetrahydrocannabinol (THC) is effective in the treatment of tics in Tourette syndrome: A 6-week randomized trial. *Journal of Clinical Psychiatry* 64(4):459–465.

NCI (National Cancer Institute). 2015. What is cancer? https://www.cancer.gov/about-cancer/understanding/what-is-cancer (accessed November 16, 2016).

NCI. 2016. Cancer statistics. https://www.cancer.gov/about-cancer/understanding/statistics (accessed October 28, 2016).

NCSL (National Conference of State Legislatures). 2016. State medical marijuana laws. http://www.ncsl.org/research/health/state-medical-marijuana-laws.aspx (accessed November 17, 2016).

NEI (National Eye Institute). n.d. What you should know. https://nei.nih.gov/glaucoma/content/english/know (accessed November 17, 2016).
Nguyen, B., D. Kim, S. Bricker, F. Bongard, A. Neville, B. Putnam, J. Smith, and D. Plurad. 2014. Effects of marijuana use on outcomes in traumatic brain injury. *American Surgeon* 80(10):979–983.
NIA (National Institute on Aging). n.d. About Alzheimer's Disease: Other Dementias. https://www.nia.nih.gov/alzheimers/topics/other-dementias (accessed December 22, 2016).
NIDA (National Institute on Drug Abuse). 2015. Research Reports: Marijuana. https://www.drugabuse.gov/sites/default/files/mjrrs_4_15.pdf (accessed December 8, 2016).
NIDDK (National Institute of Diabetes and Digestive and Kidney Diseases). 2015. Definition and facts for irritable bowel syndrome. www.niddk.nih.gov/health-information/health-topics/digestive-diseases/irritable-bowel-syndrome/pages/definition-facts.aspx (accessed October 18, 2016).
NIH (National Institues of Health). 2013. The dementias: Hope through research. file:///C:/Users/MMasiello/Downloads/the-dementias-hope-through-research.pdf (accessed December 28, 2016).
NIH. 2016a. Short-term exposure for PTSD (STEP). https://clinicaltrials.gov/ct2/show/NCT02874898 (accessed September 30, 2016).
NIH. 2016b. The impact of CBT-I on cannabis cessation outcomes. https://clinicaltrials.gov/ct2/show/NCT02102230 (accessed September 30, 2016).
NIMH (National Institute of Mental Health). 2015. Schizophrenia. https://www.nimh.nih.gov/health/publications/schizophrenia-booklet-12-2015/index.shtml (accessed October 28, 2016).
NIMH. n.d. Any mental illness (AMI) among U.S. adults. https://www.nimh.nih.gov/health/statistics/prevalence/any-mental-illness-ami-among-us-adults.shtml (accessed November 17, 2016).
NINDS (National Institute of Neurological Disorders and Stroke). 2014. Tourette syndrome fact sheet. http://www.ninds.nih.gov/disorders/tourette/detail_tourette.htm (accessed December 2, 2016).
NINDS. 2015. Parkinson's disease: Challenges, progress, and promise. https://catalog.ninds.nih.gov/pubstatic//15-5595/15-5595.pdf (accessed December 28, 2016).
NINDS. 2016a. Dystonias fact sheet. http://www.ninds.nih.gov/disorders/dystonias/detail_dystonias.htm (accessed November 18, 2016).
NINDS. 2016b. The epilepsies and seizures: Hope through research. http://www.ninds.nih.gov/disorders/epilepsy/detail_epilepsy.htm (accessed November 16, 2016).
NINDS. 2016c. Traumatic brain injury: Hope through research. http://www.ninds.nih.gov/disorders/tbi/detail_tbi.htm (accessed November 16, 2016).
OHA (Oregon Health Authority). 2016. Oregon medical marijuana program statistics. https://public.health.oregon.gov/DiseasesConditions/ChronicDisease/MedicalMarijuanaProgram/Pages/data.aspx (accessed October 28, 2016).
Pandyan, A. D., G. R. Johnson, C. I. Price, R. H. Curless, M. P. Barnes, and H. Rodgers. 1999. A review of the properties and limitations of the Ashworth and modified Ashworth scales as measures of spasticity. *Clinical Rehabilitation* 13(5):373–383.
Pandyan, A. D., M. Gregoric, M. P. Barnes, D. E. Wood, F. v. Wijck, J. H. Burridge, H. J. Hermens, and G. R. Johnson. 2005. Spasticity: Clinical perceptions, neurological realities and meaningful measurement. *Disability and Rehabilitation* 27(1-2):1–2.
Pazos, M. R., O. Sagredo, and J. Fernandez-Ruiz. 2008. The endocannabinoid system in Huntington's disease. *Current Pharmaceutical Design* 14(23):2317–2325.
PDF (Parkinson's Disease Foundation). 2016a. What is Parkinson's disease? http://www.pdf.org/en/about_pd (accessed October 18, 2016).
PDF. 2016b. Statistics on Parkinson's. http://www.pdf.org/en/parkinson_statistics (accessed October 18, 2016).

Pertwee, R. G. 2012. Targeting the endocannabinoid system with cannabinoid receptor agonists: Pharmacological strategies and therapeutic possibilities. *Philosophical Transactions of the Royal Society of London - Series B: Biological Sciences* 367(1607):3353–3363.

Phillips, R. S., A. J. Friend, F. Gibson, E. Houghton, S. Gopaul, J. V. Craig, and B. Pizer. 2016. Antiemetic medication for prevention and treatment of chemotherapy-induced nausea and vomiting in childhood. *Cochrane Database of Systematic Reviews* (2):CD007786.

Pinto, L., A. A. Izzo, M. G. Cascio, T. Bisogno, K. Hospodar-Scott, D. R. Brown, N. Mascolo, V. Di Marzo, and F. Capasso. 2002. Endocannabinoids as physiological regulators of colonic propulsion in mice. *Gastroenterology* 123:227–234.

Prud'homme, M., R. Cata, and D. Jutras-Aswad. 2015. Cannabidiol as an intervention for addictive behaviors: A systematic review of the evidence. *Substance Abuse: Research and Treatment* 9:33–38.

Prum, Jr., B. E., L. F. Rosenberg, S. J. Gedde, S. L. Mansberger, J. D. Stein, S. E. Moroi, L. W. Herndon Jr, M. C. Lim, and R. D. Williams. 2016. Primary open-angle glaucoma preferred practice pattern® guidelines. *Ophthalmology* 123(1):P41–P111.

Redler, R. L., and N. V. Dokholyan. 2012. Chapter 7–The Complex Molecular Biology of Amyotrophic Lateral Sclerosis (ALS). *In Progress in Molecular Biology and Translational Science*. Volume 107, edited by B. T. David: Cambridge, Massachusetts, Academic Press. Pp. 215–262.

Richards, B. L., S. L. Whittle, D. M. Van Der Heijde, and R. Buchbinder. 2012. Efficacy and safety of neuromodulators in inflammatory arthritis: A Cochrane systematic review. *Journal of Rheumatology* 39(Suppl 90):28–33.

Rocha, F. C. M., J. G. dos Santos Jr., S. C. Stefano, and D. X. da Silveira. 2014. Systematic review of the literature on clinical and experimental trials on the antitumor effects of cannabinoids in gliomas. *Journal of Neuro-Oncology* 116(1):11–24.

Rosenberg, E. C., R. W. Tsien, B. J. Whalley, and O. Devinsky. 2015. Cannabinoids and epilepsy. *Neurotherapeutics* 12(4):747–768.

Rossi, S., G. Bernardi, and D. Centonze. 2010. The endocannabinoid system in the inflammatory and neurodegenerative processes of multiple sclerosis and of amyotrophic lateral sclerosis. *Experimental Neurology* 224(1):92–102.

Russo, E. B., G. W. Guy, and P.,J. Robson. 2007. Cannabis, pain, and sleep: Lessons from therapeutic clinical trials of Sativex, a cannabis-based medicine. *Chemistry & Biodiversity* 4(8):1729–1743.

Sandyk, R., and G. Awerbuch. 1988. Marijuana and Tourette's syndrome. *Journal of Clinical Psychopharmacology* 8:444–445

Sateia, M. J. 2014. International classification of sleep disorders, third edition: Highlights and modifications. *Chest* 146(5):1387–1394.

Schauer, G. L., B. A. King, R. E. Bunnell, G. Promoff, and T. A. McAfee. 2016. Toking, vaping, and eating for health or fun: Marijuana use patterns in adults, U.S., 2014. *American Journal of Preventive Medicine* 50(1):1–8.

Shen, M., and S. A. Thayer. 1998. Cannabinoid receptor agonists protect cultured rat hippocampal neurons from excitotoxicity. *Molecular Pharmacology* 54:459–462.

Sieradzan, K. A., S. H. Fox, M. Hill, J. P. R. Dick, A. R. Crossman, and J. M. Brotchie. 2001. Cannabinoids reduce levodopa-induced dyskinesia in Parkinson's disease: A pilot study. *Neurology* 57(11):2108–2111.

Smith, L. A., F. Azariah, T. C. V. Lavender, N. S. Stoner, and S. Bettiol. 2015. Cannabinoids for nausea and vomiting in adults with cancer receiving chemotherapy. *Cochrane Database of Systematic Reviews* (11):CD009464.

Snedecor, S. J., L. Sudharshan, J. C. Cappelleri, A. Sadosky, P. Desai, Y. J. Jalundhwala, and M. Botteman. 2013. Systematic review and comparison of pharmacologic therapies for neuropathic pain associated with spinal cord injury. *Journal of Pain Research* 6:539–547.

Strasser, F., D. Luftner, K. Possinger, G. Ernst, T. Ruhstaller, W. Meissner, Y. D. Ko, M. Schnelle, M. Reif, and T. Cerny. 2006. Comparison of orally administered cannabis extract and delta-9-

tetrahydrocannabinol in treating patients with cancer-related anorexia-cachexia syndrome: A multicenter, phase III, randomized, double-blind, placebo-controlled clinical trial from the cannabis-in-cachexia-study-group. *Journal of Clinical Oncology* 24(21):3394–3400.

Timpone, J. G., D. J. Wright, N. Li, M. J. Egorin, M. E. Enama, J. Mayers, and G. Galetto. 1997. The safety and pharmacokinetics of single-agent and combination therapy with megestrol acetate and dronabinol for the treatment of HIV wasting syndrome. *AIDS Research and Human Retroviruses* 13(4):305–315.

Todaro, B. 2012. Cannabinoids in the treatment of chemotherapy-induced nausea and vomiting. Journal of the National Comprehensive Cancer Network 10(4):487–492.

Tomida, I., A. Azuara-Blanco,H. House, M. Flint, R. Pertwee, and P. Robson. 2007. Effect of sublingual application of cannabinoids on intraocular pressure: A pilot study. *Journal of Glaucoma* 15(5):349–353.

Tzadok , M., S. Uliel-Siboni, I. Linder, U. Kramer, O. Epstein, S. Menascu, A. Nissenkorn, O. B. Yosef, E. Hyman, D. Granot, M. Dor, T. Lerman-Sagie, and B. Ben-Zeev. 2016. CBD-enriched medical cannabis for intractable pediatric epilepsy: The current Israeli experience. *Seizure* 35:41–44.

Uribe Roca, M., F. Micheli, and R. Viotti. 2005. Cannabis sativa and dystonia secondary to Wilson's disease. *Movement Disorders* 20(1):113–115.

van den Elsen, G. A. H., A. I. A. Ahmed, M. Lammers, C. Kramers, R. J. Verkes, M. A. van der Marck, and M. G. M. O. Rikkert. 2014. Efficacy and safety of medical cannabinoids in older subjects: A systematic review. *Ageing Research Reviews* 14(1):56–64.

van den Elsen, G. A. H., A. I. A. Ahmed, R. J. Verkes, C. Kramers, T. Feuth, P. B. Rosenberg, M. A. Van Der Marck, and M. G. M. Olde Rikkert. 2015. Tetrahydrocannabinol for neuropsychiatric symptoms in dementia: A randomized controlled trial. *Neurology* 84(23):2338–2346.

van Laere, K., C. Casteels, I. Dhollander, K. Goffin, L. Grachev, G. Bormans, and W. Vandenberghe. 2010. Widespread decrease of type 1 cannabinoid receptor availability in Huntington disease in vivo. *Journal of Nuclear Medicine* 51(9):1413–1417.

Volicer, L., M. Stelly, J. Morris, J. McLaughlin, and B. J. Volicer. 1997. Effects of dronabinol on anorexia and disturbed behavior in patients with Alzheimer's disease. *International Journal of Geriatric Psychiatry* 12(9):913–919.

Wade, D. T., C. Collin, C. Stott, and P. Duncombe. 2010. Meta-analysis of the efficacy and safety of sativex (nabiximols) on spasticity in people with multiple sclerosis. *Multiple Sclerosis* 16(6):707–714.

Wallace, M. S., T. D. Marcotte, A. Umlauf, B. Gouaux, and J. H. Atkinson. 2015. Efficacy of inhaled cannabis on painful diabetic neuropathy. *Journal of Pain* 16(7):616–627.

Walther, S., R. Mahlberg, U. Eichmann, and D. Kunz. 2006. Delta-9-tetrahydrocannabinol for nighttime agitation in severe dementia. *Psychopharmacology* 185(4):524–528.

Weber, M., B. Goldman, and S. Truniger. 2010. Tetrahydrocannabinol (THC) for cramps in amyotrophic lateral sclerosis: A randomised, double-blind crossover trial. *Journal of Neurology, Neurosurgery & Psychiatry* 81(10):1135–1140.

Whiting, P. F., R. F. Wolff, S. Deshpande, M. Di Nisio, S. Duffy, A. V. Hernandez, J. C. Keurentjes, S. Lang, K. Misso, S. Ryder, S. Schmidlkofer, M. Westwood, and J. Kleijnen. 2015. Cannabinoids for medical use: A systematic review and meta-analysis. *Journal of the American Medical Association* 313(24):2456–2473.

Wilsey, B. L., R. Deutsch, E. Samara, T. D. Marcotte, A. J. Barnes, M. A. Huestis, and D. Le. 2016. A preliminary evaluation of the relationship of cannabinoid blood concentrations with the analgesic response to vaporized cannabis. *Journal of Pain Research* 9:587–598.

Wong, B. S., M. Camilleri, D. Eckert, P. Carlson, M. Ryks, D. Burton, and A. R. Zinsmeister. 2012. Randomized pharmacodynamic and pharmacogenetic trial of dronabinol effects on colon transit in irritable bowel syndrome–diarrhea. *Neurogastroenterology & Motility* 24(4):358-e169.

Wright, K., N. Rooney, M. Feeney, J. Tate, D. Robertson, M. Welham, and S. Ward. 2005. Differential expression of cannabinoid receptors in the human colon: Cannabinoids promote epithelial wound healing. *Gastroenterology* 129(2):437–453.

Zadikoff, C., P. Wadia, J. Miyasaki, R. Char, A. Lang, J. So, and S. Fox. 2011. Cannabinoid, CB1 agonists in cervical dystonia: Failure in a phase IIa randomized controlled trial. *Basal Ganglia* 1(2):91–95.

Zajicek, J., J. Hobart, A. Slade, and P. Mattison. 2012. Multiple sclerosis and extract of cannabis: Results of the MUSEC trial. *Journal of Neurology, Neurosurgery, and Psychiatry* 83(11):1125–1132.

Part III
Other Health Effects

5
Cancer

Chapter Highlights
• The evidence suggests that smoking cannabis does not increase the risk for certain cancers (i.e., lung, head and neck) in adults. • There is modest evidence that cannabis use is associated with one sub-type of testicular cancer. • There is minimal evidence that parental cannabis use during pregnancy is associated with greater cancer risk in offspring.

Cancer is a major public health problem in the United States. With 1,685,210 new cancer cases and 595,690 cancer-related deaths expected to occur in 2016, it is a leading cause of disease and death among Americans (NCI, 2016). Cannabis use has been associated with cigarette smoking—to which 28.6 percent of all cancer deaths in the United States in 2014 have been attributed—and, like tobacco smoke, cannabis smoke contains carcinogens (Lortet-Tieulent et al., 2016; Tashkin, 2013). These potential risk factors for cancer have prompted epidemiological research examining the association between cannabis use and the risk of developing several types of cancer, including lung, head and neck, testicular, esophageal, and other cancers that occur in adults, as well as cancers that occur in children. The present chapter reviews the findings of three recent, good- to fair-quality systematic reviews, including one pooled analysis, as well as three primary literature articles that best address the committee's research questions of interest. Study limitations and research gaps are noted, and the strength of the available evidence is weighed in six formal conclusions.

CANCER

Is There an Association Between Cannabis Use and the Incidence of Lung Cancer?

Systematic Reviews

Zhang et al. (2015) pooled data on 2,159 lung cancer cases and 2,985 controls from six case-control studies, four of which were unpublished. The impact of key characteristics of cannabis smoking (e.g., intensity and duration of cannabis smoking, cumulative exposure, age at start of smoking) on lung cancer incidence was evaluated for all study participants and for a sub-group who were not tobacco smokers. Among all study participants, there was no statistically significant difference in the risk of lung cancer for habitual cannabis smokers as compared to non-habitual smokers (odds ratio [OR] 0.96, 95% confidence interval [CI] = 0.66–1.38);

similarly, among participants who did not smoke tobacco, the risk of lung cancer was not significantly higher or lower for habitual cannabis smokers than for non-habitual cannabis smokers (OR 1.03, 95% CI = 0.51–2.08).[1] When only adenocarcinoma cases were compared to controls, Zhang et al. (2015, p.898) observed a "suggestive," but still statistically non-significant, association between lung cancer incidence and either smoking more than 1 joint/day (OR 1.73, 95% CI = 0.75–4.00) or having a cumulative exposure of more than 10 joint-years (OR 1.74, 95% CI = 0.85–3.56).

Primary Literature

Huang et al. (2015) conducted an epidemiologic review on the association between cannabis use and the incidence of several cancers, including lung cancer. They evaluated six studies on lung cancer, including Zhang et al. (2015) and two studies included in that review. Of the three remaining studies, two were described by Zhang et al. (2015) as having several limitations, including an inability to adequately control for tobacco use and potential reporting bias, and are not discussed here. The third study evaluated lung cancer risk among 49,321 Swedish male military conscripts over a 40-year period and found that, compared with participants who had reported never using cannabis, those who reported using cannabis more than 50 times at baseline had a statistically significant risk of developing lung cancer (hazard ration [HR] 2.12, 95% CI = 1.08–4.14) after adjusting for tobacco and alcohol use and other confounders (Callaghan et al., 2013).[2]

Discussion of Findings

Zhang et al. (2015) found no statistically significant association between smoking cannabis and lung cancer incidence; this was true for all study participants as well as for the sub-group of study participants who were not tobacco smokers. Although the risk of lung cancer increased as the duration and intensity of cannabis use increased, even participants who smoked most often and for the longest periods of time were not at significantly greater risk than non-habitual smokers. Huang et al. (2015) did not perform a meta-analysis of the lung cancer studies; studies included in that review but not in Zhang et al. (2015) indicate an increased risk for lung cancer associated with smoking cannabis.

Both studies noted several limitations. Zhang et al. (2015) were unable to account for potential effect measure modifiers, including those related to variations in cannabis smoking techniques and in the characteristics of the cannabis smoked. The authors also noted that the small number of participants who were heavy and chronic cannabis users rendered effect estimates for these subgroups imprecise. Finally, the study relied on self-report without biological validation to assess patterns of cannabis, making it impossible to verify the accuracy of cannabis use data. Regarding Callaghan et al. (2013), detailed information on cannabis and tobacco use before and after baseline was lacking, the study did not adjust or account for tobacco

[1] Non-habitual cannabis smokers were defined as those with cumulative cannabis consumption of less than 1 joint-year, including never users. Subjects who did not smoke tobacco were those who reported smoking less than 100 cigarettes over their lifetime, or who fit the cut-offs used in the pooled studies.

[2] There were 49,321 participants at the start of the study, and 44,257 participants involved in the assessment of cannabis risk. Hazard ratio (HR) includes adjustments for tobacco smoking, alcohol consumption, respiratory conditions, and socioeconomic status at time of conscription.

or cannabis during the 40-year follow-up period, the authors were unaware whether study participants mixed tobacco and cannabis, and the self-reporting process was not anonymized.

CONCLUSION 5-1 There is moderate evidence of no statistical association between cannabis smoking and the incidence of lung cancer.

Is There an Association Between Cannabis Use and the Incidence of Head and Neck Cancers?

Systematic Reviews

De Carvalho et al. (2015) conducted a systematic review and meta-analysis of nine case-control studies derived from 6 articles and totaling 13,931 study participants (5,732 cases and 8,199 controls) in order to evaluate the association between cannabis use and the incidence of head and neck cancers, including upper aerodigestive tract, oral cavity, and nasopharyngeal cancers as well as on head and neck squamous cell carcinoma. After adjusting for tobacco use, age, gender, and race, the meta-analysis found no significant association between cannabis use and head and neck cancers (OR 1.021, 95% CI = 0.912–1.143). The authors concluded that there was "insufficient epidemiological evidence to support a positive or negative association of marijuana use and the development of [head and neck cancers]" (de Carvalho et al., 2015, p. 1755).

Primary Literature

The committee did not identify any good-quality primary literature that reported on the association between cannabis use and head and neck cancers and were published subsequent to the data collection period of the most recently published good- or fair-quality systematic review addressing the research question.

Discussion of Findings

In their review, de Carvalho et al. (2015) noted several limitations particular to individual studies. First, although a non-significant association was observed for head and neck cancers as a group, this finding does not preclude the existence of a significant positive or negative association between cannabis use and the incidence of specific types of head and neck cancer. The systematic review also relied on cohort studies, which may not detect less pronounced risks or risks that emerge over longer periods. Finally, differences in the methods employed in these studies prevented an analysis of how the characteristics of cannabis use (e.g., frequency, duration, method) affect the risk of head and neck cancers.

CONCLUSION 5-2 There is moderate evidence of no statistical association between cannabis use and the incidence of head and neck cancers.

Is There an Association Between Cannabis Use and the Incidence of Testicular Cancer?

Systematic Reviews

Gurney et al. (2015) conducted a systematic review and meta-analysis on the association between cannabis use and testicular germ cell tumors. The authors identified three case-control studies totaling 2,138 study participants (719 cases and 1,419 controls). Compared to participants who never smoked cannabis, participants who reported ever smoking cannabis had a statistically non-significant increased risk of developing testicular germ cell tumors (OR 1.19, 95% CI = 0.72–1.95). By comparison, statistically significant associations between cannabis use and the risk of developing testicular germ cell tumors were seen for the subgroups of participants who were current smokers (OR 1.62, 95% CI = 1.13–2.31) or who reported smoking cannabis at least once a week (OR 1.92, 95% CI = 1.35–2.72) or for 10 years or longer (OR 1.50, 95% CI = 1.08–2.09). Among current users, including the subgroups of those who used cannabis at least once weekly or for at least 10 years, the risk of developing non-seminoma tumors was higher than the risk of developing seminoma tumors. For example, compared to never smokers, participants who smoked at least once per week had a statistically significant risk of developing non-seminoma tumors (OR 2.59, 95% CI = 1.60–4.19), while the risk for developing seminoma tumors was not statistically significant (OR 1.27, 95% CI = 0.77–2.11). Gurney et al. (2015) observed that, because non-seminoma tumors are frequently diagnosed at a younger age than seminoma tumors, the stronger association between cannabis use and non-seminoma tumors suggests "puberty (rather than later in life) as the key point of exposure" (Gurney et al., 2015, p. 8).

Primary Literature

Huang et al. (2015) conducted a review and meta-analysis of the same three studies reviewed by Gurney et al. (2015) and found no association between participants who had ever smoked cannabis and the risk of developing testicular cancer. However, compared to participants who had never smoked cannabis, heavy users who had smoked one or more times per day or week (OR 1.56, 95% CI = 1.09–2.23) and chronic users who had smoked for 10 years or longer (OR 1.50, 95% CI = 1.08–2.09) had a statistically significant risk of developing testicular cancer.

Discussion of Findings

Gurney et al. (2015) found a statistically significant association between current, frequent, or chronic cannabis use and the incidence of non-seminoma-type testicular germ cell tumors. By comparison, cannabis use was not associated with a statistically significant risk of developing seminoma-type testicular germ cell tumors. Lacking further evidence, an extrapolation of this association to other types of testicular cancer is unwarranted. Huang et al. (2015) found an association between the incidence of testicular cancer (without further specification) and cannabis use that was frequent or of long duration.

Gurney et al. (2015) highlighted several limitations of their review. First, each of the three case-control studies informing the review relied on self-report without biological validation, and the two studies that utilized interviews to collect this data did not indicate whether the interviewers were blinded to the case-control status of the participants. Self-report data cannot be verified and unblended interviewers are a potential source of bias. Second, two of

the studies reported responses rates that were both low and unequal: 67.5 percent to 38.2 percent response rate for cases and 73.3 percent to 43.3 percent response rate for controls. Differences in the prevalence of cannabis use among participants who did and did not respond could bias the odds ratios calculated in these studies. Third, the high and growing prevalence of cannabis use in the general population may render the category "ever-smoker" uninformative, since it will encompass not only frequent and chronic users but also individuals who have only minimal exposure to the drug. A final limitation is that the studies informing the review did not all control for the same, potentially relevant confounders: three studies controlled for age and a history of cryptorchidism, two controlled for alcohol and drug use, and only one controlled for other substance use.

As noted in Gurney et al. (2015), Huang et al. (2015) did not distinguish between seminoma and non-seminoma-type tumors and also failed to assess the quality of the reviewed studies. Additionally, the review included limited information on the methods used to conduct the meta-analysis.

CONCLUSION 5-3 There is limited evidence of a statistical association between current, frequent, or chronic cannabis smoking and non-seminoma-type testicular germ cell tumors.

Is There an Association Between Cannabis Use and the Incidence of Esophageal Cancers?

Systematic Reviews

The committee did not identify a good- or fair-quality systematic review that reported on the association between cannabis use and esophageal cancer.

Primary Literature

The committee identified one primary research study that addressed a potential association with esophageal cancer. To assess the association between cannabis use and the incidence of lung and upper aerodigestive tract cancers, Hashibe et al. (2006) conducted a large population-based case-control study involving 1,040 controls and 1,212 cases, 108 of which were diagnosed with esophageal cancer. Investigators collected data on the use of cannabis, tobacco, and alcohol as well as relevant medical, environmental, and socioeconomic information. After adjustments were made for demographic factors and alcohol and tobacco use, study participants with cumulative cannabis exposure equal to 1 to 10 joint-years were found to have a statistically non-significant decreased risk of developing esophageal cancer compared to participants who never used cannabis (OR 0.77, 95% CI = 0.36–1.6). The risk was further depressed, but still not statistically significant, for participants whose cumulative cannabis exposure was equal to 30 or more joint-years (OR 0.53, 95% CI = 0.22–1.3). Among participants who never smoked cigarettes, the risk of esophageal cancer was not statistically different between those who had ever smoked cannabis and those who had never smoked cannabis (OR 0.79, 95% CI = 0.30–2.1).

Discussion of Findings

In conducting their investigation, Hashibe et al. (2006) addressed several methodological issues of previous studies of the association between cannabis use and cancer incidence. These issues included accounting for tobacco use and other confounders, avoiding measurement errors, and protecting the anonymity of participants. On account of these efforts to preemptively address methodological issues, few limitations were identified that could account for the lower risk of esophageal cancer among cannabis smokers as compared to non-smokers—an unexpected, though not statistically significant, result. The participation rate among esophageal cases was low at 35 percent, creating a potential source of bias if the prevalence of cannabis use was much higher or lower among non-participants with esophageal cancer than among participants with esophageal cancer. The subgroup of participants with esophageal cancer and high levels of cumulative cannabis exposure (i.e., ≥30 joint-years) was relatively small (n = 9), thereby limiting the ability to detect an association between cannabis use and cancer incidence in this group. As with other studies, confounders may not have been entirely controlled for, and measurement errors may have persisted. The authors note these potential limitations, but also speculate that "it is possible that such inverse associations may reflect a protective effect of marijuana" (Hashibe et al., 2006, p. 1833).

CONCLUSION 5-4 There is insufficient evidence to support or refute a statistical association between cannabis smoking and the incidence of esophageal cancer.

Is There an Association Between Cannabis Use and the Incidence of Other Cancers in Adults?

Systematic Reviews

The committee identified no systematic reviews on the association between cannabis exposures and the incidence of other cancers.

Primary Literature

In an epidemiologic review, Huang et al. (2015) reported on the association between cannabis use and the risk of several types of cancer. A cohort study involving 27,920 men and 36,935 women age 15–49 years found that, compared to participants who did not smoke cannabis, self-reported current or former use of cannabis on more than 6 occasions was associated with prostrate cancer in men that never smoked cigarettes (relative risk [RR] 3.1, 95% CI = 1.0–9.5) and with cervical cancer in women that never smoked cigarettes (RR 1.6, 95% CI = 1.2–2.2), after adjusting for age, race, education, and alcohol use (Sidney et al., 1997). However, when compared to participants who did not smoke cannabis or who had smoked cannabis on only 1–6 occasions, those who were current or former cannabis smokers were not at statistically significant risk of developing prostate or cervical cancer, after adjusting for tobacco and alcohol use and other potential confounders.

Another large cohort study involving 133,881 participants aged 25 years and older found that, compared to non-use of cannabis, self-reported cannabis use at least once a month was associated with a statistically significant risk of malignant adult-onset glioma compared to non-

use of cannabis, after controlling for potential confounders, including demographic and socioeconomic factors and alcohol and tobacco use (RR 2.8, 95% CI = 1.3–6.2) (Efird et al., 2004). Compared to participants who did not use cannabis, there was statistically signficant risk of developing brain tumor among those participants who reported using cannabis weekly (RR 3.2, 95% CI = 1.1–9.2) or monthly (RR 3.6, 95% CI = 1.3–10.2).

Huang et al. (2015) also reviewed two studies on non-Hodgkin lymphoma risk. Holly et al. (1999) conducted a population-based case-control study involving 3,376 women and heterosexual men to determine risk factors for non-Hodgkin lymphoma. Compared to participants who never used cannabis, those who reported using cannabis less than 40 times had a statistically significant decreased risk of developing non-Hodgkin lymphoma, after adjusting for age, sex, and education (OR 0.68, 95% CI = 0.55–0.84). Among participants who used cannabis on 40 or more occasions, the risk of non-Hodgkin lymphoma was further depressed (OR 0.57, 95% CI = 0.44–0.74). In another population-based case-control study, 378 HIV-negative men and women diagnosed with non-Hodgkin lymphoma were matched by age, biological sex, race, language of interview, and neighborhood of residence at time of diagnosis to HIV-negative controls (Nelson et al., 1997). There was no statistically significant difference in the risk of developing non-Hodgkin lymphoma among participants who reported using cannabis at any time, as compared to those who reported never using cannabis (OR 0.86, 95% CI = 0.50–1.48). The lack of a statistical difference in non-Hodgkin lymphoma risk between cannabis users and non-users was true whether participants reported using cannabis only 1–5 times (OR 0.68, 95% CI = 0.34–1.38) or on more than 900 occasions (OR 1.09, 95% CI = 0.48–2.48).

Other studies reviewed by Huang et al. (2015) examined the association between cannabis use and the risk of Kaposi's sarcoma, and penile and anal cancer. Maden et al. (1993) conducted a case-control study involving 110 cases and 355 age matched controls to identify risk factors for penile cancer. After adjusting for alcohol and cigarette use, age, and number of sexual partners, there was no statistically significant difference in the risk of developing penile cancer among participants who reported ever using cannabis as compared to those who never used cannabis (OR 1.5, 95 % CI = 0.7–3.2). In a case-control study on risk factors for anal cancer, 148 men and women diagnosed with anal cancer were matched by age, biological sex, year of diagnosis, and area of residence to 166 male and female controls diagnosed with colon cancer (Daling et al., 1987). There was no statistically significant difference in the risk of anal cancer among participants who had ever used cannabis, as compared to those who had never used cannabis, after adjsuting for age, residence, and cigarette use (RR 0.8, 95% CI = 0.2–4.0). Chao et al. (2009) conducted a cohort study to determine the association between use of cannabis and other recreational drugs and the risk of Kaposi's sarcoma in homosexual men coinfected with HIV and human herpes virus 8 (HHV-8). Among 1,335 participants, those who used cannabis in the 6 months preceding data collection were not significantly more likely to develop Kaposi's sarcoma than participants who did not use cannabis during that period (HR 1.00, 95% CI = 0.79–1.28), after adjusting for potential confounders including alcohol use, tobacco smoking, and characteristics of sexual activity.

To assess the association between cannabis use and bladder cancer risk, Thomas et al. (2015) reviewed data from 84,170 men aged 45-69 years old who were participants in the California Men's Health Study. After adjusting for age, race, and body mass index, the risk of developing bladder cancer was significantly reduced for participants who used cannabis but not tobacco, compared to those who used neither cannabis nor tobacco (HR 0.55, 95% CI = 0.31–1.00). After stratifying cannabis use by levels of cumulative cannabis exposure, the authors

found that the depression in bladder cancer risk was statistically significant only for participants who reporting smoking cannabis on 3–10 occasions (HR 0.57, 95% CI = 0.34–0.96). Similarly, stratification by participant age revealed that, among participants who smoked cannabis but not tobacco, the risk of bladder cancer was significantly decreased only for those were age 45–54 years (HR 0.26, 95% CI = 0.07–0.92). In a case-control study involving 52 Veterans Affairs patients younger than 61 years old and age-matched to 104 controls, Chacko et al. (2006) found that a significantly higher proportion of cases as compared to controls reported ever using cannabis (88.5 percent versus 69.2 percent, p = 0.008). The mean number of joint-years of cannabis smoked was also signficantly higher among cases than controls (48.0 joint-years versus 28.5 joint-years, p = 0.022). After adjusting for potential confounders, including tobacco use, a statistically significant association between increasing joint-years of cannabis and the risk of transitional cell carcinoma remained (p trend = 0.01).

Discussion of Findings

Huang et al. (2015, p.26) reviewed eight studies that reported on the association between cannabis use and prostate, cervical, anal, bladder, and penile cancer, as well as glioma, non-Hodgkin lymphoma, and Kaposi's sarcoma, and concluded that "there are still insufficient data to make any conclusions on an association with marijuana". Separately, Thomas et al. (2015) found no statistically significant difference in the risk of developing bladder cancer among participants who used cannabis but not tobacco as compared to those who used neither. These studies have several limitations.

In the study on cervical and prostate cancers, Sidney et al. (1997, p.727) relied on self-report to determine patterns of cannabis use and did not assess for changes in those patterns during follow-up. The study cohort included no participants older than 49 years old age at baseline, and participants were followed for a mean of 8.6 years; consequently, the study was unable to ascertain whether there is an association between cannabis use and the incidence of cancer in older populations. The authors stated that they "do not consider any of the findings to be conclusive".

In the study on malignant adult-onset glioma, investigators did not assess for changes in patterns of cannabis use after baseline, only a small number of cases (n = 8) reported using cannabis at least once a month, and more than 1 in 4 cases (26 percent) did not provide data on cannabis use (Efird et al., 2004). Holly et al. (1999) note that responses to questions concerning events that occurred many years previously (e.g., lifetime cannabis use) or addressing sensitive topics (e.g., illegal drug use) can be affected by recall and response biases, respectively. Nelson et al. (1997) also list recall bias as a potential limitation. Of these two studies, Huang et al. (2015) note that the association between cannabis use and risk of non-Hodgkin lymphoma may be the result of confounding cause by the observed protective association of sexual behavior and cocaine use. For a discussion on the effectiveness of cannabis and cannabinoids as a treatment for glioma and other cancers, see chapter 4.

Maden et al. (1993) assert that the low rate of participation among cases (50.2 percent) and controls (70.3 percent) was a major limitation of their study on penile cancer. In the study on anal cancer, Daling et al. (1987) note that all control participants were diagnosed with colon cancer. Other investigators have noted that this control group may not be appropriate for assessing the association between cannabis use and anal cancer incidence, as cannabis smoking is a potential risk factors for colorectal cancer (Hashibe et al., 2005). Limitations of the study on

Kaposi's sarcoma include the lack of consistent HHV-8 testing for all participants, the use of non-continuous categories for describing frequency of cannabis use and the resultant potential for ambiguous reporting, and the use of self-report to collect data on patterns of cannabis use (Chao et al., 2009).

Thomas et al. (2015) note that the observational design of their study creates the potential for participation and response biases. Other limitations of the study include the failure to differentiate the risks for bladder cancer associated with current as opposed to former cannabis use, the lack of an evaluation of other potential risk factors for bladder cancer, and the fact that the study findings apply only to men. Findings from Chacko et al. (2006) are limited by a high proportion of ever tobacco smokers among both cases (94.2 percent) and controls (93.3 percent). According to Huang et al. (2015), the limitations of this study also include its small size, the use of self-report to collect data on cannabis use, and failing to adjust for tobacco smoking–an acknowledged bladder cancer risk factor.

Further research is needed to better characterize whether and how cannabis use is associated with the risk of developing these cancers. Additionally, since important biological distinctions exist among cancers that occur in a given organ, including histological and molecular sub-types, such research will need to separately investigate and identify the risk factors associated with each.

CONCLUSION 5-5 There is insufficient evidence to support or refute a statistical association between cannabis use and the incidence of prostate cancer, cervical cancer, malignant gliomas, non-Hodgkin lymphoma, penile cancer, anal cancer, Kaposi's sarcoma, or bladder cancer.

Is There an Association Between Parental Cannabis Use and the Incidence of Cancer in Offspring?

Systematic Reviews

The committee did not identify a good- or fair-quality systematic review that reported on the association between parental cannabis use and subsequent cancer incidence in offspring.

Primary Literature

Huang et al. (2015) reviewed 3 studies on the association between parental cannabis use and the risk of leukemia. Robison et al. (1989) conducted a case-control study involving 204 cases diagnosed with acute non-lymphoblastic leukemia (ANLL) by 17 years of age that were matched to controls by age, race, and residential location. Maternal use of cannabis during, and in the year preceding, pregnancy was associated with a statistically significant risk of ANLL (RR 10, $p = 0.005$). By comparison, the risk of ANLL associated with paternal use of cannabis during the same period was not statistically significant (RR 1.47, $p = 0.32$). Children whose mothers used cannabis during, or in the year preceding, pregnancy, were significantly younger in the age at diagnosis of ANLL than children whose mothers did not use cannabis during this period (37.7 months [mean] versus 96.1 months [mean], $p = 0.007$). There was also a statistically significant difference in the distribution of morphological types of ANLL cases between cases and controls ($p = 0.02$). For example, M1/M2 and M4/M5 morphologic types respectively comprised 10 percent and 70 percent of ANLL cases among children whose mothers used cannabis, while they

comprised respectively 58 percent and 31 percent of cases among children whose mothers did not use cannabis. Logistic regression to identify independent risk factors for ANLL found that "maternal marijuana use was the single most predictive factor" identified in the study (Robison et al., 1989, p. 1907).

In contrast to these findings, Trivers et al. (2006) conducted a case-control study involving 517 case diagnosed with acute myeloid leukemia (AML) by 17 years of age and matched to 610 controls by age, race, and residential location, and found that children whose mothers used cannabis during, or in the 3 months preceding, pregnancy were at significantly lower risk of developing AML than children whose mothers did not use cannabis during that period, after adjusting for household income and parental age and education (OR 0.43, 95% CI = 0.23–0.80).[3] Among children whose mothers reported using cannabis in the 3 months before pregnancy, those whose mothers used cannabis at least once weekly had a lower risk of developing AML than those whose mothers used cannabis less than once weekly (OR 0.19, 95% CI = 0.06–0.59 versus OR 0.57, 95% CI = 0.26–1.29). Although overall paternal use of cannabis was significantly associated with the risk of AML (OR 1.37, 95% CI = 1.02–1.83), there was no statistically significant association between paternal use of cannabis during, and in the three months preceding, pregnancy and the risk of AML (OR 1.02, 95% CI = 0.67–1.53). The authors concluded that "[p]arental marijuana use is unlikely as a strong risk factor for childhood AML" (Trivers et al., 2006, p. 117).

Finally, Wen et al. (2000) conducted a case-control study to evaluate the association between exposures related to paternal military service, such as cannabis use, and the incidence of AML or acute lymphoblastic leukemia (ALL) in their children. Among 2,343 cases diagnosed with AML or ALL and matched by age, race, biological sex, and residential location to 2,723 controls, participants whose fathers had ever used cannabis had a statistically significant risk of developing ALL or AML compared to those whose fathers had never used cannabis (OR 1.5, $p < 0.01$).

Huang et al. (2015) also reviewed studies on the association between parental cannabis use and the incidence of rhabdomyosarcoma, neuroblastoma, and astrocytoma in pediatric populations. A case-control study of 322 children younger than 21 years of age and diagnosed with rhabdomysarcoma matched by age, race, and biological sex to 322 controls found that children whose mothers used cannabis in the 12 months before their child's birth were significantly more likely to develop the disease than children whose mothers had not used cannabis during this period (OR 3.0, 95% CI = 1.4–6.5), after adjusting for complications during pregnancy and other potential confounders (Grufferman et al., 1993). Similarly, children whose fathers used cannabis in the year prior to their child's birth were at significantly greater risk of developing rhabdomyosarcoma than children whose fathers did not use cannabis at this time (OR 2.0, 95% CI = 1.3–3.3). However, use of cannabis and cocaine were highly correlated, as was maternal and paternal use of cannabis, making it impossible to isolate the effects of maternal and paternal cannabis use from each other or from the effects of parental cocaine use.

Kuijten et al. (1990) conducted a case-control study involving 163 cases diagnosed by 14 years of age with astrocytoma or related tumors and matched to controls by age, race, and residential location, and found a borderline statistically significant association between maternal use of cannabis in the 10 months preceding their child's birth and the risk of astrocytoma (OR

[3] Acute myeloid leukemia and acute non-lymphoblastic leukemia refer to the same type of cancer.

2.8, 95% CI = 0.9–9.9, p = 0.07).[4] By comparison, maternal use in the 9 months preceding their child's birth was not associated with the risk of astrocytoma (OR 4.0, p = 0.11).

Bluhm et al. (2006) examined the association between maternal cannabis use and the risk of neuroblastoma in their offspring. Among 538 cases diagnosed with neuroblastoma by 19 years of age age-matched to 504 controls, maternal use of cannabis during pregnancy, as compared to non-use of cannabis during any measured time period, was significantly associated with greater risk of neuroblastoma in their offspring, after adjusting for use of other recreational drugs (OR 2.51, 95% CI = 1.18–5.83). After stratifying maternal use of cannabis by time period, the authors found a statistically significant association between the incidence of neuroblastoma and maternal use of cannabis during the first trimester (OR 4.75, 95% CI = 1.55–16.48), but not between neuroblastoma incidence and maternal cannabis use in the second or third trimester, in the month preceding conception, or in the period between birth and diagnosis. Age at diagnosis, but not frequency of maternal cannabis use, had large effects on neuroblastoma risk. For example, among children diagnosed with neuroblastoma before 12 months of age, maternal cannabis use was significantly associated with risk of neuroblastoma (OR 15.61, 95% CI = 3.07–285.89), while the risk was similar for children whose mothers used either less than one or more than one pipeful of cannabis during the first trimester (OR 4.16, 95% CI = 1.52–14.61 and OR 4.42, 95% CI = 1.09–29.58).

Discussion of Findings

Findings on the association between parental cannabis use and risk of pediatric leukemia were mixed: maternal cannabis use in the months preceding birth was determined to be at once a risk factor for, and protective against, the development of ANLL/AML in children (Robison et al., 1989; Trivers et al., 2006). Differences in the design of questionnaires employed in these studies, including the extent to which questions on recreational drug use were distinguished from other exposure questions, may have affected participant reporting and contributed to these contradictory results. Limitations of Robison et al. (1989) include findings based on small sample sizes (9 cases), wide confidence intervals for risk estimates, and the possibility that, as a consequence of the large number of parameters analyzed in the study, the association between ANLL incidence and maternal cannabis use was a chance finding. Although the reported frequency of maternal cannabis use was considerably lower in Robison et al. (1989) than in other studies, there was no evidence of difference in reporting between cases and controls. In Trivers et al. (2006), reported rates of maternal cannabis use were lower among cases and higher among controls than in other studies, suggesting the potential for differences in reporting by cases and controls.

While Robison et al. (1989) and Trivers et al. (2006) found that paternal cannabis use during and in the months preceding pregnancy was not associated with ANLL/AML incidence in their offspring, Wen et al. (2000) found that any paternal cannabis use was significantly associated with the incidence of AML or ALL in their offspring. Limitations in Wen et al. (2000) included the potential for selection bias due to a lower participation rate among controls than cases, and potential for residual confounding due to the lack of data on the duration and frequency of exposure to cigarette smoking. A similar lack of data on patterns of cannabis use

[4] Cases were diagnosed with astrocytoma, glioblastoma multiforme, mixed glioma with astrocytic elements, or brainstem glioma.

(e.g., duration, frequency, cumulative exposure) prevented investigation of a dose-response relationship between paternal cannabis use and risk of ALL in their offspring.

Grufferman et al. (1993) found that parental cannabis use was significantly associated with the incidence of rhabdomyosarcoma in their offspring, and Bluhm et al. (2006) found that maternal cannabis use during the first trimester was significantly associated with neuroblastoma. In the latter study, very few mothers reported using cannabis more than once per day during any of the measured time periods, suggesting the potential for underreporting the frequency of cannabis use. Additionally, there was insufficient data to assess dose-response relationships, findings on paternal cannabis use were limited due to low response rates, and confidence intervals were wide due to the small number of women reporting cannabis use during and just before pregnancy. In Grufferman et al. (1993), 25 percent of cannabis users were also cocaine users. As a result of this correlation, any association between parental cannabis use and risk of rhabdomyosarcoma is confounded by polysubstance use. In addition, the authors did not collect data on frequency and duration of cannabis use, and were therefore unable to assess for a dose-response relationship.

CONCLUSION 5-6 There is insufficient evidence to support or refute a statistical association between parental cannabis use and a subsequent risk of developing acute myeloid leukemia/acute non-lymphoblastic leukemia, acute lymphoblastic leukemia, rhabdomyosarcoma, astrocytoma, or neuroblastoma in offspring.

RESEARCH GAPS

To address the research gaps relevant to cancer incidence, the committee suggests the following:

- There is need for robust epidemiological studies to investigate the association between cannabis exposure and several types of cancers, including but not limited to lung, head and neck, testicular, and esophageal cancers.
- Further investigation is needed to resolve any contradictory findings on, and to characterize the nature and strength of, any potential associations between parental cannabis use and the risk of cancer in their offspring.
- To promote the development of a body of high-quality evidence on the association between cannabis exposure and cancer incidence, researchers need to prioritize rigorous study designs and implement data collection protocols and methods that allow them to control for key confounders and to precisely measure cannabis exposure.
- Because of changing exposures to cannabis and the fact that many associations are based on single studies, replication of existing studies in targeted areas is needed.

SUMMARY

The committee identified good or fair quality systematic reviews on the association between cannabis use and the risk of lung, testicular, and head and neck cancers. Good quality primary literature on the association between cannabis use and lung, testicular, esophageal,

childhood, and several other cancers was also identified. Due to a paucity of research, mixed findings, and numerous methodological limitations, the committee judged the evidence from the studies on childhood cancers, esophageal cancer, and various other cancers in adults to be insufficient to support or refute a statistically significant association between cannabis use and the incidence of these cancers. More conclusive findings and less extensive methodological limitations in the literature on lung, testicular, and head and neck cancers allowed the committee to conclude that there is moderate evidence that there is no statistically significant association between cannabis use and the incidence of lung or head and neck cancer, and limited evidence that there is a statistically significant association between current, frequent, or chronic cannabis use and the incidence of non-seminoma-type testicular germ cells tumors. Below, Box 5-1 summarizes the chapter conclusions.

Epidemiological studies that investigate the association between cannabis use and the risk of various cancers risk face methodological challenges similar to those found in studies of other clinical outcomes. These challenges include but are not limited to small sample sizes and low participation rates, the inability to verify cannabis use data based on self-report alone, and difficulties in controlling for potential confounders and accounting for potential effect modifiers. Additionally, some special—if not unique—methodological challenges pertain to cancer studies. For example, cancer is a diverse set of diseases that occur in different organs and organ systems, and have different histopathological characteristics and risk factors. Some of these risk factors, such as family cancer history, occupational exposures, and diet, are difficult to measure and were often not accounted for by the studies review in this chapter. Additionally, the long incubation period of many cancers requires a similarly extended observation period, and makes it difficult to fully characterize the relevant cannabis exposure and to control for other relevant exposures.

Future research will need to address the limited scope and quality of epidemiological studies on the association between cannabis use and cancer incidence. Investigators will need to confirm existing evidence on lung and head and neck cancers, and to expand the evidence base on testicular, esophageal, and childhood cancers, as well as other cancers in adults. To address the methodological limitations described above, future studies will also need to be well-designed and to employ rigorous methods of data collection and measurement.

BOX 5-1
Summary of Chapter Conclusions*

There is moderate evidence of *no* statistical association between cannabis use and:

- Incidence of lung cancer (cannabis smoking) (5-1)
- Incidence of head and neck cancers (5-2)

There is limited evidence of a statistical association between cannabis smoking and:

- Non-seminoma-type testicular germ cell tumors (current, frequent, or chronic cannabis smoking) (5-3)

There is no or insufficient evidence to support or refute a statistical association between cannabis use and:

- Incidence of esophageal cancer (cannabis smoking) (5-4)
- Incidence of prostate cancer, cervical cancer, malignant gliomas, non-Hodgkin lymphoma, penile cancer, anal cancer, Kaposi's sarcoma, or bladder cancer (5-5)
- Subsequent risk of developing acute myeloid leukemia/acute non-lymphoblastic leukemia, acute lymphoblastic leukemia, rhabdomyosarcoma, astrocytoma, or neuroblastoma in offspring (parental cannabis use) (5-6)

*Numbers in parentheses correspond to chapter conclusion numbers.

REFERENCES

Bluhm, E. C., J. Daniels, B. H. Pollock, and A. F. Olshan. 2006. Maternal use of recreational drugs and neuroblastoma in offspring: A report from the children's oncology group (United States). *Cancer Causes & Control* 17(5):663–669.

Callaghan, R. C., P. Allebeck, and A. Sidorchuk. 2013. Marijuana use and risk of lung cancer: A 40-year cohort study. *Cancer Causes & Control* 24(10):1811–1820.

Chacko, J. A., J. G. Heiner, W. Siu, M. Macy, and M. K. Terris. 2006. Association between marijuana use and transitional cell carcinoma. *Urology* 67(1):100–104.

Chao, C., L. P. Jacobson, F. J. Jenkins, D. Tashkin, O. Martinez-Maza, M. D. Roth, L. Ng, J. B. Margolick, J. S. Chmiel, Z. F. Zhang, and R. Detels. 2009. Recreational drug use and risk of kaposi's sarcoma in HIV- and HHV-8-coinfected homosexual men. *AIDS Research and Human Retroviruses* 25(2):149–156.

Daling , J. R., N. S. Weiss , T. G. Hislop , C. Maden , R. J. Coates , K. J. Sherman , R. L. Ashley , M. Beagrie , J. A. Ryan , and L. Corey 1987. Sexual practices, sexually transmitted diseases, and the incidence of anal cancer. *New England Journal of Medicine* 317(16):973–977.

de Carvalho, M. F., M. R. Dourado, I. B. Fernandes, C. T. Araujo, A. T. Mesquita, and M. L. Ramos-Jorge. 2015. Head and neck cancer among marijuana users: A meta-analysis of matched case-control studies. *Archives of Oral Biology* 60(12):1750–1755.

Efird, J. T., G. D. Friedman, S. Sidney, A. Klatsky, L. A. Habel, N. V. Udaltsova, S. Van den Eeden, and L. M. Nelson. 2004. The risk for malignant primary adult-onset glioma in a large, multiethnic, managed-care cohort: Cigarette smoking and other lifestyle behaviors. *Journal of Neuro-Oncology* 68(1):57–69.

Grufferman, S., A. G. Schwartz, F. B. Ruymann, and H. M. Maurer. 1993. Parents'use of cocaine and marijuana and increased risk of rhabdomyosarcoma in their children. *Cancer Causes & Control* 4(3):217–224.

Gurney, J., C. Shaw, J. Stanley, V. Signal, and D. Sarfati. 2015. Cannabis exposure and risk of testicular cancer: A systematic review and meta-analysis. *BMC Cancer* 15:897.

Hashibe, M., K. Straif, D. P. Tashkin, H. Morgenstern, S. Greenland, and Z. F. Zhang. 2005. Epidemiologic review of marijuana use and cancer risk. *Alcohol* 35(3):265–275.

Hashibe, M., H. Morgenstern, Y. Cui, D. P. Tashkin, Z. F. Zhang, W. Cozen, T. M. Mack, and S. Greenland. 2006. Marijuana use and the risk of lung and upper aerodigestive tract cancers: Results of a population-based case-control study. *Cancer Epidemiology, Biomarkers & Prevention* 15(10):1829–1834.

Holly, E. A., C. Lele, P. M. Bracci, and M. S. McGrath. 1999. Case-control study of non-Hodgkin's lymphoma among women and heterosexual men in the San Francisco Bay Area, California. *American Journal of Epidemiology* 150(4):375–389.

Huang, Y. H., Z. F. Zhang, D. P. Tashkin, B. Feng, K. Straif, and M. Hashibe. 2015. An epidemiologic review of marijuana and cancer: An update. *Cancer Epidemioloy, Biomarkers & Prevention* 24(1):15–31.

Kuijten, R. R., G. R. Bunin, C. C. Nass, and A. T. Meadows. 1990. Gestational and familial risk factors for childhood astrocytoma: Results of a case-control study. *Cancer Research* 50(9):2608-2612.

Lortet-Tieulent, J., A. Goding Sauer, R. L. Siegel, K. D. Miller, F. Islami, S. A. Fedewa, E. J. Jacobs, and A. Jemal. 2016. State-level cancer mortality attributable to cigarette smoking in the United States. *JAMA Internal Medicine*. 176(12), 1792–1798.

Maden, C., K. J. Sherman, A. M. Beckmann, T. G. Hislop, C. Z. Teh, R. L. Ashley, and J. R. Daling. 1993. History of circumcision, medical conditions, and sexual activity and risk of penile cancer. *Journal of the National Cancer Institute* 85(1):19–24.

NCI (National Cancer Institute). 2016. *SEER stat fact sheet: Cancer of any site*. https://seer.cancer.gov/statfacts/html/all.html (accessed December 9, 2016).

Nelson, R. A., A. M. Levine, G. Marks, and L. Bernstein. 1997. Alcohol, tobacco and recreational drug use and the risk of non-Hodgkin's lymphoma. *British Journal of Cancer* 76(11):1532–1537.

Robison, L. L., J. D. Buckley, A. E. Daigle, R. Wells, D. Benjamin, D. C. Arthur, and G. D. Hammond. 1989. Maternal drug use and risk of childhood nonlymphoblastic leukemia among offspring. An epidemiologic investigation implicating marijuana (a report from the Childrens Cancer Study Group). *Cancer* 63(10):1904–1911.

Sidney, S., C. P. Quesenberry, Jr., G. D. Friedman, and I. S. Tekawa. 1997. Marijuana use and cancer incidence (California, United States). *Cancer Causes & Control* 8(5):722–728.

Tashkin, D. P. 2013. Effects of marijuana smoking on the lung. *Annals of the American Thoracic Society* 10(3):239–247.

Thomas, A. A., L. P. Wallner, V. P. Quinn, J. Slezak, S. K. Van Den Eeden, G. W. Chien, and S. J. Jacobsen. 2015. Association between cannabis use and the risk of bladder cancer: Results from the California men's health study. *Urology* 85(2):388–392.

Trivers, K. F., A. C. Mertens, J. A. Ross, M. Steinbuch, A. F. Olshan, and L. L. Robison. 2006. Parental marijuana use and risk of childhood acute myeloid leukaemia: A report from the children's cancer group (United States and Canada). *Paediatric and Perinatal Epidemiology* 20(2):110–118.

Wen, W. Q., X. O. Shu, M. Steinbuch, R. K. Severson, G. H. Reaman, J. D. Buckley, and L. L. Robison. 2000. Paternal military service and risk for childhood leukemia in offspring. *American Journal of Epidemiology* 151(3):231–240.

Zhang, L. R., H. Morgenstern, S. Greenland, S. C. Chang, P. Lazarus, M. D. Teare, P. J. Woll, I. Orlow, B. Cox, Y. Brhane, G. Liu, and R. J. Hung. 2015. Cannabis smoking and lung cancer risk: Pooled analysis in the international lung cancer consortium. *International Journal of Cancer* 136(4):894–903.

6
Cardiometabolic Risk

Chapter Highlights
• The evidence is unclear as to whether and how cannabis use is associated with heart attack, stroke, and diabetes.

An estimated 85.6 million American adults have at least one cardiovascular disease such as heart disease, stroke, heart failure, or hypertension (Mozaffarian et al., 2016). Each year cardiovascular diseases account for more than 800,000 deaths (i.e., is the underlying cause listed on the death certificate), or 30 percent of all deaths in the United States (Mozaffarian et al., 2016).

Heart disease is the leading cause of mortality in the United States, accounting for more than 600,000 deaths per year (Kochanek et al., 2016). Within subcategories of heart disease, coronary heart disease (CHD) is by far the largest, with 364,000 deaths annually (Kochanek et al., 2016). CHD is a disease in which a waxy substance called plaque builds up inside the blood vessels supplying the heart (i.e., the coronary arteries). Over the course of years or decades, the plaque can harden or rupture, resulting in an inadequate supply of blood to the heart which may, in some instances, result in death of heart muscle (myocardial infarction).

Both coronary heart disease and stroke are associated with aging, with nearly 93 percent of CHD deaths and 94 percent of stroke deaths occurring in individuals 55 years and older (Kochanek et al., 2016). More than one-third (about 36 percent) of CHD deaths occur in individuals of ages 85 years and older, while 43 percent of stroke deaths occur in this age group (Kochanek et al., 2016).

Current (past-month) cannabis use is fairly low in the older populations most likely to experience cardiovascular diseases—in particular, about 2 percent past-month prevalence in those aged 50 years and older. In younger adults, by contrast, the prevalence of cannabis use has been estimated to be as high as 19.6 percent for past-month use among those aged 18–25 years (Azofeifa et al., 2016), but these rates decline dramatically with aging. In contrast, tobacco smoking, a known risk factor for heart disease and stroke, has a much higher prevalence among older adults; 18 percent in those of ages 45–64 years and 8.5 percent older than 65 years of age smoke (Jamal et al., 2015).

Cardiometabolic disorders result in a substantial economic burden on the United States. From 2011 to 2012 the estimated annual cost of cardiovascular diseases, including heart disease, stroke, hypertensive disease, and other circulatory conditions, was $316.6 billion ($207.3 billion for heart disease, $33.0 billion for stroke). The total estimated cost of diagnosed diabetes in 2012 was $245 billion (Mozaffarian et al., 2016).

The objective of the review of cannabis and cardiometabolic conditions was to assess the independent association of cannabis with these conditions in studies in which the association has

been quantified. The justification for examining cannabis use in relation to cardiometabolic conditions is that these conditions are among the leading causes of death, are highly prevalent in the United States, account for high levels of medical care utilization and cost, and are caused, in significant part, by modifiable lifestyle risk factors, including diet, physical activity, and cigarette smoking. The high prevalence of these conditions means that a behavior that is associated with a small degree of increased risk for heart disease, stroke, or diabetes can be associated with a high level of attributable risk, that is, the number of cases of disease that result from that behavior. While the prevalence of cardiometabolic conditions is concentrated in the older-adult age groups which have low rates of cannabis use, it is expected that the expanding legalization of cannabis use will cause the rates of use to increase.

The discussion in this review is limited to acute myocardial infarction, stroke, metabolic dysregulation and metabolic syndrome, and diabetes. Sudden death and arrhythmias such as atrial fibrillation were other topics of interest for which no data were available to quantify the association with cannabis use. The 1999 IOM report *Marijuana and Medicine: Assessing the Science Base* (IOM, 1999) reviewed the cardiovascular system; however, no conclusions or recommendations related to cannabis use and cardiometabolic outcomes were included in that report. The literature search conducted by the current committee did not identify any systematic reviews that were rated as "good" or "fair" for cannabis use and acute myocardial infarction, stroke, dyslipidemia or metabolic syndrome, or diabetes, so all the available primary literature for these outcomes dating back to 1999 was reviewed and the 12 primary articles rated as "good" or "fair" by the committee have been included in this chapter.

ACUTE MYOCARDIAL INFARCTION

Each year, an estimated approximately 550,000 Americans have an incident (i.e., first-time) heart attack (acute myocardial infarction, or AMI) and about 200,000 have a recurrent attack (Mozaffarian et al., 2016). Of those who have a heart attack each year, about 116,000 die as a result of their coronary event (Mozaffarian et al., 2016). The committee responsible for the IOM report *Marijuana and Medicine: Assessing the Science Base* (IOM, 1999) did not make any conclusions or recommendations regarding cannabis use and acute myocardial infarctions.

The acute cardiovascular effects of cannabis include increases in heart rate and supine blood pressure, and postural hypotension (Beaconsfield et al., 1972; Benowitz and Jones, 1981). Smoking cannabis decreases exercise test duration on maximal exercise tests and increases the heart rate at submaximal levels of exercise (Renaud and Cormier, 1986). These acute effects provide a physiological basis for cardiac ischemia to develop in cannabis users. In fact, the time from exercise to the onset of angina pectoris is decreased by smoking one cannabis cigarette (Aronow and Cassidy, 1974). Tolerance develops to the acute effects of tetrahydrocannabinol (THC) over several days to a few weeks (Gorelick et al., 2013). Reported cardiovascular effects that may increase the risk of AMI include irregular heart rate (Khiabani et al., 2008) and impaired vascular endothelial function (demonstrated in rates from exposure to second-hand cannabis smoke) (Wang et al., 2016). Additionally, carbon dioxide production from smoked cannabis decreases the oxygen-carrying capacity of the blood and may contribute to the development of cardiac ischemia.

There have been numerous case reports suggesting that cannabis use is associated with the occurrence of AMI. The two primary studies that have quantified the risk of AMI associated with cannabis use and that were rated as good or fair are reviewed below.

Is There an Association Between Cannabis Use and Acute Myocardial Infarction?

Systematic Reviews

The committee did not identify a good- or fair-quality systematic review that reported on the association between cannabis and AMI. Three descriptive review articles provided useful background: Sidney (2002), Thomas et al. (2014), and Franz and Frishman (2016).

Primary Studies

A retrospective cohort study (Sidney, 1997, 2002) assessed the risk of hospitalization for AMI associated with cannabis use in a cohort of 62,012 men and women of ages 15 through 49 years who had, from mid-1979 through 1985, completed self-administered research questions on their cannabis, tobacco, and alcohol use. AMI was assessed by linkage to electronically maintained records of all overnight hospitalizations in Kaiser Permanente Northern California. Follow-up was conducted for up to 12 years. Current use of cannabis was reported by 22 percent and former use by 20 percent of the cohort. There were 209 incident AMIs, 173 in men and 36 in women. The relative risk associated with cannabis use was assessed by a Cox proportional hazards model with adjustments for age, race, education, body mass index, history of hypertension, smoking, and alcohol use. The relative risk for AMI in current users was 1.1 (95 percent confidence interval [CI] = 0.7–1.7) for men and 1.8 (95% CI = 0.5–6.3 for women) for women and in former users was 0.9 (95% CI = 0.6–1.5) for men and 1.0 (0.2–4.5) for women. Both current and former cannabis use were unassociated with an increased risk of AMI.

Study limitations included a reliance of self-report of cannabis use which may result in misclassification of this exposure, the lack of availability of longitudinal data on cannabis use, and the relatively young age (mean age 33 years), which meant that the AMIs occurred in a relatively young age range that is not representative of the older age range in which the vast majority of AMIs occur. Cannabis use was assessed at only one point in time.

A case crossover study design was used to examine the role of cannabis use as a possible trigger for myocardial infarction in 3,882 AMI patients in an inception cohort study identified between August 1989 and September 1996 from 64 community and tertiary medical centers in the United States that were part of the Determinants of Myocardial Onset Study (Mittleman et al., 2001). The mean ages of cannabis users and abstainers were 43.7 and 62.0 years, respectively, while 68 percent of cannabis users and 32 percent of abstainers were current tobacco smokers. Nine patients (0.2 percent) interviewed soon after admission for AMI reported cannabis use during the hour preceding the symptoms of AMI. The risk for AMI associated with cannabis use during the hour preceding symptoms of AMI was 4.8 (95% CI = 2.9–9.5) as assessed by a case-crossover analysis. The exclusion of three of the nine patients who reported other triggering behaviors during the hour prior to the AMI (cocaine use and/or sexual intercourse) resulted in a relative risk of 3.2 (95% CI = 1.4–7.3).

The major limitations of this study were its small size and its reliance on self-report for cannabis use status which meant that any misclassification could have had a significant effect on

the results. While the case-crossover design controls for confounding by traditional risk factors for cardiovascular disease, it does not control for interaction of these factors, and one cannot determine whether cannabis acts as a trigger in low-risk individuals or those who are nonsmokers of tobacco.

Discussion of Findings

While there are a number of reports of an association between cannabis use and AMI, only the two studies described above quantify risk, with the Sidney (2002) study demonstrating no association with an increased or decreased risk of AMI and the Mittleman et al. (2001) study finding that cannabis use may act as a trigger for AMI. The limitations of these studies were described. More generally, with the Mittleman study as an exception, most reports of adverse cardiovascular effects of cannabis including AMI have been conducted in a relatively young age range, while major cardiovascular events are concentrated in older adults, and the findings may not be generalizable to this age group. Other general limitations beyond those already mentioned in the description of the studies include the absence of the impact of the route of consumption (e.g, smoked, edible, etc.); dose, including accounting for the content of THC and other cannabinoids and potential additives or contaminants; and total lifetime duration/dose of cannabis use. Overall, the articles were judged to be of fair quality for assessing the risk of acute myocardial infarction associated with cannabis use.

The role of cannabis as a trigger of AMI is plausible, given its cardiostimulatory effects, which may cause ischemia in susceptible hearts. Carboxyhemoglobinemia from combustion of cannabis resulting in a decreased oxygen-carrying capacity of blood may also contribute to ischemia. Given the physiologic plausibility for a trigger effect, smoking cannabis may put individuals, particularly those at high risk for cardiovascular disease, at increased risk for AMI.

CONCLUSION 6-1

6-1(a) There is limited evidence of a statistical association between cannabis smoking and the triggering of acute myocardial infarction.

6-1(b) There is no evidence to support or refute a statistical association between chronic effects of cannabis use and the risk of acute myocardial infarction.

STROKE

Stroke is the fifth leading cause of death in the United States, accounting for 133,000 deaths annually (Kochanek et al., 2016). A stroke is the death of a portion of brain tissue due to a disruption of the blood supply. Strokes may be ischemic (inadequate blood/oxygen supply) or hemorrhagic (bleeding into the brain) in origin. Each year, approximately 795,000 people experience a new or recurrent stroke. Approximately 610,000 of these are first stoke occurrences and 185,000 are recurrent stroke events (Mozaffarian et al., 2016). The committee responsible for the IOM report *Marijuana and Medicine: Assessing the Science Base* (IOM, 1999) did not make any conclusions or recommendations regarding cannabis use and stroke.

Numerous reports have suggested that smoking cannabis increases the risk of stroke, including case series (Phillips et al., 2011), and studies describing cannabis-associated vascular changes that may be associated with stroke (Herning et al., 2001; Wolff et al., 2011, 2015). Several reports have indicated a close temporal relationship between cannabis smoking and stroke (Wolff et al., 2013). The cardiovascular effects of cannabis that have been proposed as possible mechanism in the etiology of stroke include orthostatic hypotension with secondary impairment of the autoregulation of cerebral blood flow, altered cerebral vasomotor function, supine hypertension and swings in blood pressure, cardioembolism with atrial fibrillation, other arrhythmias, vasculopathy, vasospasm, reversible cerebral vasoconstriction syndrome, and multifocal intracranial stenosis (Wolff et al., 2015).

Is There an Association Between Cannabis Use and Stroke?

Systematic Reviews

The committee did not identify a good- or fair-quality systematic review that reported on the association between cannabis use and stroke.

Primary Studies

A large reported study on the association of cannabis and stroke by Rumalla et al. (2016a) used the Nationwide Inpatient Sample, which provides admission data from a 20 percent sample of all U.S. hospitalizations, to examine the cross-sectional association between cannabis use and hospitalization for acute ischemic stroke (AIS) among patients aged 15 to 54 years during the time period 2004–2011. The primary *International Classification of Diseases* (ICD)-9-CM discharge code was used to identify AIS, and current cannabis use was identified using the ICD-9-CM code 340.30, which includes both cannabis dependence and non-dependent cannabis abuse. Current cannabis use was identified in 11,320 of 478,649 AIS events (2.4 percent). Tobacco use prevalence was higher in current cannabis users than in nonusers (64.4 percent versus 31.5 percent) as was cocaine use (26.7 percent versus 3.1 percent). The odds ratio associated with current cannabis use and hospitalization for AIS was 1.17 (95% CI = 1.15–1.20) as calculated with multivariable logistic regression adjusted for age, gender, race, substance use, payer status, Charlson's comorbidity index, and other comorbid risk factors. Analyses stratified on tobacco use status were not available. The limitations of this study include the cross-sectional design, the probable under-ascertainment of current cannabis use (2.4 percent is low for this age range), the absence of data on duration of tobacco use, and the absence of analyses that are performed stratified by tobacco and by cocaine use to determine the odds ratio in non-tobacco use and non-cocaine users, given the high prevalence of these known risk factors for ischemic stroke.

In a case-control study conducted in a New Zealand hospital (Barber et al., 2013), 160 of 218 (73 percent) of ischemic stroke/transient ischemic attack (TIA) patients, aged 18 to 55 years, had urine drug screens between January 2009 and April 2012 (150 ischemic stroke, 10 TIA). Control urine samples were obtained from 160 patients matched for age, sex, and ethnicity. Twenty-five (15.6 percent) of the stroke/TIA patients and 13 (8.1 percent) of the control patients had positive cannabis drug screens. Eighty-eight percent of cannabis-positive patients were current tobacco smokers versus 28 percent of cannabis-negative patients. The odds ratio

associated with current cannabis use was 2.30 (95% CI = 1.08–5.08), but was no longer statistically significant when an additional adjustment was made for tobacco use (1.59, 95% CI = 0.71–3.70). The strength of evidence for this study was determined to be fair.

In a cross-sectional analysis by Westover et al. (2007) of all ischemic (N = 998) and hemorrhagic strokes (N = 937) identified in 2003 by ICD-9 codes from an administrative database maintained by the State of Texas in young adults, ages 18–44 years, the odds ratios of cannabis and other illicit drugs being associated with ischemic and hemorrhagic stroke were estimated using a multivariable logistic regression adjusting for alcohol, tobacco, amphetamines, cocaine, opioids, cardiovascular risk factors, and other medical conditions associated with increased risk of these outcomes. The prevalence of cannabis use, identified by ICD-9 codes, was approximately 1 percent. Cannabis was associated with an increased risk of ischemic stroke (OR, 1.76; 95% CI = 1.15–2.71) but was not associated with a risk of hemorrhagic stroke (OR, 1.36; 95% CI = 0.90–2.06). The prevalence rate of tobacco use was not reported, and analyses stratified by category of tobacco use were not performed.

A retrospective cohort study (Sidney, 1997, 2002) assessed the risk of hospitalization for stroke associated with cannabis use in a cohort of 62,012 men and women of ages 15 through 49 years who had, from mid-1979 through 1985, completed self-administered research questions on cannabis, tobacco, and alcohol use. Stroke was assessed by linkage to electronically maintained records of all overnight hospitalizations in Kaiser Permanente Northern California. Follow-up was conducted for up to 12 years. Current use of cannabis was reported by 22 percent and former use by 20 percent of the cohort. There were 130 incident strokes, 68 in men and 62 women. The relative risk associated with cannabis use was assessed by Cox proportional hazards model with adjustments for age, race, education, body mass index, history of hypertension, smoking, and alcohol use. The relative risk for stroke in current users was 1.0 (95% CI = 0.5–1.9) for men and 0.7 (95% CI = 0.3–2.2) for women and in former users was 0.8 (95% CI = 0.4–1.8) for men and 1.5 (07–3.5) for women. Both current cannabis use and former cannabis use were not associated with increased risk of stroke.

The study's limitations included its reliance on self-report of cannabis use, which may result in misclassification of this exposure; the lack of availability of longitudinal data on cannabis use; and the relatively young age of subjects (mean age 33 years) so that the strokes occurred in a relatively young age range that is not representative of the older age range in which the vast majority of strokes occur. Cannabis use was assessed at only one point in time.

Rumalla et al. (2016b) used the Nationwide Inpatient Sample, which provides admission data from a 20 percent sample of all U.S. hospitalizations, to examine the cross-sectional association between cannabis use and hospitalization for aneurysmal subarachnoid hemorrhage (SAH) among patients 15 to 54 years of age during the time period 2004–2011. The primary ICD-9-CM discharge code was used to identify SAH, and current cannabis use was identified using the ICD-9-CM code 340.30, which includes both cannabis dependence and nondependent cannabis abuse. Current cannabis use was identified in 2,104 of the 94,052 (2.2 percent) SAH events. Tobacco use prevalence was higher in current cannabis users than in nonusers (59.3 percent versus 25.4 percent). The odds ratio associated with current cannabis use was 1.18 (95% CI = 1.12–1.24) according to a multivariate logistic regression adjusted for age, gender, race, substance use, primary payer status, Charlson's comorbidity index, and other SAH risk factors. The limitations of this study include its cross-sectional design, the probable under-ascertainment of current cannabis use (2.2 percent is low for this age range), the absence of data on duration of cannabis use, and the absence of analyses that are performed stratified by tobacco to determine

the odds ratio in non-tobacco use, given the high prevalence of this known risk factor for ischemic stroke.

Discussion of Findings

The studies by Rumalla et al. (2016a,b) and Westover et al. (2007) were cross-sectional studies using administrative data consisting of ICD-9 codes. Cross-sectional studies do not allow one to assess temporality between exposure and outcome. The miscoding of strokes does occur, although the reliability is probably reasonable for epidemiological studies. The classification of exposure status using ICD-9 is particularly concerning, given the likelihood that the percentage of cannabis users appears to be low compared to population norms in each of these studies, most notably the Westover et al. (2007) study.

With the exception of the Sidney (2002) study, none of the studies have data on the temporal relation between the cannabis or tobacco use and the stroke. A general problem was the analytic treatment of tobacco use. Given the much longer duration and frequency of tobacco smoking than of cannabis smoking for most people and the very common co-use of both substances, it is not appropriate to assume that an adjustment for tobacco use in a multivariable model will provide an accurate assessment of the risk associated with cannabis use. Additional analytic approaches, when feasible, may include testing the interaction between cannabis and tobacco use and performing stratified analyses to test the association of cannabis use with clinical endpoints in nonusers of tobacco. Other general limitations beyond those already mentioned in the description of the studies include the absence of the impact of the route of consumption (e.g., smoked, edible, etc.); the absence of information on dose, including accounting for the content of THC and other cannabinoids and potential additives or contaminants; and the lack of information on the total lifetime duration/dose of cannabis use.

All the articles were judged to be of fair quality for assessing the risk of stroke associated with cannabis use. With the exception of Sidney (2002) and Barber et al. (2013), all showed an increased risk of stroke associated with cannabis use but had significant limitations. For ischemic stroke, two of the studies indicated an increased risk while one showed a nonsignificant finding in the direction of increased risk. For subarachnoid hemorrhage, the single study found an increased risk. For the combined hemorrhagic stroke endpoint assessed by Westover et al. (2007), the study showed no association of cannabis use with the risk of this endpoint.

CONCLUSION 6-2 There is limited evidence of a statistical association between cannabis use and ischemic stroke or subarachnoid hemorrhage.

METABOLIC DYSREGULATION, METABOLIC SYNDROME, PREDIABETES, AND DIABETES MELLITUS

Ranked as the seventh-leading cause of death in the United States, diabetes accounts for more than 76,000 deaths annually (Kochanek et al., 2016). An estimated 29 million adults in the United States have diabetes (CDC, 2014a), which is a group of conditions characterized by high blood glucose (sugar) levels due to the inability to metabolize glucose effectively. The number of new (incident) cases of diabetes diagnosed annually is more than 1.4 million (CDC, 2015). Similar to the case with cardiovascular diseases, the prevalence of diabetes increases with age,

from 4.4 percent among those 20 to 44 years old, to 16.2 percent at ages 45 to 64, and 25.9 percent at ages 65 years and older (CDC, 2014a). A major risk factor for the development of the most common type of diabetes (type 2) is obesity, which results in resistance to the effect of the glucose regulating hormone, insulin. An epidemic of obesity has resulted in the prevalence of obesity increasing from 22.9 percent in 1988–1994 to 34.9 percent in 2011–2012 (Flegal et al., 2002; Ogden et al., 2014), contributing to a near tripling of the prevalence of diabetes since 1990 to its current level of 9.3 percent (CDC, 2014b). The committee responsible for the IOM report *Marijuana and Medicine: Assessing the Science Base* (IOM, 1999) did not make any conclusions or recommendations regarding cannabis use and metabolic dysregulation, metabolic syndrome, prediabetes, or diabetes mellitus.

Obesity, most notably central adiposity, is the dominant risk factor for the development of type 2 diabetes (Klil-Drori et al., 2016). Stimulation of the endogenous cannabinoid receptor system (the CB1 receptor and, to a lesser extent, the CB2 receptor) by Δ^9-THC, the major psychoactive component of cannabis, and by endogenous cannabinoids increases appetite and promotes adipogenesis, the production of body fat (Di Marzo et al., 2011). This physiological pathway suggests that cannabinoids such as Δ^9-THC may promote weight gain, which would increase the risk of an individual developing diabetes.

As noted earlier, the approximately 30-year epidemic of increasing obesity rates in the United States has been associated increasing rates of diabetes. A number of studies have examined the association of cannabis use with body mass index (BMI) and obesity. Counterintuitively, the majority of the reviewed studies showed that cannabis was associated with a lower BMI or a lower prevalence of obesity, or both (Hayatbakhsh et al., 2010; Le Strat and Le Foll, 2011; Smit and Crespo, 2001; Warren et al., 2005) or to have no association with BMI or obesity (Rodondi et al., 2006).

Because of the significance of diabetes as a highly prevalent disease, as a risk factor for cardiovascular diseases, and as a significant economic burden in our society, the question of whether cannabis use is associated with increased risk of diabetes is important. Included in this review are the assessments of three studies of cannabis use and metabolic dysregulation/metabolic syndrome, one study of cannabis use and prediabetes, and three studies of cannabis use and diabetes.

Is There an Association Between Cannabis Use and Metabolic Dysregulation, Metabolic Syndrome, Prediabetes, or Diabetes Mellitus?

Systematic Reviews

The committee did not identify a good- or fair-quality systematic review that reported on the association between cannabis and metabolic dysregulation, metabolic syndrome, prediabetes, or diabetes mellitus. A review by Sidney (2016), published after the cutoff date for literature considered in this report, informed the discussion regarding the studies described in this section.

Primary Studies

Metabolic Dysregulation and Metabolic Syndrome Three cross-sectional studies were conducted using data from the National Health and Nutrition Examination Survey (NHANES) to

examine the associations between cannabis use and glucose, insulin, and insulin resistance (Penner et al., 2013); cannabis use and the metabolic syndrome (Vidot et al., 2016); and cannabis use and tobacco cigarette smoking with metabolic syndrome (Yankey et al., 2016).

The study by Penner et al. (2013) included 4,657 NHANES participants from three exams conducted from 2005 to 2010 who were categorized as current, former, or never users of cannabis. The fasting mean glucose levels were not found to be significantly different in current users than in never users according to multivariable analyses that adjusted for age, sex, race/ethnicity, income, marital status, tobacco use, alcohol use, BMI, and physical activity. Hemoglobin A1c did not vary by cannabis use status, while fasting insulin and homeostasis models of insulin resistance (HOMA-IR) were about 12 percent lower in current cannabis users than in never users. A study by Vidot et al. (2016) of 8,478 NHANES participants from three exams conducted from 2005 to 2010 found that the odds of metabolic syndrome were lower in current users than in never users, with an odds ratio of 0.69 (95% CI = 0.47–1.00), according to a multivariable analysis that adjusted for age, sex, race/ethnicity, poverty-to-income ratio, tobacco smoking, and exam cycle year. Yankey et al. (2016) studied the association between cannabis and cigarette smoking with the prevalence of metabolic syndrome, using data from 3,051 2011–2012 NHANES participants. Compared with findings from respondents who reported never having used cannabis, regular use of cannabis (defined as smoking cannabis or hashish at least once a month for more than one year) was associated with reduced odds for metabolic syndrome (OR, 0.23; 95% CI = 0.06–0.90). The multivariable analysis controlled for age, education, family-income-to-poverty ratio, sex, medical insurance, marital status, tobacco smoking, physical activity, other drug use, and rehabilitation.

Prediabetes Bancks et al. (2015) examined the association of self-reported cannabis use with both the prevalence and incidence of prediabetes in the Coronary Artery Risk Development in Young Adults (CARDIA) study. A cross-sectional analysis for diabetes was conducted in 3,024 participants at the Year 25 exam. Cannabis use was assessed by self-administered questions. Prediabetes was defined according to American Diabetes Association criteria and was present in 45 percent of participants. Relative to never use, the current use of cannabis was associated with an odds ratios for prediabetes was of.65 (95% CI = 1.15–1.65), and lifetime cannabis use of at least 100 times was associated with an odds ratio of 1.49 (95% CI = 1.06–2.11). The multivariable analysis adjusted for age, sex, race, tobacco smoking, alcohol use, education, field center, systolic blood pressure, C-reactive protein (CRP), physical activity, and the use of other illicit drugs. The CARDIA longitudinal analysis examined the association of self-reported cannabis use at the Year 7 follow-up exam to incident prediabetes (51 percent of participants) at the four subsequent follow-up examinations, with an average of 13.8 years of follow-up. The adjusted OR for prediabetes associated with lifetime use of at least 100 times relative to never use of cannabis was 1.40 (95% CI = 1.13–1.72).

Diabetes Bancks et al. (2015) also examined the association of self-reported cannabis use and diabetes in both cross-sectional and longitudinal analyses conducted in the CARDIA study. The study population was the same for the cross-sectional analysis, and the adjustment variables were the same as described for the prediabetes analysis. Diabetes was present in 11.8 percent of Year 25 exam participants. The odds ratios for diabetes were 1.18 (95% CI = 0.67–2.10) for current use and 1.42 (95% CI = 0.85–2.38) for lifetime use of at least 100 times relative to never use of cannabis. The longitudinal analysis examined the association between Year 7 exam and self-

reported cannabis use to incident diabetes (11.1 percent of participants) at the four subsequent follow-up examinations (years 10, 15, 20, and 25). Relative to never use, the OR associated with diabetes for lifetime use of at least 100 times was 1.10 (95% CI = 0.74–1.64), adjusted for the same variables as the longitudinal analysis of prediabetes.

Two cross-sectional studies were conducted using data from the NHANES to examine the association of cannabis use with diabetes (Alshaarawy and Anthony, 2015; Rajavashisth et al., 2012). The first study (Rajavashisth et al., 2012) used interviewer-administered data regarding cannabis use and diabetes collected from 10,896 adults, ages 20–29 years, during NHANES III, conducted from 1988 to 1994. Relative to non-users, the OR for diabetes associated with current and past cannabis use was 0.36 (95% CI = 0.24–0.55), adjusted for race/ethnicity, physical activity, alcohol use, alcohol × cannabis use interaction, BMI, total cholesterol, triglyceride, CRP, and hypertension.

In the second study, Alshaarawy and Anthony (2015) examined the association of cannabis use with diabetes in eight different replication samples and in a meta-analysis. The samples were obtained from 4 NHANES surveys (2005–2006, 2007–2008, 2009–2010, 2011–2012) and from a survey performed for the National Survey on Drug Use and Health (NSDUH) during the same time periods. A composite indicator of diabetes from the NHANES data combined interview reports of diabetes, current use of insulin and/or oral hypoglycemic medication, and lab-derived glycohemoglobin. Self-report of cannabis was assessed from the NSDUH surveys. Compared to non-users, the adjusted odds ratios (ORs) for diabetes associated with current cannabis use ranged from 0.4 to 0.9, with a meta-analytic OR summary of 0.7 (95% CI = 0.6–0.8). Meta-analytic summary analyses performed within cigarette smoking strata found adjusted ORs were 0.8 (95% CI = 0.5–1.2) in respondents who reported never having smoked cigarettes and 0.8 (95% CI = 0.6–1.0) in current smokers.

Discussion of Findings

Overall, the articles reviewed by the committee were judged to be of good to fair quality for assessing the risk of metabolic dysregulation, metabolic syndrome, prediabetes, or diabetes mellitus associated with cannabis use. In their review of the evidence, the committee found that cannabis use had either an inverse association or no association with BMI, an inverse association with metabolic dysregulation and metabolic syndrome, and an inverse association or no association with diabetes mellitus. The only study showing an increased risk was the prediabetes portion of the CARDIA study analysis.

As noted earlier, these are counterintuitive findings since THC tends to stimulate appetite, promote fat deposition, and promote adipogenesis. Potential explanations include the following:

- Cross-sectional studies do not allow one to assess temporality between exposure and outcome. With the exception of the longitudinal findings reported in the CARDIA study, all the reported findings were from cross-sectional analyses.
- Dose estimates of cannabis exposure were generally imprecise and lacking information on cannabis strength, dose, frequency of use, and duration of use, although this may be because the cumulative dose for most cannabis users is not high enough to affect fat and glucose-insulin metabolism. Statistical confounders may exist in these studies which are not adequately controlled for by standard

multivariable modeling. For example, in general, high levels of cannabis use are strongly associated with younger age, which is inversely associated with the incidence and prevalence of diabetes. They are also associated with tobacco cigarette smoking, a known risk factor for diabetes (Willi et al., 2007). Cannabis use was associated with increases in physical activity in the CARDIA study (Bancks et al., 2015) and in one of the NHANES studies (Rajavashisth et al., 2012). Physical activity is protective against obesity and diabetes.

- Reverse causality might result in a chronic illness such as diabetes leading to the cessation of potentially unhealthy habits, including cannabis use. This might help to explain why cannabis use is associated with prediabetes but not with diabetes.

CONCLUSION 6-3

6-3(a) There is limited evidence of a statistical association between cannabis use and decreased risk of metabolic syndrome and diabetes.

6-3(b) There is limited evidence of a statistical association between cannabis use and increased risk of prediabetes.

RESEARCH GAPS

The major gaps and opportunities relate to the paucity of longitudinal data for all of the cardiometabolic disorders and to the lack of data on the impact of cannabis use on risk in the older-adults age groups in which the majority of cardiovascular endpoints (e.g., acute myocardial infarction, stroke) occur. To address research gaps the committee suggests the following:

- Establishing a population cohort(s) in which cannabis use is regularly evaluated with standardized questionnaires accounting for the type of preparation, THC/other cannabinoid strength, the amount smoked or consumed, assessment of frequency and duration of use, and other cardiovascular disease (CVD) risk data, and in which researchers collect medical record and toxicology data or other biological marker data for cannabis use on incident CVD events.
- The cohort(s) need to be large enough that the association of cannabis with CVD events in the presence of potential statistical confounding variables (e.g., tobacco use, physical activity) can be validly assessed.
- Promote the collection of cannabis use data in electronic health records.

An additional suggestion is that basic research needs to be carried out to better understand the mechanisms for the role of cannabis as a possible trigger of AMI.

SUMMARY

This chapter summarizes the good and fair cardiometabolic literature published since 1999. The committee found limited evidence of an association between acute cannabis use, but not chronic cannabis use, and AMI risk. The committee also determined that there is limited evidence of an association between cannabis use and an increased risk of ischemic stroke or subarachnoid hemorrhage and also prediabetes and an association between cannabis and a decreased risk of metabolic dysregulation, metabolic syndrome, and diabetes. The limitations of the reviewed studies include a lack of information on different routes of cannabis administration (e.g, smoked, edible, etc.), a lack of adequate dose information, insufficient information on potential additives or contaminants, and inadequate data on total lifetime duration/dose of cannabis use. The committee has formed a number of research conclusions related to these health endpoints; however, it is important that each of these conclusions be interpreted within the context of the limitations discussed in the Discussion of Findings sections. Box 6-1 contains a summary of the conclusions for this chapter.

BOX 6-1
Summary of Chapter Conclusions*

There is limited evidence of a statistical association between cannabis use and:

- The triggering of acute myocardial infarction (cannabis smoking) (6-1a)
- Ischemic stroke or subarachnoid hemorrhage (6-2)
- Decreased risk of metabolic syndrome and diabetes (6-3a)
- Increased risk of prediabetes (6-3b)

There is no evidence to support or refute a statistical association between *chronic effects* of cannabis use and:

- The increased risk of acute myocardial infarction (6-1b)

*Numbers in parentheses correspond with Chapter conclusion number

REFERENCES

Alshaarawy, O., and J. C. Anthony. 2015. Cannabis smoking and diabetes mellitus: Results from meta-analysis with eight independent replication samples. *Epidemiology* 26(4):597–600.

Aronow, W.S., and J. Cassidy. 1974. Effect of marihuana and placebo-marihuana smoking on angina pectoris. *New England Journal of Medicine* 291(2):65–67.

Azofeifa, A., M. E. Mattson, G. Schauer, T. McAfee, A. Grant, and R. Lyerla. 2016. National Estimates of Marijuana Use and Related Indicators—National Survey on Drug Use and Health, United States, 2002–2014. *Morbidity and Mortality Weekly Report Surveillance Summaries* 65(11):1–25.

Bancks, M. P., M. J. Pletcher, S. G. Kertesz, S. Sidney, J. S. Rana, and P. J. Schreiner. 2015. Marijuana use and risk of prediabetes and diabetes by middle adulthood: The Coronary Artery Risk Development in Young Adults (CARDIA) study. *Diabetologia* 58(12):2736–2744.

Barber, P. A., H. M. Pridmore, V. Krishnamurthy, S. Roberts, D. A. Spriggs, K. N. Carter, and N. E. Anderson. 2013. Cannabis, ischemic stroke, and transient ischemic attack: A case-control study. *Stroke* 44(8):2327–2329.

Beaconsfield, P., J. Ginsburg, and R. Rainsbury. 1972. Marihuana smoking. Cardiovascular effects in man and possible mechanisms. *New England Journal of Medicine* 287(5):209–212.

Benowitz, N. L., and R. T. Jones. 1981. Cardiovascular and metabolic considerations in prolonged cannabinoid administration in man. *Journal of Clinical Pharmacology* 21(8–9 Suppl):214S–223S.

CDC (Centers for Disease Control and Prevention). 2014a. *National diabetes statistics report: Estimates of diabetes and its burden in the United States, 2014*. Atlanta, GA: U.S. Department of Health and Human Services.

CDC. 2014b. Division of Diabetes Translation: National Diabetes Surveillance System. Long-term trends in diabetes. https://www.cdc.gov/diabetes/statistics/slides/long_term_trends.pdf. (accessed October 25, 2016).

CDC. 2015. Annual number (in thousands) of new cases of diagnosed diabetes among adults aged 18–79 Years, United States, 1980–2014. http://www.cdc.gov/diabetes/statistics/incidence/fig1.htm (accessed October 25, 2016).

Di Marzo, V., F. Piscitelli, and R. Mechoulam. 2011. Cannabinoids and endocannabinoids in metabolic disorders with focus on diabetes. *Handbook of Experimental Pharmacology* 203:75–104.

Flegal, K. M., M. D. Carroll, C. L. Ogden, and C. L. Johnson. 2002. Prevalence and trends in obesity among U.S. adults, 1999–2000. *JAMA* 288(14):1723–1727.

Franz, C. A., and W. H. Frishman. 2016. Marijuana use and cardiovascular disease. *Cardiology in Review* 24(4):158–162.

Gorelick, D. A., R. S. Goodwin, E. Schwilke, D. M. Schwope, W. D. Darwin, D. L. Kelly, R. P. McMahon, F. Liu, C. Ortemann-Renon, D. Bonnet, and M. A. Huestis. 2013. Tolerance to effects of high-dose oral Δ9-tetrahydrocannabinol and plasma cannabinoid concentrations in male daily cannabis smokers. *Journal of Analytical Toxicology* 37(1):11–16.

Hayatbakhsh, M. R., M. J. O'Callaghan, A. A. Mamun, G. M. Williams, A. Clavarino, and J. M. Najman. 2010. Cannabis use and obesity and young adults. *American Journal of Drug and Alcohol Abuse* 36(6):350–356.

Herning, R. I, W. E. Better, K. Tate, and J. L. Cadet.2001. Marijuana abusers are at increased risk for stroke. Preliminary evidence from cerebrovascular perfusion data. *Annals of the New York Academy of Sciences* 939:413–415.

IOM (Institute of Medicine). 1999. *Marijuana and medicine: Assessing the science base*. Washington, DC: National Academy Press.

Jamal, A., D. M. Homa, E. O'Connor, S. D. Babb, R. S. Caraballo, T. Singh, S. S. Hu, B. A. King. 2015. Current Cigarette Smoking Among Adults—United States, 2005–2014. *Morbidity and Mortality Weekly Report* 64(44):1233–1240.

Khiabani, H. Z., J. Mørland, and J. G. Bramness. 2008. Frequency and irregularity of heart rate in drivers suspected of driving under the influence of cannabis. *European Journal of Internal Medicine* 19:608–612.

Klil-Drori, A. J., L. Azoulay, and M. N. Pollak. 2016. Cancer, obesity, diabetes, and antidiabetic drugs: Is the fog clearing? *Nature Reviews: Clinical Oncology* August. doi:10.1038/nrclinonc.2016.120.

Kochanek, K. D., S. L. Murphy, J. Q. Xu, and B. Tejada-Vera. 2016. Deaths: Final data for 2014. *National Vital Statistics Reports* 65(4):1–121. Hyattsville, MD: National Center for Health Statistics.

Le Strat, Y., and B. Le Foll. 2011. Obesity and cannabis use: Results from 2 representative national surveys. *American Journal of Epidemiology* 174(8):929–933.

Mittleman, M. A., R. A. Lewis, M. Maclure, J. B. Sherwood, and J. E. Muller. 2001. Triggering myocardial infarction by marijuana. *Circulation* 103(23):2805–2809.

Mozaffarian, D., E. J. Benjamin, A. S. Go, D. K. Arnett, M. J. Blaha, M. Cushman, S. R. Das, S. de Ferranti, J. P. Després, H. J. Fullerton, V. J. Howard, M. D. Huffman, C. R. Isasi, M. C. Jiménez, S. E. Judd, B. M. Kissela, J. H. Lichtman, L. D. Lisabeth, S. Liu, R. H. Mackey, D. J. Magid, D. K. McGuire, E. R. Mohler 3rd, C. S. Moy, P. Muntner, M. E. Mussolino, K. Nasir, R. W. Neumar, G. Nichol, L. Palaniappan, D. K. Pandey, M. J. Reeves, C. J. Rodriguez, W. Rosamond, P. D. Sorlie, J. Stein, A. Towfighi, T. N. Turan, S. S. Virani, D. Woo, R. W. Yeh, M. B. Turner; American Heart

Association Statistics Committee, and Stroke Statistics Subcommittee. 2016. Heart disease and stroke statistics—2016 update: A report from the American Heart Association. *Circulation* 133(4):e38–e360.

Ogden, C. L., M. D. Carroll, B. K. Kit, and K. M. Flegal. 2014. Prevalence of childhood and adult obesity in the United States, 2011–2012. *JAMA* 311(8):806–814.

Penner, E. A., H. Buettner, and M. A. Mittleman. 2013. The impact of marijuana use on glucose, insulin, and insulin resistance among U.S. adults. *American Journal of Medicine* 126(7):583–589.

Phillips, M. C., J. M. Leyden, W. K. Chong, T. Kleinig, P. Czapran, A. Lee, S. A. Koblar, J. Jannes. 2011. Ischaemic stroke among young people aged 15 to 50 years in Adelaide, South Australia. *Medical Journal of Australia* 195(10):610–614.

Rajavashisth, T. B., M. Shaheen, K. C. Norris, D. Pan, S. K. Sinha, J. Ortega, and T. C. Friedman. 2012. Decreased prevalence of diabetes in marijuana users: Cross-sectional data from the National Health and Nutrition Examination Survey (NHANES) III. *BMJ Open* 2:e000494.

Renaud, A. M., and Y. Cormier. 1986. Acute effects of marihuana smoking on maximal exercise performance. *Medicine and Science in Sports and Exercise* 18(6):685–689.

Rodondi, N., M. J. Pletcher, K. Liu, S. B. Hulley, S. Sidney, and Coronary Artery Risk Development in Young Adults (CARDIA) Study. 2006. Marijuana use, diet, body mass index, and cardiovascular risk factors (from the CARDIA study). *American Journal of Cardiology* 98(4):478–484.

Rumalla, K., A. Y. Reddy, and M. K. Mittal. 2016a. Recreational marijuana use and acute ischemic stroke: A population-based analysis of hospitalized patients in the United States. *Journal of Neurological Sciences* 364:191–196.

Rumalla, K., A. Y. Reddy, and M. K. Mittal. 2016b. Association of recreational marijuana use with aneurysmal subarachnoid hemorrhage. *Journal of Stroke and Cerebrovascular Disease* 25(2):452–460.

Sidney, S. 2002. Cardiovascular consequences of marijuana use. *Journal of Clinical Pharmacology* 42(11 Suppl):64S–70S.

Sidney, S. 2016. Marijuana use and type 2 diabetes mellitus: A review. *Current Diabetes Reports* 16(11):117.

Sidney, S., J. E. Beck, I. S. Tekawa, C. P. Quesenberry, and G. D. Friedman. 1997. Marijuana use and mortality. *American Journal of Public Health* 87(4):585–590.

Smit, E., and C. J. Crespo. 2001. Dietary intake and nutritional status of U.S. adult marijuana users: Results from the Third National Health and Nutrition Examination Survey. *Public Health Nutrition* 4(3):781–786.

Thomas, G., R. A. Kloner, and S. Rezkalla. 2014. Adverse cardiovascular, cerebrovascular, and peripheral vascular effects of marijuana inhalation: What cardiologists need to know. *American Journal of Cardiology* 113(1):187–190.

Vidot, D. C., G. Prado, W. M. Hlaing, H. J. Florez, K. L. Arheart, and S. E. Messiah. 2016. Metabolic syndrome among marijuana users in the United States: An analysis of National Health and Nutrition Examination survey data. *American Journal of Medicine* 129(2):173–179.

Wang, X., R. Derakhshandeh, J. Liu, S. Narayan, P. Nabavizadeh, S. Le, O. M. Danforth, K. Pinnamaneni, H. J. Rodriguez, E. Luu, R. E. Sievers, S. F. Schick, S. A. Glantz, and M. L. Springer. 2016. One minute of marijuana secondhand smoke exposure substantially impairs vascular endothelial function. *Journal of the American Heart Association* 5(8):e003858.

Warren, M., K. Frost-Pineda, and M. Gold. 2005. Body mass index and marijuana use. *Journal of Addictive Diseases* 24(3):95–100.

Westover, A. N., S. McBride, and R. W. Haley. 2007. Stroke in young adults who abuse amphetamines or cocaine: A population-based study of hospitalized patients. *Archives of General Psychiatry* 64(4):495–502.

Willi, C., P. Bodenmann, W. A. Ghali, P. D. Faris, and J. Cornuz. 2007. Active smoking and the risk of type 2 diabetes: A systematic review and meta-analysis. *JAMA* 298(22):2654–2664.

Wolff, V., V. Lauer, O. Rouyer, F. Sellal, N. Meyer, J. S. Raul , C. Sabourdy, F. Boujan, C. Jahn, R. Beaujeux, and C. Marescaux. 2011. Cannabis use, ischemic stroke, and multifocal intracranial vasoconstriction: A prospective study in 48 consecutive young patients. *Stroke* 42(6):1778–1780.

Wolff, V., J. P. Armspach, V. Lauer, O. Rouyer, M. Bataillard, C. Marescaux, and B. Geny. 2013. Cannabis-related stroke: Myth or reality? *Stroke* 44(2):558–563.

Wolff, V., J. P. Armspach, V. Lauer, O. Rouyer, A. Ducros, C. Marescaux, and B. Gény. 2015. Ischaemic strokes with reversible vasoconstriction and without thunderclap headache: A variant of the reversible cerebral vasoconstriction syndrome? *Cerebrovascular Disease* 39(1):31–38.

Yankey, B. N., S. Strasser, and I. S. Okosun. 2016. A cross-sectional analysis of the association between marijuana and cigarette smoking with metabolic syndrome among adults in the United States. *Diabetes and Metabolic Syndrome* 10(2 Suppl 1):S89–S95.

7
Respiratory Disease

Chapter Highlights
• Smoking cannabis on a regular basis is associated with chronic cough and phlegm production. • Quitting cannabis smoking is likely to reduce chronic cough and phlegm production. • It is unclear whether cannabis use is associated with COPD, asthma, or worsened lung function.

Environmental exposures are the leading causes of respiratory disease worldwide. Exposures to tobacco smoke and household air pollution consistently rank among the top risk factors not only for respiratory disease burden but also for the global burden of disease (Lim et al., 2010). Less is known, however, about the attributable effects of cannabis use on respiratory disease despite shared similarities with that of cigarette use and the fact that cannabis is the most commonly used inhaled drug in the United States after tobacco, with an estimated 22.2 million people aged 12 years and older reporting current use (CBHSQ, 2015). Moreover, it is estimated that over 40 percent of current users smoke cannabis on a daily or near daily basis (Douglas et al., 2015). Given the known relationships between tobacco smoking and multiple respiratory conditions, one could hypothesize that long-term cannabis smoking leads to similar deleterious effects on respiratory health, and some investigators argue that cannabis smoking may be even more harmful than that of tobacco smoking. Indeed, data collected from 15 volunteers suggest that smoking one cannabis joint can lead to four times the exposure to carbon monoxide and three to five times more tar deposition than smoking a single cigarette (Wu et al., 1988). This may be in part because cannabis smokers generally inhale more deeply and hold their breath for longer than do cigarette smokers (Wu et al., 1988) and because cannabis cigarettes do not commonly have filters as tobacco cigarettes often do. On the other hand, cannabis cigarettes are not as densely packed as tobacco cigarettes (Aldington et al., 2008), and cannabis users usually smoke fewer cannabis cigarettes per day than tobacco users smoke tobacco cigarettes per day.

The committee responsible for the 1999 Institute of Medicine (IOM) report *Marijuana and Medicine: Assessing the Science Base* (IOM, 1999, p.6) concluded that cannabis smoking was an important risk factor in the development of respiratory disease and recommended that "studies to define the individual health risks of smoking marijuana should be conducted, particularly among populations in which marijuana use is prevalent". The literature search conducted by the current committee did not identify any "fair" or "good" systematic reviews for cannabis use and respiratory disease published since 2011 (the cut-off established by the current committee); however, the committee identified—and elected to include—a systematic review by Tetrault et al. (2007) that provides a detailed synthesis of the available literature through 2005. A review by Tashkin (2013) and a position statement by Douglas et al. (2015), which summarized

current evidence of the link between cannabis smoking and respiratory disease, were also considered by the committee. Thirteen primary articles published since 1999 that were not included in the systematic review from Tetrault et al. (2007) provided additional evidence on the association between smoking cannabis and respiratory diseases (Aldington et al., 2007; Bechtold et al., 2015; Hancox et al., 2015; Kempker et al., 2015; Macleod et al., 2015; Papatheodorou et al., 2016; Pletcher et al., 2012; Tan et al., 2009; Tashkin et al., 2012; Van Dam and Earleywine, 2010; Walden and Earleywine, 2008; Weekes et al., 2011; Yadavilli et al., 2014).

PULMONARY FUNCTION

Pulmonary function refers to lung size and function. Common measures of pulmonary function include forced expiratory volumes, lung volumes, airways resistance and conductance, and the diffusion capacity of the lung for carbon monoxide (DLCO). Spirometry values include the measurements of forced expiratory volumes, including forced expiratory volumes at 1 second (FEV_1), forced vital capacity (FVC), and FEV_1/FVC. The latter is a measure of airflow obstruction and, when combined with bronchodilator therapy, is used in the diagnosis of chronic obstructive pulmonary disorder (COPD).

Is There an Association Between Cannabis Use and Pulmonary Function?

Systematic Reviews

Tetrault et al. (2007) systematically reviewed the evidence found in 34 publications, of which 12 reported on the effects of airway response and 14 reported on the effects of pulmonary function. The authors found that short-term exposure to cannabis smoking resulted in bronchodilation. Specifically, acute cannabis smoking was consistently associated with improvements in specific airway conductance, peak flow measurements, and forced expiratory volume in 1 second (FEV_1) and reversed bronchospasm from challenges by either methacholine or exercise. Any short-term benefits, however, were offset by the effects of long-term cannabis smoking. Specifically, regular cannabis smoking was associated with a lower specific airway conductance on average by 16 percent and also with a lower FEV_1. There was also a dose–response effect between average daily quantity of cannabis and a lower specific airway conductance. However, the clinical significance of the association between regular cannabis smoking and a lower specific airways conductance is not known. Other studies that examined the association between long-term cannabis smoke exposure and pulmonary function have inconsistently found lower or no change in FEV_1, FVC, FEV_1/FVC, DLCO, and airway hyper-responsiveness (Tetrault et al., 2007).

Primary Studies

Aldington et al. (2007) examined the cross-sectional relationship between long-term cannabis smoking and pulmonary function in a convenience sample of 339 participants in the Wellington Research Study. The inclusion criteria for cannabis and tobacco smokers were a lifetime exposure of at least 5 joint-years of cannabis (defined as smoking 1 joint per day for 1 year) or at least 1 pack-year of tobacco, respectively. Cannabis smoking was based on self-

report. The researchers did not find an association between long-term cannabis smoking and pulmonary function variables. However, when cannabis smoking was analyzed in terms of joint-years, Aldington et al. (2007) found a significantly lower FEV_1/FVC, lower specific airways conductance, and a higher total lung capacity per joint-year smoked in cannabis smokers compared to non-smokers. Based on their analyses, the authors estimated that the negative association between each cannabis joint and a lower FEV_1/FVC was similar to that of 2.5 to 5 tobacco cigarettes. The committee identified a couple of problems with the analyses and the presentation of the results in the paper by Aldington et al. (2007). First, the authors reported main effects only from their analysis of covariance. A more conservative analysis would have considered the examination of interaction effects between cannabis smoke (or joint-years) and tobacco smoke (or pack-years) in a regression model to better dissect the contribution of cannabis smoke (or joint-years) versus tobacco smoke (or pack-years). Second, the authors incorrectly labeled the association with continuous measures of pulmonary function with cannabis smoke (or joint-years) as odds ratios in tables 3 and 4; however, their methods correctly state that a multivariable analysis of covariance methods was used for continuous data.

Papatherodoru et al. (2016) analyzed cross-sectional data from 10,327 adults who participated in the National Health and Nutrition Examination Survey (NHANES) between 2007 and 2012. Cannabis smoking was based on self-report, but the researchers could not quantify joint-years. Cannabis smokers were categorized as never smokers (n = 4,794), past cannabis smokers (n = 4,084), cannabis smokers in the past 5–30 days (n = 555), and cannabis smokers in the past 0–4 days (n = 891). Current cannabis smokers were heavier tobacco smokers than were past and never smokers of cannabis, as measured by mean pack-years. In multivariable analyses, the investigators found that current smokers had a smaller FEV_1/FVC than never smokers (−0.01 and −0.02, respectively), and they observed moderate to large increases in FEV_1 (49 mL and 89 mL, respectively) and FVC (159 mL and 204 mL, respectively) when comparing current smokers to never smokers. There was also an important decrease in exhaled nitric oxide among current smokers when compared to never smokers (−7 percent versus −14 percent), but it is unclear if this effect was confounded by the high prevalence of tobacco smoking in current cannabis users or if it represented a true decrease in exhaled nitric oxide due to cannabis smoking. The study by Papatherodoru et al. (2016) has some shortcomings. First, the researchers' analyses were based on cross-sectional data. Second, cannabis use was obtained by self-report and there may have been a bias of under-reporting. Finally, there was a lack of data on the method of smoke inhalation and the frequency of cannabis smoking, thus not allowing for an analysis of the relationship between the frequency of cannabis use and pulmonary function.

Pletcher et al. (2012) analyzed longitudinal data from 5,115 adults in the Coronary Artery Risk Development in Young Adults (CARDIA) study and concluded that occasional and low cumulative cannabis smoking was not associated with adverse effects on pulmonary function. The investigators noted that there was a trend toward decreases in FEV_1 over 20 years only in the heaviest cannabis smokers ($\geq$20 joint-years). Similar to the findings of Papatherodoru et al. (2016), CARDIA investigators found a higher-than-expected FVC among all categories of cannabis smoking intensity. Despite the large sample size, the study by Pletcher et al. (2012) had a small number of heavy cannabis smokers. Other limitations include the risk of bias due to the self-reporting of cannabis use, a lack of data on the method of cannabis smoke inhalation, and bias due to unmeasured confounders as cannabis smoking was not the main objective of this study.

The study by Hancox et al. (2010) analyzed data of a cohort of 1,037 adult participants in Dunedin, New Zealand, followed longitudinally since childhood, and asked about cannabis and tobacco use at ages 18, 21, 26, and 32 years. Cumulative exposure to cannabis was quantified as joint-years since age 17 years. Spirometry was conducted at 32 years. Cumulative cannabis use was associated with higher FVC, total lung capacity, functional residual capacity and residual volume, but not with lower FEV_1 or FEV_1/FVC.

A small feasibility study by Van Dam and Earleywine (2010) found that the use of a cannabis vaporizer instead of smoking cannabis in 12 adult participants who did not develop a respiratory illness was associated with improvements in forced expiratory volumes at approximately 1 month after the introduction of the vaporizer; however, this study did not have a control group.

Discussion of Findings

Overall, acute cannabis smoking was associated with bronchodilation, but many of the authors agreed that any benefits may be offset when cannabis is smoked regularly. The current findings are inconclusive on a variety of pulmonary function measurements, and the findings may be affected by the quality of the studies, a failure to adjust for important confounders including tobacco and other inhaled drugs, and other occupational and environmental exposures. The committee's findings are consistent with those reported in another recent review (Tashkin, 2013) and a position statement (Douglas et al., 2015).

The majority of studies, including those evaluated in the systematic review, relied on self-report for cannabis smoking. Many studies failed to control for tobacco smoking and occupational and other environmental exposures; did not control for the dose or duration of cannabis smoking; and did not use joint-years and instead based heavy cannabis smoking on having exceeded a specific threshold of joints. Even among studies that used joint-years, it is unclear how generalizable their findings are, given the potential high variability in lung-toxic content from joint to joint. Prior studies have inconsistently documented decreases or no change in FEV_1, FEV_1/FVC, DLCO, and airway hyper-responsiveness. Moreover, neither the mechanism nor the clinical significance of the association between cannabis smoking and pulmonary function deficits is known, beyond the possible impact of a high FVC in lowering the FEV_1/FVC ratio. While elevated lung volumes could be indicators of lung pathology, an elevated FVC by itself has not been associated with any lung pathology.

CONCLUSION 7-1

7-1(a) There is moderate evidence of a statistical association between cannabis smoking and improved airway dynamics with acute use, but not with chronic use.

7-1(b) There is moderate evidence of a statistical association between cannabis smoking and higher forced vital capacity (FVC).

CHRONIC OBSTRUCTIVE PULMONARY DISEASE

COPD is a clinical syndrome that consists of lower airway inflammation and damage that impairs airflow. Ranked as the fourth-leading causes of death worldwide by the World Health Organization, COPD has been estimated to cause more than 3 million deaths worldwide annually and has an estimated global prevalence of 10 percent in adults (Buist et al., 2007; Diaz-Guzman and Mannino, 2014). COPD is diagnosed with spirometry and is defined by a post-bronchodilator forced expiratory volume at 1 second divided by forced vital capacity (FEV_1/FVC) < 70 percent (fixed cutoff) or as a post-bronchodilator FEV_1/FVC below the 5th percentile of a reference population (lower limit of normal). The committee responsible for *Marijuana and Medicine: Assessing the Science Base* (IOM, 1999) suspected, but did not conclude, that chronic cannabis smoking causes COPD.

Is There an Association Between Cannabis Use and COPD?

Systematic Reviews

There is no discussion about the association between cannabis and COPD in the systematic review by Tetrault et al. (2007). In the position statement of the American Thoracic Society (Douglas et al., 2015), workshop members concluded that there was minimal impairment in occasional cannabis smokers when controlling for tobacco use. In contrast, there was a trend towards higher prevalence in heavier users based on studies of lung function decline (Pletcher et al., 2012; Tashkin et al., 1987); however, workshop members determined that this association was incompletely quantified.

Primary Studies

The study by Aldington et al. (2007) examined high-resolution computed tomography scans among the subgroups of participants with cannabis smoking only, cannabis and tobacco smoking, tobacco smoking only, and never smokers. They found inconsistent results: a decreased mean lung density, which is suggestive of emphysematous changes (mean percent of area below −950 Hounsfield units in three slices at 2.4 percent [95% confidence interval (CI) = 1.0%–3.8%] for cannabis smokers, but −0.6 percent [−2.0%–0.8%] for tobacco smokers when compared to non-smokers) but almost no evidence of macroscopic emphysema (1.3% versus 16.5% versus 18.5% versus 0% in cannabis-only smokers versus cannabis and tobacco smokers versus tobacco-only smokers versus non-smokers, respectively).

Tan et al. (2009) analyzed cross-sectional data collected in 878 adults aged ≥40 years from Vancouver, Canada, who participated in the Burden of Obstructive Lung Disease study on COPD prevalence. Current smoking of either tobacco or cannabis was defined as any smoking within the past year. Participants who had smoked at least 50 marijuana cigarettes but had no history of tobacco smoking were not at significantly greater risk of having COPD or more respiratory symptoms. There was inconsistent evidence for whether synergy from combined cannabis and tobacco smoking might affect the odds of having COPD or worse respiratory symptoms.

Specifically, the mean estimates for the tobacco and cannabis smoking versus tobacco-only smoking groups do not appear to be different and the 95% CI for the tobacco and cannabis

smoking group appears to overlap significantly with the tobacco-only smoking groups when evaluating either COPD or respiratory symptoms as the outcome.

Yadavilli et al. (2014) examined data from 709 participants over a 33-month period for hospital readmissions of COPD in illicit drug users and tobacco smokers. These investigators found that cannabis users had similar readmission rates to ex-tobacco or current tobacco users (mean readmissions at 0.22 versus 0.26) and much lower readmissions rates than other illicit drug users (mean readmissions at 1.0). The unit for mean readmissions was not specified in either the tables or methods of this paper. The limitations of the study by Yadavilli et al. (2014) include a lack of spirometry data on all patients to confirm diagnosis of COPD, the self-report of tobacco use, the risk for potential underreporting of illicit drug use, and the lack of outpatient visit frequency.

The study by Macleod et al. (2015) examined data from 500 adult participants, all of whom reported either tobacco smoking of ≥20 cigarettes per day for at least 5 years or cannabis of ≥1 joint per day for at least 1 year. There was no difference in the percent with COPD ($FEV_1/FVC < 0.7$) between tobacco-only users and tobacco and cannabis users (24.3 percent versus 25.2 percent; $p = 0.90$) for all ages or at any age group. Tobacco and cannabis users had more respiratory symptoms than did tobacco-only users (cough, phlegm, wheeze), but the investigators do not seem to report multivariable adjusted differences in the paper. The limitations of the study by Macleod et al. (2015) are that its cross-sectional design does not allow one to assess temporality between exposure and outcome, the lack of a non-smoking group, the fact that its use of as convenience sample may have oversample unwell participants, and the use of self-report for tobacco and cannabis.

Kempker et al. (2015) analyzed data from the 2007–2010 National Health and Nutrition Examination Survey (NHANES) cohorts, similar to the work done by Papatherodoru et al. (2016). Kempker et al. (2015), however, also examined the information on cumulative lifetime use of cannabis available in the 2009–2010 NHANES cohort. Main findings were that 59 percent reported using cannabis at least once during their lifetime, and 12 percent reported use during the last month. When evaluating cumulative lifetime cannabis use, those with >20 joint-years had a two times higher odds (OR, 2.1; 95% CI = 1.1–3.9) of having a pre-bronchodilator FEV_1/FVC <70 percent than those with no cannabis exposure. However, as noted by others, cannabis use was associated with a higher FVC and no association with FEV_1, which would spuriously reduce the ratio FEV_1/FVC. Beyond the limitations noted above for the paper by Papatherodoru et al. (2016) who also used NHANES data, the authors were limited to use pre-bronchodilator spirometry instead of using post-bronchodilator spirometry as commonly done in COPD studies.

Discussion of Findings

It is unclear whether regular cannabis use is associated with the risk of developing COPD or exacerbating COPD. Current studies may be confounded by tobacco smoking and the use of other inhaled drugs as well as by and occupational and environmental exposures, and these studies have failed to quantify the effect of daily or near daily cannabis smoking on COPD risk and exacerbation. There is no evidence of physiological or imaging changes consistent with emphysema. The committee's findings are consistent with those of a recent position statement from the American Thoracic Society Marijuana Workgroup which concluded that there was minimal impairment in light and occasional cannabis smokers when controlled for tobacco use and that the effects of heavy cannabis smokers remains poorly quantified (Douglas et al., 2015).

The review by Tashkin et al. (2013) concluded that the lack of evidence between cannabis use and longitudinal lung function decline (Pletcher et al., 2012) argues against the idea that smoking cannabis by itself is a risk factor for the development of COPD. This is further supported by the findings of Kempker et al. (2015), who concluded that smoking cannabis was not associated with lower FEV_1 after adjusting for tobacco smoking. However, smoking cannabis was associated with a higher FVC, which may have led to a spuriously lower FEV_1/FVC. Therefore, their analyses also do not support an association between heavy cannabis use (>20 lifetime joint-years) and obstruction on spirometry. The position statement by Douglas et al. (2015) concluded that the lack of solid epidemiologic association suggests the regular cannabis smoking may be a less significant risk factor for the development of COPD than tobacco smoking.

Cross-sectional studies are inadequate to establish temporality, and cohort studies of regular or daily cannabis users are a better design to help establish COPD risk over time. Better studies are needed to clearly separate the effects of cannabis smoking from those of tobacco smoking on COPD risk and COPD exacerbations, and better evidence is needed for heavy cannabis users.

CONCLUSION 7-2

7-2(a) There is limited evidence of a statistical association between occasional cannabis smoking and an increased risk of developing chronic obstructive pulmonary disease (COPD) when controlled for tobacco use.

7-2(b) There is insufficient evidence to support or refute a statistical association between cannabis smoking and hospital admissions for COPD.

RESPIRATORY SYMPTOMS, INCLUDING CHRONIC BRONCHITIS

Respiratory symptoms include cough, phlegm, and wheeze. Chronic bronchitis is defined as chronic phlegm production or productive cough for 3 consecutive months per year for at least 2 consecutive years (Medical Research Council, 1965). Chronic bronchitis is a clinical diagnosis and does not require confirmation by spirometry or evidence of airflow obstruction. The committee responsible for *Marijuana and Medicine: Assessing the Science Base* (IOM, 1999) concluded that acute and chronic bronchitis may occur as a result of chronic cannabis use.

Is There an Association Between Cannabis Use and Respiratory Symptoms, Including Chronic Bronchitis?

Systematic Reviews

The systematic review by Tetrault et al. (2007) summarized information from 14 studies that assessed the association between long-term cannabis smoking and respiratory symptoms. Nine of these studies were cross-sectional, three were case series, one was a case-control study, and one was a longitudinal cohort study. Data were relatively consistent in both cross-sectional and cohort studies in indicating that long-term cannabis smoking worsens respiratory symptoms including cough (odds ratio (OR), 1.7–2.0), increased sputum production (OR, 1.5–1.9), and

wheeze (OR, 2.0–3.0). Other studies have reported effects on more episodes of acute bronchitis and pharyngitis, dyspnea, hoarse voice, worse cystic fibrosis symptoms, and chest tightness.

Primary Studies

Aldington et al. (2007) reported higher prevalence of wheeze (27 percent versus 11 percent), cough (29 percent versus 5 percent), chest tightness (49 percent versus 35 percent), and chronic bronchitis symptoms (19 percent versus 3 percent) among cannabis smokers than non-smokers. There were no clear additive effects observed in the combined cannabis and tobacco smoking groups on respiratory symptoms.

Hancox et al. (2015) conducted a study in a cohort of 1,037 adults (52 percent male) in the Dunedin Multidisciplinary Health and Development Study. Cannabis and tobacco smoking histories were obtained at the ages of 18, 21, 26, 32, and 38 years. At each assessment participants were asked how many times they had used cannabis in the previous year. Frequent cannabis users were defined as those who reported using marijuana ≥52 times over the previous year. Quitters were defined as a frequent cannabis user at the previous assessment but less than frequent at the current assessment. Because it was possible to quit frequent cannabis use more than once during the follow-up from 18 to 38 years of age, only the first recorded episode of quitting was used in analyses. In this study, the investigators found that frequent cannabis use was associated with morning cough (OR = 1.97, $p < 0.001$), sputum production (OR = 2.31, $p < 0.001$), and wheeze (OR = 1.55, $p < 0.001$), but not dyspnea ($p = 0.09$) (see Figure 7-1). Quitters (open triangles) also had fewer respiratory symptoms than those who did not quit (solid squares).

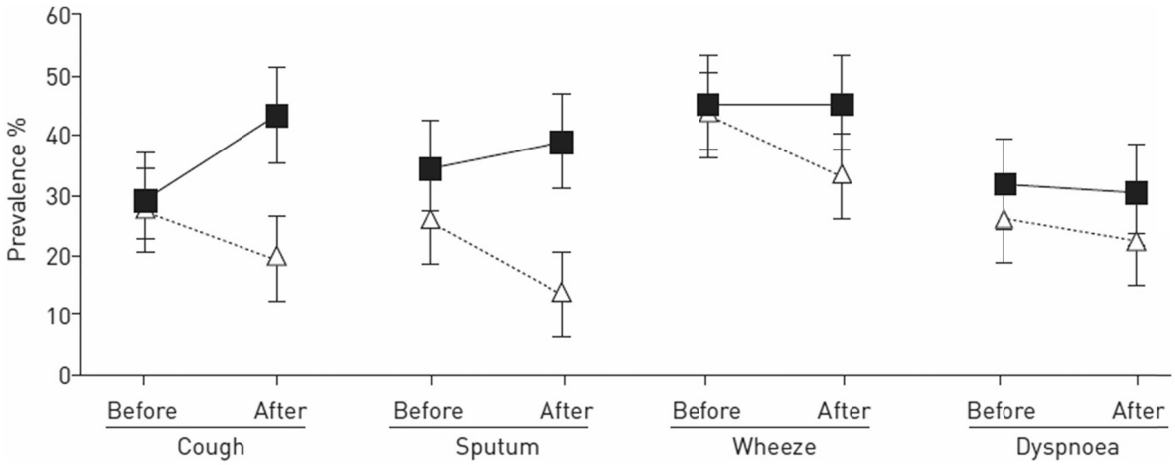

FIGURE 7-1 Prevalence of symptoms before and after quitting regular cannabis use (open triangles) and among those who used cannabis for two consecutive phases (solid squares). Vertical bars show 95% CI. SOURCE: Hancox et al., 2015.

Limitations of the study by Hancox et al. (2015) include its reliance on self-reported data of cannabis use without objective confirmation, the classification of non-users as those with <52 times of cannabis use, and a lack of data as to whether cannabis use was specifically from smoking.

Walden and Earleywine (2008) conducted a cross-sectional Internet survey of 5,987 adults worldwide who used cannabis at least once a month. They quantified frequency, amount,

and degree of usual and maximal intoxication, and they also asked about respiratory symptoms using a composite score produced from the answers to six standard questions about cough, morning phlegm, dyspnea, chest wheezing other than during colds, and night-time awakenings because of chest-tightness. They found that the frequency of use, the amount used (in quarter bags per month), and the degree of usual intoxication were all positively associated with more respiratory symptoms. Limitations for this study include its recruitment of participants from organizations that advocate drug policy reform, its reliance on self-reported data of cannabis or tobacco use without objective confirmation, and the lack of data about cannabis use for medical versus recreational purposes.

Tashkin et al. (2012) followed 299 participants from a longitudinal cohort study for at least two visits over 9.8 years and examined the relationship between symptoms for chronic bronchitis and cannabis use. They found that current cannabis users were more likely to have cough (OR = 1.7), sputum (OR = 2.1), increased bronchitis episodes (OR = 2.3), and wheeze (OR = 3.4) when compared to never users. They also found that current cannabis users were more likely to have cough (OR = 3.3), sputum (OR = 4.2), or wheeze (OR = 2.1) than former users. Similar to the studies by Hancox et al. (2015) and Walden and Earleywine (2008), these findings demonstrated the benefit of cannabis smoking cessation in resolving pre-existing symptoms of chronic bronchitis. The limitations of this study include its reliance on self-reported data of cannabis or tobacco use without objective confirmation and high rates of loss to follow-up or variable follow-up periods.

A small feasibility study by Van Dam and Earleywine (2010) of 12 adult participants who did not develop a respiratory illness during the trial found that the use of a cannabis vaporizer instead of smoking cannabis was correlated with the resolution of cannabis-related respiratory symptoms at approximately one month after the introduction of the vaporizer; however, this study did not have a control group.

Discussion of Findings

Regular cannabis use was associated with airway injury, worsening respiratory symptoms and more frequent chronic bronchitis episodes. There were no clear additive effects on respiratory symptoms observed from smoking both cannabis and tobacco. Cannabis smoking cessation was temporally associated with the resolution of chronic bronchitis symptoms, and a small feasibility study suggests that use of a vaporizer instead of smoking cannabis may lead to the resolution of respiratory symptoms. The committee's findings are consistent with those reported in a recent review (Tashkin, 2013) and position statement (Douglas et al., 2015).

The majority of studies relied on self-report for cannabis smoking. Many studies failed to control for tobacco, occupational, and other environmental exposures; did not control for the dose or duration of the cannabis smoke exposure; and did not use joint-years and instead based heavy cannabis exposure on exceeding a specific threshold of cigarettes. Even among studies that used joint-years, it is unclear how generalizable the findings are, given the potential high variability in tetrahydrocannabinol (THC) content from joint to joint and from year to year.

CONCLUSION 7-3

7-3(a) There is substantial evidence of a statistical association between long-term cannabis smoking and worse respiratory symptoms and more frequent chronic bronchitis episodes.

7-3(b) There is moderate evidence of a statistical association between cessation of cannabis smoking and improvements in respiratory symptoms.

ASTHMA

Asthma is a clinical syndrome that is associated with airways inflammation, airflow limitation, bronchial hyper-responsiveness, and symptoms of episodic wheeze and cough. It is predominantly an allergic disease. Worldwide, asthma is thought to affect 300 million people, and it is responsible for more disability-adjusted life-years lost than diabetes mellitus. Asthma was not specifically addressed in *Marijuana and Medicine: Assessing the Science Base* (IOM, 1999).

Is There an Association Between Cannabis Use and Asthma?

Systematic Reviews

The systematic review by Tetrault et al. (2007) referred to only one study that described the association between cannabis use and asthma exacerbations. Upon retrieving this study, the committee found that this was a letter to the editor which reported findings of a case-control study of 100 participants aged 18–55 years with and without asthma admitted to the emergency department. In this study, the authors found no association between THC and asthma (Gaeta et al., 1996).

Primary Studies

Bechtold et al. (2015) reported on a follow-up of a cohort of boys who participated in the Pittsburgh Youth Study. A total of 506 boys were followed longitudinally, 257 who scored ≥70th percentile of a multi-informant conduct problem score and 249 who scored below the 70th percentile. This study found no link between cannabis use and self-reported asthma symptoms. The limitations of this study include a lack of generalizability to the general population given the selection criteria for conduct problems, a lack of inclusion of women in their study, and the fact that health outcomes were based on self-report and biased to those who had sought care for health problems.

Weekes et al. (2011) studied a cohort of 110 black urban adolescents with asthma. In this study, the investigators found that 16 percent of the adolescents smoked cannabis, but there was no association between cannabis use and asthma concern or asthma severity or asthma symptoms. The limitations of this study include the use of self-report of cannabis use, which the

study authors speculated may be under-reported in black adolescents when compared to whites, and a lack of data on asthma medication adherence.

Discussion of Findings

The committee did not find evidence for an association between cannabis use and either asthma risk or asthma exacerbations, and current studies failed to control for other important confounders, including adherence to asthma medications.

The evidence linking cannabis use with asthma risk or exacerbation is limited by the scope and sample size of available studies and by the use of more standardized approaches to measure asthma prevalence or exacerbations of asthma. Few studies have examined the link between cannabis and asthma, and no clear evidence exists of a link between asthma or asthma exacerbation and cannabis use. However, asthma symptoms such as wheeze appear to be common among cannabis users.

CONCLUSION 7-4 There is no or insufficient evidence to support or refute a statistical association between cannabis smoking and asthma development or asthma exacerbation.

RESEARCH GAPS

The effects of cannabis smoke on respiratory health remain poorly quantified. Further research is needed to better elucidate the influence of exposure levels to cannabis smoke on respiratory outcomes, the chronicity of cannabis smoking, the effects of an underlying predisposition to respiratory disease, and possible interaction effects with tobacco smoke to promote airway inflammation, worsen respiratory symptoms, accelerate lung function decline, or increase exacerbation of COPD and asthma. Previous studies have not been able to adequately separate cannabis smoke effects from tobacco smoke effects, and this has meant that some important questions remain unanswered. It is unknown whether or not:

- Long-term cannabis smoking, above and beyond that of tobacco smoking, leads to a more rapid decline in lung function and to the development of chronic bronchitis or COPD.
- Cannabis smoking increases the risk of allergic disease or asthma.
- Alternative inhaled delivery methods of cannabis result in fewer respiratory symptoms.

To address the research gaps relevant to respiratory disease, the committee suggests the following:

- Design better observational studies with both self-reported and quantitative measures of cannabis smoking and systematic approaches to measure the duration and dose to determine if long-term exposure to cannabis smoke, above and beyond exposure to tobacco smoke, leads to the development of chronic bronchitis or COPD or to a higher rate of COPD exacerbation.

- Design longitudinal studies to determine if long-term cannabis smoking is associated with the development of allergic disease and risk of asthma.
- Conduct clinical trials of alternative inhaled delivery methods versus cannabis smoking to determine if they reduce respiratory symptoms.

SUMMARY

This chapter summarizes all of the respiratory disease literature that has been published since 1999 and deemed to be good or fair by the committee. Overall, the risks of respiratory complications of cannabis smoking appear to be relatively small and to be far lower than those of tobacco smoking. While heavy cannabis users may be at a higher risk for developing chronic bronchitis and COPD or at an increased risk of exacerbating COPD and asthma, current studies do not provide sufficient evidence for a link. Limitations of reviewed studies are that it is difficult to separate the effects of cannabis smoking from those of tobacco smoking from current available data, that exposures have generally been measured by self-report of cannabis smoking, and that there is a lack of cohort studies of regular or daily cannabis users, of adequate controls for environmental factors, and of generalizability of findings. The committee has formed a number of research conclusions related to these health endpoints (see Box 7-1); however, it is important that each of these conclusions be interpreted within the context of the limitations discussed in the Discussion of Findings sections.

BOX 7-1
Summary of Chapter Conclusions*

There is substantial evidence of a statistical association between cannabis smoking and:

- Worse respiratory symptoms and more frequent chronic bronchitis episodes (long-term cannabis smoking) (7-3a)

There is moderate evidence of a statistical association between cannabis smoking and:

- Improved airway dynamics with acute use, but not with chronic use (7-1a)
- Higher forced vital capacity (FVC) (7-1b)

There is moderate evidence of a statistical association between *the cessation* of cannabis smoking and:

- Improvements in respiratory symptoms (7-3b)

There is limited evidence of a statistical association between cannabis smoking and:

- An increased risk of developing chronic obstructive pulmonary disease (COPD) when controlled for tobacco use (occasional cannabis smoking) (7-2a)

There is no or insufficient evidence to support or refute a statistical association between cannabis smoking and:

- Hospital admissions for COPD (7-2b)
- Asthma development or asthma exacerbation (7-4)

*Numbers in parentheses correspond with chapter conclusion number

REFERENCES

Aldington, S., M. Williams, M. Nowitz, M. Weatherall, A. Pritchard, A. McNaughton, G. Robinson, and R. Beasley. 2007. Effects of cannabis on pulmonary structure, function and symptoms. *Thorax* 62:1058–1063.

Aldington, S., M. Harwood, B. Cox, M. Weatherall, L. Beckert, A. Hansell, A. Pritchard, G. Robinson, R. Beasley; and the Cannabis and Respiratory Disease Research Group. 2008. Cannabis use and cancer of the head and neck: Case-control study. *Otolaryngology and Head and Neck Surgery* 138(3):374–380.

Bechtold, J., T. Simpson, H. R. White, and D. Pardini. 2015. Chronic adolescent marijuana use as a risk factor for physical and mental health problems in young adult men. *Psychology and Addictive Behaviors* 29:552–563.

Buist, A. S., M. A. McBurnie, W. M. Vollmer, S. Gillespie, P. Burney, D. M. Mannino, A. M. B. Menezes, S. D. Sullivan, T. A. Lee, K. B. Weiss, R. L. Jensen, G. B. Marks, A. Gulsvik, and E. Nizankowska-Mogilnicka. 2007. International variation in the prevalence of COPD (The BOLD study): A population-based prevalence study. *Lancet* 370:741–750.

CBHSQ (Center for Behavioral Health Statistics and Quality). 2015. Behavioral health trends in the United States: Results from the 2014 National Survey on Drug Use and Health (HHS Publication No. SMA 15-4927, NSDUH Series H-50).

Diaz-Guzman, E. and D. M. Mannino. 2014. Epidemiology and prevalence of chronic obstructive pulmonary disease. *Clinics in Chest Medicine* 35(1):7–16.

Douglas, I. S., T. E. Albertson, P. Folan, N. A. Hanania, D. P. Tashkin, D. J. Upson, and F. T. Leone. 2015. Implications of marijuana decriminalization on the practice of pulmonary, critical care, and sleep medicine. A report of the American Thoracic Society Marijuana Workgroup. *Annals of the American Thoracic Society* 12:1700–1710.

Gaeta, T. J., R. Hammock, T. A. Spevack, H. Brown, and K. Rhoden. 1996. Association between substance abuse and acute exacerbation of bronchial asthma. *Academic Emergency Medicine* 3(12):1170–1172.

Hancox, R. J., R. Poulton, M. Ely, D. Welch, D. R. Taylor, C. R. McLachlan, J. M. Greene, T. E. Moffitt, A. Caspi, and M. R. Sears. 2010. Effects of cannabis on lung function: a population-based cohort study. *The European Respiratory Journal* 35(1):42–47.

Hancox, R. J., H. H. Shin, A. R. Gray, R. Poulton, and M. R. Sears. 2015. Effects of quitting cannabis on respiratory symptoms. *European Respiratory Journal* 46:80–87.

IOM (Institute of Medicine). 1999. *Marijuana and medicine: Assessing the science base*. Washington, DC: National Academy Press.

Kempker, J. A., E. G. Honig, and G. Martin. 2015. The effects of marijuana exposure on respiratory health in U.S. adults. *Annals of the American Thoracic Society* 12:135–141.

Lim, S. S., T. Vos, A. D. Flaxman, G. Danaei, K. Shibuya, H. Adair-Rohani, et al. 2012. A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990–2010: A systematic analysis for the Global Burden of Disease Study 2010. *Lancet* 380:2224–2260.

Macleod, J., R. Robertson, L, Copeland, J. McKenzie, R. Elton, and P. Reid. 2015. Cannabis, tobacco smoking, and lung function: A cross-sectional observational study in a general practice population. *British Journal of General Practice* 65:e89–e95.

Medical Research Council. 1965. Definition and classification of chronic bronchitis for clinical and epidemiological purposes. A report to the Medical Research Council by their Committee on the Aetiology of Chronic Bronchitis. *Lancet* 1:775–779.

Papatheodorou, S. I., H. Buettner, M. B. Rice, and M. A. Mittleman. 2016. Recent marijuana use and associations with exhaled nitric oxide and pulmonary function in adults in the United States. *Chest* 149:1428–1435.

Pletcher, M. J., E. Vittinghoff, R. Kalhan, J. Richman, M. Safford, S. Sidney, F. Lin, and S. Kertesz. 2012. Association between marijuana exposure and pulmonary function over 20 years. *JAMA* 307:173–181.

Tan, W. C., C. Lo, A. Jong, L. Xing, M. J. Fitzgerald, W. M. Vollmer, S. A. Buist, and D. D. Sin. 2009. Vancouver Burden of Obstructive Lung Disease (BOLD) Research Group. Marijuana and chronic obstructive lung disease: A population-based study. *Canadian Medical Association Journal* 180:814–820.

Tashkin, D. P. 2013. Effects of marijuana smoking on the lung. *Annals of the American Thoracic Society* 10:239–247.

Tashkin, D. P., A. H. Coulson, V. A. Clark, M. Simmons, L. B. Bourque, S. Duann, G. H. Spivey, and H. Gong. 1987. Respiratory symptoms and lung function in habitual heavy smokers of marijuana alone, smokers of marijuana and tobacco, smokers of tobacco alone, and nonsmokers. *American Review of Respiratory Disease* 135:209–216.

Tashkin, D. P., M. S. Simmons, and C. H. Tseng. 2012. Impact of changes in regular use of marijuana and/or tobacco on chronic bronchitis. *COPD* 9:367–374.

Tetrault, J. M., K. Crothers, B. A. Moore, R. Mehra, J. Concato, and D. A. Fiellin. 2007. Effects of marijuana smoking on pulmonary function and respiratory complications: A systematic review. *Archives of Internal Medicine* 167:221–228.

Van Dam, N. T., and M. Earleywine. 2010. Pulmonary function in cannabis users: Support for a clinical trial of the vaporizer. *International Journal of Drug Policy* 21:511–513.

Volkow, N. D., R. D. Baler, W. M. Compton, and S. R. Weiss. 2014. Adverse health effects of marijuana use. *New England Journal of Medicine* 370:2219–2227.

Walden, N., and M. Earleywine. 2008. How high: Quantity as a predictor of cannabis-related problems. *Harm Reduction Journal* 5:20.

Weekes, J. C., S. Cotton, and M. E. McGrady. 2011. Predictors of substance use among black urban adolescents with asthma: A longitudinal assessment. *Journal of the National Medical Association* 103:392–398.

Wu, T. C., D. P. Tashkin, B. Djahed, and J. E. Rose. 1988. Pulmonary hazards of smoking marijuana as compared with tobacco. *New England Journal of Medicine* 318:347–351.

Yadavilli, R., A. Collins, W. Y. Ding, N. Garner, J. Williams, and H. Burhan. 2014. Hospital readmissions with exacerbation of obstructive pulmonary disease in illicit drug smokers. *Lun*g 192:669–673.

8
Immunity

Chapter Highlights
• There exists a paucity of data on the effects of cannabis or cannabinoid-based therapeutics on the human immune system. • There is insufficient data to draw overarching conclusions concerning the effects of cannabis smoke or cannabinoids on immune competence. • There is limited evidence to suggest that regular exposure to cannabis smoke may have anti-inflammatory activity. • There is insufficient evidence to support or refute a statistical association between cannabis or cannabinoid use and adverse effects on immune status in individuals with HIV.

The immune system is composed of many different cells that perform a wide variety of functions in order to provide immunity against pathogens and other foreign bodies. Many assays and methods exist to evaluate specific components of the immune system and to assess changes in immune function and status. Toward this end, there is a sizable literature reporting on investigations into the effects of plant-derived, synthetic, and endogenous cannabinoids on various aspects of immune competence in experimental animals and in cell-based assays. The scientific literature is full of studies that used these animal- and cell-based immunological approaches to show that cannabinoids modulate (either suppressing or enhancing) the functions of most of the type of immune cells that have been evaluated. By contrast, the investigations into the effects of cannabis or cannabinoid-based therapeutics on immunity in human subjects are quite limited.

The majority of studies investigating the association between cannabis or cannabinoid use and effects on human immunity have assessed one or more immunological parameters in patients infected with human immunodeficiency virus (HIV) or viral hepatitis C (HCV). For example, in the case of HIV patients, who are extensively studied within the context of cannabis exposure, these investigations have evaluated only a small number of immunological endpoints, the most common being the number of certain types of T cells (i.e., $CD4^+$ and $CD8^+$ T cells) in circulation and also the viral load. The limited measurements provide little information about the effect of cannabis use on overall immune status among individuals with HIV. Other studies have evaluated the effects of cannabis on immune endpoints in healthy individuals or on their susceptibility to infectious agents. In healthy individuals, these evaluations have focused primarily on the effects of cannabis use on circulating cytokines concentrations, principally inflammatory cytokines. Again, these examples emphasize the very limited and extremely narrow scope of assessments that have been conducted to examine the effects of cannabis on immune competence in humans to date.

This chapter reviews the current evidence on the association between cannabis use and immune competence in healthy populations and in individuals with infectious disease. Because the immune system plays a primary role in fighting and protecting against disease, the chapter will review evidence on the potential association between cannabis use and indicators of immune functioning as well as the potential association between cannabis use and susceptibility to, and progression of, infectious disease and cancer. Due to the paucity of human studies evaluating the effects of cannabis on the immune system, the committee identified no good- or fair-quality systematic reviews reporting on the health endpoints addressed in this chapter. Consequently, this chapter's conclusions are based on a review of 14 primary literature articles that best address the committee's research questions of interest. Study limitations and research gaps are noted, and the strength of the available evidence is weighed in five formal conclusions.

IMMUNE COMPETENCE

In several of the studies reviewed below, the effects of cannabis use on immune competence were assessed via direct measurement of specific immune effector functions in healthy individuals. The primary advantage of evaluating specific immune responses is that the immune system is composed of many different cell types, each of which performs several distinct functions. Assessing specific immune responses provides more information on whether, how, and to what extent an agent such as cannabis affects particular cells in the immune system. Although the perturbations in immune competence discussed in this section are not health effects in the sense used throughout this report, they may alter a person's susceptibility to infection or have broad effects on immune competence, and they are reviewed for that reason.

The challenge with this type of information is that it is difficult to ascertain whether a deficit in a specific immune function, unless extreme, necessarily results in greater susceptibility to infection by a pathogen. Conversely, it is difficult to extrapolate results showing enhanced immune responsiveness due to exposure to an agent and determine whether that exposure may lead to an increased incidence of hypersensitivity or autoimmune disease. Therefore, the evaluation of immune competence requires a comprehensive assessment of a broad range of different cell types and their functions, which to date has not been conducted in cannabis users.

Is There an Association Between Cannabis Use and Immune Competence in Individuals Without an Infectious Disease?

Systematic Reviews

The committee did not identify a good- or fair- quality systematic review that reported on the association between cannabis use and immune competence in individuals without an infectious disease.

Primary Literature

Keen and Turner (2015) evaluated the serum levels of two inflammatory cytokines, interleukin-1 alpha (IL-1α) and tumor necrosis factor (TNF), in a total of 168 African American study participants of whom 46 were lifetime cannabis users and 77 did not use any illicit drugs.

After adjusting for demographic and physiological variables, study participants who did not use illicit drugs were not significantly more likely to have higher background serum IL-1α levels than lifetime cannabis users (odds ratio [OR] 0.77, 95% confidence interval [CI] = 0.34–1.74). By contrast, study participants who did not use illicit drugs were significantly more likely to have higher serum TNF levels than lifetime cannabis users (OR 2.73, 95% CI = 1.18–6.31).

In another study, several immune parameters were evaluated in adult Egyptians (Abo-Elnazar et al., 2014). The study included 20 cannabis users and 10 controls with no history of drug abuse. $CD4^+$ peripheral blood T cells from cannabis users showed a statistically significant decrease in proliferative response to mitogenic stimulation (phytohemagglutinin) in culture as measured by the methyl thiazolyl tetrazolium (MTT) Stimulation Index when compared to $CD4^+$ T cells from controls (mean = 1.14 ± 0.28 versus mean = 1.47 ± 0.35, p = 0.001). Supernatants from these cultures were quantified for T cell cytokines; interleukin-10 (IL-10), which is an anti-inflammatory cytokine; and interleukin-17 (IL-17), which is a proinflammatory cytokine. When compared to $CD4^+$ T cells from non-drug-using controls, $CD4^+$ T cells from cannabis users showed an approximately 50 percent decrease in proinflammatory IL-17 (129.05 pg/ml ± 44.24 pg/ml versus 206.30 pg/ml ± 51.05 pg/ml, p <0.001) and a two-fold increase in anti-inflammatory IL-10 (mean = 258.10 pg/ml ± 79.91 pg/ml versus mean = 138.70 pg/ml ± 38.11 pg/ml, p = 0.002). A major limitation of Abo-Elnazar et al. (2014) is the very small number of study participants.

Pacifici et al. (2007) conducted a longitudinal study which included an evaluation of total leukocytes as well as the number of $CD4^+$ T cells, $CD8^+$ T cells, B cells, and natural killer (NK) cells at the beginning of the study and 12 months later in 34 healthy controls who had not used illicit drugs in the previous 12 months and 23 study participants who were occasional or regular users of cannabis. There was a statistically significant difference between controls and cannabis-using study participants with respect to the number of NK cells at the initiation of the study (mean = 205.1 cells/µl ± 83.4 cells/µl versus 126.1 cells/µl ± 80.0 cells/µl) or when evaluated at 12 months (mean = 196.8 cells/µl ± 79.3 cells/µl versus mean = 101.7 cells/µl ± 48.5 cells/µl). By contrast, differences between controls and cannabis-using study participants in the number of CD4+ T cells, CD8+ T cells, and CD19 B cells were not statistically significant at the initiation of the study or 12 months later. In addition, phytohemagglutinin (PHA)-induced proliferation, supernatant interleukin-2 (IL-2) (a measure of T cell function), and transforming growth factor beta1 (TGF-β1) (a proinflammatory cytokine) were assessed at the initiation of the study. Statistically significant differences were observed between controls and cannabis users in terms of PHA-induced proliferation (mean = 96.9% ± 15.6% versus mean = 72.3% ± 32.1%) and the activity units per ml of IL-2 (mean = 10.7 U/ml ± 3.8 U/ml versus mean = 6.3 U/ml ± 4.4 U/ml), whereas the difference between controls and cannabis-users in the activity units per ml of TGF-β1was not statistically significant.

Jatoi et al. (2002) conducted a study involving 85 study participants with advanced cancer and weight loss to compare the effect of megestrol acetate (800 mg/day) and oral dronabinol tablets (2.5 mg twice daily), separately and in combination, on levels of serum interleukin-6 (IL-6), a cytokine associated with anorexia and weight loss. There was no statistically significant change in serum IL-6 levels 1 month after study initiation among study participants receiving dronabinol alone (mean difference = −0.62 pg/ml ± 3.5pg/ml) or in combination with megestrol acetate (mean difference = −0.2 pg/ml ± 3.1 pg/ml).

A longitudinal study followed study participants from birth to 38 years of age in order to investigate potential associations between cannabis use occurring between 18 and 38 years of

age and physical health problems at age 38, including systemic inflammation as measured by C-reactive protein levels (Meier et al., 2016). Among 947 study participants, there was no statistically significant association between joint-years of cannabis use and systemic inflammation after controlling for biological sex and tobacco use (β 0.00, 95% CI = −0.07–0.08). After controlling for biological sex, systemic inflammation at 26 years of age, and tobacco use, the association between joint-years of cannabis use and changes in systemic inflammation between 26 and 38 years of age was not statistically significant (β 0.05, 95% CI = −0.03–0.13).

Discussion of Findings

One trend that appeared to be supported by several studies was the observation that regular exposure to cannabis smoke decreased several regulatory factors that are secreted by leukocytes and that are well established in mediating inflammation. Consistent with the premise that cannabinoids may possess anti-inflammatory activity, one study showed an enhanced production of an anti-inflammatory mediator, which could be indicative of a decline in immune competence (Abo-Elnazar et al., 2014). By contrast, anti-inflammatory activity of cannabis, under certain conditions, could be beneficial as inflammation is a key event in many diseases processes. For example, chronic inflammation is believed to be central in HIV-associated neurocognitive disorders and anti-inflammatory activity of cannabis could potential be beneficial in decreasing the progression neurocognitive decline (Gill and Kolson, 2014). The finding that cannabinoids may possess anti-inflammatory activity is consistent with findings in studies conducted in experimental animal and in cell culture experiments (Klein, 2005).

The limitations of the studies conducted to date are numerous, with the most significant being the absence of a comprehensive evaluation of the effects of cannabis smoke on immune competence. In addition, several of the studies used a small number of study participants with very limited information on the study participants' level of exposure to cannabis. Based on the very limited evaluations of only a few immune parameters, it is not possible to draw overarching conclusions concerning the effects of cannabis smoke or cannabinoids on immune competence.

CONCLUSION 8-1

8-1(a) There is limited evidence of a statistical association between cannabis smoking and a decrease in the production of several inflammatory cytokines in healthy individuals.

8-1(b) There is insufficient evidence to support or refute a statistical association between cannabis smoking and other adverse immune cell responses in healthy individuals.

SUSCEPTIBILITY TO AND PROGRESSION OF INFECTIOUS DISEASE

The primary role of the immune system is to protect against infectious agents (e.g., bacteria, viruses, parasites). The immune system confers this protection by its ability to recognize what is foreign, often termed as "non-self," which it then seeks to destroy using a broad repertoire of different cell types and mechanisms. Significant changes in immune competence can result in serious adverse health effects. For example, inappropriate or

exaggerated immune responses can result in autoimmunity or allergy. Conversely, the suppression of immune function can lead to an increased susceptibility to infectious agents, an increased duration of infection, or a reduced ability to recognize and destroy cancer cells. A large body of literature using animal models and cell cultures has described the immunosuppressive properties of cannabinoids. Reduced immune competence due to cannabis smoke or cannabinoid treatment would be especially relevant in cases when immunocompromised HIV patients used the cannabis to stimulate their appetite or cancer patients used it to relieve the nausea associated with cancer chemotherapeutic drugs. Very few studies have investigated the effects of cannabis smoke or cannabinoids on the susceptibility to, or clearance of, infectious agents or on progression of cancer in human subjects. This section discusses findings from the few studies that have evaluated the association between cannabis use and immune status, in terms of an individual's susceptibility to infection and the health status of individuals with HIV, viral hepatitis C, and other infectious diseases.

Is There an Association Between Cannabis Use and Immune Status in Individuals with HIV?

Systematic Reviews

The committee did not identify a good- or fair-quality systematic review that reported on the association between cannabis use and immune status in individuals with HIV.[1]

Primary Literature

Several studies have been conducted with the specific objective of determining whether cannabis smoking or therapeutic dronabinol produces adverse effects on immune competence in HIV patients. In a prospective randomized controlled trial (RCT), 62 study participants aged 18 years and older who were infected with HIV were randomized to receive cannabis (up to 3 cigarettes daily), dronabinol (2.5 mg oral tablet three times daily), or oral placebo, over a 21-day period (Bredt et al., 2002). The change in absolute lymphocyte concentration among study participants receiving cannabis was statistically significantly greater than among study participants receiving placebo (median change = 300 cells/µl versus 0.00 cells/µl, $p = 0.1$). As compared to study participants receiving placebo, those receiving dronabinol experienced significantly greater changes in %CD8+CD38+HLA-DR+ cells (median change −3.50 versus 0.05, $p = 0.001$) and in %CD8+CD69+ cells (median change −0.30 versus 0.05, $p = 0.04$) during the study period. Bredt et al. (2002) state that these statistically significant changes "do not constitute meaningful pattern of changes in immune phenotype of function" (Bredt et al. 2002, p. 87S).

By contrast, study participants in neither of the cannabinoid study arms experienced statistically significantly greater changes in lymphoproliferative responses to various mitogenic stimuli than did study participants in the placebo arm. No cannabis- or dronabinol-related changes were observed. Likewise, changes in cytokine (i.e., IFNγ, IL-2, TNFα) production among study participants in the cannabinoid study arms, and in NK activity among study

[1] Chapter 4 discusses Lutge et al. (2013), a systematic review that investigates the medical use of cannabis by patients with HIV/AIDS, but does not specifically address the association between cannabis use and immune competence in this population.

participants in the dronabinol arm, were not significantly greater than among study participants receiving placebo. No cannabis- or dronabinol-associated adverse effects were observed over the 21-day exposure period on the percentage of circulating $CD4^+$ or $CD8^+$ cells or on disease progression, as measured by viral load (Abrams et al., 2003). Overall, there were no "clear discernible negative changes" (p. 87S) among study participants who received dronabinol or cannabis as compared to those who received placebo. Significant limitations of this study were the very short time period of cannabinoid exposure and the small number of study participants included in the study.

A longitudinal study evaluated the effects of recreational cannabis use on $CD4^+$ and $CD8^+$ T cell populations and disease progression in men infected with HIV (3,236 participants, of which 59 percent used cannabis) and men not infected with HIV (481 participants, of which 61 percent used cannabis) (Chao et al., 2008). HIV-negative and HIV-positive study participants were followed for a maximum of 18 and 11 years, respectively. After controlling for health risk behaviors and other potential confounders, any cannabis use and monthly or less frequent cannabis use were both associated with a statistically significant 1 percent decrease in $CD4^+$ cell count among men not infected with HIV, while weekly or more frequent cannabis use was associated with a 5 percent decrease in $CD8^+$ cell count among men infected with HIV. However, Chao et al. (2008, p. 5) state that there were no "clinically meaningful associations, adverse or otherwise, between use of marijuana …. and T cell counts and percentages in either HIV-uninfected or HIV-infected men.". A major shortcoming of this study was the absence of information concerning the frequency and level of exposure to cannabis.

Thames et al. (2016) examined the independent and combined effects of HIV and cannabis smoking on neurocognitive function in 55 HIV positive and 34 HIV negative study participants who reported previously using cannabis for 12 months or more. As part of this study, the percentage of $CD4^+$ T cells was monitored. Differences in the frequency of cannabis use were not associated with statistically significant differences in the nadir count of $CD4^+$ T cells. A modest but statistically significant increase in the percentage of circulating $CD4^+$ T cells ($p = 0.04$) and a statistically significant decrease in viral load ($p = 0.03$) were associated with light (i.e., 2–14 times per week) and moderate to heavy (i.e., 18–90 times per week) cannabis use as compared to nonusers. A shortcoming of this study was the small number of study participants.

Discussion of Findings

Collectively, the studies suggest that cannabis smoke and/or cannabinoids do not adversely affect the immune status of HIV patients. However, each of the four studies possessed major shortcomings in experimental design which could have contributed to the absence of adverse effects being observed in HIV patients who used cannabis or cannabinoids; these shortcomings include study durations that where insufficient to observe adverse effects in the endpoints being measured, small numbers of study participants, and poorly defined and variable levels of cannabinoid exposure.

CONCLUSION 8-2 There is insufficient evidence to support or refute a statistical association between cannabis or dronabinol use and adverse effects on immune status in individuals with HIV.

Is There an Association Between Cannabis Use and the Immune Status of Individuals Infected with Viral Hepatitis C?

Systematic Reviews

The committee did not identify a good- or fair-quality systematic review that reported on the association between cannabis use and the immune status of individuals infected with viral hepatitis C.

Primary Literature

Viral hepatitis C (HCV) is a chronic disorder of the liver which can lead to fibrosis and progress to cirrhosis and ultimately to end-stage liver disease or hepatocellular carcinoma. Liver fibrosis is mediated, in part, through a chronic immune-mediated inflammatory response. A study of liver biopsies from 270 untreated patients with chronic hepatitis C was conducted in which patients were categorized as either non-users, occasional cannabis users, or daily cannabis users (Hezode et al., 2005). A significantly higher proportion of daily cannabis users (68.5 percent) as compared occasional cannabis users (42.5 percent) or non-users (39.7 percent) had a fibrosis progression rate faster than the median fibrosis progression rate for the cohort as a whole. There was a statistically significant association between daily cannabis use and faster than median fibrosis progression rate, when no cannabis use was the referent (OR 3.4, 95% CI = 1.5–7.4). After controlling for potential confounders including alcohol and tobacco use, daily cannabis use was also determined to be an independent predictor of severe fibrosis (OR 2.3, 95% CI = 1.1–4.8). A subsequent prospective study investigated 690 patients infected with both HIV and HCV and who had no significant liver fibrosis or end-stage liver disease at baseline, of whom 40 percent smoked cannabis daily at study baseline (Brunet et al., 2013). This study found no statistically significant association between daily cannabis use and progression to significant liver fibrosis (HR 1.02, 95% CI = 0.93–1.12). Finally, Liu et al. (2014) conducted a study to evaluate potential associations between cannabis use and liver disease progression and outcomes from treatment for HCV. Among 376 participants for whom liver biopsies and cannabis use information was available, cannabis use as compared to non-use was not significantly associated with fibrosis stage ($p = 0.66$) or with hepatic inflammation grade ($p = 0.75$). Among 348 participants, cannabis use as compared to non-use was not significantly associated with steatosis as assessed by biopsies ($p = 0.32$). Compared to non-use of cannabis, there was no statistically significant association between cannabis use and treatment outcomes as measured by rates of sustained viral response among 359 participants receiving interferon-based HCV antiviral treatment ($p = 0.13$).

Discussion of Findings

Although all three studies were of good quality, their results were mixed. Two studies suggested that cannabis use was not significantly associated progression of liver disease or with fibrosis stage in HCV patients. Since chronic inflammation is a significant contributing factor to the progression of liver fibrosis, these findings appear to be consistent with the anti-inflammatory activity of cannabinoids observed in the immune competence literature reviewed above. However, a third study found that daily cannabis use was significantly associated with the

severe fibrosis and faster progression of fibrosis, thereby complicating any conclusions about the association between liver disease progression and cannabis use. Overall, the available evidence that cannabis use is not associated with the progression of liver fibrosis and hepatic disease in individuals with HCV is stronger than the available evidence that cannabis use is associated with the progression of liver fibrosis and hepatic disease in individuals with HCV.

CONCLUSION 8-3 There is limited evidence of no statistical association between daily cannabis use and the progression of liver fibrosis or hepatic disease in individuals with viral Hepatitis C (HCV).

Is There an Association Between Cannabis Use and Susceptibility to Oral Human Papilloma Virus (HPV)?

Systematic Reviews

The committee did not identify a good- or fair- quality systematic review that reported on the association between cannabis use and susceptibility to oral HPV.

Primary Literature

Risk factors associated with oral HPV infection were investigated in a cross-sectional study involving 128 HIV-negative and 161 HIV-positive study participants (Muller et al., 2015). Cannabis use was identified as a statistically significant risk factor for detection of oral HPV in HIV-negative study participants (OR 4.0, 95% CI = 1.3–12.4), although this risk was statistically nonsignificant after adjusting for other variables including tobacco, alcohol, and other drug use (OR 2.1, 95% CI = 0.6–7.5). By comparison, cannabis use was not a statistically significant risk factor for detection of oral HPV in HIV-positive individuals, whether before (OR 1.6, 95% CI = 0.7–3.4) or after (OR 1.3, 95% CI = 0.4–3.9) adjusting for potential confounders. The factors responsible for the differential effects between HIV-negative and HIV-positive individuals are unclear. Likewise, Kahn et al. (2015) conducted a cross-sectional study to evaluate the prevalence of oral HPV infection and to investigate associations between vaccination and oral infection in HIV-infected youth. The study included 272 HIV-infected study participants between the ages of 12 and 24 years, with a mean age of 21.5 years. In univariable analyses, no statistically significant association between lifetime cannabis use, as compared to non-use, and oral HPV infection was identified (OR 0.68, 95% CI = 0.36–1.30). A significant limitation of both studies was the inability to determine whether regular cannabis use increased risky behavior that would predispose study participants to oral HPV infection. Likewise there was no follow-up on whether cannabis altered the course of HPV infection or its downstream consequences.

Discussion of Findings

Kahn et al. (2015) reported no statistically significant association between cannabis use and oral HPV. Muller et al. (2015) reported that, prior to adjusting for potential confounders, cannabis use was significantly associated with oral HPV in HIV-negative individuals, but not in HIV-positive individuals. The plausibility of this finding is questionable in light of the fact that HIV-infected patients have decreased T cell-mediated immunity, which is critical in anti-viral

immune responses, including against HPV. Therefore, it would be expected that HIV-infected patients would be at least as, if not significantly more, susceptible to HPV infection as HIV-negative patients. A major limitation of Kahn et al. (2015) is that it is not possible to determine, based on the study design, whether the reported association between regular cannabis use and increased incidence of oral HPV in HIV-negative individuals is attributable to cannabis-mediated immune suppression or to other causes, such as increased high-risk behavior.

CONCLUSION 8-4 There is insufficient evidence to support or refute a statistical association between regular cannabis use and increased incidence of oral human papilloma virus (HPV).

Is There an Association Between Cannabis Use and Aspergillus Infection?

Systematic Reviews

The committee did not identify a good- or fair-quality systematic review that reported on the association between cannabis use and infection with *Aspergillus*.

Primary Literature

Infection with *Aspergillus* species can be life-threatening in immunocompromised patients, including those with prolonged neutropenia, hematopoietic stem cell transplant, solid organ transplant, inherited or acquired immunodeficiencies, diabetes, corticosteroid use, or diabetes (Cescon et al., 2008; Denning et al., 1991). Cannabis has been demonstrated to harbor *Aspergillus* spores, and case reports suggest cannabis use may be associated with aspergillosis in immunocompromised patients. For example, a letter published in the *Annals of Internal Medicine* in 1975 described a case of *Aspergillus fumigatus* pneumonitis in a 17-year-old male with chronic granulomatous disease. Heavy growth of *Aspergillus fumigatus* was observed in a culture taken from the patient's cannabis and pipe, and the author states that the "infection may have been acquired through inhalation of smoke from marijuana contaminated with fungi" (Chusid et al., 1975, p. 682). More recent case reports and case series have described aspergillosis in current or former cannabis users with acute myelogenous leukemia (Szyper-Kravitz et al., 2001), chronic myelogenous leukemia post bone marrow transplant (Hamadeh et al., 1988), small-cell lung cancer (Sutton et al., 1986), colorectal cancer (Cescon et al., 2008), renal transplant (Marks et al., 1996; Vethanayagam et al., 2000), chronic obstructive pulmonary disease (Sakkour et al., 2008), diabetes (Remington et al., 2015), and HIV/AIDS (Denning et al., 1991; Johnson et al., 1999). Aspergillosis has also been observed in current or former cannabis users with structural lung damage but who were not immunocompromised (Gargani et al., 2011) Many of the case reports involved smoking cannabis, although one involved a diabetic patient who inhaled vaporized cannabis for treatment of neuropathic pain (Remington et al., 2015). Box 8-1 describes a case series and a case-control study on the association between cannabis use and aspergillosis.

BOX 8-1
Cannabis and *Aspergillosis*

Denning et al. (1991) reported on 13 cases of pulmonary aspergillosis in patients with AIDS or asymptomatic HIV infection. Cannabis use was listed as a "possible underlying factor" in 4 of the 13 cases. However, the actual prevalence of cannabis use in this group may have higher, since data on cannabis use was not available for seven patients (Denning et al., 1991, p. 656). Between November 1988 and March 1994, *Aspergillus* species were detected in induced sputum or bronchoalveolar lavage specimens collected from 19 HIV positive participants in the Pulmonary Complication of HIV Infection Study (Wallace et al., 1998). A nested case-control study of these 19 participants found that cannabis use at the time of entry into the study was not significantly associated with *Aspergillus* infection (Wallace et al., 1998). By contrast, neutropenia (i.e., neutrophil count <1,000 cells per cubic millimeter), a CD4 count <30 cells per cubic millimeter, corticosteroid use, and *Pneumocystis carinii* pneumonitis were among the factors that were significantly associated with *Aspergillus* infection.

Discussion of Findings

Sporadic case reports published over the last 40 years suggest that *Aspergillus* infection may be associated with cannabis use. The case-control study of *Aspergillus* infection in HIV positive patients did not find cannabis use to be significantly associated with the presence of the fungus in induced sputum or bronchoalveolar lavage specimens, although the number of study participants was small (Wallace et al., 1998). Despite the limited nature of the literature on Aspergillosis and cannabis use, consensus guidelines and scientists suggest that immunocompromised patients avoid cannabis use due to its potential for increasing the risk of *Aspergillus* infection (Remington et al., 2015; Sullivan et al., 2001).

RESEARCH GAP

Research is needed to determine whether chronic cannabis smoke or cannabinoid treatment alters immune competence in healthy or immune-compromised individuals as evidenced by an increased incidence of infectious diseases; an extended duration of time to resolution of infectious diseases; and altered progression of cancer through the modulation of immune competence.

SUMMARY

One challenge associated with determining whether an agent alters immune competence is the diversity of the cellular elements that constitute the immune system and the many functions that these different cell types perform. The committee found a very limited number of studies in which the effects of cannabis use on the human immune system were assessed. Almost without exception, these evaluations were very narrow in scope, assessing only one or a few immunological endpoints and thus providing little information concerning the effects of cannabis use on immune status. Some studies were limited to determining the number of circulating leukocyte populations, such as T cells, with no assessments of cell function.

Although based on limited evidence, an interesting finding was the association between cannabis use in health y individuals and a decrease in the production of certain inflammatory cytokines. Similar findings have been reported in animal- and cell-based experiments. More studies will need to be conducted to verify the anti-inflammatory activity of cannabis in humans. Presently, there is either insufficient or no data to ascertain whether cannabis use alters other immune responses in healthy individuals. In addition, several studies have evaluated the effects of cannabis on either susceptibility to, or progression of, infectious diseases, namely HIV, HCV, or the papilloma virus. There is insufficient evidence to determine whether there is an association between regular use of cannabis and increased incidence of papilloma virus or between cannabis or cannabinoid (e.g., dronabinol) use and adverse effects on immune status among individuals with HIV. In addition, there is limited evidence to support the conclusion that cannabis use does not enhance the progression of liver disease in HCV patients. Box 8-2 provides a summary of the findings from this chapter.

It is important to emphasize that many of the studies in which the effects of cannabis on the immune system were evaluated possess significant shortcomings in experimental design, such as small numbers of study participants, a study that was insufficient to determine adverse effects, a narrow scope of immunological assessments, and limited information concerning the levels of cannabis exposure. Each of these limitations precludes drawing conclusions concerning the effects of cannabis on immune competence in humans with any reasonable level of certainty.

BOX 8-2
Summary of Chapter Conclusions*

There is limited evidence of a statistical association between cannabis smoking and:

- A decrease in the production of several inflammatory cytokines in healthy individuals (8-1a)

There is limited evidence of no statistical association between cannabis use and:

- The progression of liver fibrosis or hepatic disease in individuals with viral Hepatitis C (HCV) (daily cannabis use) (8-3)

There is no or insufficient evidence to support or refute a statistical association between cannabis use and:

- Other adverse immune cell responses in healthy individuals (cannabis smoking) (8-1b)
- Adverse effects on immune status in individuals with HIV (cannabis or dronabinol use) (8-2)
  Increased incidence of oral human papilloma virus (HPV) (regular cannabis use) (8-4)

* Numbers in parentheses correspond to chapter conclusion numbers.

REFERENCES

Abo-Elnazar, S., M. Moaaz, H. Ghoneim, T. Molokhia, and W. El-Korany. 2014. Th17/Treg imbalance in opioids and cannabinoids addiction: Relationship to NF-kB activation in CD4+ T cells. *Egyptian Journal of Immunology* 21(2):33–47.

Abrams, D. I., J. F. Hilton, R. J. Leiser, S. B. Shade, T. A. Elbeik, F. T. Aweeka, N. L. Benowitz, B. M. Bredt, B. Kosel, J. A. Aberg, S. G. Deeks, T. F. Mitchell, K. Mulligan, P. Bacchetti, J. M. McCune, and M. Schambelan. 2003. Short-term effects of cannabinoids in patients with HIV-1

infection: A randomized, placebo-controlled clinical trial. *Annals of Internal Medicine* 139(4):258–266.

Bredt, B. M., D. Higuera-Alhino, S. B. Shade, S. J. Hebert, J. M. McCune, and D. I. Abrams. 2002. Short-term effects of cannabinoids on immune phenotype and function in HIV-1-infected patients. *Journal of Clinical Pharmacology* 42(11 Suppl):82S–89S.

Brunet, L., E. E. M. Moodie, K. Rollet, C. Cooper, S. Walmsley, M. Potter, and M. B. Klein. 2013. Marijuana smoking does not accelerate progression of liver disease in HIV-hepatitis C coinfection: A longitudinal cohort analysis. Clinical Infectious Diseases 57(5):663–670.

Cescon, D. W., A. V. Page, S. Richardson, M. J. Moore, S. Boerner, and W. L. Gold. 2008. Invasive pulmonary aspergillosis associated with marijuana use in a man with colorectal cancer. *Journal of Clinical Oncology* 26(13):2214–2215.

Chao, C., L. P. Jacobson, D. Tashkin, O. Martinez-Maza, M. D. Roth, J. B. Margolick, J. S. Chmiel, C. Rinaldo, Z. F. Zhang, and R. Detels. 2008. Recreational drug use and T lymphocyte subpopulations in HIV-uninfected and HIV-infected men. *Drug and Alcohol Dependence* 94(1–3):165–171.

Chusid, M. J., J. A. Gelfand, C. Nutter, and A. S. Fauci. 1975. Letter: Pulmonary aspergillosis, inhalation of contaminated marijuana smoke, chronic granulomatous disease. *Annals of Internal Medicine* 82(5):682–683.

Denning, D. W., S. E. Follansbee, M. Scolaro, S. Norris, H. Edelstein, and D. A. Stevens. 1991. Pulmonary aspergillosis in the acquired immunodeficiency syndrome. *New England Journal of Medicine* 324(10):654–662.

Gargani, Y., P. Bishop, and D. W. Denning. 2011. Too many mouldy joints—marijuana and chronic pulmonary aspergillosis. *Mediterranean Journal of Hematology and Infectious Diseases* 3(1):e2011005.

Gill, A. J., and D. L. Kolson. 2014. Chronic inflammation and the role for cofactors (hepatitis C, drug abuse, antiretroviral drug toxicity, aging) in HAND persistence. *Current HIV/AIDS Reports* 11(3):325–335.

Hamadeh, R., A. Ardehali, R. M. Locksley, and M. K. York. 1988. Fatal aspergillosis associated with smoking contaminated marijuana, in a marrow transplant recipient. *Chest* 94(2):432–433.

Hezode, C., F. Roudot-Thoraval, S. Nguyen, P. Grenard, B. Julien, E. S. Zafrani, J. M. Pawlostky, D. Dhumeaux, S. Lotersztajn, and A. Mallat. 2005. Daily cannabis smoking as a risk factor for progression of fibrosis in chronic hepatitis C. *Hepatology* 42(1):63–71.

Jatoi, A., J. I. Yamashita, J. A. Sloan, P. J. Novotny, H. E. Windschitl, and C. L. Loprinzi. 2002. Does megestrol acetate down-regulate interleukin-6 in patients with cancer-associated anorexia and weight loss? A North central cancer treatment group investigation. *Supportive Care in Cancer* 10(1):71–75.

Johnson, T. E., R. R. Casiano, J. W. Kronish, D. T. Tse, M. Meldrum, and W. Chang. 1999. Sino-orbital aspergillosis in acquired immunodeficiency syndrome. *Archives of Ophthalmology* 117(1):57–64.

Kahn, J. A., B. J. Rudy, J. Xu, E. A. Secord, B. G. Kapogiannis, S. Thornton, and M. L. Gillison. 2015. Behavioral, immunologic, and virologic correlates of oral human papillomavirus infection in HIV-infected youth. *Sexually Transmitted Diseases* 42(5):246–252.

Keen, L., II, and A. D. Turner. 2015. Differential effects of self-reported lifetime marijuana use on interleukin-1 alpha and tumor necrosis factor in African American adults. *Journal of Behavioral Medicine* 38(3):527–534.

Klein, T. W. 2005. Cannabinoid-based drugs as anti-inflammatory therapeutics. *Nature Reviews Immunology* 5(5):400–411.

Liu, T., G. T. Howell, L. Turner, K. Corace, G. Garber, and C. Cooper. 2014. Marijuana use in hepatitis C infection does not affect liver biopsy histology or treatment outcomes. *Canadian Journal of Gastroenterology & Hepatology* 28(7):381–384.

Lutge, E. E., A. Gray, and N. Siegfried. 2013. The medical use of cannabis for reducing morbidity and mortality in patients with HIV/AIDS. *Cochrane Database of Systematic Reviews* (4):CD005175.

Marks, W. H., L. Florence, J. Lieberman, P. Chapman, D. Howard, P. Roberts, and D. Perkinson. 1996. Successfully treated invasive pulmonary aspergillosis associated with smoking marijuana in a renal transplant recipient. *Transplantation* 61(12):1771–1774.

Meier, M. H., A. Caspi, M. Cerda, R. J. Hancox, H. Harrington, R. Houts, R. Poulton, S. Ramrakha, W. M. Thomson, and T. E. Moffitt. 2016. Associations between cannabis use and physical health problems in early midlife: A longitudinal comparison of persistent cannabis versus tobacco users. *JAMA Psychiatry* 73(7):731–740.

Muller, K., J. Kazimiroff, M. Fatahzadeh, R. V. Smith, M. Wiltz, J. Polanco, R. M. Grossberg, T. J. Belbin, H. D. Strickler, R. D. Burk, and N. F. Schlecht. 2015. Oral human papillomavirus infection and oral lesions in HIV-positive and HIV-negative dental patients. *Journal of Infectious Diseases* 212(5):760–768.

Pacifici, R., P. Zuccaro, M. Farre, S. Poudevida, S. Abanades, S. Pichini, K. Langohr, J. Segura, and R. De La Torre. 2007. Combined immunomodulating properties of 3,4-methylenedioxy-methamphetamine (MDMA) and cannabis in humans. *Addiction* 102(6):931–936.

Remington, T. L., J. Fuller, and I. Chiu. 2015. Chronic necrotizing pulmonary aspergillosis in a patient with diabetes and marijuana use. *Canadian Medical Association Journal* 187(17):1305–1308.

Sakkour, A., T. Wang, and D. Tashkin. 2008. A 56-year-old woman with COPD and multiple pulmonary nodules. *Chest* 133(2):566–569.

Sullivan, K. M., C. A. Dykewicz, D. L. Longworth, M. Boeckh, L. R. Baden, R. H. Rubin, and K. A. Sepkowitz. 2001. Preventing opportunistic infections after hematopoietic stem cell transplantation: The Centers for Disease Control and Prevention, Infectious Diseases Society of America, and American Society for Blood and Marrow Transplantation practice guidelines and beyond. *Hematology* 2001(1):392–421.

Sutton, S., B. L. Lum, and F. M. Torti. 1986. Possible risk of invasive pulmonary aspergillosis with marijuana use during chemotherapy for small cell lung cancer. *Drug Intelligence & Clinical Pharmacy* 20(4):289–291.

Szyper-Kravitz, M., R. Lang, Y. Manor, and M. Lahav. 2001. Early invasive pulmonary aspergillosis in a leukemia patient linked to aspergillus contaminated marijuana smoking. *Leukemia & Lymphoma* 42(6):1433–1437.

Thames, A. D., Z. Mahmood, A. C. Burggren, A. Karimian, and T. P. Kuhn. 2016. Combined effects of HIV and marijuana use on neurocognitive functioning and immune status. *AIDS Care: Psychological and Socio-Medical Aspects of AIDS/HIV* 28(5):628–632.

Vethanayagam, D., S. Pugsley, E. J. Dunn, D. Russell, J. M. Kay, and C. Allen. 2000. Exogenous lipid pneumonia related to smoking weed oil following cadaveric renal transplantation. *Canadian Respiratory Journal* 7(4):338–342.

Wallace, J. M., R. Lim, B. L. Browdy, P. C. Hopewell, J. Glassroth, M. J. Rosen, L. B. Reichman, and P. A. Kvale. 1998. Risk factors and outcomes associated with identification of aspergillus in respiratory specimens from persons with HIV disease. Pulmonary complications of HIV infection study group. *Chest* 114(1):131–137.

9
Injury and Death

Chapter Highlights
• Cannabis use prior to driving increases the risk of being involved in a motor vehicle accident. • In states where cannabis use is legal, there is increased risk of unintentional cannabis overdose injuries among children. • It is unclear whether and how cannabis use is associated with all-cause mortality or with occupational injury.

This chapter discusses the association between cannabis use and all-cause mortality, occupational injury, motor vehicle accidents, and overdose injuries and death. These health endpoints are distinguished not only by their status as significant public health issues, but by the extent to which directed public health actions and policy changes hold the potential for lessening their detrimental impacts on population health. Motor vehicle accidents are a leading cause of death and injury in the United States, and occupational injuries, especially those that permanently limit an individual's capacity to perform tasks at home and in the workplace, impose substantial economic burdens on workers, employers, and communities. If research indicates that cannabis use is positively associated with either occupational injury or motor vehicle accidents, evidence-based policies limiting the use of cannabis while driving or in the workplace could potentially reduce the incidence of cannabis-related accident and injury. Similarly, research suggesting that cannabis use is linked to mortality could prompt the development of programs to educate health professionals and the general public on the effects of cannabis use and positively influence cannabis-related mortality rates.

In this chapter, the committee reviews and draws conclusions from the findings of six good- to fair-quality systematic reviews and 18 primary literature articles that best address the committee's research questions of interest. Study limitations and research gaps are noted, and the strength of the available evidence is weighed in five formal conclusions.

ALL-CAUSE MORTALITY

The Institute of Medicine (IOM) report *Marijuana and Medicine: Assessing the Science Base* states that "epidemiological data indicate that in the general population marijuana use is not associated with increased mortality" (IOM, 1999, p. 109). More recently, modeling studies have estimated that a substantial disease burden—and the associated decrements in the quality and length of life—can be attributed to cannabis use (Degenhardt et al., 2013; Imtiaz et al., 2016). By contrast, a recent systematic review informed by epidemiological data did not report a statistically significant association between cannabis use and mortality (Calabria et al., 2010).

This section reviews the available literature to assess the evidence and develop conclusions about cannabis-related mortality.

Is There an Association Between Cannabis Use and All-Cause Mortality?

Systematic Reviews

Calabria et al. (2010) conducted a systematic review to determine the association between cannabis use and all-cause mortality in the general population, and they identified two prospective epidemiological cohort studies relevant to this health endpoint.[1] A meta-analysis of these studies was not performed; consequently, the results of the individual studies are presented below.

Sidney et al. (1997) assessed the risk of mortality associated with cannabis use in a cohort of 65,171 individuals aged 15 to 49 years who were enrolled in the Kaiser Permanente Medical Care Program and followed for a mean length of 10 years. Compared to men who never smoked or who smoked experimentally (i.e., cannabis use on 1–6 occasions), those who were current smokers were at a significantly increased risk of all-cause mortality after adjusting for several potential confounders, including cigarette smoking, alcohol use, and demographic and socioeconomic factors (relative risk [RR] 1.33, 95% confidence interval [CI] = 1.11–1.59). Notably, among men who currently smoked cannabis, the relative risk of mortality due to AIDS was significantly elevated (RR 1.90, 95% CI = 1.33–2.73), while the risk of mortality due to known causes other than AIDS was not significantly elevated (RR 1.12, 95% CI = 0.89–1.39). After accounting for potential confounders, women who currently smoked cannabis were not at a significantly increased risk of all-cause mortality compared to those who had never smoked or who had smoked experimentally (RR 1.09, 95% CI = 0.80–1.48). Among men who currently smoked cannabis, the frequency of use had only a small effect on the risk of all-cause mortality: those who smoked at least once a week and those who smoked daily were at, respectively, 46 percent (RR 1.46, 95% CI = 1.19–1.79) and 43 percent (RR 1.43, 95% CI = 1.08–1.90) greater relative risk of all-cause mortality than non-users and experimental users. In women, the frequency of use among current smokers had a larger impact on the risk of mortality: those who smoked at least once a week had a less elevated risk of mortality than those who smoke daily, as compared to non-users and experimental users (RR 1.23, 95% CI = 0.84–1.80 versus RR 1.44, 95% CI = 0.80–2.56).

Andreasson and Allebeck (1990) reported that among 45,540 Swedish male military conscripts followed for 15 years, the relative risk of mortality was elevated for those who reported having smoked cannabis more than 50 times by the time of conscription, compared to non-smokers (RR 2.8, 95% CI = 1.9–4.1). After adjusting for multiple confounders, including smoking tobacco, alcohol use, and other drug use, the relative risk of mortality for heavy cannabis smokers was no longer significantly elevated compared with non-smokers (RR 1.2, 95% CI = 0.7–1.9). Similarly, participants who reported having smoked cannabis on fewer than 50 occasions by the time of conscription were not at significantly greater risk than non-smokers after adjustments (RR 0.7, 95% CI = 0.4–1.2).

[1] The review also addressed the association between cannabis use and health endpoints that are often or always fatal, such as motor vehicle accidents, cancer, and suicide. These health endpoints are not reviewed in this section, as they are discussed elsewhere in the report.

Primary Literature

Muhuri and Gfroerer (2011) assessed the risk of all-cause mortality associated with the use of cannabis and other illegal drugs among 20,983 adults over a 15-year follow-up period. After adjusting for confounders, including alcohol use, cigarette smoking, and demographic factors, individuals who reported using cannabis, but not other substances (i.e., cocaine, heroin, hallucinogens, inhalants), at baseline were not at increased risk of all-cause mortality compared with individuals who reported not using cannabis or other substances at baseline (hazard ratio [HR] 1.07, 95% CI = 0.85–1.33). Manrique-Garcia et al. (2016) conducted a follow-up study of a cohort of 50,373 Swedish male military conscripts, to characterize the potential association between mortality and heavy cannabis use (i.e., using cannabis more than 50 times by 18 years of age). Among the cohort as a whole, heavy cannabis use was associated with a significantly increased risk of mortality compared with non-use (HR 1.4, 95% CI = 1.1–1.8). Notably, heavy cannabis use as compared with non-use did not appreciably affect the risk of mortality among individuals with psychotic disorders—for whom the risk of mortality was particularly elevated (HR 3.8, 95% CI = 2.6–6.2 versus HR 3.7, 95% CI = 3.1–4.4).

Discussion of Findings

Sidney et al. (1997) found a statistically significant association between cannabis use and increased risk of all-cause mortality among men diagnosed with AIDS, but not among men without this diagnosis or among women. The authors suggest that the relationship between cannabis use and all-cause mortality among male AIDS patients was not causal; instead, it "most likely represented uncontrolled confounding by male homosexual behavior" (Sidney at al., 1997, p. 589). Limitations in Sidney et al. (2007) include the use of self-report without biological validation to assess patterns of cannabis use; the lack of post-baseline assessments of cannabis use, by which changes over time in the frequency of use could be documented; a lack of data on other substance use, creating the possibility for residual confounding; and, the inability to follow participants into later age, where potential long-term health effects of cannabis use may have emerged.

After accounting for potential confounders, Andreasson and Allebeck (1990) found no statistically significant association between cannabis use and mortality. Furthermore, although a high proportion of deaths among participants who reported smoking cannabis on 50 or more occasions by the time of conscription were due to suicide or uncertain suicide, use of narcotics was also common in these incidents, leading the authors to suggest that a "significant share of the mortality associated with cannabis abuse in this study is attributable to intravenous drug abuse" (Andreasson and Allebeck, 1990, p. 14). Limitations of the study include the use of non-anonymous self-report to collect data on patterns of cannabis use, and the lack of any post-baseline assessments of cannabis use.

Findings from Muhuri and Gfroerer (2011) are based on data from the 1991 National Health Interview Survey's Drug and Alcohol Use supplemental questionnaire, and indicate a lower prevalence of cannabis use than that seen the 1991 National Household Survey on Drug Abuse (45.2 percent versus 52.7 percent). If this discrepancy in the prevalence of cannabis use reported by two national surveys conducted in the same year is the result of underreporting by participants who died during the follow-up period, the mortality risk associated with cannabis use could have been underestimated. Other limitations include the use of self-report to collect

data on patterns of cannabis use, and the lack of post-baseline assessments to detect changes in cannabis use. Strengths of the study include a base population from a national household sample, and an analysis that excluded users of other important illicit drug categories—heroin, cocaine, hallucinogens, and inhalants.

Findings from Manrique-Garcia et al. (2016) have several limitations. Risk estimates are based on cannabis use as of the time of conscription rather than lifetime cannabis exposure, and therefore do not account for cannabis use during the ~40 year follow-up period. Similarly, data on potential confounders after the time of conscription is unavailable, so the extent to which they affected study participants and potentially impacted all-cause mortality risk is unknown. Finally, since data on cannabis use was collected by non-anonymous self-report without biological validation, cannabis use may have been underreported.

There is an overall dearth of cohort studies empirically assessing general population cannabis use and all-cause mortality. Although the available evidence suggests that cannabis use is not associated with an increased risk of all-cause mortality, the limited nature of that evidence makes it impossible to have confidence in these findings. These conclusions are not informed by the results of existing large-scale modeling studies that synthesized data from a variety of sources to estimate the burden of disease attributable to cannabis use (Degenhardt et al., 2013; Imtiaz et al., 2016). Although these studies were methodologically rigorous, their direct applicability to actual cannabis-related mortality rates in the United States is uncertain. Consequently, the committee chose not to include them in this review. Also excluded from review were studies of mortality among persons with known cannabis addiction or dependence, those who have been under medical treatment for these disorders, or those who were identified through a country's criminal justice system, due to presence in these populations of important and often inadequately controlled confounders such as concurrent mental illness and poly-substance abuse.

CONCLUSION 9-1 There is insufficient evidence to support or refute a statistical association between self-reported cannabis use and all-cause mortality.

OCCUPATIONAL INJURY

The Bureau of Labor Statistics reported that 4,821 fatal occupational injuries occurred in the United States in 2014, or about 3.4 fatal injuries for every 100,000 full-time equivalent workers (BLS, 2016). Private industry and state and local government employers reported another 3,486,400 non-fatal occupational injuries in the same year (BLS, 2015). The economic impact of these injuries is considerable. Leigh (2011) estimated that the average medical costs per non-fatal and fatal injury in 2007 were $5,369 and $55,595, respectively. Nationally, the medical and indirect costs of occupational injuries (fatal and non-fatal) totaled $191.83 billion in 2007 (Leigh, 2011). Marucci-Wellman et al. (2015) estimated that in the United States the direct workers compensation cost of the most severe, non-fatal occupational injuries was over $51 billion in 2010.[2]

[2] Cost estimate is in 2010 dollars.

Concurrent with this economic and public health burden is the increasing prevalence of cannabis use among employed U.S. adults aged 18 and older (Azofeifa et al., 2016). In 2015, 14.4 percent of U.S. adults aged 18 and older with full-time employment reported using cannabis during the previous year (CBHSQ, 2016, pp. 246–247). Among those employed part-time, the proportion was higher, at 17.8 percent (CBHSQ, 2016, pp. 246–247).[3]

Determining whether an association exists between cannabis use and occupational injury is the subject of ongoing research. According to the 1994 IOM report, *Under the Influence? Drugs and the American Workforce*, evidence on the relationship between employee drug use and accidents in the workplace is mixed (NRC/IOM, 1994, p. 144). This section updates these findings with a review of the current evidence on cannabis use and occupational injury.

Is There an Association Between Cannabis Use and Occupational Injury?

Systematic Review

The committee did not identify a good- or fair-quality systematic review that reported on the association between cannabis use and occupational injury.

Primary Literature

The committee identified six primary literature articles addressing the association between cannabis use and occupational injury. Case series of occupational fatalities, with or without forensic investigation, were not considered if there was no consideration of risk compared to non-cannabis-exposed groups.

To investigate the potential association between cannabis use and work-related and non-work-related injuries and accidents, Wadsworth et al. (2006) sent questionnaires on drug use, history of accidents and injuries, and problems with memory or attention to 30,000 residents of two communities in Wales. Based on data from 7,979 completed questionnaires, there was no statistically significant association between cannabis use in the previous year and the risk of minor occupational injuries (i.e., work-related injuries not requiring medical attention) (odds ratio [OR] 1.17, 95% CI = 0.74–1.86), work-related accidents at work requiring medical attention (OR 0.91, 95% CI = 0.43–1.89), or work-related traffic accidents (OR 3.01, 95% CI = 0.89–10.17), as compared to no illicit drug use and after adjusting for potentially confounding risk factors (e.g., mental and physical health problems, history of risk taking behavior, limited work experience).

Wadsworth et al. (2006) also stratified the study population into groups with low and high levels of potential risk factors for work-related accidents and injuries, and determined the association between cannabis use and the risk for occupational injury for each. Compared to participants who did not use illicit drugs in the previous year and who had few other risk factors, those who used cannabis in the previous year had a significantly elevated risk of suffering minor occupational injuries in the past year if they also had several other risk factors (OR 8.49, 95% CI = 5.37–13.42), but not if they had few other risk factors (OR 1.10, 95% CI = 0.47–2.57). The risk of suffering a work-related accident requiring medical attention in the previous year was also

[3] These percentages correspond to 17,042,000 and 5,770,000 U.S. adults ages 18 or older with full-time and part-time employment, respectively.

significantly elevated for participants who used cannabis in the previous year and had several other risk factors (OR 3.85, 95% CI = 1.89–7.82), but not for participants who used cannabis in the previous year and had few other risk factors (OR 0.92, 95% CI = 0.22–3.92), when compared to those who reported no illicit drug use in the previous year and who had few other risk factors. When individuals who used no illicit drugs in the previous year and who had few other risk factors were the referent, the risk of work-related traffic accidents in the previous year was significantly increased for individuals who used cannabis in the previous year, whether or not they had high levels (OR 6.06, 95% CI = 1.37–26.77) or low levels (OR 3.24, 95% CI = 1.19–8.79) of other risk factors.

Hoffmann and Larison (1999) used data on 9,097 full- and part-time employees ages 18 and older who participated in the 1994 National Household Survey on Drug Abuse (NHSDA) to evaluate the potential association between cannabis use and the risk of work-related accidents (i.e., accidents that occur at work and that result in damage to property or equipment, injury to oneself, and/or injury to others). They found no statistically significant association between any category of former cannabis use (i.e., used 3 or more years ago, used 1–3 years ago) or any category of current use (i.e., used 1–2 days in past year, used 3–51 days in the past year, used at least weekly in past year) and the risk of work-related accidents, as compared to never using cannabis.[4]

Shipp et al. (2005) conducted a cross-sectional study to assess the association between self-reported non-fatal occupational injuries and the self-reported use of substances among 3,265 students attending high school in Texas who indicated that they currently (or had previously) worked for pay. Compared to currently employed students who did not smoke cannabis, those who reported using cannabis on one to nine occasions in the previous 30 days reported a significantly increased risk of occupational injury (OR 1.37, 95% CI = 1.06–1.77) after adjusting for potential confounders, including year in high school, biological sex, and ethnicity. Heavier cannabis use was associated with higher risk: students who reported using cannabis more than 40 times in the past 30 days were more than twice as likely to have suffered a nonfatal occupational injury as those who did not use cannabis (OR 2.47, 95% CI = 1.64–3.71) during this period. Adjusting for intensity of work (hours of work per week) decreased the strength of the association between cannabis use and occupational injury; nevertheless, that association remained statistically significant for students who had used cannabis one or more times over the course of their lifetimes (1 to 9 times: OR 1.45, 95% CI = 1.10–1.90; 10 to 39 times: OR 1.46, 95% CI = 1.01–2.12); 40+ times: OR 1.87, 95% CI = 1.38–5.34) or 40 or more times in the previous 30 days (OR 2.23, 95% CI = 1.34–3.71), as compared to students who did not used cannabis during these periods.

To investigate the association between cannabis use and occupational injury, urine samples collected from individuals working in the United States who had experienced an occupational injury were tested for the presence of cannabis metabolites, and compared to samples collected from individuals selected for a random employee drug test (Price, 2014). To control for the potential confounding effect of other substances, individuals with samples containing amphetamines, phencyclidine, or cocaine or opiate metabolites were removed from

[4] ORs for these variables ranged from 1.51 for "used 1–2 days in past year" to 0.98 for "used 3–51 days in past year," where the referent was never use of cannabis. Hoffman and Larison (1999) did not provide confidence intervals for these ORs, though they indicated in the text that none achieved statistical significance at the $p < 0.05$ level.

the analysis. Among the remaining 961 cases and 2,834 controls, individuals whose urine samples contained detectable levels of cannabis metabolites were not significantly more likely to have suffered an occupational injury than those whose samples did not (OR 0.814, 95% CI = 0.625–1.060).

Macdonald et al. (2010) conducted a literature review to answer several research questions related to workplace drug testing for cannabis, including whether employees who report using cannabis or who test positive for cannabis are at an increased risk for occupational injuries. Findings from the reviewed studies were mixed, with not all studies showing a statistically significant association between cannabis use and occupational injury. The authors also sought to determine whether chronic cannabis users have cognitive deficits that place them at an increased risk for occupational injuries, and reported that although some studies suggest an association between cannabis use and reduced cognitive functioning, the impact of any such deficits on the risk of occupational injury has not been determined.

Dong et al. (2015) evaluated longitudinal data on 12,686 participants in the National Longitudinal Survey of Youth in order to identify factors associated with work-related incidents resulting in injury or illness. Among participants ages 14 to 22 years at study baseline and who reported working in construction between 1988 and 2000, there was no statistically significant association between either lifetime cannabis use on 1–10 occasions (OR 1.04, 95% CI = 0.94–1.15) or lifetime cannabis use on 11 or more occasions (OR 1.10, 95% CI = 0.99–1.21) and the incidence of occupational injury or illness, when never use of cannabis was the referent.

In addition to the articles reviewed above, the committee identified several articles that—while relevant—were published prior to 1999 (Kaestner and Grossman, 1995, 1998; Zwerling et al., 1990), or that considered research questions closely related—but not identical—to the one addressed here (Fransen et al., 2006). Although these articles did not directly inform the committee's conclusions, they aided the committee in orienting themselves to the broader literature on risk factors for occupational injury.

Discussion of Findings

Although Wadsworth et al. (2014, p. 11) concluded that their findings "suggest a detrimental impact of cannabis use on safety that is apparent both in and out of the workplace," they also list several limitations of the study and recommend caution in interpreting its results. Data on cannabis use was derived from self-report and did not measure duration or frequency of cannabis use, nor the timing of cannabis use in relation to accidents or injuries. Further, the study may not have completely controlled for the effect of potential confounders, which may work independently of, or interactively with, cannabis use to modify the risk of occupational injuries or accidents. Finally, the risk for occupational injury posed by cannabis use may be attenuated by processes of self-selection, in which cannabis users choose on average to work in lower-risk occupations and non-users choose to work in higher-risk occupations.

Findings from Hoffman and Larison (1999) also have several limitations. First, the study did not distinguish between work-related accidents resulting in damage to property and those resulting in injury. Second, the study did not determine whether cannabis use took place while at work; consequently, this type of cannabis use could pose a risk for occupational injury, even if current or former cannabis use in general does not. Third, it is not possible to determine from the NHSDA data whether cannabis use occurred proximate to the injury, or whether it preceded or followed an occupational accident.

Shipp et al. (2005) note that the scarcity of research on the association between substance abuse and occupational injuries in adolescent populations prevents the comparison of their results with those from other studies. Since the students who were absent from school on the day of the survey may have had a higher or lower risk of injury compared to students who completed the survey, the potential for selection bias exists. Other limitations of the study include the inability to determine whether cannabis use occurred during work hours or at another time, whether cannabis use preceded or followed the injury, or how closely in time the two events occurred.

In Price (2014), urine samples were collected from men and women of different ages living in different states and employed in a variety of industries with unequal levels of safety sensitivity. The analysis did not control for these variables or determine whether they affect the risk of occupational injury. Furthermore, the study results could not be used to distinguish between recent and remote cannabis use, or to determine the chronicity of cannabis use or the extent of an individual's tolerance for cannabis.

Results from Dong et al. (2015) were limited to those participants who reported working in construction, and do not address the potential association between cannabis use and the risk of occupational injury in other industries. Participants who stated they had experienced an occupational injury during a specific time period were not asked how many such injuries occurred. As a result, the study may have underestimated the true number and risk of occupational injuries. Finally, the reference period for survey questions were long and changed over the course of the study, creating the possibility for recall bias.

In addition to these limitations, the studies were extremely diverse in terms of the characteristics of study participants and their occupations, the specificity and scope of data on cannabis use and occupational injuries, and the extent to which the authors effectively controlled or accounted for potential confounders or effect modifiers. In light of the diversity among and limitations of these studies, it was not possible to determine whether general, non-medical cannabis use is associated with a clearly increased risk of occupational accidents and injuries across a broad range of occupational and industrial settings in the absence of other important risk factors.

CONCLUSION 9-2 There is insufficient evidence to support or refute a statistical association between general, non-medical cannabis use and occupational accidents or injuries.

MOTOR VEHICLE CRASHES

In 2011, motor vehicle crashes (MVCs) were the leading cause of death among U.S. adolescents and adults aged 16–25 years (NHTSA, 2015). Among all age groups, MVCs occurring in 2014 resulted more than 32, 000 fatalities and more than 2 million non-fatal injuries in the United States (CDC, 2016a; NHTSA, 2016).[5] Nationally, the combined medical and work

[5] NHTSA defines a fatal crash as "a police-reported crash involving a motor vehicle in transport on a trafficway in which at least one person dies within 30 days of the crash." Total includes drivers and passengers of motor vehicles, motorcyclists, pedestrians, and cyclists (NHTSA, 2016). Data on non-fatal injuries obtained from Centers for Disease Control and Prevention's (CDC's) Web-based Injury Statistics Query and Reporting System

loss costs associated with these fatal and non-fatal injuries is substantial at $44 and $51.3 billion, respectively (Bergen et al., 2014; CDC, 2015).[6]

In 2014, 3.2 percent of individuals aged 16–25 years reported driving while intoxicated by cannabis (Azofeifa et al., 2015), and the prevalence of THC metabolites detected in the blood or oral fluids of weekend nighttime drivers participating in the National Roadside Survey rose from 8.6 percent in 2007 to 12.6 percent in 2013–2014 (Berning et al., 2015). Given the public health burden of MVC-related morbidity and mortality and the presence of cannabis use and intoxication while driving, there is a need for research to understand the effects on cannabis use on the incidence and severity of motor vehicle crashes and the safety and performance of drivers.

Is There an Association Between Cannabis Use and Motor Vehicle Crashes?

Systematic Reviews

The committee identified a total of six systematic reviews of fair- or good-quality that summarized the association between driving under the influence of cannabis (DUIC) and MVCs (Asbridge et al., 2012; Calabria et al., 2010; Elvik, 2013; Hartman and Huestis, 2013; Li et al., 2012; Rogeberg and Elvik, 2016). Rogeberg and Elvik (2016) was both the most comprehensive and most recently published systematic review. This review pooled studies reviewed in three earlier meta-analyses (Asbridge et al., 2012; Elvik, 2013; Li et al., 2012) and also performed a structured search of online databases. Calabria et al. (2010) evaluated the association between DUIC and fatal MVCs only, but, with the exception of Bedard et al. (2007), all of the studies in this earlier review were also included in Rogeberg and Elvik (2016). Bedard et al. (2007) was excluded by Rogeberg and Elvik (2016) because it was an analysis of cross-sectional data collected by the U.S. Fatal Accident Reporting System registry.

The meta-analysis by Rogeberg and Elvik (2016) summarized evidence from 21 case-control or culpability studies in 13 countries with a combined sample count of 239,739 participants. There were a total of 28 estimates available from these 21 observational studies. The authors of this systematic review limited their analysis to evidence from either case-control studies or culpability studies, and did not include evidence from cross-sectional or cohort studies. The primary criterion for inclusion in the review was the quality of information that indicated cannabis use (i.e., laboratory analyses of blood samples, saliva samples, and urine samples; prescriptions; or self-report) and whether cannabis had been used while driving or enough time prior to driving for effects to still persist. The authors included a wide range of recent studies, including non-peer-reviewed data published by Compton and Berning (2015). Rogeberg and Elvik (2016) argued that culpability studies need to be adjusted for baseline culpability rates because the odds of culpable MVCs associated with DUIC are de facto higher than the overall

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(WISQARS). Total includes all unintentional injuries that occurred on a public road or highway and were traffic-related, and that resulted in an emergency department visit (CDC, 2016a).

[6] Total lifetime medical and work loss costs associated with fatal injuries consequent to MVC, based on MVCs occurring in 2013 was $44 billion (CDC, 2015). Total lifetime medical ($18.4 billion) and work loss ($32.9 billion) costs associated with non-fatal injuries consequent to MVC, based on MVCs occurring in 2012 was $51 billion (Bergen et al., 2014). Work loss costs are defined as "estimates of how much a person who died in a motor vehicle crash would have earned over the course of their life, had they not died," and include salary, estimated benefits, and value of household work (CDC, 2015).

increase in crash risk. Another important strength of this review is the careful adjustment for potential confounders, including alcohol, in the analysis.

Overall, the meta-analysis by Rogeberg and Elvik (2016) found that DUIC, as indicated by self-reported cannabis use or the presence of THC metabolite in blood, saliva, or urine, was associated with 20 to 30 percent higher odds of an MVC. The authors described the magnitude of this association as low to moderate in range, and the committee agrees with that assessment. Specifically, the estimated ORs were 1.36 (95% CI = 1.15–1.61) for an analysis that used a random-effects approach and 1.22 (95% CI = 1.10–1.36) for a meta-regression analysis using a precision-effect estimate with standard errors (PEESE) technique. Subgroup analyses that accounted for alcohol intoxication found that the magnitude of these ORs weakened to 1.11 (95% CI = 1.04–1.18) when using random-effects and to 1.18 (95% CI = 1.07–1.30) when using PEESE; by contrast, an analysis that did not account for alcohol intoxication found that the ORs were 1.79 (95% CI = 1.28–2.51) and 1.69 (95% CI = 1.25–2.28), respectively.

Primary Literature

The committee did not identify any relevant, good-quality primary literature that reported on the association between cannabis use and motor vehicle crashes and were published subsequent to the data collection period of the most recently published good- or fair- quality systematic review addressing the research question. Of the three identified papers with publication dates during or after 2015 that were not included in Rogeberg and Elvik (2016), none contributed new data on the association between DUIC and MVC risk (Allen et al., 2016; Lemos et al., 2015; Meibodi et al., 2015).

Discussion of Findings

Two important methodological limitations of Rogeberg and Elvik (2016) were noted by other researchers (Gjerde and Morland, 2016). First, DUIC may have not just referred to acute intoxication. Indeed, many of the studies considered in this review scored case and control counts as positive using criteria that would also be satisfied by drivers with recent or regular cannabis use but who were neither intoxicated nor impaired while driving (Gjerde and Morland, 2016). Moreover, the association between THC levels in blood and either acute intoxication or driving impairment remains a subject of controversy, and could represent an important limitation in the interpretation of findings in culpability studies based on blood THC levels (Desrosiers et al., 2014; Khiabani et al., 2006; Logan et al., 2016; Menetrey et al., 2005; Papafotiou et al., 2005). Second, 3 of the 21 studies used different methods to assess cases and controls, which may lead to a non-differential misclassification of exposure. A missing component in this review is a better determination of the dose at which driving becomes sufficiently unsafe as to increase MVC risk. Finally, Rogeberg and Elvik (2016) did not provide evidence from cohort studies to address DUIC in MVC.

Simulator studies were also not included in Rogeberg and Elvik (2016). Some laboratory and simulator studies that have examined the effects of acute cannabis intoxication on driving performance have found that the psychomotor skills necessary for safe driving become increasingly impaired at higher doses of cannabis (Sewell et al., 2009). While these experiments may have high internal validity regarding dose-related effects on psychomotor performance, they do not necessarily reflect the complex nature of driving ability and MVC risk attributed to DUIC

in a real-world scenario. Epidemiological studies of MVC in populations may help to address these limitations and are the only reasonable and ethical alternative to controlled experiments outside the laboratory. However, cannabis smokers have demographic characteristics that are similar to those of other groups with a high crash risk, including youth, males, and those with a high prevalence of drugged and drunk driving (Bergeron and Paquette, 2014; Richer and Bergeron, 2009). In particular, confounding or effect modification with alcohol is an important driver-related factor that needs to be better taken into account. The bulk of the evidence available describing the association between DUIC and MVCs comes from case-control studies that evaluate the odds of a MVC by DUIC status and from culpability studies which evaluate the odds of culpability in drivers involved in collisions by DUIC status.

CONCLUSION 9-3 There is substantial evidence of a statistical association between cannabis use and increased risk of motor vehicle crashes.

OVERDOSE INJURIES AND DEATH

According to the American Association of Poison Control Centers (AAPCC), 2,047 calls to position control centers in the United States made in 2014 were in response to single-substance exposures to cannabis, up from 1,548 such exposures in 2013 (Mowry et al., 2014, 2015) . Of these exposures, 37 were classified as having major effects, and death was the outcome in one (Mowry et al., 2015).[7] However, these data do not account for overdose injuries or deaths that did not prompt calls to poison control centers. Data from the Wide-ranging Online Data for Epidemiologic Research (WONDER) database of the Center for Disease Control and Prevention indicate that in 2014 there were 16,822 deaths in the United States due to accidental poisoning by and exposure to narcotics and psychodysleptics—a broad category that includes cannabis as well as cocaine, heroin, codeine, morphine, and several other narcotics (CDC, 2016b; WHO, 2016). Due in part to the limitations of current surveillance tools and medical record coding systems, there is a limited amount of more comprehensive and precise data on the association between cannabis use and overdose injury or death.

Meanwhile, the increasing availability, diversity, and potency of cannabis products create the potential for an increased risk of adverse health effects related to cannabis use, including overdose injury and death. Accidental ingestion of cannabis by young children can result in respiratory failure and coma, as noted by several case reports (Amirav et al., 2011; Appelboam and Oades, 2006; Carstairs et al., 2011), and the consumption of cannabis edibles has been identified as a contributing factor in the accidental death of at least one adolescent (Hancock-Allen et al., 2015).

Thus, the emerging cannabis products market creates the potential for an increased risk of cannabis-related overdose injury or death, while limitations in the current clinical and public health surveillance system hinder efforts to detect, characterize, and respond to this population health issue. This section reviews the available evidence on the association between cannabis use

[7] Major effects are defined as those that are "life-threatening or [that] resulted in significant residual disability or disfigurement" (Mowry et al., 2015, p. 1125). Exposures classified as resulting in death are those where "the patient died as a result of the exposure or as a direct complication of the exposure" (Mowry et al., 2015, p. 1125).

and overdose injury and death and discusses possible actions to improve the state of research on this health endpoint.

Is There an Association Between Cannabis Use and Overdose Injuries or Death?

Systematic Reviews

The committee did not identify a good- or fair-quality systematic review that reported on the association between cannabis use and overdose injuries or death.

Primary Literature

The committee identified a number of studies that directly or indirectly reported on the association between acute cannabis intoxication and overdose death in either adults or children. An analysis of the National Poison Data Systems database involving more than 2 million human exposure cases in 2012 did not list cannabis among the top causes of death related to pharmaceutical products (Dart et al., 2015). According to AAPCC annual reports, among all calls to U.S. poison centers in involving single-substance exposures to cannabis, death was the outcome in two cases in 2012, no cases in 2013, and one case in 2014 (Mowry et al., 2013, 2014, 2015), although the reports do not indicate whether cannabis exposure was a contributing factor in these outcomes. Cannabis was not found to be the main cause of death in any of the fatal intoxications among drug addicts submitted for medico-legal autopsy and toxicological analysis in Denmark, Finland, Iceland, Norway, or Sweden in either 2007 or 2012 (Simonsen et al., 2011, 2015). Nonetheless, tetrahydrocannabinol was commonly identified (21 percent to 38 percent of cases) in the blood samples of these fatal intoxications.

Case reports on cannabis-related deaths are also uncommon. In Colorado, cannabis intoxication was determined to be a chief contributing factor in the death by trauma of a teenager, who jumped from a fourth floor balcony after ingesting a cookie containing 65 mg of THC (Hancock-Allen et al., 2015). Postmortem analyses revealed no evidence of polysubstance abuse and a delta-9 carboxy-THC whole blood concentration of 49 ng/ml—almost 9 times the legal limit for driving in Colorado. Colorado law states that a single-serving edible cannabis product should contain no more than 10 mg of THC; however, currently available edible cannabis products such as cookies and brownies, which are otherwise generally understood as single-serving products, may contain as much as 100 mg (or 10 servings) of THC.[8] In a study on unintentional pediatric cannabis exposure, Wang et al. (2016) described a case where hospital staff members were unable to resuscitate an unresponsive 11-month-old child who presented with tachycardia and metabolic acidosis and who tested positive for THC in a urine drug screen. The authors noted that any relationship between cannabis exposure and the patient's symptoms or outcome was unclear. Although presented here for discussion, these case reports did not inform the committee's conclusions on the association between cannabis use and overdose death.

By comparison with the minimal literature on cannabis-related overdose death in adults or children, several studies reported on potentially serious symptoms associated with cannabis exposure in pediatric populations. Le Garrec et al. (2014) reported that, over a 3.5-year period,

[8] Colorado Code of Regulations. Department of Revenue. Marijuana Enforcement Division. Retail Marijuana Rules. 1 CCR 212-2 R604 (C5) (2).

seven children aged 11–33 months were admitted to a pediatric intensive care unit in Paris with accidental cannabis poisoning. All of the children had central nervous system symptoms, including drowsiness and coma, and three were intubated and placed on mechanical ventilation for less than 24 hours. Between 2010 and 2013, an Arizona poison control center received 49 calls related to unintentional medical marijuana ingestions among children aged 7 and younger (Lovecchio and Heise, 2015). Among the 39 records with complete information, the most commonly reported symptoms were lethargy (48 percent of cases), an inability to walk (53 percent), coma (10 percent), and vomiting (21 percent). These and other symptoms, including respiratory depression and aspiration pneumonia, underscore the importance of observation in children suspected or known to have unintentionally ingested cannabis. Although presented here for discussion, these case series were published as letters in scientific journals, and therefore did not inform the committee's conclusions on the association between cannabis use and overdose injuries.

These findings are supported by retrospective reviews and cohort studies. Wang et al. (2013) retrospectively reviewed cases of unintentional cannabis ingestions among children aged 11 and younger who required medical attention at a children's hospital in Colorado between 2005 and 2011. Out of 1,378 unintentional ingestions, only 14 were cannabis-related, of which 13 were observed in the ER or admitted to the hospital. Symptoms included lethargy, ataxia, dizziness, and respiratory insufficiency. The proportion of unintentional ingestions that were cannabis-related increased from 0 percent in 2005–2009 to 2.4 percent in 2009–2013, a statistically significant increase coinciding with the October 2009 decision by the U.S. Department of Justice to no longer prosecute users and suppliers of cannabis who act in accordance with state laws. In a subsequent study, Wang et al. (2016) reported the prevalence of unintentional pediatric cannabis exposures occurring between 2009 and 2015 at a children's hospital and a poison center in Colorado. The average number of cannabis-related calls per 1000 calls to the poison center increased significantly from 0.9 in 2012–2013 to 2.3 in 2014–2015, periods corresponding to the two years before and after legalization of recreational cannabis in Colorado. Between these same periods, the average number of cannabis-related emergency department visits per 1,000 visits also increased, though non-significantly, from 4.3 to 6.4. Symptoms reported in the 163 calls received by the poison center included drowsiness and/or lethargy (49 percent of cases), ataxia and/or dizziness (12 percent), and agitation (8 percent). Out of 81 cases received by the children's hospital, 40 percent were observed in the emergency department, 22 were admitted to an inpatient ward or the intensive care unit, and 2 required respiratory support. Onders et al. (2016) reviewed data from the National Poison Data System and found that between 2000 and 2013, U.S. poison centers received 1,969 calls related to cannabis exposure among children younger than 6 years old. Most exposures were unintentional (92.2 percent) and occurred as a result of ingesting cannabis or a cannabis product (75.0 percent). Drowsiness and/or lethargy accounted for nearly half of reported clinical symptoms (45.5 percent), while more serious effects, including coma (0.9 percent), cardiovascular symptoms (4.1 percent), and respiratory depression (0.7 percent), occurred less frequently. The annual rate of exposures increased over time, from a national average of 4.21 per million children in 2006 to 10.42 per million children in 2013, corresponding to a statistically significant increase of 147.5 percent. During the same period, the increase in the annual rate of exposures among states that had legalized medical cannabis prior to 2000 was significant, at 609.6 percent.

Collectively, these findings indicate that state-based legalization of cannabis is associated with a subsequent increase in pediatric cannabis exposures in those states. A similar trend

emerges when comparing exposure rates among states where cannabis is legal to exposure rates in states where it is not. Wang et al. (2014) reported that between 2005 and 2011 the rate of calls to poison centers for unintentional pediatric cannabis exposures did not increase in states where cannabis remained illegal as of 2012, increased by 11.5 percent (95% CI = −0.4%–24.7%) in states where legislation to legalize cannabis was passed between 2005 and 2011, and increased by 30.3 percent (95% CI = 22.5%–38.5%) in states where cannabis was legalized before 2005. Among children unintentionally exposed to cannabis, those living in states where cannabis was legalized before 2005 more likely to be evaluated in a health care facility (OR 1.9, 95% CI = 1.5–2.6), to experience major or moderate effects (OR 2.1, 95% CI = 1.4–3.1) and to be admitted to critical care units (OR 3.4, 95% CI = 1.8–6.5) as compared to those living in states where cannabis remained illegal as of 2012. Accounting for 78 percent of all incidents, ingestion was the most common route of unintentional pediatric exposure. Onders et al. (2016) reported that between 2000 and 2013 the annual rate of poison center calls related to cannabis exposures among children younger than 6 was 2.82 times higher in states that had legalized medical cannabis prior to 2000 than in states where medical cannabis remained illegal as of 2013. Another study found that the mean number of calls to poison control centers for unintentional pediatric cannabis exposures increased by 34 percent per year between 2009 and 2015—a significant increase that was also significantly greater than the 19 percent annual increase in cannabis-related calls received by poison control centers throughout the rest of the United States during that same period (Wang et al., 2016). Informed in part by these and other findings, a special committee of the Colorado Department of Public Health and Environment found moderate evidence that more unintentional pediatric cannabis exposures have occurred in states with increased legal access to cannabis and that the exposures can lead to significant clinical effects requiring medical attention (CDPHE, 2015).

Discussion of Findings

The committee identified few studies that report on the association between cannabis use and overdose death. Cannabis was not identified as a main cause in the intoxication deaths of drug addicts in five Nordic countries or a top cause of U.S. deaths related to pharmaceutical products. However, studies on the risks to Nordic populations posed by cannabis products available in those countries may not reflect the risks to U.S. populations posed by domestically available cannabis products, and cannabis might still be associated with overdose deaths without also being a top cause among pharmaceutical-related exposure deaths. Data from the National Poison Data System indicate that death was the outcome in a small number of single-substance exposures to cannabis; however, lacking further information, it is not possible to determine whether and to what extent cannabis contributed to these deaths. Case reports implicate acute cannabis intoxication in one accidental death and suggest cannabis use may pose a risk for sudden cardiac death. However, these individual case reports cannot be used to infer a general association between cannabis use and overdose deaths. Overall, the committee identified no study in which cannabis was determined to be the direct cause of overdose death.

Several studies report that unintentional pediatric cannabis exposure is associated with potentially serious symptoms, including respiratory depression or failure, tachycardia and other cardiovascular symptoms, and temporary coma. Similar symptoms were not reported in adults exposed to cannabis. Most study limitations were related to the origin, quality, and completeness of data. For example, Wang et al. (2013) noted that findings based on data from a single

children's hospital or regional poison centers may not be generalizable to other health care facilities or poison centers, especially those in areas where laws regarding cannabis use are different than in Colorado. Search strategies employed in retrospective reviews of records from hospitals and poison centers may fail to capture all pertinent records, and some records may be incomplete (Wang et al., 2016). Data from poison centers will capture only the subset of cannabis-related overdose injuries or deaths that resulted in a call to a poison center and may overrepresent serious cases or cases from states where cannabis is legal (Wang et al., 2014). Moreover, Onders et al. (2016) observed that cannabis exposures are not identical to poisonings and overdoses; consequently, data on trends in cannabis exposures does not necessarily allow for an estimation of trends in cannabis overdose or poisoning.

CONCLUSION 9-4

9-4(a) There is insufficient evidence to support or refute a statistical association between cannabis use and death due to cannabis overdose.

9-4(b) There is moderate evidence of a statistical association between cannabis use and increased risk of overdose injuries, including respiratory distress, among pediatric populations in U.S. states where cannabis is legal.

RESEARCH GAPS

To address the research gaps relevant to injury and death, the committee suggests the following:

- There is a need for long-term, well-designed cohort studies to determine the association between cannabis use and all-cause and cause-specific mortality among large, representative populations. These studies will need to assess the effects of the various characteristics of cannabis use (e.g., frequency, duration, cumulative exposure) on mortality among demographic and clinical subgroups of interest, to use credible measures of cannabis exposure, and to control for known confounders.
- The association between cannabis use and occupational injury needs to be explored across a broad range of regions, populations, workplace settings, workplace practices (e.g., drug use prevention programs, safety standards), worker characteristics (e.g., medical history, history of drug and alcohol use), work patterns, and occupations.
- There is a need for research to evaluate whether and how the form of cannabis (e.g., edibles, flower, concentrates) affects the risk of overdose and to characterize the incidence and prevalence of overdose deaths in children and adults due to accidental or intentional exposure to edible cannabis.
- There is a need for well-designed surveillance studies to determine the prevalence of acute cannabis use and intoxication among U.S. drivers. Research is also needed to explore how patterns of cannabis use, the degree of acute cannabis intoxication, and geographic and demographic variables affect MVC incidence, driver and passenger outcomes, and driver safety and performance. Finally, research is needed to identify the causal channels through which cannabis use may adversely or therapeutically affect MVC risk.

- There is a need for research on the association between cannabis use and injury and mortality among unstudied and understudied demographic groups, such as minority groups, working adolescents, and employed older populations.

SUMMARY

This chapter discussed the associations between cannabis use and all-cause mortality, occupational injury, motor vehicle crash, and death and injury due to overdose. Below, Box 9-1 provides a summary of the conclusions from this chapter. Notably, the committee found substantial evidence of a statistical association between cannabis use and motor vehicle crashes. These findings suggest the need for research to further specify the strength of this association and to identify any mediating factors, as well as the need for broader surveillance efforts to track patterns of cannabis use, especially where cannabis use may pose risks to personal and public health.

Apart from illuminating potential research objectives, these findings also suggest enacting policies, such as making DUIC a direct target for both policy and policing. Such efforts could include checkpoints for DUIC in conjunction with those for sobriety, the development of point-of-care kits for DUIC testing, and a consideration of zero tolerance laws. These proposals find parallels in policies that restrict or prohibit the use of alcohol while driving, and there is both domestic and international precedent for policing the use of cannabis while operating motor vehicles. In Colorado and Washington, an individual whose blood contains 5 ng/ml or more of THC while driving is considered to be under the influence and is guilty of DUIC.[9] In Australia, it is illegal to drive with any level of THC in oral fluid or blood samples (Boorman and Owens, 2009).[10] Some research suggests that policies that legalize cannabis for medical use have been associated with a decrease in the incidence of MVC. For example, an ecological study found a net reduction in traffic crashes associated with the introduction of laws for medical cannabis use (Anderson et al., 2013).

The committee also found moderate evidence of a statistical association between cannabis use and an increased risk of overdose injuries among pediatric populations in states in where cannabis is legal. The potential risks associated with the use of highly potent cannabis products suggest a need for public health policies, such as regulations that require packaging for cannabis products to include child-focused safety features, warnings that ingested cannabis can have different effects from smoked cannabis, and guidance on how to respond to potential emergencies. Again, precedents for such policies exist. For example, Colorado regulations require that medical and retail cannabis products be sold in packages that are child-resistant, that list the potency of the product in mg of THC and cannabidiol, and that contain several warning statements, including the direction to keep the product out of the reach of children.[11,12]

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[9] Wash. Rev. Code Ann. § 46.61.502 (1) (b). Colo. Rev. Stat. Ann. § 42-4-1301 (6) (a) (IV).

[10] Road Traffic Act 1974, Part V, Division 2, Section 64AC (1).

[11] Colorado Code of Regulations. Department of Revenue. Marijuana Enforcement Division. Medical Marijuana Rules. 1 CCR 212-1 M1004.5 (B) and M1005 (B).

[12] Colorado Code of Regulations. Department of Revenue. Marijuana Enforcement Division. Retail Marijuana Rules. 1 CCR 212-2 R1006 (A–B).

The available evidence was insufficient to draw any conclusions regarding the association between cannabis use and occupational injury or all-cause mortality. The high economic and social costs associated with occupational injuries in this country suggest the need for further research to determine whether these injuries are associated with cannabis use. In pursuing this research, it will be important to determine which individual and work-related factors protect against, or expose workers to, the risk of injury. Emerging evidence suggests that access to legal cannabis can increase the incidence of accidental cannabis ingestion among pediatric populations and that such ingestion can lead to depressed respiratory function and other symptoms of overdose. If state-level changes in cannabis policy continue to make cannabis more accessible, there will be an increased need for research to assess the prevalence of injuries and death due to cannabis overdose, especially among children and other vulnerable populations.

BOX 9-1
Summary of Chapter Conclusions*

There is substantial evidence of a statistical association between cannabis use and:

- Increased risk of motor vehicle crashes (9-3)

There is moderate evidence of a statistical association between cannabis use and:

- Increased risk of overdose injuries, including respiratory distress, among pediatric populations in U.S. states where cannabis is legal (9-4b)

There is no or insufficient evidence to support or refute a statistical association between cannabis use and:

- All-cause mortality (self-reported cannabis use) (9-1)
- Occupational accidents or injuries (general, non-medical cannabis use) (9-2)
- Death due to cannabis overdose (9-4a)

* Numbers in parentheses correspond to chapter conclusion numbers.

REFERENCES

Allen, J. A., K. C. Davis, J. C. Duke, J. M. Nonnemaker, B. R. Bradfield, M. C. Farrelly, S. P. Novak, and G. A. Zarkin. 2016. Association between self-reports of being high and perceptions about the safety of drugged and drunk driving. *Health Education Research* 31(4):535–541.

Amirav, I., A. Luder, Y. Viner, and M. Finkel. 2011. Decriminalization of cannabis–potential risks for children? *Acta Paediatrica* 100(4):618–619.

Anderson, D. M., B. Hansen, and D. I. Rees. 2013. Medical Marijuana Laws, Traffic Fatalities, and Alcohol Consumption. *The Journal of Law and Economics* 56(2):333–369.

Andreasson, S., and P. Allebeck. 1990. Cannabis and mortality among young men: A longitudinal study of Swedish conscripts. *Scandinavian Journal of Social Medicine* 18(1):9–15.

Appelboam, A., and P. J. Oades. 2006. Coma due to cannabis toxicity in an infant. *European Journal of Emergency Medicine* 13(3):177–179.

Asbridge, M., J. A. Hayden, and J. L. Cartwright. 2012. Acute cannabis consumption and motor vehicle collision risk: Systematic review of observational studies and meta-analysis. *BMJ* 344:e536.

Azofeifa, A., M. E. Mattson, and R. Lyerla. 2015. Driving under the influence of alcohol, marijuana, and alcohol and marijuana combined among persons aged 16–25 years—United States, 2002–2014. *Morbidity and Mortality Weekly Report* 64(48):1325–1329.

Azofeifa, A., M. E. Mattson, G. Schauer, T. McAfee, A. Grant, and R. Lyerla. 2016. National estimates of marijuana use and related indicators—National Survey on Drug Use and Health, United States, 2002–2014. *Morbidity and Mortality Weekly Report Surveillance Summaries* 65(11):1–28.

Bedard, M., S. Dubois, and B. Weaver. 2007. The impact of cannabis on driving. *Canadian Journal of Public Health* 98(1):6–11.

Bergen, G., C. Peterson, D. Ederer, C. Florence, T. Haileyesus, M. J. Kresnow, and L. Xu. 2014. Vital signs: Health burden and medical costs of nonfatal injuries to motor vehicle occupants - United States, 2012. *Morbidity and Mortality Weekly Report* 63(40):894–900.

Bergeron, J., and M. Paquette. 2014. Relationships between frequency of driving under the influence of cannabis, self-reported reckless driving and risk-taking behavior observed in a driving simulator. *Journal of Safety Research* 49:19–24.

Berning, A., R. Compton, and K. Wochinger. 2015. Results of the 2013–2014 national roadside survey of alcohol and drug use by drivers. *Traffic Safety Facts Research Note.* Report No. DOT HS 812 118. Washington, DC: National Highway Traffic Safety Administration.

BLS (Bureau of Labor Statistics). 2015. *Employer-reported workplace injuries and illnesses - 2014.* Report No. USDL-15-2086. Washington, DC: Bureau of Labor Statistics. https://www.bls.gov/news.release/archives/osh_10292015.pdf (accessed November 16, 2016).

BLS. 2016. *Injuries, illnesses, and fatalities: Revisions to the 2014 census of fatal occupational injuries (CFOI)*. http://www.bls.gov/iif/cfoi_revised14.htm (accessed November 16, 2016).

Boorman, M., and K. Owens. 2009. The Victorian legislative framework for the random testing drivers at the roadside for the presence of illicit drugs: an evaluation of the characteristics of drivers detected from 2004 to 2006. *Traffic Injury Prevention* 10(1):16–22.

Calabria, B., L. Degenhardt, W. Hall, and M. Lynskey. 2010. Does cannabis use increase the risk of death? Systematic review of epidemiological evidence on adverse effects of cannabis use. *Drug and Alcohol Review* 29(3):318–330.

Carstairs, S. D., M. K. Fujinaka, G. E. Keeney, and B. T. Ly. 2011. Prolonged coma in a child due to hashish ingestion with quantitation of thc metabolites in urine. *Journal of Emergency Medicine* 41(3):e69–e71.

CBHSQ (Center for Behavioral Health Statistics and Quality). 2016. *2015 national survey on drug use and health: Detailed tables.* http://www.samhsa.gov/data/sites/default/files/NSDUH-DetTabs-2015/NSDUH-DetTabs-2015/NSDUH-DetTabs-2015.pdf (accessed December 27, 2016).

CDC (Centers for Disease Control and Prevention). 2015. *State-specific costs of motor vehicle crash deaths*. https://www.cdc.gov/motorvehiclesafety/statecosts/index.html (accessed October 18, 2016).

CDC. 2016a. *WISQARS: Nonfatal injury reports, 2001–2014*. http://webappa.cdc.gov/sasweb/ncipc/nfirates2001.html (accessed October 18, 2016).

CDC. 2016b. *WONDER: About underlying cause of death, 1999-2014*. https://wonder.cdc.gov/ucd-icd10.html (accessed October 18, 2016).

CDPHE (Colorado Department of Public Health and Environment). 2015. *Monitoring health concerns related to marijuana use in Colorado: 2014*. http://www2.cde.state.co.us/artemis/hemonos/he1282m332015internet/he1282m332015internet01.pdf (accesssed December 27, 2016).

Compton, R. P., and A. Berning. 2015. Drug and alcohol crash risk. *Traffic Safety Facts Research Note*. DOT HS 812 117. Washington, DC: National Highway Traffic Safety Administration. http://www.nhtsa.gov/staticfiles/nti/pdf/812117-Drug_and_Alcohol_Crash_Risk.pdf (accessed December 20, 2016).

Dart, R. C., A. C. Bronstein, D. A. Spyker, L. R. Cantilena, S. A. Seifert, S. E. Heard, and E. P. Krenzelok. 2015. Poisoning in the United States: 2012 emergency medicine report of the national poison data system. *Annals of Emergency Medicine* 65(4):416–422.

Degenhardt, L., H. A. Whiteford, A. J. Ferrari, A. J. Baxter, F. J. Charlson, W. D. Hall, G. Freedman, R. Burstein, N. Johns, R. E. Engell, A. Flaxman, C. J. Murray, and T. Vos. 2013. Global burden of

disease attributable to illicit drug use and dependence: Findings from the global burden of disease study 2010. *Lancet* 382(9904):1564–1574.

Desrosiers, N. A., S. K. Himes, K. B. Scheidweiler, M. Concheiro-Guisan, D. A. Gorelick, and M. A. Huestis. 2014. Phase I and II cannabinoid disposition in blood and plasma of occasional and frequent smokers following controlled smoked cannabis. *Clinical Chemistry* 60(4):631–643.

Dong, X. S., X. Wang, and J. A. Largay. 2015. Occupational and non-occupational factors associated with work-related injuries among construction workers in the USA. *International Journal of Occupational and Environmental Health* 21(2):142–150.

Elvik, R. 2013. Risk of road accident associated with the use of drugs: A systematic review and meta-analysis of evidence from epidemiological studies. *Accident Analysis & Prevention* 60:254–267.

Fransen, M., B. Wilsmore, J. Winstanley, M. Woodward, R. Grunstein, S. Ameratunga, and R. Norton. 2006. Shift work and work injury in the New Zealand blood donors' health study. *Occupational and Environmental Medicine* 63(5):352–358.

Gjerde, H., and J. Morland. 2016. Risk for involvement in road traffic crash during acute cannabis intoxication. *Addiction* 111(8):1492–1495.

Hancock-Allen, J. B., L. Barker, M. VanDyke, and D. B. Holmes. 2015. Notes from the field: Death following ingestion of an edible marijuana product—Colorado, March 2014. *Morbidity and Mortality Weekly Report (MMWR)* 64(28):771–772.

Hartman, R. L., and M. A. Huestis. 2013. Cannabis effects on driving skills. *Clin Chem* 59(3):478-492.

Hoffmann, J., and C. Larison. 1999. Drug use, workplace accidents and employee turnover. *Journal of Drug Issues* 29(2):341–364.

Imtiaz, S., K. D. Shield, M. Roerecke, J. Cheng, S. Popova, P. Kurdyak, B. Fischer, and J. Rehm. 2016. The burden of disease attributable to cannabis use in Canada in 2012. *Addiction* 111(4):653–662.

IOM (Institute of Medicine). 1999. *Marijuana and medicine: Assessing the science base*. Washington, DC: National Academy Press.

Kaestner, R., and M. Grossman. 1995. Wages, workers' compensation benefits, and drug use: Indirect evidence of the effect of drugs on workplace accidents. *American Economic Review* 85(2):55–60.

Kaestner, R., and M. Grossman. 1998. The effect of drug use on workplace accidents. *Labour Economics* 5(3):267–294.

Khiabani, H. Z., J. G. Bramness, A. Bjorneboe, and J. Morland. 2006. Relationship between THC concentration in blood and impairment in apprehended drivers. *Traffic Injury Prevention* 7(2):111–116.

Le Garrec, S., S. Dauger, and P. Sachs. 2014. Cannabis poisoning in children. *Intensive Care Medicine* 40(9):1394–1395.

Leigh, J. P. 2011. Economic burden of occupational injury and illness in the United States. *Milbank Quarterly* 89(4):728–772.

Lemos, N. P., A. C. San Nicolas, J. A. Volk, E. A. Ingle, and C. M. Williams. 2015. Driving under the influence of marijuana versus driving and dying under the influence of marijuana: A comparison of blood concentrations of delta9-tetrahydrocannabinol, 11-hydroxy-delta9-tetrahydrocannabinol, 11-nor-9-carboxy-delta9-tetrahydrocannabinol and other cannabinoids in arrested drivers versus deceased drivers. *Journal of Analytical Toxicology* 39(8):588–601.

Li, M. C., J. E. Brady, C. J. DiMaggio, A. R. Lusardi, K. Y. Tzong, and G. Li. 2012. Marijuana use and motor vehicle crashes. *Epidemiologic Reviews* 34:65–72.

Logan, B., S. L. Kacinko, and D. J. Beirness. 2016. *An Evaluation of Data from Drivers Arrested for Driving Under the Influence in Relation to Per se Limits for Cannabis*. AAA Foundation for Traffic Safety: Washington, DC. https://www.aaafoundation.org/sites/default/files/EvaluationOfDriversInRelationToPerSeReport.pdf (accessed December 27, 2016).

Lovecchio, F., and C. W. Heise. 2015. Accidental pediatric ingestions of medical marijuana: A 4-year poison center experience. *American Journal of Emergency Medicine* 33(6):844–845.

Macdonald, S., W. Hall, P. Roman, T. Stockwell, M. Coghlan, and S. Nesvaag. 2010. Testing for cannabis in the work-place: A review of the evidence. *Addiction* 105(3):408–416.

Manrique-Garcia, E., A. Ponce de Leon, C. Dalman, S. Andreasson, and P. Allebeck. 2016. Cannabis, psychosis, and mortality: A cohort study of 50,373 Swedish men. *American Journal of Psychiatry* 173(8):790–798.

Marucci-Wellman, H. R., T. K. Courtney, H. L. Corns, G. S. Sorock, B. S. Webster, R. Wasiak, Y. I. Noy, S. Matz, and T. B. Leamon. 2015. The direct cost burden of 13 years of disabling workplace injuries in the U.S. (1998–2010): Findings from the Liberty Mutual workplace safety index. *Journal of Safety Research* 55:53–62.

Meibodi, M. K., S. Esfandyari, V. Siyabi, and S. Roosta. 2015. Illicit drug abuse in drivers of motor vehicle collisions. *Galen Medical Journal* 4(1):39–46.

Menetrey, A., M. Augsburger, B. Favrat, M. A. Pin, L. E. Rothuizen, M. Appenzeller, T. Buclin, P. Mangin, and C. Giroud. 2005. Assessment of driving capability through the use of clinical and psychomotor tests in relation to blood cannabinoids levels following oral administration of 20 mg dronabinol or of a cannabis decoction made with 20 or 60 mg delta9-THC. *Journal of Analytical Toxicology* 29(5):327–338.

Mowry, J. B., D. A. Spyker, L. R. Cantilena, Jr., J. E. Bailey, and M. Ford. 2013. 2012 annual report of the American association of poison control centers' national poison data system (NPDS): 30th annual report. *Clinical Toxicology* 51(10):949–1229.

Mowry, J. B., D. A. Spyker, L. R. Cantilena, Jr., N. McMillan, and M. Ford. 2014. 2013 annual report of the American association of poison control centers'' national poison data system (NPDS): 31st annual report. *Clinical Toxicology* 52(10):1032–1283.

Mowry, J. B., D. A. Spyker, D. E. Brooks, N. McMillan, and J. L. Schauben. 2015. 2014 annual report of the American association of poison control centers' national poison data system (NPDS): 32nd annual report. *Clinical Toxicology* 53(10):962–1147.

Muhuri, P. K., and J. C. Gfroerer. 2011. Mortality associated with illegal drug use among adults in the United States. *American Journal of Drug and Alcohol Abuse* 37(3):155–164.

NHTSA (National Highway Traffic Safety Administration). 2015. *Motor vehicle traffic crashes as a leading cause of death in the united states, 2010 and 2011.* https://crashstats.nhtsa.dot.gov /Api/Public/ViewPublication/812203 (accessed December, 27, 2016).

NHTSA. 2016. *Fatality analysis reporting system (FARS) encyclopedia*. http://www-fars.nhtsa.dot.gov/ Main/index.aspx (accessed December 27, 2016).

NRC and IOM (National Research Council and Institute of Medicine). 1994. *Under the influence?: Drugs and the American work force*. Washington, DC: National Academy Press:.

Onders, B., M. J. Casavant, H. A. Spiller, T. Chounthirath, and G. A. Smith. 2016. Marijuana exposure among children younger than six years in the United States. *Clinical Pediatrics* 55(5):428–436.

Papafotiou, K., J. D. Carter, and C. Stough. 2005. The relationship between performance on the standardised field sobriety tests, driving performance and the level of delta9-tetrahydrocannabinol (THC) in blood. *Forensic Science International* 155(2–3):172–178.

Price, J. W. 2014. Marijuana and workplace safety: An examination of urine drug tests. *Journal of Addictive Diseases* 33(1):24–27.

Richer, I., and J. Bergeron. 2009. Driving under the influence of cannabis: Links with dangerous driving, psychological predictors, and accident involvement. *Accident Analysis & Prevention* 41(2):299–307.

Rogeberg, O., and R. Elvik. 2016. The effects of cannabis intoxication on motor vehicle collision revisited and revised. *Addiction* 111(8):1348–1359.

Sewell, R. A., J. Poling, and M. Sofuoglu. 2009. The effect of cannabis compared with alcohol on driving. *American journal on Addictions* 18(3):185–193.

Shipp, E. M., S. R. Tortolero, S. P. Cooper, E. G. Baumler, and N. F. Weller. 2005. Substance use and occupational injuries among high school students in South Texas. *American Journal of Drug and Alcohol Abuse* 31(2):253–265.

Sidney, S., J. E. Beck, I. S. Tekawa, C. P. Quesenberry, and G. D. Friedman. 1997. Marijuana use and mortality. *American Journal of Public Health* 87(4):585–590.

Simonsen, K. W., P. T. Normann, G. Ceder, E. Vuori, S. Thordardottir, G. Thelander, A. C. Hansen, B. Teige, and D. Rollmann. 2011. Fatal poisoning in drug addicts in the Nordic countries in 2007. *Forensic Science International* 207(1-3):170–176.

Simonsen, K. W., H. M. Edvardsen, G. Thelander, I. Ojanpera, S. Thordardottir, L. V. Andersen, P. Kriikku, V. Vindenes, D. Christoffersen, G. J. Delaveris, and J. Frost. 2015. Fatal poisoning in drug addicts in the Nordic countries in 2012. *Forensic Science International* 248:172–180.

Wadsworth, E. J., S. C. Moss, S. A. Simpson, and A. P. Smith. 2006. A community based investigation of the association between cannabis use, injuries and accidents. *Journal of Psychopharmacology* 20(1):5–13.

Wang, G. S., G. Roosevelt, and K. Heard. 2013. Pediatric marijuana exposures in a medical marijuana state. *JAMA Pediatrics* 167(7):630–633.

Wang, G. S., G. Roosevelt, M. C. Le Lait, E. M. Martinez, B. Bucher-Bartelson, A. C. Bronstein, and K. Heard. 2014. Association of unintentional pediatric exposures with decriminalization of marijuana in the United States. *Annals of Emergency Medicine* 63(6):684–689.

Wang, G. S., M. C. Le Lait, S. J. Deakyne, A. C. Bronstein, L. Bajaj, and G. Roosevelt. 2016. Unintentional pediatric exposures to marijuana in Colorado, 2009–2015. *JAMA Pediatrics* 170(9):e160971.

WHO (World Health Organization). 2016. Accidental poisoning by and exposure to noxious substances (X40-X49). *IDC-10 Version:2015*. http://apps.who.int/classifications/icd10/browse/2015/en#!/X40-X49 (accessed November 30, 2016).

Zwerling, C., J. Ryan, and E. J. Orav. 1990. The efficacy of preemployment drug screening for marijuana and cocaine in predicting employment outcome. *JAMA* 264(20):2639–2643.

10
Prenatal, Perinatal, and Neonatal Exposure to Cannabis

Chapter Highlights
• Smoking cannabis during pregnancy is linked to lower birth weight in the offspring • The relationship between smoking cannabis during pregnancy and other pregnancy and childhood outcomes is unclear.

The issue of exposure to cannabis during pregnancy reflects concerns that two different individuals may experience the potential adverse effects of cannabis, which is the illicit drug used most frequently by women of child-bearing age. The Substance Abuse and Mental Health Services Administration's National Survey on Drug Use and Health found that in 2015, 3.4 percent of pregnant women of ages 15 to 44 had used marijuana during the previous month (CBHSQ, 2016). This is compared to 0.8 percent of pregnant women who used pain relievers, the next most used illicit drug among pregnant women (CBHSQ, 2016). In part because cannabis is an illicit drug, there is very little information on the physiological effects of cannabis in pregnancy on the mother. Moreover, most of the data reflect cannabis administered by smoking and not cannabis exposure through other routes of administration.

Concern about the fetus and newborn stems from the fact that THC crosses the placenta (Bailey et al., 1987). A rapidly growing body of evidence indicates that endocannabinoids play roles in a broad array of critical neurodevelopmental processes, from early neural stem cell survival and proliferation to the migration and differentiation of both glial and neuronal lineages as well as neuronal connectivity and synaptic function (Lubman et al., 2014). Another potentially important issue is that tetrahydrocannabinol (THC) is secreted in breast milk and can accumulate to high concentrations (Garry et al., 2009).

This chapter focuses on exposure to cannabis from the beginning of pregnancy through the infant's first month of life. Thus, the review covers complications of pregnancy, fetal effects, exposure through breast milk, and later effects of fetal exposure. Although the general principle of the overall report is to restrict the literature reviewed to that which has emerged since the publication of *Marijuana and Medicine: Assessing the Science Base*, the last Institute of Medicine (IOM) report on marijuana, the committee chose to include information concerning longer-term outcomes from two older cohorts released in the 1980s, with the rationale that the identification of late adolescent and young adult outcomes would require that length of follow-up (IOM, 1999). The committee hand-searched additional literature to examine other prioritized long-term health outcomes not covered in these cohort studies.

The committee identified only one recent, good- to fair-quality systematic review (Gunn et al., 2016). This review sought information on a comprehensive set of complications of pregnancy and on fetal and neonatal outcomes up to 6 weeks postpartum. Several lower-quality

systematic reviews (Fryers and Brugha, 2013; Irner, 2012; Savitz and Murnane, 2010; Williams and Ross, 2007), narrative reviews (Andrade, 2016; Forray et al., 2015; Hashibe et al., 2005; Huang et al., 2015; Huizink, 2014; Metz and Stickrath, 2015; Schempf, 2007; Viteri et al., 2014), and articles from the gray literature (CDPHE, 2015) were used to identify outcomes not reviewed in Gunn et al. (2016), as was a bibliographic search of materials published from 1999 onwards. A literature search was also conducted for outcomes in Gunn et al. (2016), from 2014 to August, 2016, to identify any more recent articles. The committee identified 30 primary literature articles that best address the committee's research questions of interest.

PREGNANCY COMPLICATIONS FOR THE MOTHER

Is There an Association Between Cannabis Use and Pregnancy Complications for the Mother?

Stillbirth and Spontaneous Abortion

Systematic Reviews The committee did not identify a good- to fair-quality systematic review that reported on the association between cannabis exposure and stillbirth or spontaneous abortion.

Primary Literature Varner et al. (2014) used results from a population-based case-control study conducted by the Stillbirth Collaborative Research Network to compare illicit drug use in pregnancies that did and did not result in stillbirth.[1] Among 663 stillbirth deliveries, women who with a stillbirth were twice as likely as those with a live birth to report having been addicted to an illicit drug. Tetrahydrocannabinolic acide (THCA), the most common individual drug reported by the population, was found in 2.9 percent of women with stillbirth and 1.7 percent of controls (odds ratio (OR) for stillbirth, = 2.34; 95% CI = 1.13–4.81). However, the authors indicate that the result may have been partially confounded by exposure to cigarette smoking and that they may not have had the statistical power to disentangle this effect.

Warshak et al.'s 2015 study on the association between marijuana exposure and adverse neonatal outcomes included stillbirth in the outcomes they examined and found no association (1.1 percent among 361 cannabis users versus 1.5 percent among 6,107 cannabis non-users; $p = 0.54$).

Fetal Distress

Systematic Reviews Gunn et al. (2016) found no association between marijuana use and fetal distress based on two studies (Berenson et al., 1996; Witter and Niebyl, 1990).

Primary Literature The committee did not identify any good-quality primary literature that reported on the association between cannabis use and fetal distress and that were published subsequent to the data-collection period of the most recently published good- or fair-quality systematic review addressing the research question.

[1] Fetal death was defined in the study as 20 weeks of gestation or less (Varner et al., 2014).

Other Complications

Systematic Reviews The assessment of the literature on pregnancy complications for the mother relied primarily on Gunn et al. (2016). Of the possible complications, only the increased risk of anemia had a significant association with exposure to cannabis with a (pooled odds ratio [pOR], 1.36; 95% CI = 1.10–1.69). Mixed findings about an association with cannabis use occurred in studies of precipitate labor and the manual removal of the placenta. No associations were found between in-utero exposure to cannabis and the following health outcomes: maternal diabetes, rupture of membranes, premature onset of labor, use of prenatal care, duration of labor, placental abruption, secondary arrest of labor, elevated blood pressure, hyperemesis gravidarum, maternal bleeding after 20 weeks, ante– or postpartum hemorrhage, maternal weight gain, maternal postnatal issues, duration of maternal hospital stay, or hormone concentrations (Gunn et al., 2016).

Primary Literature Three further studies were identified; Budde et al. (2007), Leemaqz et al. (2016), and Warshak et al. (2015). These studies examined the association between cannabis exposure and the following outcomes: anemia, precipitate labor, manual removal of the placenta, maternal diabetes, rupture of membranes, premature onset of labor, use of prenatal care, duration of labor, secondary arrest of labor, elevated blood pressure, hyperemesis gravidarum, maternal bleeding after 20 weeks, ante- or postpartum hemorrhage, placental abruption, maternal weight gain, maternal postnatal problems, and duration of maternal hospital stay.

Findings in Leemaqz et al. (2016) from 313 women who used cannabis during pregnancy and Warshak et al., (2015) from 4,892 women who used cannabis during pregnancy were consistent with there being no significant association between cannabis exposure and gestational diabetes (adjusted odds ration [aOR], 1.11; 95% CI = 0.52–2.38; p = 0.949 and aOR, 0.87; 95% CI = 0.66–1.04; p = 0.04, respectively) or gestational hypertension/pre-eclampsia (aOR, 0.443; 95% CI = 0.13–3.54; p = 0.671 and aOR, 0.84; 95% CI = 0.68–1.04; p = 0.12, respectively). Warshak et al. (2015) did not find a statistically significant association between cannabis use and placental abruption (aOR, 1.17; 95% CI = 0.81 – 1.70), p = 0.25). Budde et al. (2007) reported an increased risk of placental abruption that did not achieve standard statistical significance (OR, 2.83, 95% CI = 0.86–10.78; p = 0.055).

Discussion of Findings

Despite identifying one good- to fair-quality systematic review addressing pregnancy complications for the mother, the findings of the review must be interpreted with caution. The review relied on a primary literature that is limited in the number, quality, and rigor of the studies that have been carried out to date. By and large, the existing studies have been retrospective cohort studies, many of which looked at a large number of outcomes without biological plausibility or a biological mechanism guiding the test of the hypothesis. For example, the association identified between anemia and cannabis use in pregnancy arises in the absence of a clear mechanism by which these factors would be related. In addition, many studies were underpowered to detect relatively rare pregnancy complications. Therefore, though Gunn's review reports "no association" for the vast majority of conditions selected, it remains unclear whether this represents type II error. Ethical challenges obviously preclude the ability to conduct randomized controlled trials of cannabis use in pregnancy, thereby precluding the ability to establish causal relationships. Logistical and financial constraints make even prospective cohort

studies of adequate size and duration challenging to fund and implement. Even with rigorous study designs, comorbid tobacco and polysubstance use often confound the interpretation of the data. Such considerations markedly diminish the confidence with which the committee can draw conclusions regarding how much risk can be attributed to cannabis in the area of adverse maternal events.

CONCLUSION 10-1 There is limited evidence of a statistical association between maternal cannabis smoking and pregnancy complications for the mother.

FETAL GROWTH AND DEVELOPMENT

Is There an Association Between Cannabis Use and Fetal Growth and Development?

Birthweight

Systematic Reviews Studies reviewed in Gunn et al. (2016) that examined the effect of cannabis exposure on birth weight reported both mean birth weights and the percentage of infants at low birth weight (LBW, defined as 2.2kg or 5.5 lbs). Gunn et al. (2016) found that in utero exposure to cannabis is associated with a decrease in birth weight among cannabis exposed infants (pOR = 1.77; 95% CI = 1.04–3.01; pooled mean difference (pMD), −109.42 grams; 95% CI = −38.72 to −180.12) compared to those without cannabis exposure.

Primary Literature Similar to the findings reported by Gunn et al., (2016), Gray et al. (2010) and Fergusson et al. (2002) also reported lower mean birthweights for infants prenatally exposed to cannabis. Among 9,521 mothers, Fergusson et al. (2002) showed a −84.20 gram difference (95% CI = −174.7 to −6.4; p = 0.005) in birthweight for the children of mothers who had used cannabis at least once per week before and throughout pregnancy versus non-users. Out of 86 total infants of cannabis using mothers (independent from tobacco use), Gray et al. (2010) reported a mean birth weight of 3,161 grams (standard deviation [SD], 689; p = 0.051) among 41 infants who had been exposed to cannabis and 3,417 grams (SD, 504; p = 0.051) among 45 infants who had not been exposed to cannabis. In contrast, Schempf and Strobino (2008) found that, when adjusted for other drug use (i.e., cocaine and opiates), there was no significant association between cannabis use wand low birth weight (defined as less than 2,500 grams) (aOR, 0.93; 95% CI = 0.55–1.57).

Birth Length

Systematic Reviews In their systematic review, Gunn et al. (2016) found that for the nine studies that reported neonatal length at birth (measured in centimeters), there was no statistically significant association between neonatal length and prenatal exposure to cannabis (pMD, −0.10; 95% CI = −0.65–0.45).

Primary Literature Birth length was also examined by Fergusson et al. (2002) who found that children who had been exposed to cannabis in utero had a lower birth length than children

who had not been prenatally exposed to cannabis. However, after adjusting for various confounding factors (e.g. cigarette smoking during pregnancy and alcohol concumption during pregnancy), the association was no longer significant (p = 0.225). Similarly, Gray et al. (2010) found non-significant differences in birth length between 41 infants of cannabis-using mothers (independent from tobacco use) (49.8 cm; SD = 3.8; p = 0.156) and 45 infants of non-using mothers (50.8 cm; SD = 2.2; p = 0.156).

Head Circumference

Systematic Reviews Gunn et al. (2016) found that among the 10 studies they reviewed that measured head circumference at birth, no statistical association was found between cannabis exposure in utero and neonatal head circumference (cm) (pMD, −0.31; 95% CI = −0.74–0.13).

Primary Literature The committee did not identify any good-quality primary literature that reported on the association between cannabis use and head circumference and that was published subsequent to the data collection period of the most recently published good- or fair-quality systematic review addressing the research question.

Intrauterine Growth Restriction/Small for Gestational Age

There are two ways to describe slower-than-expected growth for a particular duration of gestation. The first is intrauterine growth restriction (IUGR), an obstetric diagnosis based on serial ultrasounds during pregnancy. The second is small for gestational age (SGA), which applies to infants with a birth weight that is less than the 10th or 5th percentile on normative growth curves. The limitation of the latter is that it does not distinguish between those infants with true slow growth and those with normal growth in the lower percentiles.

Systematic Reviews Gunn et al. (2016) addressed two studies that looked at the relationship between in utero cannabis exposure and SGA and concluded that no association can be reported on the association between exposure to cannabis during pregnancy and IUGR/SGA. A pooled odds ratio was not reported.

Primary Literature Leemaqz et al. (2016) similarly did not find an association between cannabis exposure and SGA (defined as a birth weight less than the 10th percentile) when adjusted for any smoking (aOR, 1.13; 95% CI = 0.80–1.60). In a path analysis of urban black women who reported cannabis use at 50 percent of prenatal visits, Janisse et al. (2014) found a reduction in birthweight for heavy marijuana use alone (−55.2 grams), with a path coefficient of 0.05.[2] Their analysis suggests that low birth weight resulting from cannabis exposure reflects fetal growth restriction rather than premature delivery.

[2] The authors used a z-score of birth weight for duration of gestation residualized.

Congenital Malformation

In this category the committee considered infants who had malformations or anomalies diagnosed prenatally or after birth. Congenital malformations reflect abnormalities of fetal development in one or more organ systems and can occur throughout pregnancy. They may be identified before or after birth.

Systematic Reviews Gunn et al. (2016) reported no association between cannabis exposure and chromosomal anomalies. No estimate of effect was provided.

Primary Literature Warshak et al. (2015) analyzed data from among 4,892 cannabis users and 153 marijuana cannabis non-users and reported no association between cannabis exposure and fetal anomalies (aOR, 1.29; 95% CI = 0.87–1.92). In contrast, Forrester and Merz (2006) found higher rates of cannabis use to be associated with the presence of 19 defects out of a total of 54 selected conditions.[3] However, this study only performed bi-variate comparisons for exposure/no exposure without considering other substances, confounders, or multiple comparisons.

Two case-control studies of the association of cannabis exposure to specific malformations were found. Using data from the National Birth Defects Prevention Study (1997–2005), van Gelder et al. (2014) examined the association between maternal cannabis use from 1 month before pregnancy through the end of the third month of pregnancy and 20 selected anomalies (n = 13,859 case infants; n = 6,556 control infants). The authors reported an increased risk of the following anomalies: anencephaly (aOR, 2.2; 95% CI = 1.3–3.7), esophageal atresia (aOR, 1.4; 95% CI = 0.8–2.4), diaphragmatic hernia (aOR, 1.4; 95% CI = 0.9–2.2), and gastroschisis (aOR, 1.2; 95% CRI = 0.9–1.7). Williams et al. (2004) obtained an (aOR, 1.90; 95% CI = 1.29–2.81) for the risk of isolated ventricular septal defect (VSD) among 122 isolated ventricular septal defect cases and 3,029 control infants.

Discussion of Findings

The findings for birth weight are consistent with the effects of non-cannabinoid substances in smoked cannabis and cigarette smoking. It has been shown in several studies that the increases in carbon monoxide, with elevated carboxyhemoglobin blood levels, may be up to five-fold higher after marijuana than cigarettes (Wu et al., 1988). In other studies of marijuana exposure during pregnancy, the cause of the fetal growth restriction noted was proposed to be fetal hypoxia due to the shift in the oxyhemoglobin curve caused by carbon monoxide (Frank et al., 1990).

CONCLUSION 10-2 There is substantial evidence of a statistical association between maternal cannabis smoking and lower birth weight of the offspring.

[3] The authors found higher rates of association between cannabis use and the following birth defects: encephalocele, hydrocephaly, microcephaly, anotia/microtia, tetralogy of Fallot, ventricular septal defect, atrial septal defect, pulmonary valve atresia/stenosis, hypoplastic left heart syndrome, cleft palate alone, cleft lip with/without cleft palate, pyloric stenosis, anal/rectal/large-intestinal atresia/stenosis, obstructive genitourinary defect, polydactyly, syndactyly, reduction deformity of upper limbs, gastroschisis, trisomy 21 (Forrester and Merz, 2006).

NEONATAL CONDITIONS

Is There an Association Between Maternal Cannabis Use and Neonatal Conditions in the Infant?

Prematurity/Gestational Age

Systematic Reviews Gunn et al. (2016) documented a decrease in gestational age (measured in weeks) associated with cannabis use with (pMD, −0.20; 95% CI = −0.62 to −0.22) and increased odds of the risk of preterm delivery (<37 completed weeks) (pOR, 1.29; 95% CI = 0.80–2.08).

Primary Literature Two other studies, Gray et al. (2010) and van Gelder et al. (2014), found no association between cannabis use and shortened gestation. For a total of 86 infants, Gray et al. (2010) reported an median estimated gestational age at delivery of 39 weeks (p = 0.685) for both infants who were exposed to cannabis and infants who were not exposed to cannabis. van Gelder et al. (2014) found no association between cannabis use and gestational age after adjusting for gestational weight gain (aOR, 0.6; 95% CI = 0.1–2.4; n = 3 exposed; n = 335 non-exposed). The study was likely not to have power to detect a difference.

Two studies, Dekker et al. (2012) and Leemaqz et al. (2016), reported an increased risk of spontaneous preterm birth associated with cannabis use (aOR, 2.34 95% CI = 1.22–4.52 and aOR, 2.28; 95% CI = 1.49–3.60, p <0.001, respectively).

Neonatal Intensive Care Unit Admission

Systematic Reviews Gunn et al. (2016), reported increased risk of neonatal intensive care unit (NICU) admission for infants exposed to prenatal cannabis (pOR, 2.02; 95% CI = 1.27–3.21).

Primary Literature Warshak et al. (2015) also found an increased risk of NICU admission among 4,892 cannabis users and 153 non-users (aOR, 1.54; 95% CI = 1.14–2.07).

Other Neonatal Conditions

Systematic Reviews In Gunn et al. (2016) considered other neonatal conditions and found no association between maternal cannabis use and infant Apgar scores at 1 and 5 minutes. Gunn et al. (2016) did not find any differences for jaundice, resuscitation, respiratory distress syndrome, intubation following delivery, hypoglycemia, and sepsis. Studies were mixed as to whether infants exhibited abnormal behavior on neonatal behavioral assessments, in part because different assessment instruments were used in each study.

Primary Literature Warshak et al. (2015) did not find a statistically significant difference in the length of infant hospital stays (aOR, 1.12; 95% CI = 0.95–1.31). Gray et al. (2010), examined Apgar scores at 1 and 5 minutes and found no association between the scores and infant cannabis exposure (p = 0.709 and p = 0.496, respectively).

Discussion of Findings

The literature with regard to prematurity are mixed and need further study. No neonatal outcomes appeared to be associated with cannabis exposure, but the studies are limited. Findings related to health care use, such as the increase in NICU admissions, need to be treated with caution. This pattern may reflect protocols requiring admission of all infants with a history of substance use in pregnancy or failed toxicological screens during labor, rather than the health of the infant per se, particularly as there appears to be no increase in length of neonatal stay.

CONCLUSION 10-3 There is limited evidence of a statistical association between maternal cannabis smoking and admission of the infant to the neonatal intensive care unit (NICU).

LATER OUTCOMES

Is There an Association Between Maternal Cannabis Use and Later Outcomes for the Offspring?

Systematic Reviews

The committee did not identify a good- or fair-quality systematic review that reported on the association between cannabis exposure later outcomes for the child.

Primary Literature

As noted above in the introduction of this chapter, examination of later outcomes relied heavily on three cohorts with some limited results from other hand-searched studies to be reported below.

The first of these cohorts was the Ottawa Prenatal Prospective Study (OPPS) by Fried and colleagues (Fried et al., 1998). The sample of 698 pregnant women was a convenience sample obtained through advertising in doctors' offices and in the media. It could be characterized as including low-risk middle-class women of European descent. No gestational criterion was used, but most of the women were in their second trimester of pregnancy. Data collection was by interview about drug use while pregnant, including the use of cigarettes, alcohol, and cannabis, the last of which was characterized in terms of the number of joints per week. Of the original 698 study participants, 140 women reported at least some use of cannabis or drinking at least 0.85 oz. of absolute alcohol per day or smoking at least 16 mg of nicotine per day (Fried et al., 1998). A smaller group of women (n = 50) who did not use any substances during pregnancy were randomly selected as a reference group. Among these women, prenatal maternal cannabis use was categorized into three groups, with levels averaged across pregnancy: (1) no use, (2) mild/moderate use up to 6 joints/week, and (3) heavy use of at least 6 joints/week. Offspring were followed until the age of 18–22 years, with some attrition as would be expected (Fried et al., 1998).

The second study, started in 1982, was the Maternal Health Practices and Child Development Study (MHPCD) (Day and Richardson, 1991). The sample was recruited from a single inner-city outpatient prenatal clinic in Pittsburgh and thus was of mixed race/ethnicity and

lower socio-economic status. The participants had to be at least 18 years of age and in their fourth month of pregnancy. Of the 1,360 participants who met these criteria and were screened by an interview, pregnant women who used two or more joints per month were then selected for the study, with a random sample of an equal number of women chosen from the remaining non-using subjects, for a total sample of 564 (Huizink, 2014). Prenatal cannabis use was expressed as average daily joints for each trimester of pregnancy separately, although there was some overlap. Follow-up data on offspring have been reported up to the age of 14.

The most recent study was the Generation R study started in 2001, a multi-ethnic (Dutch, Surinamese, Turkish and Moroccan) population-based prospective cohort study from fetal life until adulthood in the city of Rotterdam, the Netherlands (Jaddoe et al., 2012). The sample consists of 9,778 mothers with a delivery date between April 2002 and January 2006, and the members of the sample tended to be of higher socioeconomic status (Huizink, 2014). All participating women in Generation R filled out questionnaires on their substance use at three points in pregnancy corresponding to the three trimesters. In this sample, 220 women reported using cannabis in pregnancy, generally in the first trimester (Huizink, 2014). The study discriminated between cannabis exposure, tobacco smoking, and the use of neither. Data on the resulting children up to age 6 were used in this report.

Sudden Infant Death Syndrome

Systematic Reviews The committee did not identify a good- or fair-quality systematic review that reported on the association between cannabis exposure and sudden infant death syndrome (SIDS).

Primary Literature Only one study was identified that examined the association between cannabis use and SIDS. In a case-control study of 428 infants who died of SIDS in southern California between 1989 and 1992, Klonoff-Cohen et al. (2001) found no association between SIDS and cannabis exposure at conception (aOR, 1.1; 95% CI = 0.6–2.0; p = 0.82), during pregnancy (aOR, 0.6; 95% CI = 0.3–1.6; p = 0.33), or postnatally (aOR, 0.6; 95% CI = 0.2–1.8; p = 0.42). An interesting finding is increased risk of SIDS with paternal cannabis use at conception (aOR, 2.2; 95% CI = 1.2–4.2; p = 0.01), during pregnancy (aOR, 2.0; 95% CI = 1.0–4.1; p = 0.05), and postnatally (aOR, 2.8; 95% CI = 1.1–7.3; p = 0.04).

Breastfeeding

Systematic Reviews The committee did not identify a good- or fair-quality systematic review that reported on the association between cannabis exposure and breastfeeding.

Primary Literature One narrative review (Garry et al., 2009) identified two early studies on the effects of cannabinoids in breast milk on subsequent motor function but found no consistency in the results. The authors noted the difficulty in studying this issue since prenatal exposure is also likely among other confounders of cannabis use. The committee's search identified one study of physical growth (Fried et al., 2001) which makes mention of no difference being found in choice and duration of breastfeeding relative to marijuana use.

Physical Growth

Systematic Reviews The committee did not identify a good- or fair-quality systematic review that reported on the association between cannabis exposure and physical growth in the child.

Primary Literature Postnatal growth results were obtained from the OPPS (Fried et al., 2001). Growth was measured for 152 participants at 1 year, 2–4 years, 6 years, 12 years, and 13–16 years. There was a dose-response relationship between head circumference and cannabis exposure (measured as heavy or 6 or more joints a week, moderate or between 0 and 6 joints per week, and none), with children of heavy cannabis users having the smallest head circumferences (Z, 0.84; SD = 1.3; p = 0.08), a finding that persisted through age 12 but was not seen at age 13–16 (Fried et al., 2001). In addition, infants of heavy cannabis users were the lightest at birth (Z, 0.32; SD = 0.9), but they experienced substantial weight gain such that they were the heaviest at 1 year. Furthermore, at age 13–16 no differences were seen in height, weight, ponderal index, or onset of puberty.

Cognition/Academic Achievement

Systematic Reviews The committee did not identify a good- or fair-quality systematic review that reported on the association between cannabis exposure and cognition and academic achievement of the child.

Primary Literature The committee reviewed this literature in terms of preschool cognitive development and later cognitive development. Among the studies that examined cognitive development up to 3 years of age no difference was found. In addition two studies (OPPS and MHPCD) looked at cognitive development at 36–60 months. Both studies reported a weak effect on short-term memory.

Six studies out of two cohorts were identified that addressed the association between cannabis and cognitive function between ages 5 and 16 years using a variety of assessment instruments (Bluhm et al., 2006; El Marroun et al., 2010; Fried and Watkinson, 1990; 1998; Goldschmidt et al., 2012; Richardson et al., 1995). No differences in overall cognitive scores were found, but differences with exposure to different levels of prenatal cannabis were seen for some subscale scores, although they were not replicated across studies. In their assessment of school achievement, Goldschmidt et al. (2012) found worse reading scores at age 14 as measured by the Wechsler Individual Achievement Test (WIAT Screener). The authors found a WIAT Screener basic reading score of 93.8 among non-exposed children, 93.1 among children exposed to less than one joint per day, and 87.8 among children exposed to one or more joints per day (p = 0.001).[4] No differences with cannabis exposure were seen for cognitive or motor development in Fried and Watkinson (1998), Richardson et al. (1995), or El Marroun et al. (2010).

Behavior

Systematic Reviews The committee did not identify a good- or fair-quality systematic review that reported on the association between cannabis exposure and later child behavior.

[4] This can be accounted for by attention and depression at age 10.

Primary Literature The committee sought studies linking prenatal marijuana exposure to later child behavior. Of the three cohorts assessed above, only one report dealt with child behavior problems (Bluhm et al., 2006). The remaining reports assessed behavior in testing situations, for example, variability in reactions times and errors on continuous performance tests. Because the committee felt the latter do not really capture the construct of interest, this section reports only on child behavior problems at age 18 months and 3 years. At 18 month higher aggression scores were seen in girls but not in boys; this effect did not persist at 36 months (El Marroun et al., 2010).

Substance Use and Delinquency

Systematic Reviews The committee did not identify a good- or fair-quality systematic review that reported on the association between cannabis exposure and later substance use and delinquency of the child.

Primary Literature The committee identified five reports from two cohorts (OPPS and MHPCD) addressing the association between prenatal cannabis exposure and substance use and delinquency among offspring between 14 and 22 years of age. In the study addressing delinquency at age 14 years, prenatal cannabis exposure was found to be correlated with an increased risk of delinquent behavior (OR, 1.84; 95% CI = 1.05–2.96) (Day et al., 2011). However, this effect was mediated by depression and attention difficulties at age 10. Three studies addressed prenatal exposure to cannabis on the use of both cigarettes and cannabis in offspring ages 14–22. In Porath and Fried (2005), prenatal marijuana exposure more than doubled the risk of the initiation of cigarette smoking (OR, 2.58; 95% CI = 1.11–6.00) and daily cigarette smoking (OR, 2.36; 95% CI = 1.00–5.57). The authors also found that prenatal cannabis exposure also increased the risk of initiation of cannabis use in youth (OR, 2.76; 95% CI = 1.11–6.86) and increased the risk of using marijuana regularly (OR, 0.79; 95% CI = 0.33–1.90). Sonon et al. (2015) found that prenatal cannabis exposure was a predictor of offspring marijuana use (OR, 1.22; 95% CI = 1.02–1.44) at age 22 (Sonon et al., 2015).

Mental Health and Psychosis

Systematic Reviews The committee did not identify a good- or fair-quality systematic review that reported on the association between cannabis exposure and later mental health and psychosis in the child.

Primary Literature At age 10 children in the MHPCD study with prenatal cannabis exposure in the first and third trimesters had worse scores on a measure of depressive symptoms. Using the Avon Longitudinal Study of Parents and Children (ALSPAC) cohort study Zammit et al. (2009) found no difference in definite psychotic-like symptoms (PLIKS) as measured by a PLIKS semi-structured interview at 12 years of age between those exposed prenatally and those not exposed (aOR for linear trend, 0.91; 95% CI = 0.49–1.71; $p = 0.776$). Day et al. (2015), working with the MHPCD cohort at age 22, found that prenatal marijuana exposure was associated with an increased risk of psychotic symptoms as measured by the Diagnostic Interview Schedule (incidence density ration (IDR) 1.31; $p < 0.05$). In a mediation model,

considering the effect of early initiation use of cannabis, the youth risk was essentially the same (IDR, 1.27; p = 0.06).

Discussion of Findings

The literature reviewed above does not support an effect of cannabis exposure on overall cognitive function, although some variation in subscale scores has been seen. Only one study has examined overall child behavior, and it found that the results did not persist. More consistency is seen for adolescent outcomes, with increased delinquency, greater cigarette and cannabis use, and some suggestion of increased mental health symptoms. For the later outcomes, attributing the outcomes to prenatal exposures is particularly difficult. While the studies attempted to control for the child's environment using standard measures of socioeconomic status as well as a direct assessment of the home environment, these approaches may be insufficient to detect potentially subtle differences in the family and neighborhood environments of women who smoke cannabis during pregnancy and those who do not. For example, the association of prenatal cannabis exposure and adolescent substance use may reflect family/neighborhood influences and may not be a direct effect of the prenatal exposure. Likewise, maternal distress/depression during pregnancy, which is likely to continue post-partum, may influence both the use of cannabis and child developmental outcomes. In addition, these studies did not address hereditable or epigenetic vulnerability

CONCLUSION 10-4 There is insufficient evidence to support or refute a statistical association between maternal cannabis smoking and later outcomes in the offspring (e.g., SIDS, cognition/academic achievement, and later substance use).

RESEARCH GAPS

To address the research gaps relevant to prenatal, perinatal, and neonatal outcomes, the committee suggests the following:

- There is a need for systematic inquiry using standardized questions about dose and duration at specific intervals in pregnancy to ascertain the level of prenatal cannabis exposure.
- Capitalizing, where possible, on the increase in toxicological screening at delivery to validate self-report measures.
- With the increased availability of recreational cannabis, where ethical, observational studies need to be carried out on cannabis use and potential physiologic changes, e.g., blood pressure, etc.
- Pooling, if possible, to obtain cohorts of women exposed only to THC and not to other drugs.
- A systematic follow-up of children exposed to cannabis prenatally with agreed upon protocols and tests, with an ascertainment of the home and neighborhood environment regarding concurrent substance use.

- Developing strategies for assessing the effect of cannabis on the pregnant woman and fetuses through registries or systematic use of administrative data.

SUMMARY

This chapter summarizes the literature on prenatal, perinatal, and neonatal exposure to cannabis that has been published since 1999 and deemed to be of good or fair quality by the committee. Overall, there is substantial evidence of a statistical association between cannabis smoke and lower birth weight, but there is only limited, insufficient, or no evidence in support of any other health endpoint related to prenatal, perinatal, or neonatal outcomes. This may be due to a number of limitations faced by many of the research studies reviewed in this chapter, including an almost exclusive reliance on self-report to ascertain cannabis exposure, as is true in many areas of this report. While many studies used standardized questions regarding frequency and duration of cannabis use, others relied on data extracted from the medical record. Also, as with other portions of this report, the potency of cannabis varied across time. The lack of biological validation of self-report suggests caution is warranted. Moreover, dosage and timing of exposure in pregnancy is particularly important, as exposures early in pregnancy may affect organogenesis leading to birth defects, whereas later exposures are more likely to affect the growth of the fetus.

Second, even within substantial cohorts, the number of women who used cannabis exclusively was small. These sample sizes may have limited statistical power to detect many outcomes.

Third, cannabis exposure was almost exclusively through smoking and was often confounded by the use of other substances, namely tobacco and alcohol. Although many authors relied on a variety of statistical techniques to isolate the effects of cannabis exposure, attribution of outcomes to cannabis alone was difficult. Even when cannabis is the sole exposure, it is not straightforward to attribute of outcomes to THC alone versus the mode of exposure.

Finally, caution needs to be used in interpreting the numerous findings of "no association" in this chapter. Absent a pooled estimate of effect and confidence intervals, such conclusions may be based on a small number of studies, some of which may even conflict.

The committee has formed a number of research conclusions related to these health endpoints (see Box 10-1); however, it is important that each of these conclusions be interpreted within the context of the limitations discussed in the Discussion of Findings sections.

BOX 10-1
Summary of Chapter Conclusions*

There is substantial evidence of a statistical association between maternal cannabis smoking and:

- Lower birth weight of the offspring (10-2)

There is limited evidence of a statistical association between maternal cannabis smoking and:

- Pregnancy complications for the mother (10-1)
- Admission of the infant to the neonatal intensive care unit (NICU) (10-3)

There is insufficient evidence to support or refute a statistical association between maternal cannabis smoking and:

- Later outcomes in the offspring (e.g., sudden infant death syndrome, cognition/academic achievement, and later substance use) (10-4)

* Numbers in parentheses correspond to chapter conclusion numbers.

REFERENCES

Andrade, C. 2016. Cannabis and neuropsychiatry, 1: Benefits and risks. *Journal of Clinical Psychiatry* 77(5):551–554.

Bailey, J.R., H.C. Cunny, M.G.Paule, and W. Jr. Slikker. 1987. Fetal disposition of delta 9-tetrahydrocannabinol (THC) during late pregnancy in the rhesus monkey. *Toxicology and Applied Pharmacology* 90(2):315–321.

Berenson, A.B., G.S. Wilkinson, and L.A. Lopz. 1996. Effects of prenatal care on neonates born to drug-using women. *Substance Use and Misuse* 31(8):1063–1076.

Bluhm, E.C., Daniels, J., Pollock, B.H., and Olshan, A.F. 2006. Maternal use of recrational drugs and neuroblastoma in offspring. *Cancer Causese and Control* 17(5):663–669.

Budde, M. P., T. E. De Lange, G. A. Dekker, A. Chan, and A. M. T. Nguyen. 2007. Risk factors for placental abruption in a socio-economically disadvantaged region. *Journal of Maternal–Fetal and Neonatal Medicine* 20(9):687–693.

CBHSQ (Center for Behavioral Health Statistics and Quality). 2015~~5~~6. 2015~~4~~ National Survey on Drug Use and Health: Detailed tables. Rockville, MD: Substance Abuse and Mental Health Services Administration. http://www.samhsa.gov/data/sites/default/files/NSDUH-DetTabs2014/NSDUH-DetTabs2014.pdf (accessed November 23, 2016).

CDPHE (Colorado Department of Public Health and Environment). 2015. *Monitoring health concerns related to marijuana in Colorado: 2014*. http://www2.cde.state.co.us/artemis/hemonos/he1282m332015internet/he1282m332015internet01.pdf (accessed November 23, 2016).

Day, N. L., and G. A. Richardson. 1991. Prenatal marijuana use: Epidemiology, methodologic issues, and infant outcome. *Chemical Dependency and Pregnancy* 18(1):77–91.

Day, N. L., L. Goldschmidt, R. Day, C. Larkby, and G. A. Richardson. 2015. Prenatal marijuana exposure, age of marijuana initiation, and the development of psychotic symptoms in young adults. *Psychological Medicine* 45(8):1779–1787.

Dekker, G. A., S. Y. Lee, R. A. North, L. M. McCowan, N. A. Simpson, and C. T. Roberts. 2012. Risk factors for preterm birth in an international prospective cohort of nulliparous women. *PLoS ONE* 7(7):e39154.

El Marroun, H., H. Tiemeier, E. A. P. Steegers, J. W. Roos-Hesselink, V. W. V. Jaddoe, A. Hofman, F. C. Verhulst, W. van den Brink, and A. C. Huizink. 2010. A prospective study on intrauterine cannabis exposure and fetal blood flow. *Early Human Development* 86(4):231–236.

Fergusson, D. M., L. J. Horwood, and K. Northstone. 2002. Maternal use of cannabis and pregnancy outcome. *British Journal of Obstetrics and Gynaecology* 109(1):21–27.

Forray, A., B. Merry, H. Lin, J. P. Ruger, and K. A. Yonkers. 2015. Perinatal substance use: A prospective evaluation of absinence and relapse. *Drug and Alcohol Dependence* 150:147–155.

Forrester, M., and R. Merz, R. 2006. Comparison of trends in gastroschisis and prenatal illicit drug use rates. *Journal of Toxicology and Environmental Health, Part A: Current Issues* 69(13):1253–1259.

Frank, D. A., H. Bauchner, S. Parker, A. M. Huber, K.-A. Kwabena, H. Cabral, and B. Zuckerman. 1990. Neonatal body proportionality and body composition after in utero exposure to cocaine and marijuana. *Journal of Pediatrics* 117(4):622–626.

Fried, P.A., and B. Watkinson. 1988. 12- and 23-month neurobehavioural follow-up of children prenatally exposed to marihuana, cigarettes and alcohol. *Neurotoxicology and Teratology* 10:305–313.

Fried, P.A., and Watkinson, B. 1990. 36- and 48-month neurobehavioral follow-up of children prenatally exposed to marijuana, cigarettes, and alcohol. *Developmental and Behavioral Pediatrics* 11(2) 49–58.

Fried, P. A., B. Watkinson, and R. Gray. 1998. Differential effects on cognitive functioning in 9- to 12-year olds prenatally exposed to cigarettes and marihuana. *Neurotoxicology and Teratology* 20(3):293–306.

Fried, P. A., D. S. James, and B. Watkinson. 2001. Growth and pubertal milestones during adolescence in offspring prenatally exposed to cigarettes and marihuana. *Neurotoxicology & Teratology* 23(5):431–436.

Fryers, T., and T. Brugha. 2013. Childhood determinants of adult psychiatric disorder. *Clinical Practice and Epidemiology in Mental Health* 9:1–50.

Garry, A., V. Rigourd, A. Amirouche, V. Faurox, S. Aubry, and R. Serreau. 2009. Cannabis and breastfeeding. *Journal of Toxicology* 2009(596149):1–5.

Goldschmidt, L., G. A. Richardson, J. A. Willford, S. G. Severtson, and N. L. Day. 2012. School achievement in 14-year-old youths prenatally exposed to marijuana. *Neurotoxicology & Teratology* 34(1):161–167.

Gray, T. R., R. D. Eiden, K. E. Leonard, G. J. Connors, S. Shisler, and M. A. Huestis. 2010. Identifying prenatal cannabis exposure and effects of concurrent tobacco exposure on neonatal growth. *Clinical Chemistry* 56(9):1442–1450.

Gunn, J. K. L., C. B. Rosales, K. E. Center, A. Nunez, S. J. Gibson, C. Christ, and J. E. Ehiri. 2016. Prenatal exposure to cannabis and maternal and child health outcomes: A systematic review and meta-analysis. *BMJ Open* 6(4):e009986.

Hashibe, M., K. Straif, D. P. Tashkin, H. Morgenstern, S. Greenland, and Z. Zhang. 2005. Epidemiologic review of marijuana use and cancer risk. *Alcohol* 35:265–275.

Huang, Y. J., Z. Zhang, D. P. Tashkin, B. Fend, K. Straif, and M. Hashibe. 2015. An epidemiologic review of marijuana and cancer: An update. *Cancer Epidemiology, Biomarkers, and Prevention* 24(1):15–31.

Huizink, A. 2014. Prenatal cannabis exposure and infant outcomes: Overview of studies. *Progress in Neuro-Psychopharmacology and Biological Psychiatry* 52:45–52.

IOM. 1999. *Marijuana and medicine: Assessing the science base*. Washington, DC National Academy Press.

Irner, T. B. 2012. Substance exposure in utero and developmental consequences in adolescence: A systematic review. *Child Neuropsychology* 18(6):521–549.

Jaddoe, V. W. V., C. M. van Duijn, O. H. Franco, A. K. van der Heijden, M. H. van IIzendoorn, J. C. de Jongste, A. van der Lugt, J. P. Mackenbach, H. A. Moll, H. Raat, F. Rivadeneira, E. A. P.

Steegers, H. Tiemier, A. G. Uitterlinder, F. C. Verhulst, and A. Hofman. 2012. The Generation R study: Design and cohort update 2012. *European Journal of Epidemiology* 27(9):739–756.

Janisse, J. J., B. A. Bailey, J. Ager, and R. J. Sokol. 2014. Alcohol, tobacco, cocaine, and marijuana use: Relative contributions to preterm delivery and fetal growth restriction. *Substance Abuse* 35(1):60–67.

Klonoff-Cohen, H., and P. Lam-Kruglic. 2001. Maternal and paternal recreational drug use and sudden infant death syndrome. *Pediatrics and Adolescent Medicine* 155(7):765–770.

Leemaqz, S. Y., G. A. Dekker, L. M. McCowan, L. C. Kenny, J. E. Myers, N. A. Simpson, L. Poston, and C. T. Roberts. 2016. Maternal marijuana use has independent effects on risk for spontaneous preterm birth but not other common late pregnancy complications. *Reproductive Toxicology* 62:77–86.

Lubman, D., Cheetham, A., Yucel, M. (2014) Cannabis and adolescent brain development. *Pharmacology and Therapeutics* (148):1–16.

Metz, T. D., and E. H. Stickrath. 2015. Marijuana use in pregnancy and lactation: A review of the evidence. *American Journal of Obstetrics & Gynecology* 213(6):761–778.

Porath, A. J., and P. A. Fried. 2005. Effects of prenatal cigarette and marijuana exposure on drug use among offspring. *Neurotoxicology & Teratology* 27(2):267–277.

Richardson, G. A., N. L. Day, and L. Goldschmidt. 1995. Prenatal alcohol, marijuana, and tobacco use: Infant mental and motor development. *Neurotoxicology and Teratology* 17(4):479–487.

Savitz, D. A., and P. Murnane. 2010. Behavioral influences on preterm birth: A review. *Epidemiology* 21(3):291–299.

Schempf, A. H. 2007. Illicit drug use and neonatal outcomes: A critical review. *Obstetrical & Gynecological Survey* 62(11):749–757.

Schempf, A. H., and D. M. Strobino. 2008. Illicit drug use and adverse birth outcomes: Is it drugs or context? *Journal of Urban Health* 85(6):858–873.

Sonon, K.E., G.A. Richardson, J.R. Cornelius, K.H. Kim, and N.L. Day. 2015. Prenatal marijuana exposure predicts marijuana use in young adulthood. *Neurotoxicology and Teratology* 47:10–15.

van Gelder, M. M., A. R. Donders, O. Devine, N. Roeleveld, J. Reefhuis, and the National Birth Defects Prevention Study. 2014. Using Bayesian models to assess the effects of under-reporting of cannabis use on the association with birth defects, National Birth Defects Prevention Study, 1997–2005. *Paediatric and Perinatal Epidemiology* 28(5):424–433.

Varner, M. W., R. M. Silver, C. J. Rowland Hogue, M. Willinger, C. B. Parker, V. R. Thorsten, R. L.Goldenberg, G. R. Saade, D. J. Dudley, D. Coustan, B. Stoll, R. Bukowski, M. A. Koch, D. Conway, H. Pinar, U. M. Reddy, and the Eunice Kennedy Shriver National Institute of Child Health and Human Development Stillbirth Collaborative Research Network. 2014. Association between stillbirth and illicit drug use and smoking during pregnancy. *Obstetrics & Gynecology* 123(1):113–125.

Viteri, O. A., E. E. Soto, R. O,. Bahado-Singh, C. W. Christensen, S. P. Chauhan, and B. M. Sibai. 2015. Fetal anomalies and long-term effects associated with substance abuse in pregnancy: A literature review. *American Journal of Perinatology* 32(5):405–415.

Warshak, C.R., J. Regan, B. Moore, K. Magner, S. Kritzer, and J. Van Hook. 2015. Association between marijuana use and adverse obstetrical and neonatal outcomes. *Journal of Perinatology* 35(12):991–995.

Williams, J. H., and L. Ross. 2007. Consequences of prenatal toxin exposure for mental health in children and adolescents: A systematic review. *European Child & Adolescent Psychiatry* 16(4):243–253.

Williams, L. J., A. Correa, and S. Rasmussen. 2004. Maternal lifestyle factors and risk for ventricular septal defects. *Birth Defects Research* 70(2):59–64.

Witter, F.R. and Niebyl, J.R. 1990. Marijuana use in pregnancy and pregnancy outcom. *American Journal of Perinatology* 7(1):36–38.

Wu, T. C., D. P. Tashkin, B. Djahed, and J. E. Rose. 1988. Pulmonary hazards of smoking marijuana as compared with tobacco. *New England Journal of Medicine* 318(6):347–351.

Zammit, S., K. Thomas, A. Thompson, J. Horwood, P. Menezes, D. Gunnell, C. Hollis, D. Wolke, G. Lewis, and G. Harrison. 2009. Maternal tobacco, cannabis and alcohol use during pregnancy and risk of adolescent psychotic symptoms in offspring. *British Journal of Psychiatry* 195(4):294–300.

11
Psychosocial

Chapter Highlights
• Recent cannabis use impairs the performance in cognitive domains of learning, memory, and attention. Recent use may be defined as cannabis use within 24 hours of evaluation. • A limited number of studies suggest that there are impairments in cognitive domains of learning, memory, and attention in individuals who have stopped smoking cannabis. • Cannabis use during adolescence is related to impairments in subsequent academic achievement and education, employment and income, and social relationships and social roles.

Adolescence and emerging adulthood are the periods where most youth begin to experiment with substances of abuse, including cannabis (Johnston et al., 2015). Exploration for many substances of abuse have maintained historical consistency for the past few decades, with approximately 24.9 percent youth having used cannabis at least one time by eighth grade to 51.4 percent having tried cannabis by the time they graduate (Johnston et al., 2015). Yet, recent changes in recreational cannabis use laws have been linked to adolescents' changing perception around accessibility and availability of cannabis and decreased risk of harm from cannabis use, two factors that have been historically connected with rising rates of substance use (Feldstein Ewing et al., 2016; Schmidt et al., 2016). The result is that we are at the forefront of a changing cannabis landscape for youth and young adults.

This is relevant because it is during this precise period of adolescence and young adulthood that the neural substrates that underlie the development of cognition are most active. Indeed, adolescence marks one of the most impressive stretches of neural and behavioral change (Giedd, 2015), with substantial and protracted development in terms of both brain structure and function throughout the teenage years and into the late 20s and early 30s (e.g., Conrod and Nikolaou, 2016). As a result, cannabis and other substance use during this period may incur relatively greater interference in neural, social, and academic functioning as compared to later developmental periods (e.g., adulthood) (Brumback et al., 2016; Jacobus et al., 2015). However, with the paucity of data on the impact of changes of cannabis policy, coupled with existing limitations in the field of addiction neurodevelopment (e.g., predominance of cross-sectional studies) (Feldstein Ewing et al., 2014), we are still very much at the forefront of beginning to understand how cannabis impacts adolescent through adult cognitive health and broader psychosocial functioning.

COGNITION

Despite what appears, on first glance, to be a very broad existing literature, a surprisingly small number of empirical studies have examined how cannabis impacts the psychosocial domains targeted here. The questions addressed in this section revolve around how cannabis affects three aspects of cognition — memory, learning, and attention — areas that have continued to be prevalent across the self-report, neuropsychological, and magnetic resonance imaging (MRI)/functional magnetic resonance imaging (fMRI) literature since the mid-1970s. Further, these are aspects of cognition that are often explored in other studies. In other words, evaluation of these aspects of cognition increases the potential to compare these findings to other studies, including the 10-year prospective examination of 10,000 youth across 21 sites (the ABCD study; Adolescent Brain Cognitive Development Study, 2016). In terms of the relevance of these aspects of cognition, the domains of memory, learning and attention are central, as they undergird an individual's success — or failure — across areas such as academic, employment, and social/relationship functioning. This subsequently renders these three domains of cognition as strong proxies for examining interference in functioning, one of the key metrics of cannabis use disorder symptomology *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM–5).

These domains are defined broadly, in order to be as inclusive as possible of how they were measured within the included systematic analyses and component primary manuscripts, and to allow maximal potential for generalization to the broader literature. Thus, within this review, "memory" is defined as the wide array of function that involves the abilities to remember, temporarily store, more extensively store, process, manipulate, recall, and reproduce data (e.g., verbal, auditory, written). In this review, "learning" is defined as the wide array of function that involves the ability to observe, comprehend, absorb, and appropriate new information into an individual's cognitive repertoire (e.g., verbal, auditory, visual). Finally, in this review, "attention" is defined as an individual's ability to stay focused on the task at hand without being distracted, but also cognitively flexibility enough to transfer to a different task or set of information when the time requires (e.g., including brain regions relevant to visual, auditory, and verbal processing, as well as executive control).

To investigate how cannabis affects these three domains of human cognition (memory, learning, attention), a search was conducted to identify systematic reviews of the existing published literature since the publication of *Marijuana and Medicine: Assessing the Science Base*, the last Institute of Medicine (IOM) report on marijuana (IOM, 1999). There were a total of 94 systematic reviews identified that responded to the topic of cannabis and cognition during the period of 2000–2016. Of these, five systematic reviews were considered of good quality (Batalla et al., 2013; Broyd et al., 2016; Grant et al., 2003; Martin-Santos et al., 2010; Schreiner and Dunn, 2012). No primary manuscripts were utilized in this section as all study questions were addressed by the systematic reviews.

In contrast to other sections of this report, given the diversity of the metrics and constructs in memory, learning, and attention, and the different coverage of these domains within the five different systematic reviews, we present summaries from each of the systematic reviews in these domains, rather than only presenting one representative systematic review for the topic are of cognition. Further, reflective of the field of cognition at this time, the presented systematic reviews reflect data from the fields of neuropsychology, computer-administered cognitive tests,

as well as brain structure and function (e.g., MRI/fMRI). The latter represent some of our most contemporary, sensitive and specific metrics of cognitive function at this time.

It should be noted that Chapter 12: Mental Health highlights the multi-directional and complex relationship between cannabis use and cannabis use disorder and cognitive performance among individuals with psychotic disorders. For further information on this topic, please refer to Chapter 12.

The collection of systematic reviews used in this chapter represents a large body of work. Broyd et al. (2016) systematic review is the most recent, evaluating 3,021 total manuscripts, yielding a final number of 105 manuscripts in their review. Within their systematic review, they evaluated cannabis' interference with cognition across a number of assessment methodologies. Further, they evaluated the impact of these cognitive domains across developmental periods, including adolescence, emerging adulthood, and adulthood (for additional information about developmental implications among adolescents, see Box 11-1). Batalla began with 142 studies, which they narrowed to 43 manuscripts. As with the Broyd et al. (2016) team, Batalla et al. (2013) included studies across the age span, including adolescents and adults. One of the older systematic reviews, Grant et al. (2003) commenced their review with 1,830 manuscripts, which were reduced to a group of 117 papers in their final evaluation. Martin-Santos et al. (2010) began their examination with 66 manuscripts, which resulted in a final set of 41 studies of cannabis on cognition. Schreiner and Dunn (2012) started with more than 800 studies, which they narrowed to a final set of 13 studies.

In these systematic reviews, "acute" generally reflects cognitive domains assessed within a short window (often within several hours) immediately after cannabis use. The individual may or may not still be intoxicated during this examination. In contrast, "sustained" generally reflects cognitive domains assessed after a period of abstinence from cannabis. Within the reviewed studies, that ranges from several hours to months after discontinuing cannabis use.

Is There An Association Between Cannabis Use and Learning?

Systematic Reviews

Of our final set of five systematic reviews, three addressed cannabis use on the cognitive domain of learning (Broyd et al. 2016; Grant et al., 2003; Schreiner and Dunn, 2010).

In terms of acute impact of cannabis use on learning, primarily relying on word list learning, data from 11 manuscripts within the Broyd et al. (2016) systematic review contributed to "strong" support of acute cannabis use on interference in learning. However, in terms of sustained effects, Broyd et al. (2016) only showed "mixed" support. Grant et al. (2003) assessed sustained impact of cannabis use on learning via neuropsychological tests (e.g., California Verbal Learning Test–Learning Trials; Rey Auditory Verbal Learning Test–Learning Trial). Across nine component studies, Grant et al. (2003) found a small negative effect size of −0.21 (99% Confidence interval [CI] = −0.39 to −0.022) for the sustained impact of cannabis on learning. Schreiner and Dunn (2010) also examined sustained impact on learning, with component studies also relying on neuropsychological metrics (e.g., California Verbal Learning Test—Learning Trials; Rey Auditory Verbal Learning Test−Learning Trials; VIG−Visual Learning). Using the criteria of cannabis abstinence for at least month (measured as ≥25 days) within their 13 examined studies, they found a very small effect size of −0.16 (95% CI = −0.33–0.02).

One example study of the component studies within this section includes a study by Hanson et al. (2010). In this study, 19 adolescent marijuana users (mean age = 18 years) with limited other alcohol and/or other substance use were compared with 21 demographically-similar non-using controls (mean age = 17.4 years). Participants completed neuropsychological batteries assessing learning, and other cognitive domains at several points post-cessation (e.g., 3 days; 2 weeks; 3 weeks). Abstinence was verified via decreasing tetrahydrocannabinol metabolite values assess via serial urine drug screens. Marijuana users showed initial poorer performance on learning as compared with non-using controls in acute assessments (at 3 days; $p < 0.01$). However, they showed significant improvements with cessation, with no differences observed on learning between the cannabis using and non-cannabis using groups at either of the sustained time points (e.g., 2 weeks; 3 weeks).

Primary Literature

In this review of cannabis, the primary literature was searched when the systematic review content did not fully cover or address study questions. Given the breadth and scope of the existing systematic reviews in this domain, additional primary literature was not searched for the domain of learning.

Is There An Association Between Cannabis Use and Memory?

Systematic Reviews

Of the final set of five systematic reviews, three addressed cannabis use on the cognitive domain of memory (Batalla et al., 2013; Broyd et al., 2016; Martin-Santos et al., 2010).

In terms of acute impact of cannabis use on memory, the Broyd et al. (2016) systematic review was the only one to address this question. In this review, 22 studies assessed memory including working memory and other memory function using various neuropsychological tests such as the Sternberg task, Trails B, *n*-back, and Wechsler tests, including spatial working memory, digit span, and digit recall. These studies showed moderate to strong evidence for acute interference of cannabis on memory. In terms of long-term sustained relationship between cannabis use and learning following abstinence, the 11 studies examined by Broyd et al. (2016) showed mixed to no evidence for interference in memory functioning after cessation from cannabis use. Similarly, Batalla et al. (2013) examined memory using seven MRI/fMRI studies. The range in mean days of abstinence in these studies extended from 7 days to 201 days post-cannabis cessation. Batalla et al. (2013) found that although there was no difference in task performance between cannabis users and cannabis non-users, cannabis users engaged slightly different parts of their brains as compared to non-users to accomplish the task, often described as in the neuroimaging literature as the utilization of "compensatory" efforts. Similar to Batalla et al. (2013), Martin-Santos et al. (2010) examined 5 empirical MRI/fMRI studies. Individuals in these studies had been abstinent from cannabis for an average of 24 hours to 26 days. As with Batalla et al (2013), cannabis users showed equivalent performance across the neuroimaging tasks to the non-users, but could have engaged compensatory efforts to achieve these outcomes.

One example study in the memory systematic analyses includes a recent study by Roten and colleagues (2015). This is a pharmacotherapy trial of 78 youth seeking treatment for cannabis dependence (ages 15–21). Youth were evaluated to ensure abstinence from cannabis via

urine cannabinoid testing. Youth received a computer-administered battery of tests, including verbal memory, visual memory and composite memory. Youth who were recently abstinent and continuously abstinent 4 weeks showed significantly better memory performance as compared to youth who were still using cannabis at the 4 week measurement (difference [*d*] = 7.2 ± 2.1, p <0.001 and *d* = 7.5 ± 2.4, p = 0.002, respectively).

Primary Literature

In this review of cannabis, the primary literature was searched when the systematic review content did not fully cover or address study questions. Given the breadth and scope of the existing systematic reviews in this domain, additional primary literature was not search for the domain of memory.

Is There An Association Between Cannabis Use and Attention?

Systematic Reviews

Of our final set of five systematic reviews, four addressed cannabis use on the cognitive domain of attention (Batalla et al., 2013; Broyd et al., 2016; Grant et al., 2003; Schreiner and Dunn, 2010).

To determine the acute impact of cannabis use on attention, Broyd et al. (2016) reviewed 17 studies that assessed attention using several approaches, including using neuropsychological metrics of continuous task performance, divided attention tasks, reaction time, attention control tasks. The synthesized findings from studies showed strong evidence for acute interference of cannabis on attention, as reported by the authors.

In terms of the long-term, sustained relationship between cannabis use and attention following abstinence, 10 studies examined by Broyd et al. (2016) showed mixed evidence for impairment in attention functioning after cessation from cannabis use. Likewise, using a series of MRI and fMRI measures (e.g., attention network task, functional connectivity via Multi-Source Interference Task), with three studies Batalla et al. (2013) showed limited evidence of differences in task performance, but as with the other domains, found evidence that cannabis users may be engaging different neural network to achieve similar outcomes during the task (e.g., compensatory efforts). In a review of 11 studies, Grant et al. (2003) also examined the long-term sustained relationship between cannabis use and attention following abstinence. In their study, Grant et al. (2003) examined attention primarily using neuropsychological measures, finding a small effect size for the influence of cannabis use on attention (effect size [ES]; −0.083; 99% CI = −0.32–0.15). Finally, Schreiner and Dunn (2010) primarily examined neuropsychological test performance to determine sustained impact of cannabis on attention performance, including the Continuous Performance Task and Iowa Gambling Task. With the 13 component studies, the authors found small effect size for the sustained impact of cannabis on attention (ES,-0.20; 95% CI = −0.49–0.09).

An example of a component study from this section includes Crane et al. (2013). This study included 69 cannabis using 18- to 24-year-olds (mean age = 21 years). Attention was measured with four neuropsychological measures, including the Iowa Gambling Task (IGT), Balloon Analogue Risk Task, Monetary Choice Questionnaire, and the GoStop Task. Interestingly, cannabis use was only associated with a significant difference on 1 measure (IGT

and past year cannabis use, p <0.03; IGT and past month cannabis use, p<.003). There were no significant sustained associations between cannabis use on the other three measures of inhibition (ns's for past year cannabis use and past month cannabis use across Balloon Analogue Risk Task, Monetary Choice Questionnaire, and the GoStop Task).

Primary Literature

In this review of cannabis, the primary literature was searched when the systematic review content did not fully cover or address study questions. Given the breadth and scope of the existing systematic reviews in this domain, additional primary literature was not search for the domain of attention.

Discussion of Findings

In sum, within the domain of learning, the Broyd et al. (2013) systematic review and the component study highlighted from within that review showed strong data for the acute (immediate) impact of cannabis use on learning. However, results from three systematic reviews (Batalla et al., 2013; Broyd et al., 2013; Martin-Santos et al., 2010) reflected limited to no support for the association between the sustained effects of cannabis use after cessation and the cognitive domain of learning. Similarly, for the domain of memory, the Broyd et al., (2013) systematic review and the component study within it showed moderate to strong evidence for the acute (immediate) impact of cannabis use on memory. However, as with learning, there were limited to no data to support the association between the sustained effects of cannabis use after cessation and the cognitive domain of memory in the 3 systematic reviews that addressed this question (Batalla et al., 2013; Broyd et al., 2016; Martin-Santos et al., 2010). Of interest, the neuroimaging studies reflected that while there was no difference in terms of performance on memory tasks, cannabis users may recruit different parts of their brain to achieve equivalent performance to control subjects on these tasks, suggesting the need to examine how cannabis may impact the neural regions that drive the processing of memory in future research. Finally, for the domain of attention, the Broyd et al. (2016) systematic review showed strong evidence for the acute (immediate) impact of cannabis on attention. However, as with the other domains, the evidence from other systematic reviews (Batalla et al., 2013; Broyd et al., 2016; Grant et al., 2003; Martin-Santos et al., 2010; Schreiner and Dunn, 2010) suggest that there were limited to no data to support the association between the sustained effects of cannabis use after cessation and the cognitive domain of attention.

CONCLUSION 11-1

11-1(a) There is moderate evidence of statistical association between acute cannabis use and impairment in the cognitive domains of learning, memory, and attention.

11-1(b) There is limited evidence of a statistical association between sustained abstinence from cannabis use and impairments in the cognitive domains of learning, memory, and attention.

BOX 11-1
Developmental Implications Among Adolescents

While adolescents were clustered into many of these systematic reviews (e.g., Broyd et al., 2016), it is important to note that they were the minority, often less than 20 percent of the full sample, and rarely examined independently (e.g., Batalla et al., 2013) to uncover potential developmental differences in cognitive function and/or its interference between the age groups. Much work needs to be done specifically examining the impact of cannabis on these cognitive contexts in adolescents and emerging adults specifically (e.g., ages 14–25). This is highly important for three reasons. First, data in the cited systematic reviews and elsewhere (e.g., Batalla et al., 2013, and Filbey et al., 2015) continue to indicate that an early age of initiation tends to be connected to bigger differences in brain function during adulthood. Second, the brain does not complete development until approximately age 25 (e.g., Giedd, 2015), and data from the field of alcohol use reflect that substance use exposure during this period when the brain undergoes rapid transformation could have a more lasting impact on cognitive performance (e.g., Lisdahl et al., 2013). This interference in cognitive function during the adolescent and emerging adult years, which overlap with the critical period in which many youth and young adults' primary responsibility is to be receiving their education, could very well interfere with these individuals' ability to optimally perform in school and other educational settings.

While the evidence for an association between cannabis use and effects on cognitive development during adolescence is limited at this time, the committee recognizes the important initiative recently begun by the National Institutes of Health (NIH) for the landmark study on brain development and child health, Adolescent Brain Cognitive Development Study (ABCD) (Adolescent Brain Cognitive Development Study, 2016). The ABCD Study is the largest long-term study on cognitive development, tracking the biological and behavioral development of at least 10,000 children beginning at ages 9–10 for 10 years through adolescence into adulthood using neuropsychological evaluations and advanced brain imaging to observe brain growth with precision. This study, which began in 2015, will examine how biology and environment interact and relate to developmental outcomes such as physical health, mental health, and life achievements.

ACADEMIC ACHIEVEMENT

Is There an Association Between Cannabis Use and Academic Achievement and Education?

For the psychosocial areas that go beyond cognition, there was one systematic review (Macleod et al., 2004) that examined the effects of cannabis on a number of psychosocial outcomes as reported in longitudinal studies of general population samples. Specifically, this review contributed to our evaluation of the research literature related to the effects of cannabis on academic achievement as well as social relationships and other social roles. There was no systematic review of the research literature on the effects of cannabis on employment and income.

Because only one systematic review was available, we also focused on the primary literature to address questions related the effect of cannabis on (1) academic achievement; (2) employment and income; and (3) social relationships and other social roles. The primary literature to be reviewed and summarized is based on studies published subsequent to 1999. In

selecting that literature, we focused on studies that met criteria derived from the Newcastle-Ottawa quality assessment scale. In particular, (1) prospective studies in which cannabis use occurred prior to the outcomes of interest; (2) multiple assessments of the variables of interest over time; (3) samples that are representative, either of the nation or a major subgroup; (4) multiple measures of cannabis use, involving frequency and/or quantity of use; (5) a relatively large sample size; and (6) consideration of relevant sociodemographic control variables such as sex/gender, age, family income, ethnicity/race and/or history related to the outcome of interest.

Systematic Reviews

In their systematic review, Macleod et al. (2004) identified 16 high-quality longitudinal studies of the general population in which the effects of cannabis use on psychosocial outcomes, including educational attainment, were examined. The authors reported that cannabis use was consistently related to negative educational outcomes (measured primarily by drop-out rates), but also noted that the strength of the association varied across the studies reviewed. In addition, including the appropriate control variables in the analyses typically resulted in a substantial decrease in the strength of the association. There was no evidence of a causal relationship between cannabis use and lower educational attainment.

Primary Literature

The primary literature published subsequent to Macleod et al.'s 2004 review continues to show that it is difficult to document a direct link between cannabis use and negative educational outcomes because other variables play a role. At best, indirect relationships have been reported. For example, Arria et al. (2013) used longitudinal growth curve modeling to analyze cannabis use and grade point average (GPA) data across 4 years of university education. They found no direct links from cannabis to GPA, but they did report an indirect path in which increased cannabis use led to increased skipping of classes, which resulted in lower GPA. Using data from the CARDIA study, Braun et al. (2000) initially found an inverse relationship between past-month cannabis use and becoming a college graduate over 10 years. When analyses were adjusted for variables such as age and parental education this relationship disappeared, so that cannabis use was unrelated to college graduation.

There is some evidence to suggest that a higher frequency and persistence of cannabis use are associated with some negative educational outcomes. Using data from the Victoria Adolescent Health Cohort (1992–2003), Degenhardt et al. (2010) examined a cohort of a representative sample of Australian students (n = 1,943) from an average age of 14.9 years through an average of 24.1 years. Individuals who were persistent or weekly users of cannabis in adolescence and young adulthood had poorer post-school outcomes at age 24 years (adusted odds ratio [aOR], 0.84; 95% CI = 0.55–1.3; n = 190),[1] compared with individuals who never used cannabis. Adjustment for background factors and cigarette smoking reduced this association.

The age at which cannabis use is initiated may be important in determining negative educational outcomes. Using data from three Australian cohort studies involving over 6,000 participants, Horwood et al. (2010) reported that individuals who began to use cannabis before

[1] Adjusted for non-Australian birth, symptoms of depression and anxiety in adolescence, high-risk alcohol use, and maximum level of cigarette smoking in adolescence.

age 15 years experienced significantly greater negative educational outcomes, even after reductions in odds ratios (ORs) based on an adjustment for confounding variables. Pooled estimates indicated that the educational achievement of those who never used cannabis by age 18 years were 1.9 to 2.9 times greater than for those who used cannabis before the age of 15 years. The researchers found that individuals who had not used cannabis by age 18, they were more likely to complete high school (pOR, 2.9; 95% CI = 1.8–4.6; $p < 0.001$), enroll in university (pOR, 1.9; 95% CI = 1.5–2.4; $p < 0.001$), and earn a university degree (pOR, 2.5; 95% CI = 1.8–3.5; $p < 0.001$) compared to individuals who had used cannabis before age 18. In related findings, Brook et al. (2002) reported that minority youth 10–19 years old who used cannabis had higher rates of being suspended or expelled from school (aOR, 2.68; 95% CI = 1.73–4.14; $p < 0.001$).

Educational outcomes related to cannabis use tend to be confounded with the use of other substances, particularly tobacco/smoking cigarettes. Mokrysz et al. (2016), analyzed data from the Avon Longitudinal Study of Parents and Children, a propective study of 2,235 adolescents, 24 percent of whom reported using cannabis by the age of 15 years. When analyses included appropriate confounding variables (particularly tobacco use) even heavy ($\geq$50 times) cannabis users (mean educational performance,[2] 69.2 percent; 95% CI = 65.0–73.3) did not significantly differ from never-users in their and educational performance at age 16 (mean educational performance, 80.8 percent; 95% CI = 80.2–81.4).

Similarly, McCaffrey et al. (2010) followed 4,500 adolescents for 4 years through high school, and reported a positive association between cannabis use and drop out rates (OR, 5.6; risk ratio [RR] = 3.8). However, the remaining association (OR = 2.4; RR = 1.7) became statistically insignificant when the data were adjusted for cigarette use. Degenhendt et al.'s 2010 study found that occasional cannabis use was linked to lower educational outcomes (i.e., dropping out of school), but that the initial relationship was attenuated by tobacco use, which was relatively high in their sample. Green and Ensminger (2006) found that heavy use of cannabis during adolescence was assocaited with dropping out of school.

Discussion of Findings

Researchers have hypothesized and some studies have reported that cannabis use is linked to negative educational outcomes. However, the relationships among these variables are complex as are the ways in which the specific variables of interest are measured. In addition, all such research requires the careful consideration of a wide range of control variables that include sociodemographic confounders (e.g., gender/sex, family socioeconomic status [SES]) and educational confounds (e.g., parental education, intelligence quotient [IQ], student's cognitive ability) (Fergusson and Boden, 2008; Horwood et al., 2010). This complexity requires that researchers use sophisticated data-analytic techniques (e.g., propensity scoring to reduce confounding by measured factors) (McCaffrey et al., 2010). Use of less sophisticated approaches (e.g., correlations, logistic regression) can lead to an overestimation of the association between cannabis use and negative educational outcomes (McCaffrey et al., 2010). Typically, the primary literature cannot elucidate the mechanisms through which cannabis use may produce negative educational outcomes, although some have speculated that these outcomes may be related to cannabis' effects on the brain, including cognitive impairment.

In all of the primary research literature reviewed on the effects of cannabis on academic achievement, employment and income, as well as social relationships and other social roles,

[2] Measured in percentage of General Certificate of Secondary Education points.

there were a number of limitations. Below, we summarize aspects of various studies that make it difficult to draw definitive conclusions regarding the causal relationships among cannabis use and the different psychosocial outcomes that we examined. They include the following:

1. Sample heterogeneity (e.g., differences related to sample's SES, age, gender, ethnicity)
2. Inconsistent measures of cannabis use (Yes/No; cross-sectional reports of frequency and/or quantity/amount; categories based on history of use.
3. Inconsistent/varying measures of the duration of cannabis use and outcome variables.
4. Even in longitudinal studies, the measures of interest often are cross-sectional snapshots.
5. The history and persistence of cannabis use is not always considered. In adolescence through adulthood, patterns of cannabis use can vary (groupings include: consistent never users, occasional users, persistent heavy users, and so on).
6. In almost every study, the measure of cannabis use is based only on self-report, which cannot be validated.
7. Failure to consider individual characteristics (e.g., attitudes related to the outcomes of interest).
8. Multiple substances being used, so difficult to separate out effects of cannabis relative to use of other drugs, including alcohol and smoking tobacco. Often cannabis effects are less strongly related to outcomes of interest.
9. The complexity of the relationships means that confounds must be considered and statistical analyses must be sophisticated. Many studies meet criteria for design and samples, but report outcomes based on less sophisticated analyses (e.g., correlations, logistic regressions).

CONCLUSION 11-2 There is limited evidence of a statistical association between cannabis use and impaired academic achievement and education outcomes.

EMPLOYMENT AND INCOME

Is There an Association Between Cannabis Use and Employment and Income?

Systematic Reviews

The committee did not identify a good- or fair-systematic review that reported on the association between cannabis use and employment and income.

Primary Literature

The primary literature to be reviewed and summarized is based on studies published subsequent to 1999. In selecting that literature, the committee focused on studies that met criteria derived from the Newcastle–Ottawa criteria (Wells et al., 2014), as described in the previous section.

Popovici and French (2014) analyzed two waves of panel data from the nationally representative National Epidemiologic Survey on Alcohol and Related Conditions. Initial analyses suggested a significant association between cannabis and employment status (implying poorer labor market outcomes also see Fergusson and Boden, 2008). However, more sophisticated (fixed-effect) data analyses that considered individual sources of heterogeneity resulted in smaller and less significant relationships between cannabis and unemployment for men and women (OR, 0.813; 95% CI = 0.237–2.791 and OR, 0.777, 95% CI = 0.269–2.239, respectively). The researchers concluded that cannabis use is less detrimental to labor market participation than suggested in previous research. A similar conclusion was reached by Lee et al. (2015a) who found that cannabis use was not related to unemployment (OR, 0.96; 95% CI = 0.91–1.01), but rather that it is confounded with the use of other substances such as drinking alcohol and tobacco use, which are associated with unemployment.

There are some studies that suggest that the persistent use of cannabis over longer periods of time is associated with unemployment. Zhang et al. (2016) reported that chronic cannabis users (who started in adolescence) were more likely to be unemployed in at age 43 (across 3 decades) than non/experimental users (aOR, 3.51; 95% CI = 1.13–10.91). Braun et al. (2000) also found cannabis users to be less likely to be employed than non-users. Those who were employed tended to have lower prestige occupations (measured by the Occupational Prestige Score [OPS]; across 10 years) compared to nonusers. Some of this may be related to lessened commitment to work among those who use cannabis over time. Hyggen (2012) found low work commitment (as measured by the Work Involvement Scale) among cannabis users compared to abstainers, starting from young adulthood (ages 17 to 20 years) through to middle age (early to mid-40s).

Some of the negative effects of cannabis use on unemployment may be exacerbated among those from low SES backgrounds (Lee et al., 2015a). Other studies of low SES and minority samples also report that chronic cannabis use is related to increased unemployment (Green and Ensminger, 2006; Lee et al., 2015b). Disentangling the effects of cannabis use from other variables related to having a low SES and/or disadvantaged background may be fruitful areas for future research.

Discussion of Findings

All of the committee's conclusions are based on primary literature. In some cases, especially with more sophisticated data analyses, cannabis use has not been linked to outcomes such as labor market participation and unemployment. In other cases, a longer duration of cannabis use has been associated with unemployment. A lower socioeconomic status may exacerbate these negative outcomes. Along with the limitations described on page 11-10, our examination of the literature on the relationship between cannabis use and employment was limited by the difficulty in determining causality. Because employment status is not static, it is possible that the relationships may be cyclical (e.g., depending on context, unemployment could contribute to the use of cannabis and other substances [Lee et al., 2015a] and cannabis/substance use could contribute to unemployment).

CONCLUSION 11-3 There is limited evidence of a statistical association between cannabis use and increased rates of unemployment and/or low income.

SOCIAL RELATIONSHIPS AND OTHER SOCIAL ROLES

Is There an Association Between Cannabis Use and Social Functioning and Social Roles?

Systematic Reviews

There was one systematic review that examined the effects of cannabis on social functioning as one of a number of outcomes in longitudinal studies of general population samples. In their systematic review, Macleod et al. (2004) identified 16 high-quality longitudinal studies of the general population in which the effects of cannabis use on psychosocial outcomes, including social functioning, were examined. The authors found that cannabis use was inconsistently related to social functioning, as manifested by antisocial behaviors such as conduct disorder or delinquency, offending, and contact with police. Associations related to an individual's gender and ethnicity also produced inconsistent findings. Using data from the Christchurch Health and Development Study (n = 1,265), Fergusson et al. (1996) reported that cannabis use at younger ages (<15 years) was consistently associated with antisocial behavior (aOR, 1.0; 95% CI = 0.5–2.1). Interestingly, the use of tobacco and alcohol showed similar associations.

Primary Literature

The primary literature has shown that there is a statistical association between cannabis use and social functioning, as manifested by negative relationships with others, but there are too few good-quality studies to provide conclusive evidence of causation. Palamar et al. (2014) examined various psychosocial outcomes in a nationally representative sample of high school seniors (n = 7,437) from the Monitoring the Future study. They found that participants who had used cannabis 40 or more times had compromised relationships with teachers, supervisors, and parents. Cannabis users reported less interest in activities and more trouble with police. Interestingly, the adverse psychosocial outcomes for cannabis were less than those for alcohol. In a sample of African American and Puerto Rican young adults, cannabis use was associated with rebelliousness and engagement with fewer productive activities (Brook et al., 2002).

Chassin et al. (2010) reported that in a sample of juvenile offenders, cannabis use in adolescence was inversely related to "psychosocial maturity" (i.e., a measure of responsibility, temperance, and perspective taking) in young adulthood (χ 2 (5) = 13.49, p = 0.02; comparative fit index [CFI] = 0.991, RMSEA = 0.038). Such maturity is integral to being able to successfully engage in social relationships and to transition into adult social roles. Interestingly, in some cases the temporal sequencing of cannabis use and maturity fluctuated over time, suggesting that these relationships were not static; increases in cannabis use were associated with reduced maturity, and reductions in cannabis use were associated with increases in maturity.

There is some evidence to suggest that a higher frequency and persistence of cannabis use or, in particular, cannabis use during adolescence is associated with some negative social outcomes. Among a low-income sample of 274 African Americans, Green and Ensminger (2006) found that "heavy" (>20 times) cannabis use during adolescence (i.e., before age 17 years) was associated with poorer functioning in some social roles at ages 32–33 years. Compared to never using or experimenting with cannabis, heavy cannabis use was associated with unemployment

(effect size [ES], −0.159; 95% CI = −0.303 to −0.155; p = 0.030) and to parenting outside of marriage (ES, 0.109; 95% CI = −0.042–0.261).

Discussion of Findings

In the systematic review and primary literature, the findings indicate inconsistent relationships between cannabis use and social functioning. The primary literature included studies in which there was a relationship between cannabis use and adverse outcomes such as compromised relationships with authority figures and poorer functioning in social roles such as employment and parenting. Various limitations faced by the primary literature are described on page 11-10.

Researchers have hypothesized —and some studies have reported—that cannabis use is linked to negative social functioning and the ability to appropriately handle social roles. The relationships among these variables are complex, as are the ways in which the specific variables of interest are measured. In addition, all such research requires the careful consideration of a wide range of control variables that include sociodemographic confounds (e.g., gender/sex, family SES), the use of other substances (alcohol, other illicit drugs), and psychological problems such as depression or a personality disorder (Macleod et al., 2004). This complexity requires that researchers use sophisticated data-analytic techniques (e.g., propensity scoring to reduce selection bias; see Chassin et al., 2010). The use of less sophisticated approaches (e.g., correlations, logistic regression) can lead to an overestimation of the association between cannabis use and negative social outcomes (Macleod et al., 2004).

CONCLUSION 11-4 There is limited evidence of a statistical association between cannabis use and impaired social functioning or engagement in developmentally appropriate social roles.

BOX 11-2
Special Consideration for Psychosocial Systematic Reviews

The quality assessment of the systematic reviews in this chapter followed the methods used in this report. Most of the systematic reviews focused on the literature on cognition (i.e., learning, memory, attention) as related to behavioral, neuropsychological, and neuroimaging findings (Batalla et al., 2013; Broyd et al., 2016; Grant et al., 2003; Martin-Santos et al., 2010; Schreiner and Dunn, 2012). There was only one systematic review (Macleod et al., 2004) that included outcomes related to academic achievement/education and social functioning/social roles. In the systematic reviews on cognition, it important to note that the broad reporting standards for the field of behavioral, neuropsychological, and neuroimaging findings included limitations related to the failure to consistently describe the methods for scoring the evidence for each endpoint. For example, within this examination of the literature, many systematic reviews followed the standards typically used to evaluate findings from the primary literature. That is, the reviews include scores of the strength and consistency of the evidence for each outcome, but provided less information about issues such as study design and statistical analyses. As a result, the reviews did not include the conventions generally found within quantitatively based systematic

examinations of a topic, or such as would be found in meta-analytic reviews (e.g., empirical demarcations of synergy or dissonance, as reported via effect sizes and confidence intervals). Reasons for this may include variations in study methodologies, instrumentation, populations, and research designs, which may be relatively more prevalent within psychosocial research. Other reasons may reflect the relatively small body of literature that meets the quality criteria for inclusion in the systematic review. For example, Broyd et al. (2016) evaluated 3,021 manuscripts that yielded a final sample of only 105 manuscripts that addressed the cognitive outcomes of interest. The state-of-the-science in such research often includes confounds that make it difficult to identify effects that unequivocally can be linked to cannabis. Thus, research designed to examine the impact of cannabis on the developing brain often has to contend with confounds related to polysubstance use (which is characteristic of adolescent cannabis use), which obscures the ability to answer questions about the effects of "cannabis only" on the developing brain and cognitive functioning. In some cases, samples included different populations (adolescents vs. adults), cannabis use history (i.e., chronic versus acute), and patterns of use (i.e., frequency, dose, quantity) all of which provide mixed or inconsistent evidence as to the effects of cannabis on a specific outcome. In their systematic review, Macleod et al. (2004) noted that when analyses were appropriately adjusted to address such confounds, there was a substantial decrease in the strength of associations between cannabis use and negative educational outcomes. Similar conclusions can be reached when examining the literature in a broad range of topics. All of these issues provide the basis for recommendations regarding future research on psychosocial outcomes. The findings from such research will begin to provide the evidence base for future systematic reviews and meta-analyses that can better articulate the effects of cannabis on behavior and functioning.

RESEARCH GAPS

To address the research gaps relevant to cognitive health and psychosocial functioning, the committee suggests the following:

- The systematic reviews that were reviewed by the committee did not necessarily parallel those in other fields of research that are covered in this report. As such, more studies that report quantitative data on the psychosocial effects of cannabis use are required to allow for a greater degree of comparison with the effects of cannabis use on the other health endpoints discussed in this report.
- It will be necessary to conduct further research on the developmental implications of cannabis use across age groups, particularly among adolescents, children, and the older populations. While the National Institute on Drug Abuse's Adolescent Brain Cognitive Development study is in progress (see Box 11-2), at the time that this report was released, the findings of that study had not been published.

SUMMARY

This chapter summarizes the good- and fair-quality psychosocial literature published since 1999. The committee found that there is moderate evidence of an association between

cannabis use and the impairment of the cognitive domains of verbal learning and attention but insufficient evidence for an association between cannabis use and the impairment of working memory. There is mixed evidence for the persistence of impairments or the recovery of function following an abstinence period of 24 hours or several weeks (25–32 days) without cannabis use in the domains of working memory, attention, and verbal learning (Broyd et al., 2016).

The committee found that it is difficult to document a direct link between cannabis use and negative educational outcomes, because other variables play a role. There is some evidence to suggest that a higher frequency and persistence of cannabis use is associated with some negative educational outcomes. The age at which cannabis use is initiated may be important in determining negative educational outcomes. Educational outcomes related to cannabis use tend to be confounded with the use of other substances, particularly tobacco/smoking cigarettes. The primary literature has shown that there is an association between cannabis use and social functioning, as manifested by negative relationships with others, but there are too few good-quality studies to provide conclusive evidence. There is some evidence to suggest that a higher frequency and persistence of cannabis use or cannabis use during adolescence is associated with some negative social outcomes. The literature provides limited evidence to support the hypothesis that cannabis use contributes to negative social functioning (e.g., conduct disorder, immature behavior) or to a failure to engage in developmentally appropriate social roles (e.g., marriage, parenting). The committee has formed a number of research conclusions related to these health endpoints (see Box 11-3); however, it is important that each of these conclusions be interpreted within the context of the limitations discussed in the Discussion of Findings sections.

BOX 11-3
Summary of Chapter Conclusions*

There is moderate evidence of a statistical association between cannabis use and:

- The impairment in the cognitive domains of learning, memory, and attention (acute cannabis use) (11-1a)

There is limited evidence of a statistical association between cannabis use and:

- Impaired academic achievement and education outcomes (11-2)
- Increased rates of unemployment and/or low income (11-3)
- Impaired social functioning or engagement in developmentally appropriate social roles (11-4)

There is limited evidence of a statistical association between *sustained abstinence from* cannabis use and:

- Impairments in the cognitive domains of learning, memory, and attention (11-1b)

*Numbers in parenthesis correspond with chapter conclusion number.

REFERENCES

Adolescent Brain Cognitive Development Study. 2016. A*dolescent Brain Cognitive Development Study (ABCD)*. http://abcdstudy.org/ (accessed October 11, 2016).

Arria, A. M., L. M. Garnier-Dykstra., E. T. Cook,K. M. Caldeira, K. B. Vincent, R. A. Baron, and K. E. O'Grady. 2013. Drug use patterns in young adulthood and post-college employment. *Drug and Alcohol Dependence* 127(1):23–30.

Batalla, A., S. Bhattacharyya, M. Yucel, P. Fusar-Poli, J. A. Crippa, S. Nogue, M. Torrens, J. Pujol, M. Farre, and R. Martin-Santos. 2013. Structural and functional imaging studies in chronic cannabis users: A systematic review of adolescent and adult findings. *PLoS ONE* 8(2):e55821.

Braun, B. L., P. Hannan, M. Wolfson, R. Jones-Webb, and S. Sidney. 2000. Occupational attainment, smoking, alcohol intake, and marijuana use: Ethnic-gender differences in the CARDIA study. *Addictive Behaviors* 25(3):399–414.

Brook, J. S., R. E. Adams, E. B. Balka, and E. Johnson. 2002. Early adolescent marijuana use: Risks for the transition to young adulthood. *Psychological Medicine* 32(1):79–91.

Broyd, S. J., H. H. Van Hell, C. Beale, M. Yucel, and N. Solowij. 2016. Acute and chronic effects of cannabinoids on human cognition—A systematic review. *Biological Psychiatry* 79(7):557–567.

Brumback, T., N. Castro, J. Jacobus, and S. Tapert. 2016. Effets of marijuana use on brain structure and function: neuroimaging findings from a neurodevelopmental perspective. *International Review of Neurobiology* 129:33–65.

Chassin, L., J. Dmitrieva, K. Modecki, L. Steinberg, E. Cauffman, A. R. Piquero, G. P. Knight, and S. H. Losoya. 2010. Does adolescent alcohol and marijuana use predict suppressed growth in psychosocial maturity among male juvenile offenders? *Psychology of Addictive Behaviors* 24(1):48–60.

Conrod, P.K., and K. Nikolaou. 2016. Annual research review: On the developmental neuropsychology of substance use disorders. *Journal of Child Psychology and Psychiatry* 57(3):371–394.

Crane, N.A., R. M. Schuster, and R. Gonzalez. 2013. Preliminary evidence for a sex-specific relationship between amount of cannabis use and neurocognitive performance in young adult cannabis users *Journal of the International Neuropsychological Society* 19:1009–1015.

Degenhardt, L., C. Coffey, J. B. Carlin, W. Swift, E. Moore, and G. C. Patton. 2010. Outcomes of occasional cannabis use in adolescence: 10-year follow-up study in Victoria, Australia. *The British Journal of Psychiatry* 196(4):290–295.

Feldstein Ewing, S.W., S. J. Blakemore, and A. Sakhardande. 2014. The effect of alcohol consumption on the adolescent brain: A systematic review of MRI and fMRI studies of alcohol-using youth. *NeuroImage: Clinical* 5:420–437.

Feldstein Ewing, S.W., T. I. Lovejoy, and E. Choo. in press. How has legal recreational cannabis impacted adolescents in your state? A window of opportuntiy. *American Journal of Public Health.*

Fergusson, D. M., and J. M. Boden. 2008. Cannabis use and later life outcomes. *Addiction* 103(6):969–976.

Fergusson., D. M., M. T. Lynskey, and L. J. Horwood. 1996. The short-term consequences of early onset cannabis use. *Journal ofAbnormal Child Psychology* 24:499–512.

Filbey, F. M., T. McQueeny, S. Kadamangudi, C. Bice, and A. Ketcherside. 2015. Combined effects of marijuana and nicotine on memory performance and hippocampal volume. *Behavioural Brain Research* 293:46–53.

Giedd, J. N. 2015. The amazing teen brain. *Scientific American* 312(6):32–37.

Grant, I., R. Gonzalez, C. L. Carey, L. Natarajan, and T. Wolfson. 2003. Non-acute (residual) neurocognitive effects of cannabis use: A meta-analytic study. *Journal of the International Neuropsychological Society* 9:679–689.

Green, K. M., and M. E. Ensminger. 2006. Adult social behavioral effects of heavy adolescent marijuana use among African Americans. *Developmental Psychology* 42(6):1168–1178.

Hanson, K.L., J. L. Winward, A. D. Schweinsburg, K. L. Medina, S. A. Brown, and S. F. Tapert. 2010. Longitudinal study of cognition among adolescent marijuana users over three weeks of abstinence. *Addictive Behaviors* 35(11):970–976.

Horwood, L. J., D. M. Fergusson, M. R. Hayatbakhsh, J. M. Najman, C. Coffey, G. C. Patton, E. Silins, and D. M. Hutchinson. 2010. Cannabis use and educational achievement: Findings from three Australasian cohort studies. *Drug and Alcohol Dependence* 110(3):247–253.

Hyggen, C. 2012. Does smoking cannabis affect work commitment? *Addiction* 107(7):1309–1315.

IOM. 1999. *Marijuana and medicine: Assessing the science base*. Washington, DC National Academy Press.

Jacobus, J., L. K. Squeglia, A. D. Meruelo, N. Castro, T. Brumback, J. N. Giedd, and S. F. Tapert. 2015. Cortical thickness in adolescent marijuana and alcohol users: A three-year prospective study from adolescence to young adulthood. *Developmental Cognitive Neuroscience* 16:101–109.

Johnston, L.D., P M. O'Malley, R. A. Miech, J. G. Bachman, and J. E. Schulenberg. 2015. *Monitoring the future national survey results on drug use: 1975–2014. Overview, key findings on adolescent drug use.* Ann Arbor, MI: Institute for Social Research, the University of Michigan.

Lee, J. O., K. G. Hill, L. A. Hartigan, J. M. Boden, K. Guttmannova, R. Kosterman, J. A. Bailey, and R. F. Catalano. 2015a. Unemployment and substance use problems among young adults: Does childhood low socioeconomic status exacerbate the effect? *Social Science and Medicine* 143:36–44.

Lee, J. Y., J. S. Brook, S. J. Finch, and D. W. Brook. 2015b. Trajectories of marijuana use from adolescence to adulthood predicting unemployment in the mid 30s. *American Journal on Addictions* 24(5):452–459.

Lisdahl, K. M., E. R. Gilbart, N. E. Wright, and S. Shollenbarger. 2013. Dare to delay? The impacts of adolescent alcohol and marijuana use onset on cognition, brain structure, and function. *Frontiers in Psychiatry* 4(53):1–19.

Macleod, J., R. Oakes,A. Copello, I. Crome, M. Egger, M. Hickman, T. Oppenkowski, H. Stokes-Lampard, and G. Davey Smith. 2004. Psychological and social sequelae of cannabis and other illicit drug use by young people: A systematic review of longitudinal, general population studies. *Lancet* 363(9421):1579–1588.

Martin-Santos, R., A. B. Fagundo, J. A. Crippa, Z. Atakan, S. Bhattacharyya, P. Allen, P. Fusar-Poli, S. Borgwardt, M. Seal, G. F. Busatto, and P. McGuire. 2010. Neuroimaging in cannabis use: A systematic review of the literature. *Psychological Medicine* 40(3):383–398.

McCaffrey, D. F., R. L. Pacula, B. Han, and P. Ellickson. 2010. Marijuana use and high school dropout: The influence of unobservables. *Health Economics* 19(11):1281–1299.

Mokrysz, C., R. Landy, S. H. Gage, M. R. Munafo, J. P. Roiser, and H. V. Curran. 2016. Are IQ and educational outcomes in teenagers related to their cannabis use? A prospective cohort study. *Journal of Psychopharmacology.* doi: 0269881115622241.

Palamar, J. J., M. Fenstermaker, D. Kamboukos, D. C. Ompad, C. M. Cleland, and M. Weitzman. 2014. Adverse psychosocial outcomes associated with drug use among U.S. high school seniors: A comparison of alcohol and marijuana. *American Journal of Drug and Alcohol Abuse* 40(6):438–446.

Popovici, I., and M. T. French. 2014. Cannabis use, employment, and income: Fixed-effects analysis of panel data. *Journal of Behavioral Health Services & Research* 41(2):185–202.

Roten, A., N. L. Baker, and K. M. Gray. 2015. Cognitive performance in a placebo-controlled pharmacotherapy trial for youth with marijuana dependence. *Addictive Behaviors* 45:119–123.

Schmidt, L.A., L. M. Jacobs, and J. Spetz. 2016. Young people's more permissive views about marijuana: Local impact of state laws or national trend? *American Journal of Public Health* 106(8):1498–1503.

Schreiner, A. M., and M. E. Dunn. 2012. Residual effects of cannabis use on neurocognitive performance after prolonged abstinence: A meta-analysis. *Experimental and Clinical Psychopharmacology* 20(5):420–429.

Wells, G. A., B. Shea, D. O'Connel, J. Peterson, V. Welch, M. Losos, and P. Tugwell. 2014. The Newcastle–Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp (accessed November 24, 2016).

Zhang, C., J. S. Brook, C. G. Leukefeld, and D. W. Brook. 2016. Trajectories of marijuana use from adolescence to adulthood as predictors of unemployment status in the early forties. *American Journal on Addictions* 25(3):203–209.

12
Mental Health

Chapter Highlights
• Cannabis use is likely to increase the risk of developing schizophrenia and other psychoses; the higher the use the greater the risk. • In individuals with schizophrenia and other psychoses, a history of cannabis use may be linked to better performance on learning and memory tasks. • Cannabis use does not appear to increase the likelihood of developing depression, anxiety, and posttraumatic stress disorder. • For individuals diagnosed with bipolar disorders, near daily cannabis use may be linked to greater symptoms of bipolar disorder than non-users. • Heavy cannabis users are more likely to report thoughts of suicide than non-users. • Regular cannabis use is likely to increase the risk for developing social anxiety disorder.

The relationship between substance use and mental health has been a long-standing and complex public health issue. In 2014, a national survey from the Substance Abuse and Mental Health Services Administration found that 20.2 million adults had a substance use disorder, and of these individuals, 7.9 million had both a mental health disorder and a substance use disorder (SAMSHA, 2015). These statistics emphasize the importance of conducting cross-disciplinary research in order to appropriately inform public health decisions and ultimately improve population health. In this chapter, the committee reviews the current evidence on the association between cannabis use and prioritized mental health outcomes.

The mental health outcomes selected for review in this report were derived from the committee's statement of task and the sponsors' expressed interest, and based on committee consensus. Specifically, mental health outcomes with high prevalence (e.g., depression and anxiety disorders) were included, as were outcomes with significant public health implications such as suicide. Studies on the association between cannabis use and schizophrenia and psychosis were included based on the large volume of literature on the subject, and in an effort to evaluate cannabis effects across mental health diagnostic spectrum, studies on the association between cannabis use and bipolar disorder were reviewed as well.

Concerning each disorder, the committee focused on two key questions: What is the effect of cannabis use on the risk of developing the disorder? And in patients with the disorder, what are the effects of cannabis use on the symptoms or course of the disorder? An initial search of the primary literature (see Appendix B) produced a substantial number of primary articles (e.g., cross-sectional studies, case-control studies, cohort studies, randomized controlled trials [RCTs], or non-systematic literature reviews) for the committee to review. Due to the time constraints of the study, additional search constraints were added to zero in on the types of studies that would likely produce the clearest research conclusions. For example, for the health endpoints discussed below, literature searches were limited to articles that included the following

search terms: longitudinal, prospective, and case-control.[1] The committee's review of the literature focused on identifying studies relevant to answering these specific questions. In this chapter the committee will discuss the findings from 14 of the most recent, good- to fair-quality systematic reviews and from 31 primary literature articles that best address the committee's research questions of interest.

It is important to note that the present review does not include findings from controlled laboratory studies. These studies have been used to assess the effect of cannabis on behavior, to understand how cannabis interacts with alcohol and other drugs to influence behavior, and to characterize the dose-dependent effects of cannabis as they relate to its potential for addiction. Evidence from this body of research—though illuminating at the mechanistic level—does not provide information on the mental health effects of cannabis use in real-world conditions, and was excluded for this reason.

BOX 12-1
Co-Morbidity in Substance Abuse and Mental Illness

National survey studies suggest that it is not uncommon for individuals with mental health disorders to use substances of abuse and, likewise, that it is not uncommon for individuals who abuse or are dependent on drug substances to also meet diagnostic criteria for a mental health disorder. In fact, in a 2014 national survey, almost 8 million adults in the United States reported co-occurring substance abuse and mental health disorders. This co-occurrence is also termed, *co-morbidity*.

There are a number of proposed explanations for why the co-morbidity of substance abuse and mental health disorders exists. Three of the most commonly explored hypotheses are:

1. *Substance use may be a potential risk factor for developing mental health disorders.* Given the overlap in associated neurochemical substrates (e.g., dopamine, serotonin), specific neurobiological alterations due to drug use, may have resulting effects on the neural processes regulating mental health.
2. *Mental illness may be a potential risk factor for developing a substance abuse disorder.* Research suggests that individuals who are at risk for a mental health disorder, or those who experience subclinical symptoms, may be more likely than others to use drugs as a form of self-medication.
3. *An overlap in predisposing risk factors (e.g., genetic vulnerability, environment) may contribute to the development of both substance abuse and a mental health disorder.* Studies suggest that the development of mental health disorders and substance abuse disorders may be a symptomatic outcome of pre-existing neurobiological abnormalities (e.g., receptor abnormalities, epigenetic modifications).

Although the precise explanation is still unclear, it is reasonable to assume that co-morbidity between substance abuse and mental health disorders may occur due to a mixture of proposed scenarios. With this context in mind, however, it is important to note that the issue of co-morbidity directly affects the ability to determine causality and/or directionality in associations between substance use and mental health outcomes. This is a complex issue, one that certainly warrants further investigation.

SOURCES: Center for Behavioral Health Statistics and Quality, 2015; EMCDDA, 2016; NIDA, 2011.

[1] The initial search of the primary literature produced a relatively small literature base for the posttraumatic stress disorder section, and as such, the additional search restrictions were not applied.

SCHIZOPHRENIA AND OTHER PSYCHOSES

Schizophrenia spectrum disorders and other psychotic disorders are mental health disorders characterized by three different classes of symptoms: positive symptoms (e.g., delusions, hallucinations, or disorganized or abnormal motor behavior), negative symptoms (e.g., diminished emotional expression, lack of interest or motivation to engage in social settings, speech disturbance, or anhedonia), and impaired cognition (APA, 2013, p. 87; NIMH, 2015). Evidence suggests that the prevalence of cannabis use among people with schizophrenia is generally higher than among the general population (McLoughlin et al., 2014). In most of the studies reviewed below, schizophrenia, schizophreniform disorder, schizoaffective disorder, and psychotic disorders are used as aggregate endpoints. Therefore, conclusions regarding the association between cannabis use and psychosis are in general not diagnosis specific.

Is There an Association Between Cannabis Use and the Development of Schizophrenia or Other Psychoses?

Systematic Reviews

Five systematic reviews of fair or higher quality were identified that addressed the committee's research question (Large et al., 2011, Marconi et al., 2016, Moore et al., 2007, Myles et al., 2012, van der Meer et al., 2012). While the systematic review by Marconi et al was the most recent, it excluded studies that did not consider at least three levels of cannabis exposure because the researchers' main purpose was to address dose–response relationships. In addition to reporting on the systematic review by Marconi et al., the systematic review conducted by Moore et al is also discussed.This study addressed the broad question of cannabis use and psychotic outcome and included meta-analysis results. The remaining systematic reviews, which are not reported on here, focused on the time to onset of psychosis (or the age of onset of psychosis), the role of concomitant tobacco use, and psychotic symptomatology in patients at high risk of psychosis.

The systematic review by Marconi et al. (2016) included a search of the literature through December 31, 2013, and selected 10 studies for inclusion in the meta-analysis. A key feature of the researchers' inclusion criteria was the requirement that studies assess cannabis use with a dose criterion and classify cannabis use into at least three exposure groups. Thus, high-quality studies with cannabis assessed as a dichotomous variable were excluded from the analysis. Studies that reported psychotic symptoms on a continuous, rather than categorical, scale were also excluded from the analysis. The 10 studies reviewed were conducted in Australia, Europe, New Zealand, and the United States and reported results for 66,816 individuals. The age and sex of the subjects were not reported. Cannabis use was classified based on lifetime frequency, the frequency of use at baseline, the duration/frequency of current use, and frequency within the last year. The authors did not assess the quality of the papers included in the meta-analysis, but they did conduct analyses to assess publication bias and heterogeneity. They considered the publication bias to be low and acknowledged the existence of heterogeneity within their sample of studies. Marconi et al., (2016) found an association between cannabis use and psychosis (odds ratio [OR], 3.9; 95% confidence interval [CI] = 2.84–5.34) among the most severe cannabis users, as compared to the nonusers. The investigators also report a dose-response relationship with an OR of 1.97 (95% CI = 1.68–2.31) for those at the median of any cannabis use and an OR

of 3.40 (95% CI = 2.55–4.54) for those in the top 20 percent of cannabis use. In addition, they reported associations of cannabis use with the presence of psychotic symptoms (pooled odds ratio [pOR], 3.59: 95% CI = 2.42–5.32), as well as with a diagnosis of schizophrenia or psychotic disorder (pOR,5.07; 95% CI = 3.62–7.09). Subgroup analysis stratified by study design revealed a pooled odds ratio of 3.99 (95% CI = 2.50–6.37) for cross-sectional studies and 3.83 (95% CI = 2.34–6.29) for cohort studies.

Moore et al. (2007) searched multiple databases from their inception through September 2006 and included only studies that were longitudinal, population-based, or case-control studies nested within longitudinal designs. They assessed study quality by recording information on sampling strategy, response rates, missing data, attrition, attempts to address reverse causation, intoxication effects, and other potential confounders. Their search identified 32 studies, with 11 studies reporting the incidence of psychosis from 7 cohort studies, 5 of which were adult population-based cohorts and 2 of which were birth cohorts. They found no evidence of the presence of publication bias using Egger's test ($p = 0.48$). The authors noted that some individual studies adjusted for psychotic symptoms at previous assessments or baseline and excluded people with psychotic symptoms or diagnosis at baseline to help clarify the temporal order of events. The authors also noted that individual studies excluded psychotic symptoms that arose solely from drug use by using scales to measure drug intoxication. In addition, this group of studies collectively adjusted for approximately 60 different potential confounders, including other substance use, personality traits, sociodemographic markers, intellectual ability, and other mental health problems. In a pooled analysis, the authors found that in individuals that have ever used cannabis, there was an associated increased risk of a psychotic outcome (adjusted odds ratio [aOR], 1.41; 95% CI = 1.20–1.65). When the analysis was restricted to studies examining the effects of frequent cannabis use, the investigators found a stronger association (aOR, 2.09; 95% CI = 1.54–2.84), suggesting a dose–response relationship between cannabis use and the risk of a psychotic outcome.

Primary Literature

Auther et al. (2015) used the North American Prodrome Longitudinal Study[2] phase 1 sample to examine the impact of the level of cannabis use on conversion to psychosis.[3] From the subjects that contributed to the data, 370 were determined to be at a high risk for developing a psychotic disorder. After excluding subjects that were missing necessary outcome data, or who met criteria for attenuated positive symptom syndrome, brief intermittent psychotic syndrome, genetic high-risk, and deterioration syndrome, a total of 283 subjects (mean age = 18.3 years) were included in the study's analysis. Using the subjects' reported level of lifetime use, subjects were divided into three subgroups: no use, use without impairment, and abuse and dependence. The primary outcome, conversion to psychosis, was determined by meeting the full criteria for Presence of Psychotic Syndrome on the Structured Interview for Prodromal Syndrome.In a follow-up assessment (approximately 17 months after the initial baseline assessment), the researchers found that cannabis abuse/dependence was associated with a greater risk of

[2] The North American Prodrome Longitudinal Study is a collaborative database formed in 2007. The database contains data on various clinical, cognitive, and functioning variables collected from eight independent research centers.

[3] Auther et al. defined this outcome as having a psychotic level positive symptom that is either seriously disorganizing or dangerous, or that occurs for at least 1 hour per day for an average of 4 days in the past month.

conversion to psychosis within the chronic high-risk population; however, when alcohol use was incorporated into the Cox regression model, cannabis abuse/dependence was no longer significantly related to conversion (hazards ratio [HR], 1.875; 95% CI = 0.963–3.651). Similar research conclusions were reached in a longitudinal study by Valmaggia et al. (2014), where they examined the assocation between lifetime cannabis use, and the development of psychosis. Valmaggia et al. (2014) followed 182 individuals at ultra-high risk for psychosis disorder for two years and found that varying degrees of cannabis use (i.e., lifetime use, frequent use, early-onset use, and continued use after presentation) among lifetime cannabis users is associated with an increased transition to psychosis. It is of note, however, that within this specific ultra-high risk population, cannabis users were no more likely to develop psychosis than those who had never tried cannabis.

Using a case-control design of 410 patients with first episode psychosis and 370 population controls, Di Forti et al. (2015) showed that first-episode psychosis patients were more likely to have lifetime cannabis use, more likely to use cannabis every day, and to mostly use high potency cannabis, as compared to the controls. The cases were also more likely to have used cannabis before the age of 15. Duration of use did not differ between patients and controls, nor did other drug use. After adjusting for a variety of confounders including use of other drugs and alcohol, the researchers found an increased risk of developing psychosis in subjects who used cannabis daily (OR, 3.04; 95% CI= 1.91–7.76), and in subjects who used high potency cannabis (OR, 2.91; 95% CI = 1.52–3.60). In a cross-sectional study of subjects with first-episode psychosis, Colizzi et al. (2015) examined the association between cannabis use, the risk of psychosis, and the dopamine receptor type 2 polymorphism, rs1076560. Researchers found, after adjusting for confounders (e.g., gender, age, ethnicity, polysubstance use), a significant interaction between lifetime frequency of cannabis use and dopamine receptor type 2 (DRD2) polymorphism rs1076560 on psychosis risk. Moreover, a lifetime history of cannabis use was associated with an increased risk of having psychotic disorder in T carrying subjects, relative to GG carrying subjects (OR, 3.07; 95% CI = 1.22–7.63).[4]

Discussion of Findings

The association between cannabis use and the development of a psychotic disorder is supported by data synthesized in several good-quality systematic reviews. The magnitude of this association is moderate to large and appears to be dose-dependent, and it may be moderated by genetic factors. Factors contributing to the strength of the evidence derived from the cited systematic reviews include large sample sizes, the relative homogeneity of the findings, the presence of relationships between the dose/exposure and the risk, the studies having been controlled for co-founders, and the systematic reviews having assessed for publication bias. The primary literature reviewed by the committee confirms the conclusions of the systematic reviews, including the association between cannabis use and psychotic outcome and the dose-dependency of the effects, further bolstering the overall strength of evidence for our conclusions.

The limitations of the summarized studies include their reliance of self-report for cannabis use, issues with study designs (e.g., a lack of randomization), a lack of information on

[4] T carrying subjects have at least one allele with the polymorphism. G carrying subjects do not express the polymorphism. Genotype results of the subjects included: homozygote G/G, heterozygote G/T, and homozygote T/T genotype classes. Due to the low number of subjects with TT subjects, G/T and T/TT subjects were combined and compared to G/G carriers.

the frequency of use, patterns of long-term use, and possible confounding polysubstance effects. In addition, for the primary studies cited, some are also limited in terms of their sample sizes and controlling for confounders. Overall, the accumulated evidence is suggestive that cannabis use is associated with an increase in psychosis-related outcomes, as made evident in the discussion of Auther et al., 2015, and Valmaggia et al., 2014, above.

As noted in Box 12-1, the relationship between cannabis use, cannabis use disorder and psychoses may be multi-directional and complex. The committee found this to be consistent with their review of the summarized data demonstrating a strong and consistent association between cannabis use and the subsequent development of psychosis and psychotic disorders. In addition, it is noteworthy to state that in certain societies, the incidence of schizophrenia has remained stable over the past 50 years despite the introduction of cannabis into those settings (Kirkbride et al., 2012); however, the committee did not examine ecologic data (studies of concomitant time trends) to evaluate trends in cannabis consumption and diagnosis of psychosis over time. Multiple factors (including measurement of dose and frequency of cannabis consumption over decades, and patterns of diagnosis of psychosis) limit our ability to draw conclusions from such findings. Of note, future analysis of rates of psychosis in states with increased access to cannabis could be tracked to provide valuable information regarding potential causal relationships between cannabis use and psychosis.

CONCLUSION 12-1 There is substantial evidence of a statistical association between cannabis use and the development of schizophrenia or other psychoses, with the highest risk among the most frequent users.

Is There an Association Between Cannabis Use and the Course or Symptoms of Schizophrenia or Other Psychoses?

Systematic Reviews

Positive Symptoms One systematic review was identified assessing the effects of cannabis use on positive symptoms[5] in patients with psychotic disorders, but the researchers did not conduct a quantitative synthesis of the findings (Zammit et al, 2008). An additional systematic review (Szoke et al 2014) addressed the effects of cannabis on schizotypal symptom dimensions, however, the committee will only report on the conclusions reported by Zammit et al (2008) because it provides information about patients with psychotic disorders rather than schizotypy.

After their assessment of the literature, Zammit et al. (2008) found mixed evidence for the effects of cannabis use on positive symptoms in patients with psychotic disorders, with studies reporting statistically significant but small associations between cannabis use and the severity of positive symptoms. The authors searched multiple databases through November 2006, screened 15,303 references, and identified 13 cohort studies (n = 1,413) for their review. Studies were included if they were longitudinal or were case-control studies nested in longitudinal designs to assure that cannabis use was measured before outcome ascertainment. The authors excluded cohorts of individuals with dual diagnoses (psychosis and cannabis misuse or dependence) because of the limitations on comparisons to control groups. The authors assessed the quality of the studies by comparing the response rate at baseline, loss to follow-up,

[5] Positive symptoms of schizophrenia may include delusions, hallucinations, or abnormal motor behavior.

masking of outcome assessment, adjustment for baseline severity, adjustment for alcohol and other substances, and adjustment for confounders. Their quality assessment is reported in a summary table, and the authors noted that the most likely source of confounding would be the lack of adjustment for baseline severity and a lack of adjustment for alcohol and other substances in several of the studies. The authors did not report sample sizes, the age or sex of the study participants, or the definitions of cannabis use. The authors noted that several of the reviewed studies varied in their consideration of confounders, such as the use of other substances and baseline symptom severity, and that the lack of an association may be explained by a random misclassification of exposure data, particularly self-reports of cannabis use.

Negative Symptoms In the systematic review described above, Zammit et al. (2008) identified four studies (from the 13 cohort studies identified in the larger systematic review) that assessed the effects of cannabis use on negative symptoms[6] in patients with psychotic disorders. As described above, Zammit et al. (2008) did not conduct a quantitative analysis of findings, but in their review they found that cannabis use was not associated with negative symptom scores in three studies, but that it was associated with reduced negative symptoms scores in a fourth study. It should be noted that the fourth study did not control for confounders or baseline differences in symptoms.

Cognition Three systematic reviews were identified that assessed the relationship between cannabis abuse and dependence and cognition effects (e.g., disorganized thinking) in patients with psychotic disorders (Donoghue and Doody, 2012, Rabin et al 2011, Yucel et al., 2012). A distinctive feature of this group of studies is the varying approaches to separating cannabis use from other substances. While the systematic review by Donoghue and Doody reported on all types of illegal substance abuse, it identified a sub-group of three studies focusing on cannabis use. This is in contrast to the work of Yucel and colleagues who included studies with patient groups who abused substances other than cannabis, and by Rabin et al., who considered cannabis use without other substance use, but relied on cross-sectional studies only.

Donoghue and Doody (2012) conducted a search for relevant studies published between 1980 and October 2010, and from an initial pool of 7,075 studies, the authors selected 19 studies for further review. Three of the 19 studies focused on cannabis use. The three studies (n = 551) used the *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition* (DSM-IV) criteria to define cannabis abuse or dependence, and DSM-IV criteria to define schizophrenia or schizoaffective disorders. All three studies included inpatients and outpatients, as well as patients with a dual diagnosis. In their review of these studies, the authors found that cannabis users performed better on various measures of cognition, including verbal learning and memory, attention and psychomotor, and global cognitive factor tests, than non-cannabis users. The authors conducted a meta-analysis of the three studies and reported statistically significant associations between cannabis use and verbal learning and memory (Hedges g[7] = 0.351, 95% CI = 0.179–0.523), attention and psychomotor (Hedges g = 0.316, 95% CI = 0.144–0.488), and global cognitive factor (Hedges g = 0.237, 95% CI = 0.083–0.390). Tests of association with working memory and executive function were not statistically significant.

[6] Negative symptoms of schizophrenia may include diminished emotional expression, lack of interest or motivation to engage in social settings, speech disturbance, or anhedonia.

[7] Hedges g reports the unbiased estimate of the effect size (the standardized difference between two means). It is commonly used for small sample sizes.

Rabin et al. (2011) conducted a meta-analysis on 8 cross-sectional studies, published between 2005 and 2010, with a total of 942 patients with schizophrenia. The 356 cannabis users among those patients had a mean age of 28.7 years, 81.9 percent were male, and had a mean education of 11.4 years. 586 of the 942 patients were nonusers of cannabis and had a mean age of 32.4 years, 65.8 percent were male, and had a mean education of 12.2 years. Limited information was provided about the statistical analysis, and the authors reported moderate associations with cannabis users performing better on general cognitive ability and intelligence; selective, sustained and divided attention; and visual-spatial and constructional abilities.

Yucel et al. (2012) searched the literature for the period 1987–March 2010 and included studies where cannabis was the predominant substance used by patients. They identified 10 studies involving 572 patients with schizophrenia; the studies were stratified by lifetime versus current or recent use. From their review, Yucel et al. (2012) found that patients with established schizophrenia and a history of cannabis use showed better performance on tests assessing cognitive abilities than did patients who did not use cannabis. For example, the meta-analysis conducted on 10 studies to assess global cognition, resulted in a Cohen's d[8] of 0.35 (95% CI = 0.09–0.61; p = 0.009), showing small to moderate increases in performance in cannabis users compared to non-users. Other small to moderate statistically significant effects were observed, again showing better performance by cannabis users compared to non-users for processing speed, visual memory, and planning, despite the smaller number of studies available for these comparisons. The authors stated that tests for publication bias or heterogeneity were conducted, but these were only partially reported. No differences were reported for assessments of attention, verbal memory or working memory.

Primary Literature

Positive Symptoms In a 2004 case control study with schizophrenic patients, Rehman and Farooq (2007) determined that patients with cannabis abuse had higher rates of positive symptoms than non-users. Seddon et al. (2016), in a case control study examining cannabis use in the first year following a first-episode psychosis, found that cannabis use at baseline or the 1-year assessment was associated with greater severity of positive symptoms (as measured by the Positive and Negative Syndrome Scale [PANSS] 2.14; 95% CI = 1.41–2.88) and a decrease in global functioning (as measured by the Global Assessment of Functioning symptom scale (-3.27; 95% CI = -6.04 to -0.49)). In contrast, Barrowclough et al. (2013) found no association between cannabis use and positive symptoms in patients with non-affective psychotic disorders, as assessed by PANSS; adjusted coefficient = 0.07 95% CI = -0.21–0.34). Moreover, using a longitudinal analysis over 24 months, the researchers found that changes in cannabis dose did not predict changes in positive symptoms severity, even when patients became abstinent. In their study, the researchers conducted a cross sectional analysis of 160 patients with a clinical diagnosis of non-affective psychotic disorder and a DSM-IV diagnosis of drug and/or alcohol dependence or abuse. Notable strengths of this study are its dose-response analysis and its detailed quantification of cannabis use, with mean use in the sample being 4 days/week and average of 2.4 grams per day. However, the results were not adjusted for confounders, including other drug use.

Another study, Dubertret et al. (2006) conducted a cross-sectional analysis on 205 patients with schizophrenia (n = 121 with no substance abuse; n = 38 cannabis users) and found

[8] Cohen's d is an estimate of the effect size (the standardized difference between two means).

that after controlling for other substance use, no association between cannabis use and positive symptoms was evident. A cross sectional analysis by Tosato et al. (2013) (n = 311 patients), found no association between cannabis use and the severity of positive symptoms in a population of first-episode psychosis patients. Similarly, in a prospective, longitudinal, cross-sectional study by Barrowclough et al. (2015) found no specific association between cannabis dose and positive symptoms (n = 102; adjusted coefficient, 0.01; 95% CI = −0.24–0.25), and reductions in cannabis use during follow-up (longitudinal analysis up to 18 months) were not associated with improvements in positive PANSS symptoms in cannabis-using subjects after adjusting for confounders including other drug use (n = 65; adjusted coefficient, -0.12; 95% CI = −0.45–0.22). After adjustment for confounders, abstinence from cannabis (90 days preceding the assessment) was found to be related to improved global functioning (adjusted coefficient, 4.95; 95% CI = 0.46–9.44). After controlling for confounders, van Dijk et al. (2012) found no difference between cannabis users (n = 68) and non-users (n = 77) with schizophrenia with regard to the severity of baseline schizophrenia symptoms (p = 0.61; assessed by the Clinical Global Impression scale). The researchers also found no relationship between amount of cannabis used and the level of psychopathology (p = 0.676; as measured by PANSS).

Negative Symptoms Dubertret et al. (2006), using a cross-sectional analysis, found that after controlling for other drug substances, cannabis use was strongly associated with fewer negative symptoms of avolition—apathy (p = 0.0001), as compared to non-cannabis users. Barrowclough et al. (2013), also using a cross sectional analysis, found that previous 90-day cannabis use was not significantly associated with the severity of negative symptoms (adjusted coefficient, 0.12; 95% CI = -0.05–0.29). The longitudinal analysis of data from this cohort (up to 24 months) revealed no association between cannabis dose and negative symptom severity (adjusted coefficient, 0.18; 95% CI = -0.14–0.51). Similarly, a prospective longitudinal study by Barrowclough et al. (2015) found no association between cannabis dose and negative symptoms after adjustment for confounders including other drug use (adjusted coefficient, 0.28; 95% CI = -0.04–0.61. Seddon et al. (2016) found that cannabis use at baseline or the 1-year assessment was not associated with differences in negative symptoms relative to non-users (as measured by PANSS; -0.07; 95% CI = -1.11–0.97)).

Cognition Power et al. (2015) found no association between lifetime cannabis use or cannabis dependence and cognitive function after controlling for confounding variables including the onset of illness and co-morbid cognitive functioning in Australian patients with an established *International Classification of Diseases-10* (ICD-10) diagnosis of psychotic disorder. Sanchez-Torres et al. (2013) used a longitudinal study to examine the impact of lifetime and current cannabis use on cognition in 42 patients with schizophrenia and found a negative effect of longitudinal cannabis use specifically in the social cognition domain (Pearson correlation, -0.34; $p < 0.05$). Van Winkle et al. (2011) found that cannabis use before the onset of psychosis interacted significantly with the rs2494732 single nucleotide polymorphism of the AKT1 gene to affect patient reaction time and accuracy as measured by the Continuous Performance Test. Cannabis-using patients with the a priori vulnerability (i.e., homozygous for the polymorphism) were slower and less accurate on the CPT than non-users.

Discussion of Findings

With regard to the effects of cannabis use on positive symptoms the data are considered mixed. Studies report both worsening and no effect of cannabis use on positive symptoms in schizophrenia. The limitations observed in the reviewed studies included variable adjustment for other drug use and baseline symptom severity, issues with study design (observational), a reliance on self-reports, and variable analyses of cannabis use (i.e., dose/amount/frequency, current versus lifetime). However, these studies combined with human experimental studies demonstrating that cannabis can worsen positive symptoms in patients with schizophrenia were also considered when determining the strength of evidence. With regard to negative symptoms, the data reviewed were generally more homogenous with most studies reporting either an absence of association between cannabis use and negative symptoms, or else reduced negative symptoms in cannabis users. Variable adjustments for other drug use and baseline symptom severity were noted as limitations in some studies. Overall, the data provide support for the conclusion that cannabis use does not worsen negative symptoms in patients with psychotic disorders. With regard to cognition in patients with psychotic disorders, the data reviewed in the systematic reviews suggest better cognitive performance in some cognitive domains in patients with psychotic disorders and cannabis use disorders, and in patients with a history of cannabis use, as compared to patients with psychotic disorders and no cannabis use disorder diagnosis. The limitations of two of the systematic reviews, Yucel et al. (2012) and Rabin et al. (2011), include their study design (cross-sectional only), variable adjustments made for confounders, including other drug use, and variable definitions and inclusion criteria for cannabis using and non-using control groups. This study found better cognitive performance only in subjects with a lifetime history of cannabis use, but not recent cannabis use. The systematic review by Donoghue and Doody (2012) focused on longitudinal studies in schizophrenic subjects with and without co-morbid cannabis use and found that cannabis users performed better on some measures of cognition, including verbal learning and memory, attention and psychomotor, and global cognitive factor tests, than non-cannabis users. The three reviewed studies showed similar effects; however, the largest study was more precise and had narrower confidence intervals. Estimates for the size of the effect are small to moderate. The primary articles reviewed indicate more mixed results than the systematic reviews.

Overall, the totality of data favor the conclusion that a history of, but not recent, cannabis use is associated with statistically significant performance improvement on measures of cognitive function in patients with psychotic disorders. It is not clear how the difference in scores might translate with respect to overall improved outcomes in functioning beyond the test setting. Furthermore, other data do not support the notion that acute cannabis exposure improves cognitive performance in patients with psychotic disorders, as acute intoxication is associated with impaired cognitive performance in cognitive domains of learning, memory, and attention (see Chapter 11). Among the multiple potential explanations of the data indicating better performance on certain measures of cognition in patients using cannabis, is that these patients represent a higher-functioning subgroup of psychotic patients, or that cannabis users who achieve abstinence have better premorbid cognitive status. Additionally, it has been proposed that a history of cannabis use may have exerted neuroprotective effects in patients with psychotic disorders. Finally, we find insufficient data from which to draw conclusions regarding the effects of cannabis on risk for suicide in patients with psychotic disorders.

CONCLUSION 12-2

12-2(a) There is moderate evidence that, among individuals with psychotic disorders, there is a statistical association between a history of cannabis use and better cognitive performance.

12-2(b) There is limited evidence of a statistical association between cannabis use and an increase in positive symptoms of schizophrenia (e.g., hallucinations) among individuals with psychotic disorders.

12-2(c) There is moderate evidence for no statistical association between cannabis use and worsening of negative symptoms of schizophrenia (e.g., blunted affect) among individuals with psychotic disorders.

BIPOLAR DISORDER

Bipolar and related disorders are categorized by episodes and/or symptoms of mania, hypomania, and depression (APA, 2013). The risk factors for developing bipolar disorder are not clear; however, research suggests that brain structure, genetics, and family history may contribute to its onset (NIMH, 2016). Given that cannabis is reportedly the most commonly used illicit drug by individuals with bipolar disorders (Zorrilla et al., 2014), it is worthwhile for this report to explore the potential association between cannabis use and the development and course of bipolar disorder.

Is There an Association Between Cannabis Use and the Development of Bipolar Disorder or Mania?

Systematic Reviews

The committee identified one systematic review, Gibbs et al., 2015, that assessed the association between cannabis use and bipolar disorder or mania. The authors searched multiple databases for English language studies published through 2014 and included studies that were experimental, prospective, cohort or longitudinal. The overall search strategy yielded six studies with a total of 14,918 participants that met the inclusion criteria.Two of these studies, published in 2006 (n = 4815) and 2010 (n = 705) were used in the analysis. The meta-analysis showed an association between cannabis use and new onset of manic symptoms in individuals without pre-existing bipolar disorder (OR, 2.97; 95% CI = 1.80–4.90). However, the researchers did not report information about the patient characteristics, the total number of subjects, age, gender, cannabis form, the ascertainment of mania symptoms, or other features of the two studies. Furthermore, due to the low number of studies that contributed to their research findings, the authors describe their conclusions as prelimnary and tentative.

Primary Literature

Data from the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC)[9] (Feingold et al., 2014) found that that any past-year use of cannabis was associated with the onset of bipolar disorder (OR, 2.24; 95% CI = 1.44–3.51) in unadjusted analyses. However, after adjusting for sociodemographic and clinical variables, the association was attenuated and no longer statistically significant (aOR, 1.17; 95% CI = 0.65–2.11).

Using the same NESARC dataset as Feingold, Cougle and colleagues (2015)[10] found that the risk of a past-year bipolar disorder diagnosis was elevated in regular (e.g., weekly use) cannabis users at Wave 2 follow-up: (OR, 1.37; 95% CI = 1.11–1.69). Cougle and collaborators reminded readers about the correlational nature of the study design and noted that causality could not be inferred from their conclusions. They also cautioned that the increased risk in bipolar disorders might be due to augmenting the psychotic features in frequent cannabis users (i.e., manic symptoms) that need further investigation. Also, Cougle and collaborators warned that in adjusting for other psychiatric comorbidities, they only adjusted for those that fulfilled diagnostic thresholds, but not other psychiatric symptoms that could explain the relationships of interest.

Discussion of Findings

Overall there is some evidence to support the association between cannabis use and the increased incidence of bipolar disorders. Although there is support for this association, more information is needed on the potential mediators that could explain the relationship as well as whether the risk is likely to occur only in conjunction with the use of other substances such as alcohol or nicotine. For example, panel studies that have evaluated the relationship found the magnitude of the relationship to be similar, but once alcohol or other substances were adjusted for in the statistical models, the associations diminished or become insignificant. This suggests that the constellation of behaviors that includes the use of cannabis, alcohol, and other substances might be all play roles in the risk for bipolar disorders, with those different roles being difficult to disentangle. See Box 12-1 for additional discussion on the complex relationship between substance use and mental health disorders.

CONCLUSION 12-3 There is limited evidence of a statistical association between cannabis use and the likelihood of developing bipolar disorder, particularly among regular or daily users.

[9] The NESARC is a longitudinal and nationally representative survey. Data on psychiatric disorders and quality of life were assessed from two waves of subjects. Wave 1: 2001–2002; n = 43,093, Wave 2: 2004–2005; n = 34,653.

[10] Cougle et al. (2015) and Feingold et al. (2104) used the same dataset, but they chose to use different outcome variables: one analyzed past-year cannabis use, while the other examined past- year weekly cannabis use.

Is There an Association Between Cannabis Use and the Course or Symptoms of Bipolar Disorder?

Systematic Reviews

The committee identified Gibbs et al. (2015) as a systematic review that assessed the relationship between cannabis use and the course, symptoms, or other endpoints in individuals with bipolar disorder. Gibbs et al. (2015) concluded, based on their narratives of three studies, that cannabis use may worsen the course of bipolar disorder by increasing the likelihood, severity or duration of manic phases.Their narrative summarizes the findings of the three studies: the duration of active cannabis use was associated with duration of mania syndrome/symptoms; cannabis use within a quarter (3-month time period) was associated with manic symptoms or episodes; and a report of "any cannabis use" was associated with mania symptoms over 1 year in a sample of 3,426 in- and outpatients patients. The three studies were published in 2000, 2008, and 2009. The studies used clinical samples of 50 new-onset bipolar patients aged 16–54, 166 first-episode DSM-IV bipolar I patients aged 18–72, and 3,426 bipolar in- and outpatients and outpatients (age not reported). No other information (gender, country, etc.) about the study populations was reported.

Primary Literature

Zorrilla and colleagues (2015), using the European Mania in Bipolar Longitudinal Evaluation of Medication study (n = 1,922 patients) showed that previous users of cannabis had similar outcomes to never users (all $p > 0.05$) in terms of bipolar disorders, whereas current users had lower rates of recovery ($p = 0.004$) and remission ($p = 0.014$) and higher rates of recurrence of bipolar disorder ($p = 0.014$). They also demonstrated that the median time to remission was longer in the current cannabis use group (571 days, 95% CI = 539–588) compared with the other two groups (never users: 236 days, 95% CI = 209–345; previous users: 189 days, 95% CI = 1.5–357), while the times to relapse and recurrence were shorter in current use group. Using Cox regression models, Zorrilla and colleagues found that cannabis use (versus no use) was associated with time to recovery (HR, 0.53; 95% CI = 0.298–0.959), relapse (HR, 1.61; 95% CI = 1.116–2.316), and recurrence (HR, 1.67; 95% CI = 1.206–2.320). However, when alcohol and other substance use variables were included in the model as confounders, only the time to recurrence remained significantly associated with cannabis use (HR, 1.47; 95% CI = 1.030–2.092).

Using the NESARC data with two waves, Feingold et al. (2014) examined the relationship between weekly cannabis use and almost daily cannabis use and found a steady association with the incidence of mania/hypomania symptoms in all adjusted models (OR, 2.47; 95% CI = 1.03–5.92). In contrast, daily cannabis use was not associated with mania/hypomania symptoms (OR, 0.52, 95% CI = 0.17–1.55).

Discussion of Findings

The evidence on the association between cannabis use and the course and symptoms in patients with bipolar disorder is modest, but it is suggestive that cannabis use moderates the

course of bipolar disorder by increasing the time to recovery, relapse, and recurrence of manic phases. As discussed in the section above, when adjustments for alcohol and other substance use variables are included in the model as confounders, only the time to recurrence remains as significantly associated to cannabis use. There is also moderate evidence that weekly cannabis use to almost daily cannabis use can lead to the onset of mania/hypomania symptoms in adjusted models, but there is less evidence of this association for daily users of cannabis. The authors report that given the inconclusive nature of the relationship between very frequent cannabis use (daily/almost daily) or less than weekly cannabis use and the onset of mania/hypomania symptoms in adjusted models (i.e., dose–response), other factors that have not been identified might mediate the relationship. The authors suggest that part of the problem of being able to find a conclusive relationship between the frequency of cannabis use and mania or hypomania symptoms might be due to the resemblance of mania and hypomania symptoms to psychotic symptoms, making it difficult to discriminate between these types of symptoms. It should also be noted that in some of the studies reviewed above, the analyzed patient populations were undergoing treatment for bipolar disorder, adding an additional layer of limitations to the research findings.

In reviewing the literature on the relationship between cannabis use and bipolar disorder, the committee identified various limitations in the studies discussed above, including a lack of biogenetic covariates that could relate to both cannabis use and bipolar disorders, as well as other psychological symptoms that are not adjusted in these studies. Many of these studies do not take into account the variance among the subtypes of cannabis or in the potency or route of administration, all of which that could lead to difference in results. Also, the lack of precision in measuring the frequency of cannabis use at baseline and in measuring follow-up data remains a problem.

CONCLUSION 12-4 There is moderate evidence of a statistical association between regular cannabis use and increased symptoms of mania and hypomania in individuals diagnosed with bipolar disorders.

DEPRESSION

Depression is one of the nation's most common mental health disorders (ADAA, 2016). Across the many depressive disorders that exist (e.g., persistent depressive disorder, major depressive disorder, pre-menstrual dysphoric disorder) there are common symptomatic features of feelings of sadness, emptiness, or irritable mood, accompanied by somatic and cognitive changes that affect the individual's capacity to function (APA, 2013, p. 155). The endocannabinoid system is known to play a role in mood regulation (NIDA, 2015); and therefore, the committee decided to explore the association between cannabis use and depressive disorders or symptoms.

Is There an Association Between Cannabis Use and the Development of Depressive Disorders or Symptoms?

Systematic Reviews

The committee identified two systematic reviews that assessed the association between cannabis use and the risk of developing depressive disorders or symptoms (Lev-Ran et al., 2013; Moore et al., 2007). The most recent systematic review is discussed.

Lev-Ran et al. (2013) searched the published literature through 2012 and included studies with: population-based data that were collected longitudinally and prospectively; an exposure variable referring specifically to cannabis use (not "substance use"); outcome measures that referred specifically to depression (and not, for example, mixed anxiety–depressive symptoms); the outcome variable (depression) controlled for at baseline, or individuals with baseline depression being excluded; and data either presented as odds of developing depression following cannabis use or that allowed the odds ratio (OR) to be calculated. When the authors identified multiple studies reporting on the same population cohort at different time points, only one study (the most recent) reporting on the respective cohort was included. The authors identified 14 studies published between 1977 and 2012. Seven were conducted in the United States, and one each were conducted in Australia, Canada, Colombia, the Netherlands, New Zealand, Norway, and Sweden. Sample sizes ranged from 736 to 45,087, with 10 of the samples having 1,000 or more participants. The ages of patients at cannabis assessment included high school age, subjects ages 12–17 or 12–16, and older groups (18–64). A wide range of measures were used to assess cannabis use: (i.e. any cannabis use in the previous 30 days, any previous cannabis use, cannabis use disorder, cannabis use one or more times per month, any cannabis use in the previous year or heavy use (at least once per week in the previous month), at least five previous occasions of cannabis use or heavy use (at least weekly), any use in the previous 6 months, or than 4 occasions of use per month in a 5-year period). Studies also varied in the definition of comparison groups with some studies contrasting any cannabis use to no cannabis use, and other studies comparing "heavy cannabis use" to a group with some or no cannabis use. Thus, the comparison group (lower level of exposure to cannabis) in the latter studies included non-users, as well as individuals using cannabis less than weekly, or individuals not having a cannabis use disorder. Studies varied in their approaches to adjust for confounding factors, ranging from none to adjustment for more than 20 variables. One half of the studies accounted for other types of substance use and or mental health issues as potential confounders. The analysis showed that cannabis use was associated with a small increase in risk for depressive outcome (pOR, 1.17; 95% CI = 1.05–1.30). The analysis further revealed a dose–response relationship, with a slightly higher OR observed in seven studies comparing heavy cannabis use to non-cannabis users (pOR, 1.62; 95% CI = 1.21–2.16).

Primary Literature

Although several primary research studies found a positive association, the confounding factors of polydrug use or unspecified cannabis use made it difficult for the committee to make conclusions on the overall findings (Brook, 2016; Nkansah-Amankra, 2016; Rasic, 2013). Additional studies reviewed provided mixed findings on the association between cannabis use and depression or depressive symptoms (Crane, 2015; Gage, 2015; Silins, 2015; Wilkinson,

2016). A consideration of the confounding factors led to several of these mixed findings. For example, Sillins et al. (2015) published an analysis of interview data from three longitundal studies from Australia and New Zealand. The investigators sought to determine the association between the maximum frequency of cannabis use before age 17 and seven developmental outcomes, including depression. The number of participants varied by the outcome assessed, but ranged from n = 2,537 to 3,765. Because this was an integrated study, the outcomes of depression were assessed by different measures (i.e., Composite International Diagnostic Interview, Clinical Interveiw Schedule, and short-form Depression Anxiety Stress Scale) and at different ages across the three studies. The investigators of this study created a dichotomous measure of moderate or severe depression in the past week to the past month between ages 17 and 25 years. Using combined data adjusted for study-specific effects, the investigators found a significant asssociation between adolescent cannabis use and the study's measure of depression (less than month use, OR, 1.12; 95% CI = 1.01–1.25; monthly or more, OR, 1.26; 95% CI = 1.02–1.56; weekly or more, OR, 1.42; 95% CI = 1.03–1.94; daily use OR, 1.59; 95% CI = 1.04–2.42), as well as an apparent potential dose–response relationship. However, after adjusting for relevant covariates in the analysis, this association became insignificant and negligible in size (less than monthly use, aOR, 1.01; 95% CI = 0.85–1.19; monthly or more, aOR, 1.01; 95% CI = 0.72–1.42; weekly or more, aOR, 1.02; 95% CI = 0.61–1.69; daily use aOR, 1.02; 95% CI = 0.52–2.01). The authors noted that the confounding factors spanning the individual's background and functioning as wll as parental and peer factors likely affected the change in the research findings.

Discussion of Findings

The evidence reported suggests that cannabis use, and particularly heavy cannabis use, is associated with a small increase in the risk of developing depressive disorders. This evidence is supported by a good quality, recent systematic review that included 10 longitudinal studies with sample sizes between 700 and 45,000. Although the supplemental studies from the primary literature reported mixed findings, the committee concludes that there is a strong enough evidence base to support the conclusion that there is an association between cannabis use and a small increased risk (pOR of 1.17; Lev-Ran, 2013) of developing depressive disorders, which increases with increased frequency of use (OR of 1.62; Lev-Ran, 2013) The possible relationship between heavy cannabis use and the development of depressive disorders or symptoms needs to be further explored.

Given that these relationships are associational and not necessarily causal, it is important to note possible alternative explanations for the mixed findings. For example, within the literature, a reverse association between cannabis use and depressive disorders has been documented, and the relationship may be bi-directional (Horwood et al., 2012; Wilkinson et al., 2016). This complex scenario is consistent with the known protective roles of the endocannabinoid system in the control of mood and affect, and with the propensity of cannabinoid receptors to undergo desensitization following prolonged activation. See Box 12-1 for an additional discussion on this topic.

To review the research potential therapeutic effects of cannabis or cannabinoids on major depression disorder, please refer to Chapter 4: Therapeutics.

CONCLUSION 12-5 There is moderate evidence of a statistical association between cannabis use and a small increased risk for the development of depressive disorders.

Is There an Association Between Cannabis Use and the Course or Symptoms of Depressive Disorder?

Systematic Reviews

The committee did not identify a good- or fair-quality systematic review that reported on the association between cannabis use and the course, symptoms, or other endpoints in individuals with a depressive disorder.

Primary Literature

The committee did not identify any good-quality primary literature that reported on the association between cannabis use and the course, symptoms, or other endpoints in individuals with a depressive disorder, and that were published subsequent to the data-collection period of the most recently published good- or fair-quality systematic review addressing the research question.

CONCLUSION 12-6 There is no evidence to support or refute a statistical association between cannabis use and changes in the course or symptoms of depressive disorders

SUICIDE

Suicide is the act of purposely taking one's own life. It is the 10th most common cause of death in the United States, with an estimated 13 suicidal deaths occur per 100, 000 individuals in the United States, and is often related to mental illness, substance abuse, or a major stressful event (CDC, 2014; MedlinePlus, 2016). Cannabis is widely used for both medical and recreational purposes (Azofeifa et al., 2016), and therefore, there is a public health interest to evaluate the possible association between cannabis use and suicide, suicidal attempts, and suicidal ideation.

Is There an Association Between Cannabis Use and Suicide, Suicide Attempts, and Suicidal Ideation?

Systematic Reviews

Two systematic reviews were identified that assessed the association between cannabis use and suicidal ideation, attempts, and suicide (Borges et al., 2016; Moore et al., 2007). We report here on the most recent one. Borges et al. (2016) conducted a systematic review to address multiple questions concerning acute and chronic cannabis use, suicidal ideation, suicidal attempts, and suicide. The authors reported the databases searched and their search terms, but they did not report the number of citations screened or the reasons for exclusions. The term "any

cannabis use" was defined as: life-time use, use before or at age 15, ever used, any use in past 30 days, or any use in the last year. "Chronic use" was referred to as: cannabis use patterns, symptoms of cannabis use disorder, and heavy cannabis use. "Heavy cannabis use" was defined as: used 40 or more times, DSM-IIIR abuse/dependence, ≥6 times/month, >11 times in past year, >10 times, or daily.

The authors reviewed 12 studies that were relevant to the committee's research question. Their meta-analysis of six studies showed that any cannabis use was associated with an increased risk of suicidal ideation (pOR, 1.43; 95% CI = 1.13–1.83). Similarly, a review of five studies showed that heavy cannabis use was also associated with a larger increase of suicidal ideation (pOR, 2.53; 95% CI = 1.00–6.39). The six studies included in the meta-analysis of any cannabis use and suicide ideation were published between 1997 and 2014 and conducted in Canada, New Zealand, Norway, and the United States (four studies) in populations of male and female young adults or adolescents. The five studies included in the meta-analysis of heavy cannabis use and suicidal ideation were published between 1997 and 2013 and conducted in Canada, New Zealand, Norway, and the United States (two studies) in male and female populations of all age groups.

The authors also assessed another subset of six studies to determine the association between any cannabis use and suicide attempts, reporting a pooled odds ratio of 2.23 (95% CI = 1.24–4.00). The studies used reported on male and female adolescents or young adults in Canada, Ireland, and the United States (four studies). A review of a third subset of six studies found a higher risk of suicide attempt associated with heavy cannabis use (pOR, 3.20; 95% CI = 1.72–5.94). These six studies reported on male and female adolescents, young adults, or adults in Canada, New Zealand/Australia (two studies), Norway, and the United States (two studies).

The researchers reported that any cannabis use was associated with an increased risk of death by suicide (pOR, 2.56; 95% CI = 1.25–5.27), based on a meta-analysis of four non-overlapping studies. The studies included two case-control studies and two longitudinal studies published between 2003 and 2012 which were conducted in the United States, Colombia, Denmark, and Sweden; the studies were carried out in young adults and in all age groups, in males and females, and in male-only study groups. Interestingly, the one study restricted to males only showed no association of cannabis with suicide, but the other studies, which used mixed groups of males and females, did show an association of cannabis with suicide.

Primary Literature

The committee identified one recent primary article published in 2016 (Shalit et al., 2016) that reported on the association between cannabis use and the risk of suicidality (suicidal ideation and suicide attempt). Shalit and collaborators presented their results using a general population sample of the NESARC (n = 34,653; 963 cannabis users versus 30,586 non-users). They found that in the general population, any cannabis use in Wave 1 (baseline) was not statistically significantly associated with increased risk for developing suicidality in Wave 2 (follow-up) (aOR, 1.56; 95% CI = 0.98–2.46). However, when the results were stratified by gender, the researchers found significant differences in risk for suicidality. Among men, any cannabis use was significantly associated with the incidence of suicidality in fully adjusted models (aOR, 1.91; 95% CI = 1.02–3.56) but not for women (aOR, 1.19; 95% CI = 0.64–2.20). The magnitude of the relationship with the 3-year incidence of suicide ideation is larger in men (aOR, 4.28; 95% CI = 1.32–13.82) who are daily cannabis users, but this pattern is not observed

for women (aOR, 0.75; 95% CI = 0.28–2.05). However, in adjusted models neither cannabis use (aOR, -1.91; 95% CI = 0.85–4.28), nor daily cannabis use (aOR, 1.13; 95% CI = 0.42–3.05) was statistically significantly associated with the incidence of suicide attempts. Another finding of importance was that sex moderated the association between cannabis use, particularly daily use, and suicide attempts, with a significantly increased dose–response relationship in men (any cannabis use OR, 3.35; 95% CI = 1.07–10.47; daily cannabis use OR, 32.31; 95% CI = 2.59–402.88). However, there are several limitations, including that suicidality was only assessed in participants who reported a 2-week period of depressed mood or anhedonia, so the results might underestimate the effect for those that have suicidal ideation or suicidal attempts without these symptoms. Other limitations include the use of dichotomous response categories for suicidality when there is some evidence that additional changes to the measures are needed, the lack of adjustment for some early traumatic life events associated with suicidality, and the lack of adjustments for psychotic disorders.

Discussion of Findings

The evidence reported suggests that any cannabis use is related with increased suicidal ideation, augmented suicide attempts, and greater risk of death by suicide. The studies presented demonstrate evidence of a dose–response effect, with heavy cannabis use being associated with a higher risk of suicidal ideation and suicidal attempts. Additionally, sex differences emerged from the research findings related to suicidality (Shatit et al., 2016) and death by suicide (Borges, 2016). These sex differences may have occurred due to differences in where the study samples were recruited (e.g., Australia, Canada, Denmark, New Zealand, Norway, Sweden, United States, etc.) or how the data were assessed. This might suggest that sample composition, gender, and the type of assessment could matter when examining these associations between cannabis use and suicidality and suicide completion.

Although the evidence seems to support a relationship between cannabis use and suicidality, particularly heavy cannabis use and suicidality, the limitations of the literature temper such findings. Several limitations should be noted including the lack of homogeneity in the measurement of cannabis exposure, the lack of systematic controls for known risk factors, the short period of observation for suicidality, the variability in the covariates used to adjust for confounders, the differences in the dose–response analyses, and problems of small sample size. Additionally, as reported by the authors, some studies adjust for alcohol and other comorbidities, while in other studies there is no report of such adjustments. There is a strong need for new studies that to discriminate between the acute and chronic use of cannabis and between suicidal ideation, suicide attempts and completed suicides.

CONCLUSION 12-7

12-7(a) There is moderate evidence of a statistical association between cannabis use and increased incidence of suicidal ideation and suicide attempts, with a higher incidence among heavier users.

12-7(b) There is moderate evidence of a statistical association between cannabis use and increased incidence of suicide completion.

ANXIETY

Anxiety disorders share features of excessive fear and anxiety, which induce psychological and physical symptoms that can cause significant distress or interfere with social, occupational, and other areas of functioning (APA, 2013). In a given year, an estimated 18 percent of the United States adult population will suffer from symptoms associated with an anxiety disorder (NIMH, n.d.). Given the role of the endocannabinoid system in mood regulation, it is worthwhile for this report to explore the relationship between anxiety and cannabis.

Is There an Association Between Cannabis Use and the Development of Anxiety Disorders?

Systematic Reviews

One systematic review was identified that assessed the relationship between cannabis use and anxiety disorders (Kedzior and Laeber, 2014). The authors searched two databases for articles published through 2013 to identify studies that had been conducted in non-institutionalized populations, with anxiety diagnoses based on DSM/ICD criteria, with odds ratios or data sufficient for the calculation of effects, and with comparison data from healthy non-users. They then identified five studies that examined cannabis use at baseline and anxiety at follow-up. The five studies were all longitudinal, published between 1996 and 2013, and conducted in Australia, Colombia, the Netherlands, New Zealand, and the United States. Sample sizes were more than 2,000 or greater in four studies and over 12,000 in the fifth study. Four studies were of adolescents and a fifth studied the general population (age unspecified). The five studies adjusted for confounders such as demographics, prior anxiety disorder diagnosis, alcohol and tobacco use, and other mental health problems at age 15. In their review of the five studies, Kedzior and Laeber (2014) found that cannabis use at baseline was associated with the developmment of symptoms of anxiety at follow up (OR, 1.28; 95% CI = 1.06–1.54), after adjusting for confounders (e.g., other substance use, psychiatric comorbidity, certain demographics).

Primary Literature

In a longitudinal U.S. study of a nationally representative sample of adults 18 years or older (NESARC; n = 34,653), Blanco and colleagues (2015) investigated the prospective associations of cannabis use in the past 12 months (Wave 1; years 2001–2002) with anxiety disorders 3 years later (Wave 2; years 2004–2005) and adjusted for socio-demographic characteristics, family history of substance use disorder, disturbed family environment, childhood parental loss, low self-esteem, social deviance, education, recent trauma, past and present psychiatric disorders, and respondent's history of divorce. The researchers found that cannabis use in the 12 months preceding the survey was not associated with an increased prevalence of anxiety disorders (OR, 1.0; 95% CI = 0.8–1.2) after adjustments for covariates. The researchers also reported no significant relationship of cannabis use (Wave 1) with the prevalence of panic disorder (OR, 0.8; 95% CI = 0.5–1.2), social anxiety disorder (OR, 1.2; 95% CI = 0.8–1.8), specific phobia (OR, 0.9; 95% CI = 0.7–1.2) or generalized anxiety disorder (OR,

1.0; 95% CI = 0.7–1.4) assessed 3 years later (Wave 2). The researchers also found no significant relationship between cannabis use and incident anxiety disorders (aOR, 0.9; 95% CI = 0.7–1.1). However, they did find that an increased frequency of cannabis use was related with significantly increased odds of incident social anxiety disorder (OR, 1.8; 95% CI = 1.1–2.8). Some of the limitations of this study are that cannabis use was ascertained by self-report, causality could not be established because of the possibility of residual confounding, and the follow-up period was limited to 3 years.

Feingold and colleagues (2016) used the same dataset as Blanco et al. (2015), NESARC, and also found no association of cannabis use with the increased incidence of any anxiety disorder (aOR, 1.12; 95% CI = 0.63–0.98), after adjusting for covariates. However, they did find a statistically non-significant association between daily or almost daily use of cannabis at Wave 1 (baseline) with the incidence of social anxiety at follow-up 3 years later (aOR, 1.98; 95% CI = 0.99–6.98). This relationship was found to be significant in older adults (aOR, 2.83; 95% CI = 1.26–6.35) but not for younger adults (aOR, 1.76; 95% CI = 0.44–6.98). They also found a significant relationship between cannabis use disorder at baseline and incident social anxiety disorder among young adults (aOR, 2.45; 95% CI = 1.19–5.06) but not older adults (aOR, 1.38; 95% CI = 0.58–3.25). No other associations between cannabis use disorder and other anxiety disorders proved to be significant after adjustment for covariates.

Cougle et al. (2015) also used the NESARC to examine past-year regular cannabis use (defined as at least weekly use) and current and prospective presence of anxiety disorders 3 years later. These authors found no association (OR, 1.09; 95% CI = 0.90–1.32) in the prospective analyses that adjusted for psychiatric comorbidity and sociodemographic factors. However, when looking at specific anxiety disorders, Cougle and colleagues report finding a relationship between regular cannabis use and an increased risk of developing panic disorder with agoraphobia (OR, 1.56; 95% CI = 1.11–2.19) and social phobia (OR, 1.89; 95% CI = 1.54–2.32). As with other studies using the NESARC, the authors emphasize the non-randomized nature of the study design, the possibility that the study was underpowered to find certain relationships and the relatively short time period of observation.

Bechtold and colleagues (2015), using data from the oldest cohort of the Pittsburgh Youth Study, found that there were no differences among cannabis trajectory groups (categorized as low/non-users, adolescence-limited users, increasing users, and early onset chronic users) related to a lifetime diagnosis of anxiety disorders for black or white men after controlling for confounders (i.e., socioeconomic status, co-occurring use of other substances, physical and mental health problems that predated cannabis use, and access to medical care). In this study cannabis use was evaluated with the Substance Use Questionnaire, with respondents (who were from ages 15 to 26) initially indicating the number of days they had used cannabis in the previous 6 months and then, in each of the subsequent 10 annual follow-ups, reporting their use in the previous year. At age 36, respondents were assessed with the Diagnostic Interview Schedule to determine whether they had ever met the criteria for an anxiety disorder, and an analysis shows that the patterns of cannabis use from adolescence to young adulthood were not related to anxiety disorders. However, the authors mentioned several limitations, including the possibility of selection effects, the fact that cannabis use was determined by self-report, and the use of a limited sample that used cannabis from one geographic area and only included white and black men, implying that the results might not be generalizable to the general population. A recent study by Gage and colleagues (2015) found similar results. Using data from the Avon Longitudinal Study of Parents and Children (a UK birth cohort study), they found no evidence of

an association between cannabis use at age 16 and anxiety disorder at age 18 (aOR, 0.96; 95% CI = 0.75–1.24) after adjusting for pre-birth and childhood confounders (family history of depression, maternal education, urban living, IQ, borderline personality traits, victimization, peer problems, conduct disorder, and other substance use). The authors cite as limitations of their study the use of self-reported data, poor follow-up rates, and a limited power to detect small effects.

Brook and colleagues (2014), using the Harlem Longitudinal Developmental Study, assessed urban African American and Puerto Rican participants (n = 816) with four waves of data. In this study, Brook et al. (2014) found that participants with joint chronic cannabis, tobacco, and alcohol use were at an increased risk for generalized anxiety disorder in adulthood when compared to those with occasional alcohol use and no smoking and no cannabis use (OR, 4.35; 95% CI = 1.63–11.63). Again, this study had such limitations the use of self-reports, the use of proxies to determine earlier generalized anxiety disorder (depression in Time 1), and omitted variables (such as family substance use) that could have explained such relationships.

Additional work by Brook and colleagues (2016) reported on a large community-based sample (the Children and Adults in Community study, n = 973 at Time 1), examining comorbid trajectories of substance use which included conjoint chronic cannabis with chronic alcohol and cigarette use as predictors of generalized anxiety disorder. According to their multivariate logistic regression analyses, the Bayesian posterior probability (BPP) of members who were chronic or moderate to heavy users of cannabis, alcohol, and cigarettes, when compared to the patterns of those with occasional alcohol use and no smoking and no cannabis, had an adjusted odds ratio of 6.39 (95% CI = 2.62–15.56). This suggests that the conjoint use of cannabis with alcohol and cigarettes could have biological or psychosocial effects that increased the risk for generalized anxiety disorder. However, the study had several limitations in the present study, including having a mostly white sample from upstate New York and not including environmental or social variables that could explain the relationship under study such as family substance use or childhood psychiatric disorders.

Discussion of Findings

Studies examining the relationship between cannabis use and anxiety disorder show mixed results depending on whether they assessed the development of anxiety symptoms or the incidence of anxiety disorders, whether the explanatory variable was any cannabis use or cannabis use disorder, and whether there were adjustments for psychiatric comorbidity and sociodemographic factors. For example Kedzior and Laeber (2014) found that cannabis use at baseline was associated with the development of symptoms of anxiety at follow-up. In contrast, the 2015 report by Blanco and colleagues, the 2015 report by Cougle et al., and the 2015 report by Gage and colleagues all found no association between cannabis use and an increased prevalence of anxiety disorders in adjusted models. However, both Feingold and Blanco's studies did find an association of daily or almost daily use of cannabis at Wave 1 with the incidence of social anxiety disorder at follow-up 3 years later. Age seemed to moderate this relationship since it was found to be significant in older adults, but not in younger adults.

Some of the limitations of these studies are that cannabis use was ascertained by self-report, that causality cannot be established because of the possibility of residual confounding, that the follow-up period was limited to 3 years, and that there was a high loss in the follow-up and limited power to detect small effects. Further work needs to be done to examine why the

outcomes differ depending on whether the assessment is done with anxiety symptoms or anxiety disorders and whether the explanatory variable is any cannabis use or cannabis use disorder. Morever, studies are needed to determine whether psychiatric comorbidity, sociodemographic factors, or the conjoint use of cannabis with alcohol and cigarettes have biological or psychosocial effects that increase the risk for generalized anxiety disorder.

To review the research potential therapeutic effects of cannabis or cannabinoids on anxiety, please refer to Chapter 4: Therapeutics.

CONCLUSION 12-8

12-8 (a) There is limited evidence of a statistical association between cannabis use and the development of any type of anxiety disorder, except social anxiety disorder.

12-8 (b) There is moderate evidence of a statistical association between regular cannabis use and increased incidence of social anxiety disorder.

Is There an Association Between Cannabis Use and the Course or Symptoms of Anxiety Disorders?

Systematic Reviews

The committee did not identify a good- or fair-quality systematic review that reported on the association between cannabis use and the course, symptoms, and other endpoints of anxiety disorders.

Primary Literature

Recent work by Grunberg and collaborators (2015) conducted a prospective study to examine whether cannabis use (i.e., use during the past 30 days using the Time-Line Follow Back[11]) moderates the effects of temperament on the level of anxiety symptoms (measured with Achenbach's System of Empirically Based Assessment) within late adolescence and early adulthood (n = 338; 18 to 21-year-olds). While there was no association between cannabis use groups and anxiety symptoms among the college students in this prospective study, the researchers conducted simple slope analyses investigating the relationship between harm avoidance (characterized by heightened apprehension, shyness, pessimism, and inhibition of behaviors) and prospective anxiety symptoms for those subjects who rated low (zero days of use out of 30 days) and high (approximately 26 days of use out of 30 days) on cannabis use. The researchers found that harm avoidance measured at baseline was associated with more symptoms of anxiety measured a year later—but only for those low in cannabis use ($\beta = 0.15$, $t(329) = 2.69$, $p < 0.01$). When cannabis use was high, harm avoidance was unrelated to anxiety ($\beta = -0.14$, $t(329) = -1.40$, $p = 0.16$). Study participants with higher cannabis use showed a positive association between novelty seeking and anxiety symptoms ($\beta = 0.28$, $t(329) = 3.46$, $p = 0.001$) ,

[11] Authors describe this as a calendar-assisted structured interview that allows participants to indicate the amount of cannabis used on each day over the past month.

while those lower in cannabis use showed no relation between novelty seeking and anxiety symptoms ($\beta = -0.08$, $t(329) = -1.61$, $p = 0.11$).

Discussion of Findings

Grunberg and collaborators (2015) warned however, that the findings discussed above should be taken with caution since the mechanisms underlying these relations are still not clear. In addition, although this study uses a prospective design in which cannabis use and temperment are evalutated at baseline to predict anxiety symptoms 1 year later, it is limited to college students (ages 18–21) in only one assessment site. The authors emphasized that the reason that the relationship between cannabis use and anxiety symptoms is inconsistent is that there was no consideration of cannabis effects on other factors that influence anxiety symptoms such as temperament (i.e., levels of harm avoidance and novelty seeking) within the sample. Some limitations of this study are the use of a college student sample, the use of self-report for all assessments, and the use of correlational data although cannabis use and temperament were measured 1 year before anxiety symptoms. Given the limited evidence of studies that addrdess the realtionship between cananbis use and anxiety symptoms, these findings need to be replicated in larger samples with appropriate controls.

CONCLUSION 12-9 There is limited evidence of a statistical association between near daily cannabis use and increased symptoms of anxiety.

POSTTRAUMATIC STRESS DISORDER

Posttraumatic stress disorder (PTSD) falls within the broader trauma- and stressor-related disorders categorized by the DSM-V. The diagnostic criteria of PTSD include an exposure to a traumatic event (e.g., the threat of death, serious injury, or sexual violence) and exhibiting psychological distress symptoms that occur as a result of that exposure (e.g., intrusion symptoms, such as distressing memories; avoidance of stimuli that are associated with the traumatic event; negative alterations in mood and cognition; alterations in arousal and reactivity associated with the traumatic event; functional impairment) (APA, 2015, pp. 271–272). Given the known psychoactive effects of cannabis, the committee chose to explore the association between PTSD and cannabis use in this review.

Is There an Association Between Cannabis Use and the Development of PTSD?

Systematic Reviews

The committee did not identify a good- or fair-quality systematic review that reported on the association between cannabis use and the risk of developing PTSD.

Primary Literature

The committee did not identify any good-quality primary literature that reported on the association between cannabis use and the development of PTSD and that were published subsequent to the data-collection period of the most recently published good- or fair-quality systematic review addressing the research question.

CONCLUSION 12-10 There is no evidence to support or refute a statistical association between cannabis use and the development of posttraumatic stress disorder.

Is There an Association Between Cannabis Use and the Course or Symptoms of PTSD?

Systematic Reviews

The committee did not identify a good- or fair-quality systematic review that reported on the association between cannabis use and the course, symptoms, and other endpoints in PTSD.

Primary Literature

Gentes et al. (2016) found that past 6-month cannabis use was associated with increased PTSD severity (Clinician Administered PTSD Scale; global severity score; aOR, 1.30; 95% CI = 1.01–1.66), depressive symptoms (Beck Depression Inventory; aOR, 9.25; 95% CI = 1.13–1.75), and suicidality (Beck Depression Inventory Item 9; aOR, 4.63; 95% CI = 1.02–1.54) in a population of treatment-seeking veterans (n = 719). In this study, the odds ratios were adjusted for age, race, service era, and combat exposure, but not co-occurring substance use. Conversely, Manhapra et al. (2015) found improvements in PTSD symptoms (Mississippi Scale for Combat-Related Posttraumatic Stress Disorder), violence, and suicidality after 4 months of abstinence from cannabis relative to symptoms upon entry to the study in a large population of veterans admitted for an intensive PTSD program (n = 22,948). Villagonzalo et al. (2011), in a small study of patients (n = 80; mean age 35 years) participating in a methadone maintenance program, found that the severity of cannabis use was associated with the occurrence of certain PTSD symptoms, as measured by the Posttraumatic Stress Disorder Checklist–Civilian Version. Significant findings were identified for measures of re-experiencing (i.e., repeated disturbing dreams, χ^2 (2) = 6.351; p <0.05; physical reaction at reminder of event χ^2(2) = 7.053; p <0.05), hyperarousal (i.e., difficulty concentrating, χ^2(2) = 7.517; p <0.05; "super alert" χ^2(2) = 6.778; p <0.05; easily startled χ^2(2) = 9.645, p <0.01), and overall PTSD symptoms (1-way ANOVA, F(2,65) = 3.705; p <0.05).

Of interest, the committee also identified two large observational studies that compared the effects of cannabis to controls. Both studies enrolled predominately male veterans. A large cohort study (Wilkinson et al., 2015) examined outcomes for 2,276 veterans who received specialized intensive PTSD services between 1992 and 2011. Assessments for substance use and PTSD symptoms were taken at intake and at 4 months after discharge. Veterans who continued to use or started using cannabis after discharge had significantly worse PTSD symptoms and greater drug abuse than those who had never used or who had stopped cannabis use at 4 months after discharge (p <0.0001). Starters also had more violent behavior in the 4 months after

enrollment compared to other groups ($p < 0.0001$). There were no significant differences among the groups on employment status. A second study (Johnson et al., 2016), was a matched, case-control, cross-sectional study that was conducted in 700 veterans with probable PTSD, half of whom used cannabis and half who were non-users. Cannabis users and non-users did not differ on PTSD symptom severity ($p = 0.91$) or depression severity ($p = 0.07$), as measured by the PTSD Checklist-Civilian version and the Patient Health Questionnaire, respectively. However, cannabis users were more likely to experience suicidal ideation ($p = 0.04$) and reported more alcohol use ($p < 0.001$), as measured by the Paykel questionnaire, an alcohol Timeline Follow-back assessment, and the Alcohol, Smoking, and Substance Involvement Screening Test.

Discussion of Findings

Notable in this section relative to the others in this chapter is the lack of data addressing the key questions posed by the committee. For example, using the committee's specified search strategy, we found no relevant studies directly addressing the question of whether cannabis use is associated with an increased risk of PTSD. Of the relevant studies reviewed, cannabis use appears to be associated with more severe symptoms, but limited sample sizes were an issue in certain studies, and that issue, combined with the lack of adjustment for baseline symptom severity and other drug use and the examination of specialized patient populations, limits the strength of the conclusions that can be drawn. Overall, there is limited evidence for an association between cannabis use and increased PTSD symptom severity. The direction of the association is difficult to address, however. It has been argued that PTSD is a risk factor for cannabis use, and cannabis-using patients with PTSD often cite symptom-coping motives for cannabis use, suggesting that more severe PTSD may be driving patients to increase cannabis use in an effort to self-medicate.[12] In contrast, one study (Manhapra et al., 2015) found overall improvements in several symptom domains after 4 months of abstinence from cannabis, suggesting that cannabis use may be causally related to more severe PTSD symptoms. See Box 12-1 for a discussion on why it is often difficult to conclude causality in the associations between substance use and mental health.

To review the research potential therapeutic effects of cannabis or cannabinoids on PTSD, please refer to Chapter 4: Therapeutics.

CONCLUSION 12-11 There is limited evidence of a statistical association between cannabis use and increased severity of posttraumatic stress disorder symptoms among individuals with posttraumatic stress disorder.

BOX 12-2
Special Considerations for
Systematic Reviews of Observational Studies

The quality assessment of the systematic reviews in this chapter followed the research methods used throughout this report, within the context of the mental health literature. Of note,

[12] Studies examining PTSD as a risk factor for cannabis use and cannabis use disorders were identified and are discussed in Chapter 13 of this report.

the primary literature in mental health is mostly observational (in contrast to the literature base in other fields, such as therapeutics), and it was not possible to restrict systematic reviews and meta-analyses to those that synthesized evidence from randomized clinical trials (RCTs). Accordingly, the vast majority of the studies included in the systematic reviews and meta-analyses summarized in this chapter were observational studies. In addition to receiving a lower-quality grading in most systems, the methodologic science around the synthesis of observational data is less developed than it is for RCTs. The methodology used for systematic reviews and meta-analysis originates in the synthesis of data from RCTs, where methodology is highly standardized and structured. The synthesis of observational studies presents some challenges that have not been fully met, arising out of the greater variety in study design and conceptualization and the fact that there has been generally less experience in applying the methodology of systematic reviews and meta-analysis to observational literature. For example, none of the systematic reviews discussed in this chapter mentioned a protocol, an ethics review board, or a priori published research objectives, features that have become increasingly standard in systematic reviews of RCTs. Mallen and colleagues (2006, p.765) noted, "Quality assessment does not routinely occur in systematic reviews of observational studies. Where it does occur, there is no clear consensus in the method used." Brugha and colleagues (2012, p.450), in their review of systematic reviews and meta-analyses of observational psychiatric epidemiology studies, found "a number of deficiencies in the conduct and reporting of systematic reviews and meta-analyses of observational psychiatric epidemiology studies that could have serious implications for inferences drawn or decisions made on the basis of these reviews. There were frequent omissions of descriptions of method of abstraction, study quality, publication bias, bias and confounding."

In assessing the body of evidence, it is tempting to correlate the number of systematic reviews with the strength of the evidence; however, a number of concerns arise when synthesizing evidence across systematic reviews. When multiple systematic reviews address similar research questions or slight variations on similar research questions, it is likely that the reviews will include some of the same primary studies. For example, in the Schizophrenia section above, the three systematic reviews assessing the effects of cannabis on cognition—Donoghue and Doody (2012), Rabin et al. (2011), and Yucel et al. (2012)—each cite the primary study by Schnell et al. (2009). Another four studies were included in two of the systematic reviews on cognition. Given the use of some primary studies in more than one systematic review, the number of systematic reviews or meta-analyses may not, by themselves, indicate a stronger body of evidence.

While it is easy to understand how multiple reviews might identify similar studies, it is also of concern when reviews identify different studies. For example, the systematic review on cognition by Rabin et al. (2011) identified four studies that were not included in the reviews by Donoghue and Doody (2012) or by Yucel et al. (2012), and Yucel and colleagues (2012) also identified four studies that were not included in the other systematic reviews. This may be explained by a careful examination of the search strategies and inclusion/exclusion criteria, but the reasons for such differences are not always transparent.

Exposure measurement is always of concern in observational studies, and assessment of cannabis exposure is particularly fraught because of its illegal status (in most settings) and the reliance on self-report. Inherent difficulties in accurately assessing the exposure in terms of dose, specific chemicals, mode of intake, duration, frequency, and other variables result in the variability in definitions used to operationalize cannabis exposure. For example, systematic

reviews may include studies using greatly differing definitions such as non-dependent cannabis use in past week, a history of 0.5 g cannabis/day, cannabis use in the last 6 months, and >2g cannabis/week (Rabin et al., 2011). In addition, studies focusing on mental health may use medical records showing a diagnosis of cannabis use disorder as their exposure variable, either focusing on the disorder as a construct or as a proxy for cannabis exposure. This last approach allows researchers to consider the construct of cannabis use disorder, but it may result in exposure and non-exposure groups having similar intakes of cannabis. One can imagine a scenario where a person with a cannabis use disorder diagnosis has perhaps not consumed cannabis in the preceding week, month, or other time frame and where individuals without a diagnosis of cannabis use disorder had consumed cannabis in the same time frame. In this scenario, misclassification in both directions would result in biases towards the null, although differences between individuals with and without mental health diagnoses of cannabis use disorder could be expected to be associated with other differences observed in the study groups.

RESEARCH GAPS

As noted above, we found a paucity of studies relevant to our key questions. To address the research gaps relevant to PTSD, the committee suggests the following:

- More longitudinal studies to determine whether cannabis use is associated with an increased incidence of PTSD.
- In patients with PTSD, current data do not provide a very clear picture as to whether cannabis use affects PTSD symptoms. More longitudinal studies examining the effects of cannabis use on PTSD symptoms need to be conducted, with a specific emphasis placed on detailed measures of cannabis use (amounts, potency, routes of administration), controls for baseline symptom severity and the use of other substances, and temporality (excluding patients with cannabis use at study entry).
- From a cannabis therapeutics perspective, blinded, randomized, placebo-controlled studies in patients with PTSD need to be conducted to evaluate any potential therapeutic benefits of cannabis on PTSD symptoms and course.
- There is also a research need to investigate cannabis and cannabis constituents (tetrahydrocannabinol and cannabidiol) in animal models.

SUMMARY

This chapter outlines the committee's efforts to review the current evidence base for the association of cannabis use with prioritized mental health conditions. The health conditions reviewed in this chapter include: schizophrenia and other psychotic disorders; bipolar disorder; depression; suicide; anxiety; and posttraumatic stress disorder (PTSD). The committee formed a number of research conclusions related to these health endpoints; however, it is critically important that each of these conclusions be interpreted within the context of the limitations discussed in the Discussion of Findings sections. See Box 12-3 for a summary list of the chapter's conclusions.

A conclusion weighted as substantial was reached for the research question addressing the statistical association between cannabis use and the development of schizophrenia or other psychoses. As noted in the chapter's Discussion of Findings sections, there are common trends in the types of study limitations found in this evidence base. The most common are limitations in the study design (e.g., a lack of appropriate control groups, a lack of long-term follow-ups), variable analysis of cannabis use (i.e., dose/amount/frequency current versus. lifetime), small sample sizes, and research gaps in the studies of depression and PTSD. These limitations highlight the enormous amount of available opportunity to advance the current research agenda, in the hopes of providing comprehensive and conclusive conclusions on the potential therapeutic benefits and harms of cannabis or cannabinoid use.

BOX 12-3
Summary of Chapter Conclusions*

There is substantial evidence of a statistical association between cannabis use and:

- The development of schizophrenia or other psychoses, with the highest risk among the most frequent users (12-1)

There is moderate evidence of a statistical association between cannabis use and:

- Better cognitive performance among individuals with psychotic disorders and a history of cannabis use (12-2a)
- Increased symptoms of mania and hypomania in individuals diagnosed with bipolar disorders (regular cannabis use) (12-4)
- A small increased risk for the development of depressive disorders (12-5)
- Increased incidence of suicidal ideation and suicide attempts with a higher incidence among heavier users (12-7a)
- Increased incidence of suicide completion (12-7b)
- Increased incidence of social anxiety disorder (regular cannabis use) (12-8b)

There is moderate evidence of *no* statistical association between cannabis use and:

- Worsening of negative symptoms of schizophrenia (e.g., blunted affect) among individuals with psychotic disorders (12-2c)

There is limited evidence of a statistical association between cannabis use and:

- An increase in positive symptoms of schizophrenia (e.g., hallucinations) among individuals with psychotic disorders (12-2b)
- The likelihood of developing bipolar disorder, particularly among regular or daily users (12-3)
- The development of any type of anxiety disorder, except social anxiety disorder (12-8a)
- Increased symptoms of anxiety (near daily cannabis use) (12-9)
- Increased severity of posttraumatic stress disorder symptoms among individuals with posttraumatic stress disorder (12-11)

There is no evidence to support or refute a statistical association between cannabis use and:

- Changes in the course or symptoms of depressive disorders (12-6)
- The development of posttraumatic stress disorder (12-10)

* Numbers in parentheses correspond with chapter conclusion number.

REFERENCES

APA (American Psychiatric Association). 2013. *Diagnostic and statistical manual of mental disorders,5th ed*. Arlington, VA: American Psychiatric Publishing.

Auther, A.M., K. S. Cadenhead, R. E. Carrion, J. Addington, C. E. Bearden, T. D. Cannon, T. H. McGlashan, D. O. Perkins, L. Seidman, M. Tsuang, E. F. Walker, S. W. Woods, and B. A. Cornblatt. 2015. Alcohol confounds relationship between cannabis misuse and psychosis conversion in a high-risk sample. *Acta Psychiatrica Scandinavica* 132(1):60–68.

Azofeifa, A., M. E. Mattson, G. Schauer, T. McAfee, A. Grant, and R. Lyerla. 2016. National estimates of marijuana use and related indicators—National Survey on Drug Use and Health, United States, 2002–2014. *Morbidity and Mortality Weekly Report* 65(SS-11):1–25.

Barrowclough, C., R. Emsley, E. Eisner, R. Beardmore, and T. Wykes. 2013. Does change in cannabis use in established psychosis affect clinical outcome? *Schizophrenia Bulletin* 39(2):339–348.

Barrowclough, C., L. Gregg, F. Lobban, S. Bucci, and R. Emsley. 2015. The impact of cannabis use on clinical outcomes in recent onset psychosis. *Schizophrenia Bulletin* 41(2):382–390.

Bechtold, J., T. Simpson, H. R. White, and D. Pardini. 2015. Chronic adolescent marijuana use as a risk factor for physical and mental health problems in young adult men. *Psychology of Addictive Behaviors* 29(3):552–563.

Blanco, C., D. S. Hasin, M. M. Wall, L. Florez-Salamanca, N. Hoertel, S. Wang, B. T. Kerridge, and M. Olfson. 2016. Cannabis use and risk of psychiatric disorders: Prospective evidence from a U.S. national longitudinal study. *JAMA Psychiatry* 73(4):388–395.

Borges, G., C. L. Bagge, and R. Orozco. 2016. A literature review and meta-analyses of cannabis use and suicidality. *Journal of Affective Disorders* 195:63–74.

Brook, J. S., J. Y. Lee, E. Rubenstone, D. W. Brook, and S. J. Finch. 2014. Triple comorbid trajectories of tobacco, alcohol, and marijuana use as predictors of antisocial personality disorder and generalized anxiety disorder among urban adults. *American Journal of Public Health* 104(8):1413–1420.

Brook, J. S., C. Zhang, E. Rubenstone, B. A. Primack, and D. W. Brook. 2016. Comorbid trajectories of substance use as predictors of antisocial personality disorder, major depressive episode, and generalized anxiety disorder. *Addictive Behaviors* 62:114–121.

Brugha, T.S., R. Matthews, Z. Morgan, T. Hill, J. Alonso, and D. R. Jones. 2012. Methodology and reporting of systematic reviews and meta-analyses of observational studies in psychiatric epidemiology: Systematic review. *British Journal of Psychiatry* 200(6):446–453.

CDC (Centers for Disease Control and Prevention). 2014. *Injury Prevention and Control. Fatal Injury Reports*. https://www.cdc.gov/injury/wisqars/fatal_injury_reports.html (accessed December 15, 2016).

CBHSQ (Center for Behavioral Health Statistics and Quality). 2015. *Behavioral health trends in the United States: Results from the 2014 National Survey on Drug Use and Health* (HHS Publication No. SMA 15-4927, NSDUH Series H-50). http://www.samhsa.gov/data/sites/default/files/NSDUH-FRR1-2014/NSDUH-FRR1-2014.pdf (accessed December 5, 2016).

Colizzi, M., C. Iyegbe, J. Powell, G. Ursini, A. Porcelli, A. Bonvino, P. Taurisano, R. Romano, R. Masellis, G. Blasi, C. Morgan, K. Aitchison, V. Mondelli, S. Luzi, A. Kolliakou, A. David, R. M. Murray, A. Bertolino, and M. Di Forti. 2015. Interaction between functional genetic variation of DRD2 and cannabis use on risk of psychosis. *Schizophrenia Bulletin* 41(5):1171–1182.

Cougle, J. R., J. K. Hakes, R. J. Macatee, J. Chavarria, and M. J. Zvolensky. 2015. Quality of life and risk of psychiatric disorders among regular users of alcohol, nicotine, and cannabis: An analysis of the National Epidemiological Survey on Alcohol and Related Conditions (NESARC). *Journal of Psychiatric Research* 66-67:135–141.

Crane, N. A., S. A. Langenecker, and R. J. Mermelstein. 2015. Gender differences in the associations among marijuana use, cigarette use, and symptoms of depression during adolescence and young adulthood. *Addictive Behaviors* 49:33–39.

Di Forti, M., A. Marconi, E. Carra, S. Fraietta, A. Trotta, M. Bonomo, F. Bianconi, P. Gardner-Sood, J. O'Connor, M. Russo, S. A. Stilo, T. R. Marques, V. Mondelli, P. Dazzan, C. Pariante, A. S. David, F. Gaughran, Z. Atakan, C. Iyegbe, J. Powell, C. Morgan, M. Lynskey, and R. M. Murray. 2015. Proportion of patients in South London with first-episode psychosis attributable to use of high potency cannabis: A case-control study. *The Lancet Psychiatry* 2(3):233–238.

Donoghue, K., and G. A. Doody. 2012. Effect of illegal substance use on cognitive function in individuals with a psychotic disorder: A review and meta-analysis. *Neuropsychology* 26(6):785–801.

Dubertret, C., I. Bidard, J. Ades, and P. Gorwood. 2006. Lifetime positive symptoms in patients with schizophrenia and cannabis abuse are partially explained by co-morbid addiction. *Schizophrenia Research* 86(1-3):284–290.

EMCDDA (European Monitoring Centre for Drugs and Drug Addiction). 2016. Comorbidity of substance use and mental health disorders in Europe. Perspectives on Drugs. http://www.emcdda.europa.eu/system/files/attachments/2639/Comorbidity_POD2016.pdf (accessed November 24, 2016).

Feingold, D., M. Weiser, J. Rehm, and S. Lev-Ran. 2014.The association between cannabis use and mood disorders: A longitudinal study. *Journal of Affective Disorders* 172:211–218.

Feingold, D., M. Weiser, J. Rehm, and S. Lev-Ran. 2016. The association between cannabis use and anxiety disorders: Results from a population-based representative sample. *European Neuropsychopharmacology* 26(3):493–505.

Gage, S. H., M. Hickman, J. Heron, M. R. Munafo, G. Lewis, J. Macleod, and S. Zammit. 2015. Associations of cannabis and cigarette use with depression and anxiety at age 18: Findings from the Avon Longitudinal Study of Parents and Children. *PLoS ONE* 10(4): e0122896.

Gentes, E. L., A. R. Schry, T. A. Hicks, C. P. Clancy, C. F. Collie, A. C. Kirby, M. F. Dennis, M. A. Hertzberg, J. C. Beckham, and P. S. Calhoun. 2016. Prevalence and correlates of cannabis use in an outpatient VA posttraumatic stress disorder clinic. *Psychology of Addictive Behaviors* 30(3):415–421.

Gibbs, M., C. Winsper, S. Marwaha, E. Gilbert, M. Broome, and S. P. Singh. 2015. Cannabis use and mania symptoms: A systematic review and meta-analysis. *Journal of Affective Disorders* 171:39–47.

Grunberg, V. A., K. A. Cordova, L. C. Bidwell, and T. A. Ito. 2015. Can marijuana make it better? Prospective effects of marijuana and temperament on risk for anxiety and depression. *Psychology of Addictive Behaviors* 29(3):590–602.

Horwood, L. J., D. M. Fergusson, C. Coffey, G. C. Patton, R. Tait, D. Smart, P. Letcher, E. Silins, and D. M. Hutchinson. 2012. Cannabis and depression: An integrative data analysis of four Australasian cohorts. *Drug and Alcohol Dependence* 126(3):369–378.

Johnson, M. J., J. D. Pierce, S. Mavandadi, J. Klaus, D. Defelice, E. Ingram, and D. W. Oslin.(2016). Mental health symptom severity in cannabis using and non-using Veterans with probable PTSD. *Journal of Affective Disorders* 190:439–442.

Kedzior, K. K., and L. T. Laeber. 2014. A positive association between anxiety disorders and cannabis use or cannabis use disorders in the general population—A meta-analysis of 31 studies. *BMC Psychiatry* 14:136.

Kirkbride, J. B., A. Errazuriz, T. J. Croudace, C. Morgan, D. Jackson, J. Boydell, R. M. Murray, and P. B. Jones. 2012. Incidence of schizophrenia and other psychoses in England, 1950–2009: A systematic review and meta-analyses. PLoS ONE 7(3): e31660.

Large, M., S. Sharma, M. T. Compton, T. Slade, and O. Nielssen. 2011. Cannabis use and earlier onset of psychosis: A systematic meta-analysis. *Archives of General Psychiatry* 68(6):555–561.

Lev-Ran, S., B. Le Foll, K. McKenzie, T. P. George, and J. Rehm. 2013. Bipolar disorder and co-occurring cannabis use disorders: Characteristics, co-morbidities and clinical correlates. *Psychiatry Research* 209(3):459–465.

Mallen, C., G. Peat, and P. Croft. 2006. Quality assessment of observational studies is not commonplace in systematic reviews. *Journal of Clinical Epidemiology* 59(8):765–769.

Manhapra, A., E. Stefanovics, and R. Rosenheck. 2015. Treatment outcomes for veterans with PTSD and substance use: Impact of specific substances and achievement of abstinence. *Drug and Alcohol Dependence* 156:70–77.

Marconi, A., M. Di Forti, C. M. Lewis, R. M. Murray, and E. Vassos. 2016. Meta-analysis of the association between the level of cannabis use and risk of psychosis. *Schizophrenia Bulletin* 42(5):1262–1269.

McLoughlin, B. C., J. A. Pushpa-Rajah, D. Gillies, J. Rathbone, H. Variend, E. Kalakouti, and K. Kyprianou. 2014. Cannabis and schizophrenia. Cochrane Database of Systematic Reviews 10:CD004837.

MedlinePlus. Suicide. October 19, 2016. https://medlineplus.gov/suicide.html (accessed October 26, 2016).

Moore, T. H., S. Zammit, A. Lingford-Hughes, T. R. Barnes, P. B. Jones, M. Burke, and G. Lewis. 2007. Cannabis use and risk of psychotic or affective mental health outcomes: A systematic review. *Lancet* 370(9584):319–328.

Myles, N., H. Newall, O. Nielssen, and M. Large. 2012. The association between cannabis use and earlier age at onset of schizophrenia and other psychoses: Meta-analysis of possible confounding factors. *Current Pharmaceutical Design* 18(32):5055–5069.

NIDA (National Institute on Drug Abuse). 2011. DrugFacts—comorbidity: Addiction and other mental disorders. https://www.drugabuse.gov/publications/drugfacts/comorbidity-addiction-other-mental-disorders (accessed November 24, 2016).

NIDA 2014. Drugs, brains, and behavior: The science of addiction. https://www.drugabuse.gov/publications/drugs-brains-behavior-science-addiction/drugs-brain (accessed November 24, 2016).

NIDA 2015. Research reports: Marijuana. https://www.drugabuse.gov/sites/default/files/mjrrs_4_15.pdf (accessed November 29, 2016).

NIMH (National Institute of Mental Health). 2015. Schizophrenia. https://www.nimh.nih.gov/health/publications/schizophrenia-booklet-12-2015/index.shtml (accessed October 28, 2016).

NIMH 2016. Bipolar disorder. https://www.nimh.nih.gov/health/topics/bipolar-disorder/index.shtml (accessed October 25, 2016).

NIMH n.d. Any anxiety disorder among adults. https://www.nimh.nih.gov/health/statistics/prevalence/any-anxiety-disorder-among-adults.shtml (accessed 10 26, 2016).

Nkansah-Amankra, S., and M. Minelli. 2016. "Gateway hypothesis" and early drug use: Additional findings from tracking a population-based sample of adolescents to adulthood. *Preventive Medicine Reports* 4:134–141.

Power, B. D., M. Dragovic, J. C. Badcock, V. A. Morgan, D. Castle, A. Jablensky, and N. C. Stefanis. 2015. No additive effect of cannabis on cognition in schizophrenia. *Schizophrenia Research* 168(1-2):245–251.

Rabin, R. A., K. K. Zakzanis, and T. P. George. 2011. The effects of cannabis use on neurocognition in schizophrenia: A meta-analysis. *Schizophrenia Research* 128(1–3):111–116.

Rasic, D., S. Weerasinghe, M. Asbridge, and D. B. Langille. 2013. Longitudinal associations of cannabis and illicit drug use with depression, suicidal ideation and suicidal attempts among Nova Scotia high school students. *Drug and Alcohol Dependence* 129(1-2):49–53.

Rehman, I. U., and S. Farooq, S. 2007. Cannabis abuse in patients with schizophrenia: Pattern and effects on symptomatology. *Journal of the College of Physicians and Surgeons, Pakistan* 17(3):158–161.

SAMHSA (Substance Abuse and Mental Health Services Administration). *Behavioral health trends in the United States: Results from the 2014 National Survey on Drug Use and Health*. http://www.samhsa.gov/data/sites/default/files/NSDUH-FRR1-2014/NSDUH-FRR1-2014.pdf (accessed November 24, 2016).

Sanchez-Torres, A. M., V. Basterra, A. Rosa, L. Fananas, A. Zarzuela, B. Ibanez, V. Peralta, and M. J. Cuesta. 2013. Lifetime cannabis use and cognition in patients with schizophrenia spectrum disorders and their unaffected siblings. *European Archives of Psychiatry and Clinical Neuroscience* 263(8):643–653.

Schnell, T., D. Koethe, J. Daumann, and E. Gouzoulis-Mayfrank. 2009. The role of cannabis in cognitive functioning of patients with schizophrenia. *Psychopharmacology* 205(1):45–52.

Seddon, J. L., M. Birchwood, A. Copello, L. Everard, P. B. Jones, D. Fowler, T. Amos, N. Freemantle, V. Sharma, M. Marshall, and S. P. Singh. 2016. Cannabis use is associated with increased psychotic symptoms and poorer psychosocial functioning in first-episode psychosis: A report from the UK National Eden Study. *Schizophrenia Bulletin* 42(3):619–625.

Shalit, N., G. Shoval, D. Shlosberg, D. Feingold, and S. Lev-Ran. 2016. The association between cannabis use and suicidality among men and women: A population-based longitudinal study. *Journal of Affective Disorders* 205:216–224.

Silins, E., L. J. Horwood, G. C. Patton, D. M. Fergusson, C. A. Olsson, D. M. Hutchinson, E. Spry, J. W. Toumbourou, L. Degenhardt, W. Swift, C. Coffey, R. J. Tait, P. Letcher, J. Copeland, R. P. Mattick, S. Allsop, W. Hall, R. Hayatbakhsh, K. Little, J. Najman, R. Skinner, and T. Slade. 2014. Young adult sequelae of adolescent cannabis use: An integrative analysis. *The Lancet Psychiatry* 1(4):286–293.

Szoke, A., A. M. Galliot, J. R. Richard, A. Ferchiou, G. Baudin, M. Leboyer, and F. Schurhoff. 2014. Association between cannabis use and schizotypal dimensions—A meta-analysis of cross-sectional studies. *Psychiatry Research* 219(1):58–66.

Tosato, S., A. Lasalvia, Bonetto, R. Mazzoncini, D. Cristofalo, K. De Santi, M. Bertani, S. Bissoli, L. Lazzarotto, G. Marrella, D. Lamonaca, R. Riolo, F. Gardellin, A. Urbani, M. Tansella, and M. Ruggeri. 2013. The impact of cannabis use on age of onset and clinical characteristics in first-episode psychotic patients. Data from the Psychosis Incident Cohort Outcome Study (PICOS). *Journal of Psychiatric Research* 47(4):438–444.

Valmaggia, L. R., F. L. Day, C. Jones, S. Bissoli, C. Pugh, D. Hall, S. Bhattacharyya, O. Howes, J. Stone, P. Fusar-Poli, M. Byrne, and P. K. McGuire. 2014. Cannabis use and transition to psychosis in people at ultra-high risk. *Psychological Medicine* 44(12):2503–2512.

van der Meer, F. J., E. Velthorst, C. J. Meijer, M. W. Machielsen, and L. de Haan. 2012. Cannabis use in patients at clinical high risk of psychosis: Impact on prodromal symptoms and transition to psychosis. *Current Pharmaceutical Design* 18(32):5036–5044.

van Dijk, D., M. W. J. Koeter, R. Hijman, R. S. Kahn, and W. van den Brink. 2012. Effect of cannabis use on the course of schizophrenia in male patients: A prospective cohort study. *Schizophrenia Research* 137(1–3):50–57.

van Winkel, R., N. J. van Beveren, and C. Simons. 2011. AKT1 moderation of cannabis-induced cognitive alterations in psychotic disorder. *Neuropsychopharmacology* 36(12):2529–2537.

Villagonzalo, K. A., S. Dodd, F. Ng, S. Mihaly, A. Langbein, and M. Berk. 2011. The relationship between substance use and posttraumatic stress disorder in a methadone maintenance treatment program. *Comprehensive Psychiatry* 52(5):562–566.

Wilkinson, A. L., C. T. Halpern, and A. H. Herring. 2016. Directions of the relationship between substance use and depressive symptoms from adolescence to young adulthood. *Addictive Behaviors* 60:64–70.

Wilkinson, S. T., E. Stefanovics, and R. A. Rosenheck. 2015. Marijuana use is associated with worse outcomes in symptom severity and violent behavior in patients with posttraumatic stress disorder. *Journal of Clinical Psychiatry* 76(9):1174–1180.

Yucel, M., E. Bora, D. I. Lubman, N. Solowij, W. J. Brewer, S. M. Cotton, P. Conus, M. J. Takagi, A. Fornito, S. J. Wood, P. D. McGorry, and C. Pantelis. 2012. The impact of cannabis use on cognitive functioning in patients with schizophrenia: A meta-analysis of existing findings and new data in a first-episode sample. *Schizophrenia Bulletin* 38(2):316–330.

Zammit, S., T. H. Moore, A. Lingford-Hughes, T. R. Barnes, P. B. Jones, M., Burke, and G. Lewis. 2008. Effects of cannabis use on outcomes of psychotic disorders: Systematic review. *British Journal of Psychiatry* 193(5):357–363.

Zorrilla, I., J. Aguado, J. M. Haro, S. Barbeito, S. Lopez Zurbano, A. Ortiz, P. Lopez, and A. Gonzalez-Pinto. 2015. Cannabis and bipolar disorder: Does quitting cannabis use during manic/mixed episode improve clinical/functional outcomes? *Acta Psychiatrica Scandinavica* 131(2):100–110.

13
Problem Cannabis Use

Chapter Highlights
• Greater frequency of cannabis use increases the likelihood of developing problem cannabis use. • Initiating cannabis use at a younger age increases the likelihood of developing problem cannabis use.

A recent national survey reported that 22.2 million Americans (aged 12 or older) identify as current users of cannabis (CBHSQ, 2015). A subgroup of these users, 4.2 million Americans, reported experiencing symptoms in the previous year that would qualify them for cannabis use disorder (CUD) (CBHSQ, 2015). Unfortunately, the literature remains unclear on the association or developmental link between varying levels of cannabis use and the development of "problem" cannabis use or cannabis use disorder, particularly at different age groups (e.g., 12 years or older).

In this chapter, the committee reviews the current research evidence that most directly addresses prioritized research questions related to the association between cannabis use and the development of problem cannabis use and to the risk and protective factors involved in the development or exacerbation of problem use. An initial search of the primary literature (see Appendix B) produced a substantial number of primary articles for the committee to review. Due to the time constraints of the study, additional search constraints were added to zero in on the types of studies that would likely produce the clearest research conclusions. For example, literature searches were limited to articles that included the following search terms: longitudinal, prospective, and case-control. The primary literature was further limited to studies that included a sample size of >500 participants and to studies that investigated problem cannabis use as a function of the most relevant risk factors including mental health, the age of initiation of cannabis use, risk factors during adolescence, biological sex, and other drug use. Large population-based studies that explored multiple demographic variables were also included.

It is of note, however, that due to the specific search restrictions outlined above, controlled laboratory studies with cannabis were not included in the committee's set of articles to review. There do, in fact, exist controlled lab studies that assess the direct effects of cannabis on behaviors relevant to cannabis use disorder and the dose-dependent effects of cannabis and that are related to its abuse liability. Unfortunately, because of the constraints of this study, these findings are not incorporated in the chapter's discussion. Furthermore, the committee's prioritized research questions did not examine the association between low level cannabis use or infrequent cannabis use and the development of problem cannabis use.

To inform their research conclusions, the committee reviewed two of the most recent, good- to fair-quality systematic reviews and 26 primary literature articles.

PROBLEM CANNABIS USE

As noted above, the literature is unclear on the association between cannabis use and the progression to the sort of cannabis use determined to be "problem" use. A major contributor to this issue is the lack of official distinction between "risky" or "problem" use of cannabis (Casajuana et al., 2016). In recent years, CUD[1] has been termed an official psychiatric disorder (APA, 2013; WHO, 2015). A current *Diagnostic and Statistical Manual of Mental Disorders (DSM-5)* diagnosis of CUD replaces the previous diagnoses of cannabis abuse and cannabis dependence. Although some progress has been made in standardizing terminology, explicit characterizations of cannabis use patterns that *precede* abuse or dependence still remain unclear (Casajuana et al., 2016). Given this context, for the purposes of this chapter the committee will use the broad term "problem cannabis use disorder" to encompass various levels of hazardous or potentially harmful cannabis use patterns, including those related to CUD, dependence, and abuse.

Which Characteristics of Cannabis Use Are Associated with the Progression to Developing Problem Cannabis Use?

Systematic Reviews

The committee did not identify a good- or fair-quality systematic review that reported on the association between cannabis use and cannabis use disorder, dependence, abuse, or problem cannabis use.

Primary Literature

Several studies using large population surveys have explored the rates of cannabis use disorder and the variables that affect progression from the initiation of use to problem cannabis use. According to findings from Wave 1 (baseline; 2001–2002) and Wave 2 (follow-up; 2004–2005) of the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC), a survey of a nationally representative sample of U.S. adults ages 18 years and older (n = 34,653 in Wave 2), cannabis use reported during the first wave was significantly associated with any cannabis use disorder during the second wave, (adjusted odds ratio [aOR], 9.5; 95% confidence interval [CI] = 6.4–14.1); 14.1 percent of past-year cannabis users in Wave 1 met the criteria for cannabis abuse in Wave 2, and 5.1 percent met criteria for dependence, as compared with 0.7 percent of participants who reported no past-year cannabis use during Wave 1 who met the criteria for cannabis abuse and 0.2 percent who met the criteria for cannabis dependence (Blanco et al., 2016). This study accounted for multiple socio-demographic factors that may have affected the outcome.

The progression of cannabis use to developing cannabis use disorder as a function of the frequency of cannabis use was also explored using waves 1 and 2 of the NESARC data (Cougle et al., 2016) Among the past-year weekly nondependent cannabis users in Wave 1 (n = 435), 9.7 percent progressed to cannabis dependence in Wave 2; however, an increased frequency of

[1] In brief, CUD is a diagnosable psychiatric disorder defined as a problematic pattern of cannabis use leading to clinically significant personal, social, physical, and/or psychological distress or impairment.

cannabis use per day only weakly predicted progression of cannabis use to CUD (odds ratio [OR], 1.08; CI = 1.04–1.13) in a prospective analysis. A cross-sectional analysis of Wave 1 data found that 8.0 percent of respondents who reported using cannabis at least once in the past year met the criteria for dependence, whereas among weekly and daily cannabis smokers, 17.0 percent and 18.8 percent, respectively, met the criteria for dependence.

Using data obtained from the U.S. National Household Survey on Drug Abuse conducted in 2001 with a representative sample of U.S. residents 12 years of age and older (n = 114,241), Chen and colleagues (2005) explored the rates of developing cannabis dependence syndrome after onset of use. Of the recent onset users (individuals that used cannabis within 24 months prior to assessment), an estimated 3.9 percent developed dependence during the interval since first use (median time = 1 year). Of those who initiated cannabis use more than 24 months before the assessment, and were also active cannabis users within the past year, 9.9 percent developed dependence (Chen et al., 2005).

Using data from two large U.S. surveys—the 1991 National Longitudinal Alcohol Epidemiologic Survey (NLAES) (n = 42,862) and the 2002 NESARC (n = 43,093)—Compton and colleagues (2004) assessed the rates of cannabis use disorder as a function of biological sex, ethnicity, and frequency of cannabis use. They found that the overall prevalence of DSM-IV cannabis abuse and dependence increased significantly from 1.2 percent to 1.5 percent between 1991 and 2001. The greatest increases in these rates were observed among young black men and women ($p < 0.001$), and young Hispanic men ($p = 0.006$). The increase in the rates of cannabis use disorder among cannabis users was observed in the absence of self-reported increases in frequency or quantity of use ($p = 0.002$) suggesting that the increases in cannabis use disorders may be due to the increased potency (percent tetrahydrocannabinol [THC]) of cannabis between 1991 and 2001.

Discussion of Findings

The limitations of these studies include the reliance on self-reported cannabis use, the fact that data were restricted to two time-points of assessment separated by 3 years, and that the findings are based on epidemiological data obtained over 10 years ago. A significant issue with relying on self-report methodologies to ascertain problem cannabis use is that this requires that the respondent have insight into the fact that cannabis is actually causing problems in order to meet criteria for cannabis abuse/dependence (as per the DSM-IV) or CUD (as per the DSM-V). Furthermore, while the primary literature indicates a weak association between the frequency of use and a greater risk of developing cannabis use disorder, it should be noted that the frequency of use in these studies was assessed in the absence of determining the amount of cannabis used per occasion, which is a primary variable hypothesized to affect the rates of developing problem cannabis use.

Cannabis use is increasing across the country and across age groups (Hasin et al., 2015), the strength of cannabis has increased (ElSohly et al., 2016), and different routes of cannabis administration have become popular, including vaping, dabs, and edibles (Daniulaityte et al., 2015; Kilmer et al., 2013; Pacula et al., 2016); these trends may reflect an increased vulnerability to developing problem cannabis use relative to what was estimated based on the Wave 1 and Wave 2 NESARC data collected in 2001–2001 and 2004–2005. Therefore, the estimated risk of developing problem cannabis use based on these data may not accurately reflect the risk now, given the current trends.

CONCLUSION 13-1 There is substantial evidence for a statistical association between increases in cannabis use frequency and the progression to developing problem cannabis use.

Are There Risk and Protective Factors for Developing Problem Cannabis Use?

Anxiety

Systematic Reviews Kedzior et al. (2014) searched two large databases for articles published from inception through 2013 to identify studies of cannabis use and anxiety. They included cross-sectional and longitudinal studies conducted in non-institutionalized populations, with anxiety diagnoses based on DSM/ICD criteria, odds ratios, or data sufficient for the calculation of a measure of effects, and they included comparison data from healthy non-users. Their purpose was to examine both of the possible temporal relationships between cannabis use and anxiety, i.e., the effect of anxiety on cannabis use and the effect of cannabis use on anxiety. They identified 31 studies for their review. Five of these examined cannabis use at baseline and anxiety at follow-up, and the remainder considered the role of anxiety as a risk factor for cannabis use. Sample sizes were almost 2,000 or greater in four studies and more than 12,000 in a fifth study. After analyzing various subsets of the selected articles, the authors concluded that there was a small positive association between anxiety and CUD (OR, 1.68; 95% CI = 1.23–2.31, n = 13 studies). One study included in the analysis assessed anxiety at baseline and cannabis use at follow-up and did not find an association (OR, 0.94; 95% CI = 0.86–1.03) but did not report on problem cannabis use at follow-up. The authors found little evidence of publication bias after their assessment, and they reported a moderate-high heterogeneity. They offered three possible explanations of this heterogeneity: differences in adjustment for confounding when calculating the OR, year of publication, and different methods for diagnosing anxiety. Based on this systematic review, it appears that while there is a small association between anxiety and CUD, anxiety does not seem to be a predisposing risk factor for developing CUD.

Primary Literature The committee did not identify any good-quality primary literature that reported on anxiety as a risk or protective factor for developing problem cannabis use and that were published subsequent to the data-collection period of the most recently published good- or fair-quality systematic review addressing the research question.

Stimulant Medication in Children Diagnosed with Attention Deficit Hyperactivity Disorder

Systematic Reviews Humphreys et al. (2013) conducted a systematic literature review and meta-analysis to assess the association between childhood treatment with stimulant medication and later substance use, abuse, or dependence. They searched the literature published between 1980 and 2012 and included published and unpublished studies with a longitudinal design, binary measures to identify children with attention deficit hyperactivity disorder (ADHD), binary substance use and abuse measures, and data allowing the calculation of odds ratios. Fifteen studies were included in the review; nine of these evaluated the association of stimulant medication with a lifetime history of ever using marijuana, and nine evaluated the association of

stimulant medication with cannabis abuse or dependence. All study subjects were children at the time of enrollment, and the follow-up time ranged from 4 to 28 years in the group of 9 studies reviewed, with the mean age at follow-up ranging from 15 to 26. One of the studies in this systematic review included children as young as four years of age who would not be expected to develop CUD in the follow-up time period. The percentage of study subjects who were male ranged from 0 to 100, with the majority of the studies being more than 80 percent male. The researchers reported an OR of 1.01 (95% CI = 0.68–1.50) for the association between stimulant medication and marijuana abuse or dependence. Some suggestion of publication bias was noted, and heterogeneity was noted in the group of nine studies with data about marijuana abuse or dependence. These results suggest that medication for ADHD during childhood does not constitute a risk factor for developing problem cannabis use later in life.

Primary Literature The committee did not identify any good-quality primary literature that reported stimulant medication in children diagnosed with ADHD as a risk or protective factor for developing problem cannabis use and that were published subsequent to the data collection period of the most recently published good- or fair-quality systematic review addressing the research question.

Psychopathology

Systematic Reviews The committee did not identify a good- or fair-quality systematic review that reported on psychopathology as a risk or protective factor for developing problem cannabis use.

Primary Literature Data obtained from the 2001 and 2005 NESARC, a survey of a nationally representative sample of U.S. adults of ages 18 years and older (n = 34,653 in Wave 2), explored anxiety as a risk factor for progression to cannabis use disorder. Using data from Wave 2 (comprised of 34, 653 participants from Wave 1), Feingold and colleagues (2016) found that anxiety disorders were not associated with an increased incidence of cannabis use disorders (aOR, 0.68; 95% CI = 0.41–1.14). Similarly, a prospective analysis using Wave 1 and Wave 2 NESARC data also found that anxiety disorders failed to predict progression from cannabis use to cannabis dependence in weekly cannabis users (Cougle et al., 2016).

Another analysis used these data to determine the association between baseline major depressive disorder (MDD) as a risk factor for cannabis use disorders (Pacek et al., 2013). A positive relationship was observed between baseline MDD and cannabis use disorders (OR, 2.01, 95% CI = 1.09–3.68); baseline MDD also increased the risk of co-occurring alcohol and cannabis use disorders (OR, 5.23; 95% CI = 1.28–21.34), when compared to individuals without baseline MDD. When adjusting the model to account for potential confounding variables, the association between baseline MDD and the development of cannabis use disorders alone, and co-occurring with alcohol use disorders was retained (aOR, 2.28; 95% CI = 1.28–4.05 for cannabis use disorders alone and aOR, 4.51, 95% CI = 1.31–15.60 for comorbid alcohol and cannabis use disorders). These findings support a strong association between MDD and the development of cannabis use disorders. According to a later prospective analysis (Cougle et al., 2016), among weekly, nondependent cannabis users in Wave 1, depressive disorders did not significantly predict progression to cannabis dependence in Wave 2 (OR, 0.89; 95% CI = 0.58–1.38) (Cougle et al., 2016). The discrepancy between these two findings may be due to the former study

assessing respondents who met the criteria for MDD. Also, the pool of respondents in the earlier study was not limited to those who reported weekly cannabis use during Wave 1, as was the case with the later study. Another study assessing the impact of baseline depressive symptoms on developing cannabis abuse used data from a longitudinal study involving 1,980 participants (the 1980 Baltimore Epidemiologic Catchment Area study). In this study, a subset of participants (n = 1,837) were assessed for cannabis use disorders 14 to 16 years after initial assessment (Bovasso, 2001). Depressive symptoms failed to predict cannabis abuse at follow-up assessments, which indicated that among the population studied, depression was not a risk factor for later cannabis abuse. The long duration between the initial assessment and the follow-up and the presence of significant attrition were significant limitations to this study.

In order to determine the effects of psychotic disorders on the risk for heavy cannabis use, data obtained from the Genomic Psychiatric Cohort, a clinically assessed multiethnic sample of participants (n = 9,142) with a diagnosis of schizophrenia, bipolar disorder with psychotic features, or schizoaffective disorders, was compared to a control population (n = 10,195) (Hartz et al., 2014). Relative to the control population, individuals with chronic psychotic disorders were found to have an increased risk for heavy cannabis use, defined by the researchers as cannabis use more than 21 times per year (OR, 3.5; 95% CI = 3.2–3.7). It is important note, however, that it remains difficult to determine how heavy cannabis use translates to problem cannabis use, cannabis dependence, or CUD.

A prospective analysis using data from waves 1 and 2 of the NESARC found that personality disorders failed to predict a progression from past-year, weekly nondependent cannabis use in Wave 1 to cannabis dependence in Wave 2 (OR, 0.91; 95% CI = 0.62–1.34). This same analysis demonstrated that bipolar disorder was associated with a lower risk for developing CUD (OR, 0.43; 95% CI = 0.36–0.52) (Cougle et al., 2016).

Biological Sex

Systematic Reviews The committee did not identify a good- or fair-quality systematic review that reported on biological sex as a risk or protective factor for developing problem cannabis use.

Primary Literature Data from the NLAES (n = 42,862) were analyzed in effort to determine the effect of biological sex on the risk of developing cannabis use disorders (Grant et al., 2006). Of the participants that reported cannabis use at least 12 times, women were less likely to be categorized with cannabis "abuse/moderate dependence" relative to men (8 percent versus 14 percent) or "severe abuse/dependence" (3 percent versus 6 percent). While men were consistently more likely to report hazardous cannabis use relative to women, women were more likely to report withdrawal and to have higher rates of four symptoms of dependence (i.e., emotional problems, giving up activities, using more cannabis than intended, withdrawal) in the "abuse/moderate dependence" category than men. These findings may suggest either that men and women differ in cannabis dependence symptomatology or that they differ in their willingness to self-report the symptoms.

Using data obtained from the fourth wave of the National Longitudinal Study of Adolescent Health, a nationally representative population-based survey of young adults aged 24–32 (n = 15,500; interviewed from 2008–2009), lifetime prevalence rates of cannabis dependence were determined to be 8.3 percent, and higher among males than among females (Haberstick, 2014). However, a prospective analysis using data from Wave 1 and Wave 2 of the NESARC

failed to find that biological sex predicted a progression from cannabis use to cannabis dependence in weekly nondependent cannabis users (OR, 1.17; 95% CI = 0.75–1.81) (Cougle et al., 2016).

Progression from the onset of cannabis use to the development of cannabis dependence as a function of biological sex was explored using data obtained from the U.S. National Household Survey on Drug Abuse, which was conducted in 2001 with a representative sample of US residents 12 years of age and older (n = 114,241) (Chen et al., 2005). The rate for developing cannabis dependence 24 months after onset of use was 3.9 percent for both men and women. However, it is not known if differences between men and women would have emerged if a shorter timeframe from cannabis use onset had been explored.

Other Drug Use

Systematic Reviews The committee did not identify a good- or fair-quality systematic review that reported on other drug use as a risk or protective factor for developing problem cannabis use.

Primary Literature To explore the impact of other drug use as a risk factor for developing problemcannabis use, data obtained from the U.S. National Household Survey on Drug Abuse conducted in 2001 with a representative sample of U.S. residents 12 years of age and older (n = 114,241) were analyzed. The rate of developing cannabis dependence within 24 months of first cannabis use was dou`bled among respondents who had experience with three or more other drugs (tobacco, alcohol, and other drugs) prior to cannabis use (adjusted risk ratio [aRR] = 2.2; 95% CI = 1.1–4.3; p = 0.03) (Chen et al., 2005). However, a prospective analysis using data from waves 1 and 2 of the NESARC failed to find that alcohol or nicotine dependence predicted progression from cannabis use to cannabis dependence (OR, 0.88; 95 % CI = 0.58–1.32 and OR, 0.77; 95% CI = 0.52–1.13, respectively) (Cougle et al., 2016).

Age—Older Population

Systematic Reviews The committee did not identify a good-or fair-quality systematic review that reported on older age as a risk or protective factor for developing problem cannabis use.

Primary Literature Based on the large population-based U.S. National Survey on Drug Use and Health , the prevalence of cannabis use in the United States was assessed in a population over 50 years of age (n = 10,953; data from 2005 and 2006). Only 0.12 percent of the population met the criteria for cannabis abuse and dependence demonstrating that, at the time of this survey, this is an age group that is of low risk for developing CUD (Blazer and Wu, 2009).

Age of Initiation of Cannabis Use

Systematic Reviews The committee did not identify a good- or fair-quality systematic review that reported on the age of initiation of cannabis use as a risk or protective factor for developing problem cannabis use.

Primary Literature The age of initiation of cannabis use as a risk factor for developing cannabis dependence has been explored in many studies. Chen et al. (2005) used data obtained from the U.S. National Household Survey on Drug Abuse conducted in 2001 with a representative sample of US residents 12 years of age and older (n = 114,241). Adolescent onset cannabis users were more likely to become dependent than respondents who had initiated cannabis use during adulthood. Using data obtained from adult onset users of cannabis (21 years of age and older) as a reference, Chen and colleagues found a strong association between an onset of cannabis use between 11and 13 years of age and the relative risk of becoming dependent (aRR = 10.8; 95% CI = 2.5–47.1). The estimated risk ratio of developing cannabis dependence when initiating cannabis use at 14-15 years of age was 12.0 (95% CI = 2.9–50.3).

Another study exploring early, frequent cannabis use as a risk factor for developing cannabis use disorder used data from three long-running surveys in Australia and New Zealand[2] (Silins et al., 2014). Compared to individuals who had never used cannabis, those who were daily users before 17 years of age had significantly greater odds of later developing cannabis dependence (n = 2,675; aOR,17.95; 95% CI = 9.44–34.12). This study controlled for 53 covariates including sociodemographic factors and other potential antecedents to the development of problem cannabis use that may have affected the findings.

A longitudinal study of a community-based sample of adolescents and young adults surveyed between 14 and 24 years of age in Munich, Germany, with four waves of assessments over a 10-year period (n = 3,021 at baseline) ascertained the prevalence rates of DSM-IV cannabis dependence as a function of cannabis use (Perkonigg et al., 2008). During the first assessment (at baseline), 1.5 percent of the sample met the criteria for DSM-IV cannabis dependence. Among those who reported using cannabis at that time, 4.3 percent met the criteria for dependence. At the 10-year follow-up, 6.1 percent of those reported using cannabis at baseline met the criteria for dependence. The authors concluded that the higher rates of cannabis dependence during the 10-year follow-up assessment suggested that cannabis use early in life may be indicative of increased vulnerability to developing CUD. However, there are other factors (as discussed below) that may explain why an increase in cannabis dependence was observed at the 10-year follow-up.

A later study using these data evaluated the probability and speed of going from first cannabis use to developing cannabis dependence as a function of the age of first use. The conditional probability of transition from cannabis use to dependence was estimated to be 6.2 percent (Behrendt et al., 2009). The authors also compared the time of transition from first substance use (nicotine, alcohol, or cannabis) to the development of the specific substance use disorder and found that the transition from first cannabis use to the development of CUD occurred at a faster rate than for those with alcohol or nicotine use disorders.

Other Variables Specific to Adolescents

Systematic Reviews The committee did not identify a good- or fair-quality systematic review that reported on variables that protect against or increase the risk of developing cannabis use disorders among adolescents.

[2] These surveys include the Australian Temperament Project, the Christchurch Health and Development Study, and the Victorian Adolescent Health Cohort Study.

Primary Literature Longitudinal data from the above-described community-based sample from Munich, Germany were analyzed to determine whether the age of first alcohol and nicotine affects the risk of transition from cannabis use to cannabis dependence (Behrendt et al., 2012). This analysis took into account externalizing disorders (mental disorders characterized by disruptive behaviors that are directed toward an individual's external environment) and parental substance use disorders as potential factors that may affect the trajectory to cannabis dependence. Using multiple models, the authors found that (1) a younger age of cannabis use (hazard ratio [HR], 0.77), (2) paternal alcohol dependence (HR, 1.47), and (3) externalizing disorders (HR, 1.69) were all associated with a higher risk of developing cannabis dependence. Externalizing disorders were associated with a slower transition from initial cannabis use to cannabis dependence (HR main effect, 1.14; HR interaction effect, 1.17; 95% CI = 1.03–1.33; p = 0.013). A younger age of first alcohol use was also associated with higher risk for developing cannabis dependence (HR, 0.88). In participants that used nicotine first, younger age of cannabis use and maternal alcohol dependence were associated with a higher risk of developing cannabis dependence. As such, the age of first alcohol and nicotine use interacted with other risk factors, including the age of first cannabis use, externalizing disorders, and parental alcohol use, in contributing to the risks of developing CUD.

In a population-based longitudinal study of children between the ages of 6 and 12 with yearly assessments, CUD was assessed at ages 19–21 (n = 1,803) to define the overall prevalence rates of the disorder (Pingault et al., 2013). The authors further determined whether childhood inattention and hyperactivity symptoms of ADHD, including oppositional behaviors (e.g., hostile, disobedient, or defiant behaviors), and anxiety and depressive behaviors served as risk factors for developing CUD. Overall, cannabis abuse or dependence (high, moderate, or severe) affected 9.1 percent of the participants during young adulthood. Only oppositional behaviors contributed to the risk of developing CUD (OR, 2.33; 95% CI = 1.4–3.87), whereas anxiety and depressive disorders did not.

To determine early life-course predictors of problem cannabis use in early adulthood, data obtained from a population-based birth cohort study of 2,493 young adults who had been included in the Mater Hospital and University of Queensland Study of Pregnancy (MUSP) were assessed (Hayatbakhsh et al., 2009). In this population, 21 percent of those who ever used cannabis were classified as having a CUD at the 21-year follow-up assessment. Males were 2.5 times more likely to have a CUD than females, children living in a family with the mother reporting more frequent changes in marital status had an increased risk of CUD (OR, 2.9; 95% CI = 1.7–5.0), aggressive and delinquent children were 5.4 times more likely to develop CUD, those with poor school performance at 14 years of age were more likely to have CUD (OR, 3.4; 95% CI = 2.3–4.9), and maternal smoking when the child was 14 years of age also increased risk of CUD (OR,2.0; 95% CI = 1.6–2.5). Childhood anxiety and depression were not risk factors for developing CUD.

In an effort to determine the association between cannabis use by 18 years of age and risk for CUD at 24 years of age, the frequency of cannabis use was evaluated in a 10-year representative cohort study set in Australia (n = 1,520 participants included in the final assessment) which included six surveys during adolescence (15–17.5 years of age) and two follow-up assessments during young adulthood (at 21 and 24 years of age) (Swift et al., 2008). One-third of the population reported having used cannabis during adolescence, and 37 percent of the adolescent cannabis users were using at least weekly when interviewed at 24 years of age. After adjusting for potential confounding factors, problem cannabis use at 24 years of age was

associated with adolescent cannabis use, tobacco use, and persistent mental health problems. The frequency of cannabis use was evaluated in a follow-up analysis that sought to determine whether moderation of cannabis use among adolescent cannabis users protected against the risk of CUD in young adulthood (Swift et al., 2009). In this study, participants were grouped into one of six categories that reflected their maximum level of adolescent use (i.e., non-users, occasional to abstinence, occasional persisting, weekly to abstinence, weekly to occasional, and weekly persisting). The study's outcome measures were level of cannabis use and DSM-IV cannabis dependence in youth adulthood. While 31 percent of the population reported having ever used cannabis, 71 percent of occasional users and 28 percent of weekly users were abstinent in young adulthood. Adolescent weekly or daily users who persisted with regular use (rather than decreased use or becoming abstinent) were at the greatest risk for developing CUD in young adulthood. Therefore, this suggests that moderating adolescent cannabis use can protect against the later problem use that is observed in persistent users. However, regardless of whether the adolescent users moderated their intake, the risk for developing CUD in young adulthood was still significantly greater for adolescent users than for those who never used cannabis.

The Christchurch Health and Development longitudinal, birth-cohort study (n = 1,265) from New Zealand assessed the probability of developing CUD by young adulthood as a function of various social and demographic factors (Boden et al., 2006). By 18 years of age, 4.7 percent of the population met criteria for cannabis dependence; that number increased to 12.5 percent by 25 years of age. The primary risk factors that predicted the development of CUD included being male and having poor academic performance. Respondents with four or more of the following risk factors had a 50 percent risk of developing cannabis dependence: (1) peer substance use, (2) parental history of a substance use disorder, (3) novelty seeking, (4) cigarette smoking, (5) childhood sexual abuse, and (6) conduct problems had a 50 percent risk of developing cannabis dependence.

A longitudinal study of probands from the Oregon Adolescent Depression Project (final n = 816) assessed the prevalence and age of onset of CUD over four assessments between the ages of 16 and 30 (Farmer et al., 2015). The weighted lifetime prevalence of CUD before the age of 30 was estimated to be 19.1 percent; 81.8 of these participants achieved recovery from CUD and the recurrence rate of CUD was 27.7 percent, which likely occurred within 36 months following the offset of the first CUD diagnosis. Males were more likely to have been diagnosed at some point during their lives than females.

The association between psychopathology and problem cannabis use was also assessed in a longitudinal, prospective study of adolescents (n = 1,395) that were 14 to17 years of age at baseline and who were assessed at three different time points over the course of10 years (Wittchen et al., 2007). A prospective analysis determined that mood disorders (OR, 2.5; 95% CI = 1.3–4.7), including bipolar disorder (hypomania and mania) (OR, 2.7; 95% CI = 1.1–6.2), but not including dysthymia (chronic depression) (OR, 2.3; 95% CI = 0.7–6.7), predicted progression to CUD. Generalized anxiety disorder and specific phobias were also associated with CUD (OR, 3.9; 95% CI = 1.1–13.8 and OR, 1.8; 95% CI = 1.1–3.0, respectively). Of note, ADHD, post-traumatic stress disorder, and panic-anxiety all failed to predict the development of CUD.

Data from a longitudinal survey of a representative sample (n = 2,032) of secondary students in the Australian state of Victoria who were assessed for cannabis disorders six times between the ages of 14 and 17 from 1992–1995 and again at 20 years of age were evaluated to determine the adolescent precursors of young adult cannabis dependence (Coffey et al., 2003).

Variables that independently predicted cannabis dependence in young adulthood included being male (OR = 2.6; p <0.01), regular cannabis use during adolescence (weekly use: OR = 4.9; daily use: OR = 4.6; p = 0.02), persistent antisocial behavior (linear effect p = 0.03) and persistent cigarette smoking (linear effect p = 0.02). Psychiatric comorbidity did not predict cannabis dependence (linear effect, p = 0.26). Regular cannabis use during adolescence only increased the risk for CUD in the absence of persistent problem alcohol use.

Discussion of Findings

Overall findings suggest that both biological sex and the age of initiation of cannabis use are positively associated with the development of problem cannabis use. There is also evidence that being male and smoking cigarettes are risk factors that contribute to the progression to problem cannabis use. Additional risk factors for the development of CUD during adolescence that are supported by moderate evidence include frequency of use, oppositional behaviors, younger age of first alcohol use, nicotine use, parental substance use, poor school performance, and childhood sexual abuse. The strength of association between the risk factors for developing problem cannabis use, including other drug use and psychopathology, differs between adult and adolescent onset of cannabis use. It is important to highlight that the studies reviewed above vary in their age grouping and generally include populations that cross from late adolescence into young adulthood. Therefore, the conclusions below pertain to a mixture of age subgroups, including older adolescents and young adults.

One significant limitations of any conclusions drawn from the current literature is the data cannabis use, other drug use, and the symptoms of problem cannabis use are derived from self-reports. Another concern is that the structured interviews used to assess baseline dependent variables (i.e., mental health) and outcomes (i.e., problem cannabis use) vary between studies and even for some longer longitudinal studies, within individual studies. Also, as mentioned in the first section, understanding the conclusions drawn from the currently available literature should take into account the fact that trends in cannabis use have evolved over the last 10 years and that the strength of cannabis has increased, which likely affects the strength of associations between risk factors and developing problem cannabis use. It is also important to note that there is biological plausibility for many of the risk factors noted above. Specifically, there is preclinical literature that speaks to the sex-dependent effects, exposure to nicotine as a risk factor for CUD, and the age of initiation of use affecting CUD.

CONCLUSION 13-2

Anxiety and Depression

13-2(a) There is limited evidence that childhood anxiety and childhood depression are risk factors for the development of problem cannabis use.

13-2(b) There is moderate evidence that anxiety, personality disorders, and bipolar disorders are not risk factors for the development of problem cannabis use.

13-2(c) There is moderate evidence that major depressive disorder is a risk factor for the development of problem cannabis use.

ADHD

13-2(d) There is moderate evidence that adolescent attention deficit hyperactivity disorder (ADHD) is not a risk factor for the development of problem cannabis use.

13-2(e) There is substantial evidence that stimulant treatment of ADHD during adolescence is not a risk factor for the development of problem cannabis use.

Biological Sex

13-2(f) There is moderate evidence that being male is a risk factor for the development of problem cannabis use.

Other Drug Use

13-2(g) There is moderate evidence that exposure to the combined use of abused drugs is a risk factor for the development of problem cannabis use.

13-2(h) There is moderate evidence that neither alcohol nor nicotine dependence alone are risk factors for the progression from cannabis use to problem cannabis use.

13-2(i) There is substantial evidence that being male and smoking cigarettes are risk factors for the progression of cannabis use to problem cannabis use.

Age

13-2(j) There is substantial evidence that initiating cannabis use at an earlier age is a risk factor for the development of problem cannabis use.

13-2(k) There is moderate evidence that during adolescence the frequency of cannabis use, oppositional behaviors, a younger age of first alcohol use, nicotine use, parental substance use, poor school performance, antisocial behaviors, and childhood sexual abuse are risk factors for the development of problem cannabis use.

Are There Risk And Protective Factors for Severity or Persistence of Problem Cannabis Use?

Psychopathology

Systematic Reviews The committee did not identify a good- or fair-quality systematic review that reported on psychopathology as a risk or protective factor for the severity or persistence of problem cannabis use.

Primary Literature A case-control study sought to determine the association between a history of psychiatric treatment and persistent cannabis use disorder (Arendt et al., 2007). Data from the Danish Psychiatric Case Register (n = 3,114; mean age at start of treatment = 25.7

years) were compared to a representative control group that was randomly selected from the general population and matched to the patient population for age and biological sex (n = 15,570). The authors determined that a history of psychiatric treatment was associated with increased rates of reentry into substance abuse treatment for cannabis dependence (OR, 1.26; 95% CI = 1.07–1.48) relative to the control population.

In an Israeli population (n = 1,317; ages ranged from 21–45 years and older), Walsh et al. (2014) conducted in-person structured interviews to examine the association between traumatic exposure and substance dependence (alcohol, nicotine, and marijuana) and to assess whether posttraumatic stress disorder (PTSD) accounted for this association. After controlling for alcohol and nicotine dependence, investigators found that PTSD symptoms were associated with increased odds of marijuana dependence (OR, 1.1; 95% CI = 1.04–1.24) and concluded that the severity of PTSD symptoms may increase the risk for substance dependence. It should be noted, however, that these are cross-sectional data and that the directionality and causality of these associations cannot be determined.

A study by Boden et al, (2013) was outside the scope of our primary literature search due its small sample size, but it was included because of its potential relevance to the committee's prioritized research question. In this study, researchers found that in a small population of cannabis-dependent military veterans (n = 37; mean age of starting sample = 51.3 years), a diagnosis of PTSD was significantly associated with the use of cannabis to cope with PTSD symptoms, the severity of cannabis withdrawal, and three factors of cannabis drug craving (i.e., compulsivity, emotionality, and anticipation) relative to a cannabis-dependent population without a diagnosis of PTSD (n = 57). Furthermore, the severity of PTSD symptoms was associated with an increased severity of cannabis withdrawal and factors of cannabis craving (i.e., compulsivity, emotionality, and anticipation)

Biological Sex

Systematic Reviews The committee did not identify a good- or fair-quality systematic review that reported on biological sex as a risk or protective factor for the severity or persistence of problem cannabis use.

Primary Literature Data from the NLAES (n = 42,862) were analyzed in an effort to determine the effect of biological sex on the risk and severity of cannabis use disorders (Grant et al., 2006). Of the participants who reported cannabis use at least 12 times, women were less likely to be categorized with cannabis "abuse/moderate dependence" than men (8 percent versus 14 percent) or "severe abuse/dependence" (3 percent versus 6 percent). While men were consistently more likely than women to report hazardous cannabis use, women were more likely than men to report withdrawal and to have higher rates of four symptoms of dependence in the "abuse/moderate dependence" category.

A longitudinal study of probands from the Oregon Adolescent Depression Project (final n = 816) assessed recovery from CUD as a function of biological sex (Farmer et al., 2015). Females achieved recovery from CUD at a significantly faster rate than males (females = 24.2 months, standard deviation [SD] = 24.8; males = 41.2 months, SD = 42.7; p = .006), although recurrence rates of CUD did not differ between males and females (30.0% of males, 25.4% of females, p = 0.564).

Discussion of Findings

In addition to the limitations cited for the first two sections such as issues with self-reported cannabis use, the respondents' reporting of symptoms of problem cannabis use, and data restricted to trends of cannabis use and cannabis strength that do not accurately reflect current trends, the current findings are additionally restricted to limited follow-up with participants and to only a few of the risk factors highlighted in the second section, including biological sex. The impact of the primary risk factors for developing problem cannabis use identified in the second section of this chapter, including the age of initiation of use, biological sex, and other drug use, should be explored as risk factors for both the severity and the recurrence of problem cannabis use over extended periods of time.

CONCLUSION 13-3

13-3(a) There is moderate evidence of a statistical association between the persistence of problem cannabis use and a history of psychiatric treatment.

13-3(b) There is substantial evidence of a statistical association between being male and the severity of problem cannabis use, but the recurrence of problem cannabis use does not differ between males and females.

13-3(c) There is moderate evidence of a statistical association between problem cannabis use and increased severity of posttraumatic stress disorder symptoms.

RESEARCH GAP

To address the research gaps relevant to problem cannabis use, the committee suggests the following:

- The impact of the primary risk factors for developing problem cannabis use needs to be explored as risk factors for both the severity and the recurrence of problem cannabis use over extended periods of time.

SUMMARY

This chapter outlines the committee's efforts to review the current evidence base (1) to determine likelihood of developing problem cannabis use and (2) to identify the potential risk and protective factors involved in the development or exacerbation of problem use. The vast majority of the conclusions formed within this chapter were of moderate evidence; however, the conclusions that were determined to have substantial evidence were formed by research that examined the impact of biological sex, cannabis use at an early age, and past use of cannabis on problem cannabis use. Many of the chapter conclusions pertain to a mixture of age groups, including older adolescents and young adults. See Box 13-1 for a summary list of the chapter's conclusions.

These research conclusions may have important public health implications; however, it is important that the conclusions are interpreted within the context of the limitations discussed in

the Discussion of Findings sections above. It is also important to understand that the conclusions drawn from the currently available literature should take into account the fact that trends of cannabis use have evolved over the past 10 years and note that the strength of cannabis has increased, which likely has affected strength of associations between risk factors and developing problem cannabis use. Greater attention to the research limitations (e.g., reliance on self-reported cannabis use, limited detail on the amount of cannabis used per occasion, poly drug use, limited follow up, and so on) and improvements to study design and methodological approach would bolster the evidence base and help ensure that substantial evidence concerning problem cannabis use is available.

BOX 13-1
Summary of Chapter Conclusions*

There is substantial evidence that:

- Stimulant treatment of attention deficit hyperactivity disorder (ADHD) during adolescence is *not* a risk factor for the development of problem cannabis use (13-2e)
- Being male and smoking cigarettes are risk factors for the progression of cannabis use to problem cannabis use (13-2i)
- Initiating cannabis use at an earlier age is a risk factor for the development of problem cannabis use (13-2j)

There is substantial evidence of a statistical association between:

- Increases in cannabis use frequency and the progression to developing problem cannabis use (13-1)
- Being male and the severity of problem cannabis use, but the recurrence of problem cannabis use does not differ between males and females (13-3b)

There is moderate evidence that:

- Anxiety, personality disorders, and bipolar disorders are *not* risk factors for the development of problem cannabis use (13-2b)
- Major depressive disorder is a risk factor for the development of problem cannabis use (13-2c)
- Adolescent ADHD is *not* a risk factor for the development of problem cannabis use (13-2d)
- Being male is a risk factor for the development of problem cannabis use (13-2f)
- Exposure to the combined use of abused drugs is a risk factor for the development of problem cannabis use (13-2g)
- Neither alcohol nor nicotine dependence alone are risk factors for the progression from cannabis use to problem cannabis use (13-2h)
- During adolescence the frequency of cannabis use, oppositional behaviors, a younger age of first alcohol use, nicotine use, parental substance use, poor school performance, antisocial behaviors, and childhood sexual abuse are risk factors for the development of problem cannabis use (13-2k)

There is moderate evidence of a statistical association between:

- A persistence of problem cannabis use and a history of psychiatric treatment (13-3a)
- Problem cannabis use and increased severity of posttraumatic stress disorder symptoms (13-3c)

There is limited evidence that:

- Childhood anxiety and childhood depression are risk factors for the development of problem cannabis use (13-2a)

* Numbers in parentheses correspond with chapter conclusion number.

REFERENCES

APA (American Psychiatric Association). 2013. *Diagnostic and statistical manual of mental disorders, 5th ed*. Arlington, VA: American Psychological Association.

Arendt, M., R. Rosenberg, L. Foldager, G. Perto, and P. Munk-Jorgensen. 2007. Psychopathology among cannabis-dependent treatment seekers and association with later substance abuse treatment. *Journal of Substance Abuse Treatment* 32(2):113–119.

Azofeifa, A., M. E. Mattson, G. Schauer, T. McAfee, A. Grant, and R. Lyerla. 2016. National estimates of marijuana use and related indicators—National Survey on Drug Use and Health, United States, 2002–2014. *Morbidity and Mortality Weekly Report: Surveillance Summaries* 65(SS-11):1–25.

Behrendt, S., H. U. Wittchen, M. Hofler, R. Lieb, and K. Beesdo. 2009. Transitions from first substance use to substance use disorders in adolescence: Is early onset associated with a rapid escalation? *Drug and Alcohol Dependence* 99(1-3):68–78.

Behrendt, S., K. Beesdo-Baum, M. Hofler, A. Perkonigg, G. Buhringer, R. Lieb, and H. U. Wittchen. 2012. The relevance of age at first alcohol and nicotine use for initiation of cannabis use and progression to cannabis use disorders. *Drug and Alcohol Dependence* 123(1-3):48–56.

Blanco, C., D. S. Hasin, M. M. Wall, L. Florez-Salamanca, N. Hoertel, S. Wang, B. T. Kerridge, and M. Olfson. 2016. Cannabis use and risk of psychiatric disorders: Prospective evidence from a U.S. national longitudinal study. *JAMA Psychiatry* 73(4):388–395.

Blazer, D. G., and L. T. Wu. 2009. The epidemiology of substance use and disorders among middle aged and elderly community adults: National Survey on Drug Use and Health. *American Journal of Geriatric Psychiatry* 17(3):237–245.

Boden, J. M., D. M. Fergusson, and L. J. Horwood. 2006. Illicit drug use and dependence in a New Zealand birth cohort. *Australian and New Zealand Journal of Psychiatry* 40(2):156–163.

Boden, M. T., K. A. Babson, A. A. Vujanovic, N. A. Short, and M. O. Bonn-Miller. 2013. Posttraumatic stress disorder and cannabis use characteristics among military veterans with cannabis dependence. *American Journal on Addictions* 22(3):277–284.

Bovasso, G. B. 2001. Cannabis abuse as a risk factor for depressive symptoms. *American Journal of Psychiatry* 158(12):2033–2037.

Casajuana, C., H. López-Pelayo, M. M. Balcells, L. Miguel, J. Colom, and A. Gual. 2016. Definitions of risky and problematic cannabis use: A systematic review. *Substance Use & Misuse* 51(13):1760–1770.

CBHSQ (Center for Behavioral Health Statistics and Quality). 2015. *Behavioral health trends in the United States: Results from the 2014 National Survey on Drug Use and Health* (HHS Publication No. SMA 15-4927, NSDUH Series H-50). http://www.samhsa.gov/data/ (accessed November 21, 2016).

Chen, C. Y., M. S. O'Brien, and J. C. Anthony. 2005. Who becomes cannabis dependent soon after onset of use? Epidemiological evidence from the United States: 2000–2001. *Drug and Alcohol Dependence* 79(1):11–22.

Coffey, C., J. B. Carlin, M. Lynskey, N. Li, and G. C. Patton. 2003. Adolescent precursors of cannabis dependence: Findings from the Victorian Adolescent Health Cohort Study. *British Journal of Psychiatry* 182:330–336.

Compton, W. M., B. F. Grant, J. D. Colliver, M. D. Glantz, and F. S. Stinson. 2004. Prevalence of marijuana use disorders in the United States: 1991–1992 and 2001–2002. *JAMA* 291(17):2114–2121.

Cougle, J. R., J. K. Hakes, R. J. Macatee, M. J. Zvolensky, and J. Chavarria. 2016. Probability and correlates of dependence among regular users of alcohol, nicotine, cannabis, and cocaine:

Concurrent and prospective analyses of the National Epidemiologic Survey on Alcohol and Related Conditions. *Journal of Clinical Psychiatry* 77(4):e444–e450.

Daniulaityte, R., R. W. Nahhas, S. Wijeratne, R. G. Carlson, F. R. Lamy, S. S. Martins, E. W. Boyer, G. A. Smith, and A. Sheth. 2015. Time for dabs: Analyzing Twitter data on marijuana concentrates across the U.S. *Drug and Alcohol Dependence* 155:307–311.

ElSohly, M. A., Z. Mehmedic, S. Foster, C. Gon, S. Chandra, and J. C. Church. 2016. Changes in cannabis potency over the last 2 decades (1995–2014): Analysis of current data in the United States. *Biological Psychiatry* 79(7):613–619.

Farmer, R. F., D. B. Kosty, J. R. Seeley, S. C. Duncan, M. T. Lynskey, P. Rohde, D. N. Klein, and P. M. Lewinsohn. 2015. Natural course of cannabis use disorders. *Psychological Medicine* 45(1):63–72.

Feingold, D., M. Weiser, J. Rehm, and S. Lev-Ran. 2016. The association between cannabis use and anxiety disorders: Results from a population-based representative sample. *European Neuropsychopharmacology* 26(3):493–505.

Grant, J. D., J. F. Scherrer, R. J. Neuman, A. A. Todorov, R. K. Price, and K. K. Bucholz. 2006. A comparison of the latent class structure of cannabis problems among adult men and women who have used cannabis repeatedly. *Addiction* 101(8):1133–1142.

Haberstick, B. C., S. E. Young, J. S. Zeiger, J. M. Lessem, J. K. Hewitt, and C. J. Hopfer. 2014. Prevalence and correlates of alcohol and cannabis use disorders in the United States: results from the national longitudinal study of adolescent health. *Drug and Alcohol Dependence* 136:158–161.

Hartz, S. M., C. N. Pato, H. Medeiros, P. Cavazos-Rehg, J. L. Sobell, J. A. Knowles, L. J. Bierut, and M. T. Pato. 2014. Comorbidity of severe psychotic disorders with measures of substance use. *JAMA Psychiatry* 71(3):248–254.

Hasin, D. S., T. D. Saha, B. T. Kerridge, R. B. Goldstein, S. P. Chou, H. Zhang, J. Jung, R. P. Pickering, W. J. Ruan, S. M. Smith, B. Huang, and B. F. Grant. 2015. Prevalence of marijuana use disorders in the United States between 2001–2002 and 2012–2013. *JAMA Psychiatry* 72(12):1235–1242.

Hayatbakhsh, M. R., J. M. Najman, W. Bor, M. J. O'Callaghan, and G. M. Williams. 2009. Multiple risk factor model predicting cannabis use and use disorders: A longitudinal study. *American Journal of Drug and Alcohol Abuse* 35(6):399–407.

Humphreys, K. L., T. Eng, and S. S. Lee. 2013. Stimulant medication and substance use outcomes: A meta-analysis. *JAMA Psychiatry* 70(7):740–749.

Kedzior, K. K., and L. T. Laeber. 2014. A positive association between anxiety disorders and cannabis use or cannabis use disorders in the general population—A meta-analysis of 31 studies. *BMC Psychiatry* 14:136.

Kilmer, B., J. P. Caulkins, G. Midgette, L. Dahlkemper, R. J. MacCoun, and R. L. Pacula. 2013. *Before the grand opening: Measuring Washington State's marijuana market in the last year before legalized commercial sales*. Santa Monica, CA: RAND Corporation.

Pacek, L. R., S. S. Martins, and R. M. Crum. 2013. The bidirectional relationships between alcohol, cannabis, co-occurring alcohol and cannabis use disorders with major depressive disorder: Results from a national sample. *Journal of Affective Disorders* 148(2-3):188–195.

Pacula, R. L., M. Jacobson, and E. J. Maksabedian. 2016. In the weeds: A baseline view of cannabis use among legalizing states and their neighbours. *Addiction* 111(6):973–980.

Perkonigg, A., R. D. Goodwin, A. Fiedler, S. Behrendt, K. Beesdo, R. Lieb, and H. U. Wittchen. 2008. The natural course of cannabis use, abuse and dependence during the first decades of life. *Addiction* 103(3):439–449.

Pingault, J. B., S. M. Cote, C. Galera, C. Genolini, B. Falissard, F. Vitaro, and R. E. Tremblay. 2013. Childhood trajectories of inattention, hyperactivity and oppositional behaviors and prediction of substance abuse/dependence: A 15-year longitudinal population-based study. *Molecular Psychiatry* 18(7):806–812.

SAMHSA (Substance Abuse and Mental Health Services Administration). *Behavioral health trends in the United States: Results from the 2014 National Survey on Drug Use and Health*. Rockville, MD: Substance Abuse and Mental Health Services Administration.

http://www.samhsa.gov/data/sites/default/files/NSDUH-FRR1-2014/NSDUH-FRR1-2014.pdf (accessed November 24, 2016).

Silins, E., L. J. Horwood, G. C. Patton, D. M. Fergusson, C. A. Olsson, D. M. Hutchinson, E. Spry, J. W. Toumbourou, L. Degenhardt, W. Swift, C. Coffey, R. J. Tait, P. Letcher, J. Copeland, R. P. Mattick, S. Allsop, W. Hall, R. Hayatbakhsh, K. Little, J. Najman, R. Skinner, and T. Slade. 2014. Young adult sequelae of adolescent cannabis use: An integrative analysis. *The Lancet Psychiatry* 1(4):286–293.

Swift, W., C. Coffey, J. B. Carlin, L. Degenhardt, and G. C. Patton. 2008. Adolescent cannabis users at 24 years: Trajectories to regular weekly use and dependence in young adulthood. *Addiction* 103(8):1361–1370.

Swift, W., C. Coffey, J. B. Carlin, L. Degenhardt, B. Calabria, and G. C. Patton. 2009. Are adolescents who moderate their cannabis use at lower risk of later regular and dependent cannabis use? *Addiction* 104(5):806–814.

Walsh, K., J. C. Elliott, D. Shmulewitz, E. Aharonovich, R. Strous, A. Frisch, A. Weizman, B. Spivak, B. F. Grant, and D. Hasin. 2014. Trauma exposure, posttraumatic stress disorder and risk for alcohol, nicotine, and marijuana dependence in Israel. *Comprehensive Psychiatry* 55(3):621–630.

WHO (World Health Organization). 2015. *The ICD-10 classification of mental and behavioural disorders: Clinical descriptions and diagnostic guidelines*. Geneva, Switzerland: World Health Organization.

Wittchen, H. U., C. Frohlich, S. Behrendt, A. Gunther, J. Rehm, P. Zimmermann, R. Lieb, and A. Perkonigg. 2007. Cannabis use and cannabis use disorders and their relationship to mental disorders: A 10-year prospective-longitudinal community study in adolescents. *Drug and Alcohol Dependence* 88(Suppl. 1):S60–S70.

14

Cannabis Use and the Abuse of Other Substances

Chapter Highlight
• Cannabis use is likely to increase the risk for developing substance dependence (other than cannabis use disorder).

Since the 1970s, researchers have debated about the role that cannabis may play in the "gateway hypothesis" which suggests that individuals rarely use certain substances, such as heroin or cocaine, without first having used "gateway" substances, such as alcohol, tobacco, or cannabis (Kandel, 1975; Vanyukov et al., 2012). While some research has shown an association between cannabis use and the subsequent use of other illicit drugs, the predictors of progression from cannabis use to other illicit drugs remain largely unknown (Secades-Villa et al., 2015). Emerging animal studies have begun to explore the hypothesis that cannabis exposure may enhance the susceptibility to the addictive effects of other drugs (Panlilio et al., 2012). Researchers have also begun to explore the "reverse gateway hypothesis." This hypothesis posits that cannabis use is a reverse gateway to the initiation of other addictive drugs such as nicotine and alcohol (Agrawal et al., 2008).

In the United States, the number of individuals 12 years and older using illicit drugs rose each year between 2002 and 2013. In 2014 alone, the National Survey on Drug Use and Health reported that 27 million individuals in this age range—or almost 1 in every 10 Americans—of that age were found to have used illicit drugs within the past 30 days, 66.9 million were current users of tobacco, and another 139.7 million were past month alcohol drinkers (CBHSQ, 2015). With illicit drug use on the rise, the need for understanding and addressing when and how individuals start using illicit drugs is of the utmost importance. Of similar importance is understanding the role that cannabis might play in the use of other addictive substances such as tobacco and alcohol.

The committee responsible for the 1999 Institute of Medicine (IOM) [1] report, *Marijuana and Medicine: Assessing the Science Base* (IOM, 1999) discussed the "gateway hypotheses" but did not make any specific conclusions about its relevance to cannabis use. That report questioned the designation of cannabis as a "gateway" drug since its use is often preceded by underage drinking and tobacco use, and no conclusive evidence supporting a causal link between cannabis use and the use of other illicit drugs was found at that time (IOM, 1999).

In this chapter, the committee reviews the research evidence that most directly addresses the prioritized research questions related to the associations among cannabis use and (1) the

[1] As of March 2016, the Health and Medicine Division continues the consensus studies and convening activities previously carried out by the Institute of Medicine (IOM).

initiation of use of other substances, (2) changes in the rates and use patterns of other substances and, (3) and the development of other substance dependence or substance abuse disorder. Due to the time constraints of the study, additional search constraints were added to prioritize the types of studies that would likely produce the clearest research conclusions. For example, literature searches were limited to articles that included the search terms: "longitudinal," "prospective," and "case-control," and the committee did not review controlled laboratory studies with cannabis. Although the committee did not find any fair- or good-quality systematic reviews covering these issues, 12 primary articles published since the 1999 IOM report were identified and are reviewed in this chapter.

ABUSE OF OTHER SUBSTANCES

Is There an Association Between Cannabis Use and the Initiation of Use of Other Substances?

Tobacco/Nicotine

Systematic Reviews The committee did not identify a good- or fair-quality systematic review that reported on the association between cannabis use and the initiation of tobacco/nicotine use.

Primary Literature Mayet and colleagues (2016) conducted a retrospective cohort study of the transitions between tobacco, cannabis and other illicit drugs initiations. Data on 16,421 adults of ages 18 to 34 was collected from two French nationwide health and behavior studies conducted in 2005 and 2010. The data used included the age of initiation of substance use (cannabis, tobacco, alcohol, other illicit drugs), current use, and a number of other variables (e.g., gender, socioeconomic level). A total of 436,206 observations based on yearly measures were provided by the study subjects, including 17,510 transitions from one state of use to another. A Markov multistate model was constructed to examine transitions from cannabis use to the use of other drugs. The model's results show that the probability of initiating tobacco after cannabis use (10.39 percent) was significantly greater ($p < 0.001$) than the probability of initiating cannabis after tobacco use (3.47 percent). The primary study limitations include potential recall bias on the age of initiation and the usual issues surrounding the self-reporting of substance use.

Mayet and colleagues (2011) analyzed data collected from a cross-sectional survey of 29,393 17-year old adolescents attending compulsory military information session to assess transitions from cannabis use to the use of other substances. Data from study participants were captured via a self-administered questionnaire on substance use thus participants were considered followed from birth through 2011 by way of recall data. Substance use was categorized as "no lifetime use of tobacco and cannabis," "tobacco initiation only," "cannabis initiation only," "daily use of tobacco only," "daily use of cannabis only," "daily use of both tobacco and cannabis" (Mayet et al., 2011, p. 1102). A Markov multistate model was constructed to examine the transition states among the first-substance-use cohorts from no-use/initial substance use to other substance use states.

Study participants were more likely to use tobacco (72.2 percent) than cannabis (49.4 percent), and only 2 percent of those using both tobacco and cannabis reported having used cannabis before tobacco (Mayet et al., 2011). With respect to transitions from initial substance

use, the risk of initiating tobacco use from no-lifetime use was 17.6 times greater (95% confidence interval [CI] = 16.5–18.9) than first initiating cannabis use. Among individuals initiating use with cannabis, the transition to first tobacco use was 3.2 times greater (95% CI = 2.9–3.6) than the transition from no-lifetime use of cannabis to first tobacco use (Mayet et al., 2011). However, the transition of first tobacco use to cannabis was 42.1 times greater (95% CI = 39.3–45.1) than the transition from no-lifetime use of tobacco to first cannabis use. The transition from daily use of cannabis to daily use of both cannabis and tobacco was 3.0 times greater (95% CI = 2.0–4.4) than the transition from daily tobacco use to daily use of both cannabis and tobacco (Mayet et al., 2011). The authors also found that cannabis initiation did not increase the risk of a tobacco user transitioning to a daily cannabis smoker. The study's limitations include potential problems with recall bias and self-reporting of substance use.

Opioids

Systematic Reviews The committee did not identify a good- or fair-quality systematic review that reported on the association between cannabis use and the initiation of use of opioids.

Primary Literature Mayet and colleagues (2016) in the retrospective cohort study described earlier also explored the transition from cannabis use to the use of other illicit drugs. They found that the probability of initiating other illicit drugs after cannabis did not differ significantly from the probability of starting with other illicit drugs.

Mixed Drug Use

Systematic Reviews The committee did not identify a good- or fair-quality systematic review that reported on the association between cannabis use and the initiation of use of other substances.

Primary Literature Novins and colleagues (2004) reported on risk factors for the initiation of substance use and transition to other substance use among American Indian adolescents living west of the Mississippi. Survey data collected as part of the Voices of Indian Teens longitudinal study from 1993 to 1996 were used to calculate the conditional probability that an adolescent who reported lifetime use of cannabis (Stage 1) would progress to report a lifetime use of stimulants, sedatives, cocaine, or other drugs such as hallucinogens, phencyclidine, or heroin (Stage 2).

For analysis purposes, the initial sample of 2,356 adolescents was reduced to 1,244 adolescents due to exclusions related to continued lifetime abstention or transition to Stage 2 before the study began and to inconsistent responses between the two waves of data collection, as well as those lost to follow-up (Novins et al., 2004). The hazard ratio (HR) for the progression of cannabis use (Stage 1) to a harder substance (Stage 2) was 2.737 ($p < 0.01$). The authors noted that the study had a number of limitations, including generalizability to other populations, the self-reporting of substance use data, an inability to include tobacco use in the analysis because the survey did not differentiate between ceremonial and non-ceremonial tobacco use, and the potential for underestimating the results because of the potential bias created by individuals lost to follow-up who may have had different (higher) patterns of substance use than those remaining in the study.

Discussion of Findings

The small number of studies reviewed provide limited evidence that cannabis use increases the rates of initiation of other drug use, mainly tobacco. Two studies had relatively large samples. The data do not provide compelling evidence that cannabis is associated with the initiation of other drugs of abuse, although this is one possibility. Other possibilities that could explain these findings include easier access to cannabis than other illicit substances and common risk factors for both cannabis use and the use of other substances. Although cannabis use is associated with increased odds of transitioning to tobacco use relative to non-cannabis users, tobacco use was associated with far greater odds of transitioning to cannabis use relative to non-tobacco users. These data highlight tobacco use as a key risk factor for the initiation of cannabis use.

CONCLUSION 14-1 There is limited evidence of a statistical association between cannabis use and the initiation of tobacco use.

Is There an Association Between Cannabis Use and the Rates and Use Patterns of Other Substances?

Alcohol

Systematic Reviews The committee did not identify a good- or fair-quality systematic review that reported on the association between cannabis use and the rates and use patterns of drinking alcohol.

Primary Literature Buu and colleagues (2015) conducted a secondary data analysis of eight waves of data collected from 850 high-risk adolescents participating in the longitudinal Flint Adolescent Study to assess risk and protective factors for substance use and other health risk behaviors through adulthood (ages 14 through 24 years). The impact of early or later onset (i.e., age at first use) and of the quantity and frequency of cannabis use on heavy drinking were specific research questions. A linear mixed model was used to determine the longitudinal effects of nicotine and marijuana on heavy drinking while controlling for the early onset of alcohol use. Model results indicate that both early onset cannabis users (β, 0.2263; standard error [SE] = 0.0445; $p < 0.0001$), late onset cannabis users (β, 0.1838; SE = 0.0461; $p<0.0001$), and those who used cannabis more frequently (β, 0.2667; SE = 0.0119; $p<0.0001$) were all at a higher risk of heavy alcohol drinking than those who did not use cannabis at all (Buu et al., 2015). Among this population, about 80 percent of the study participants were black and had grade point averages of 3.0 or below and thus are not representative of the general population of youth. Further, the lifetime prevalence of substance use was higher in the study population than in the general population. The impact of cannabis use on nicotine use was not reported.

Opioids

Systematic Reviews The committee did not identify a good- or fair-quality systematic review that reported on the association between cannabis use and the rates and use patterns of opioids.

Primary Literature In a longitudinal study of a random sample of 120 adolescents aged 12 to 18 years who were admitted to a level 1 trauma center or an emergency department for injury, Whiteside and colleagues (2016) found that preinjury cannabis use was an independent predictor of continued prescription opioid use up to 12 months after discharge (relative risk, 1.69; 95% CI = 1.09–2.6). Cannabis use was assessed via a single-item question regarding cannabis use (yes/no) in the year before the injury and the use of a range of prescription opioids (codeine, hydrocodone, oxycodone, etc.) was assessed and categorized as yes or no at months 2, 5, and 12. At 1 year post injury, 12.5 percent of adolescents were still using prescribed opioids. The study's limitations include the use of self-reported data to determine preinjury cannabis use and opioid use as well as the reliance on a small study sample and the fact that the sample was collected at an urban, academic trauma center, which thus limited the generalizability of the findings.

Tobacco/Nicotine

Systematic Reviews The committee did not identify a good- or fair-quality systematic review that reported on the association between cannabis use and the rates and use patterns of tobacco and nicotine dependence.

Primary Literature Agrawal and colleagues (2008) studied women cannabis users and patterns of smoking and nicotine dependence. Data were collected as part of the Missouri Female Twin Study (MOAFTS), a cohort study of 3,787 young adult twin females ages 18 to 29 years, who were originally interviewed in 1994–1999 and subsequently re-interviewed in 2002–2005. Data collection included lifetime cannabis use (ever used cannabis and other measures of frequency and use) and cannabis dependence (determined by a lifetime history of one or more 4 *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition* [DSM-IV] abuse or 1 or more of 6 DSM-IV dependence criteria). Regular cigarette smoking among participants was determined by responding positively to having smoked 100 or more cigarettes lifetime and smoking 20–99 cigarettes at least once per week for a period of 2 months or longer. Nicotine dependence was defined using the 7 DSM-IV dependence criteria with at least 3 symptoms clustering within the same 12-month period. Data on a number of covariates were also collected including measures of behavioral disinhibition, negative affect regulation and other measures of psychopathology. In this sample, 44.2 percent of the participants were cannabis users, 34.7 percent were classified as regular cigarette smokers and 17.4 percent were designated as nicotine dependent based on DSM-IV criteria. It is also important to note that only 6.8 percent of participants reported smoking their first cigarette before using cannabis for the first time.

Survival analyses were used to examine whether women who smoked cannabis were at an increased risk of moving from experimenting with smoking (but not first time smoking) to becoming a regular smoker. After adjusting for covariates, the results indicate that women with a prior history of cannabis use were 4.4 times more likely (HR, 4.41; 95% CI = 3.57–5.44) to transition from experimenting with smoking to becoming regular smokers. An additional analysis was conducted to assess spurious associations caused by the onset of cannabis use and

regular smoking in the same year. The results of this analysis showed a diminished effect size; the effect size of the hazards of regular smoking in cannabis users was reduced to 1.8 (95% CI = 1.5–2.2) for those meeting this condition.

Mixed Drug Use

Systematic Reviews The committee did not identify a good- or fair-quality systematic review that reported on the association between cannabis use and the rates and use patterns of substances other than cannabis.

Primary Literature To examine trajectories of adolescent cannabis and alcohol users Patton and colleagues (2006) analyzed data from a 10-year cohort study of health in 2,032 adolescents and young adults living in Victoria, Australia. Data were collected in eight waves over the study period from an initial study sample of adolescents who were in mid-secondary school in 1992. About 95 percent of students from the initial study sample participated in waves 1 through 6, and 75 percent of the students participated in wave 8. The frequency of cannabis and alcohol use was categorized in three categories: "any alcohol or cannabis use," "at least moderate-risk alcohol or cannabis use," and "high-risk alcohol or cannabis use" (Patton et al., 2006, p. 609). Logistic regression modeling was used to explore the associations between substance use in adolescence (at about 15 years old in Wave 1) and later substance use in early adulthood (at about 25 years old in Wave 8).

After adjusting for a number of social and behavioral factors and persistent substance use measures, the researchers found that adolescents with moderate-risk cannabis use were seven times as likely to develop high-risk cannabis use (odds ratio [OR], 7.4; 95% CI = 3.3–17) and twice as likely to develop high-risk alcohol use in early adulthood (OR, 2.2; 95% CI = 1.1–4.5) compared with students with no hazardous alcohol use or daily cannabis use (Patton et al., 2006).

Among this population, the risk was also elevated for daily cigarette smoking (OR, 3.0; 95% CI = 1.7–5.4), for the use of amphetamines (OR, 6.0; 95% CI = 3.6–10.0), for the use of ecstasy (OR, 7.2; 95% CI = 4.3–12.0), and for the use of cocaine (OR, 4.7; 95% CI = 2.3–9.7) within the past 12 months, as reported in Wave 8 (Patton et al., 2006). The study's limitations include a 25 percent reduction in the initial sample between Wave 1 and Wave 8 (imputation techniques were used to mitigate potential bias related to students missing waves of the survey), the use of self-reports to determine substance use, and questions about the generalizability of the study to other populations.

The use of cannabis and relapse after discharge from a substance abuse program were the focus of a study conducted by Aharonovich and colleagues (2005). This longitudinal study followed 349 patients who had undergone and successfully completed inpatient treatment for a DSM-IV diagnosis of alcohol, cocaine, or heroin dependence; patients had not experienced mania or non-affective psychosis. Patients were followed up after discharge at months 6, 12, and 18 to update the Psychiatric Research Interview for Substance and Mental Disorders. Responses were analyzed to assess cannabis use and return to substance abuse, sustained remission from substance abuse, and relapse to substance abuse after sustained remission. Of the 349 patients participating in the study, 250 contributed data through at least one follow-up interview; the study results are based on this subset of patients. Of the 250 patients dependent on alcohol, cocaine, or heroin at baseline who did not achieve sustained remission from using these substances, 41.4 percent used cannabis during follow-up after hospital discharge compared to

15.4 percent of those who had achieved remission ($p < 0.0001$) (Aharonovich et al., 2005). Among the patients dependent on alcohol at baseline who failed to achieve sustained remission, 38.7 percent used cannabis ($p < 0.004$), and among patients dependent on cocaine at baseline who failed to achieve sustained remission 52.5 percent used cannabis during follow-up after hospital discharge ($p < 0.03$). Relapse after sustained remission was also seen among patients who used cannabis during follow-up.

A Cox proportional model that adjusted for socio-demographic variables and diagnoses of substance dependence and a number of psychiatric symptoms and disorders was developed to examine the effects of cannabis use on a number of outcomes, including the return to substance use (multiple substance use, alcohol only, cocaine only, and heroin only), sustained remission from substance use, and relapse to substance use. Hazard ratios were significant ($p < 0.0001$) for cannabis use and a return to the use of multiple substance, alcohol only, and cocaine only. Cannabis use was associated with a statistically significant reduced hazard of achieving a sustained remission from multiple substance use and cocaine use specifically ($p < 0.05$). In addition, cannabis use was found to increase the hazard of relapse to alcohol use ($p < 0.05$).

Discussion of Findings

The primary literature reviewed presents limited evidence that cannabis use affects the rates and patterns of the use of other substances. With regard to alcohol use, cannabis users were found to be at a higher risk than non-users for heavy drinking. With regard to opioids, cannabis use predicted continued opioid prescriptions 1 year after injury. Finally, cannabis use was associated with reduced odds of achieving abstinence from alcohol, cocaine, or polysubstance use after inpatient hospitalization and treatment for substance use disorders. The limitations of these studies include their lack of generalizability due to their use of restricted study populations, their limited assessment of cannabis use, the lack of dose-response relationships, and the potential for self-report bias.

CONCLUSION 14-2 There is limited evidence of a statistical association between cannabis use and changes in the rates and use patterns of other licit and illicit substances.

Is There an Association Between Cannabis Use and the Development of Other Substance Dependence or Other Substance Abuse Disorder?

Alcohol

Systematic Reviews The committee did not identify a good- or fair-quality systematic review that reported on the association between cannabis use and the development of alcohol dependence or alcohol use disorder.

Primary Literature Buu and colleagues (2014) assessed the long term effects of cannabis use on alcohol problems and alcohol use disorder (AUD) using data from the Michigan Longitudinal Study. The researchers followed a sample of 160 female–male sibling pairs from high-risk families (sample total of 320 individuals) from ages 3–5 to 21–23 years, assessing the participants every 3 years using the Drinking and Drug History Questionnaire, Diagnostic Interview Schedule, Diagnostic Interview Schedule for Children and the Health and Daily Living

Questionnaire. Data were collected on age at first use of alcohol, cannabis, and nicotine as well as the quantity and frequency of use and were analyzed using a linear mixed model. The authors concluded that a higher frequency of cannabis use was related to greater odds of developing drinking problems (β, 0.55; SE = 0.08; $p < 0.05$) and to meeting an AUD diagnosis (β, 0.59; SE = 0.09; $p < 0.05$) (Buu et al., 2014). However, the odds were not as high as those associated with the frequency of alcohol consumption on the odds of developing drinking problems (β, 1.90; SE = 0.10; $p < 0.05$) and the odds of meeting an AUD diagnosis (β, 1.75; SE = 0.31; $p < 0.05$) (Buu et al., 2014). Further, an early onset of cannabis use was not found to contribute to AUD. A major limitation of this study is that the participant population included children who had intact families in early childhood, families that were at high risk for developing AUD, and families of minority race/ethnicity, thus limiting the generalizability of the study results.

Tobacco/Nicotine

Systematic Reviews The committee did not identify a good- or fair-quality systematic review that reported on the association between cannabis use and the development of tobacco or nicotine dependence or tobacco or nicotine abuse disorder.

Primary Literature Timberlake and colleagues (2007) conducted a study to examine the role of cannabis use in adolescence and the likelihood of developing nicotine dependence and initiating daily tobacco smoking at an earlier age. Survey data were collected from 90,118 students participating in the National Longitudinal Study of Adolescent Health conducted in 132 U.S. schools (public and private) between September 1994 and April 1995. A subsample of participants was followed up at three points with more in depth surveys, a baseline survey (wave I) and two subsequent surveys (wave II, one year after the baseline survey and Wave III) six years later). Of these, 5,963 unrelated participants formed the primary sample and included individuals who had not smoked cigarettes by the baseline survey (wave I) but smoked at least one cigarette by wave III. Participants ranged in age from 18.3 to 27.7 years. Data on lifetime use of cannabis and prior month use at wave I, age at daily cigarette smoking, and lifetime and current nicotine dependence at wave III were available for these participants. A smaller sample of 1,447 participants who had tried cannabis by wave I and for which data on the age of first use was available was used to examine lifetime and current nicotine dependence 6 years later. Cannabis use was classified as no lifetime use, experimental use (1–10 times), and regular use (greater than 10 times). Age at first use was also collected from adolescents who had experimented with cannabis by wave I of the survey. Nicotine dependence was defined using the Fagerstrom Test for Nicotine Dependence. Demographic risk factor data were also collected. Survey–based logistic regression analysis and censored regression techniques were used to predict outcomes.

Results from this study indicate that regular lifetime users of cannabis at wave I were 1.89 times more likely to develop lifetime nicotine dependence ($t = 2.3$ $p < 0.05$, adjusted odds ratio [aOR], 1.89; 95% CI = 1.09–3.30) than non-users. Past month users (both experimental and regular) at wave I were 1.83 times more likely to develop lifetime nicotine dependence ($t = 2.3$ $p < 0.05$, aOR, 1.83; 95% CI = 1.08–3.11) than non-users. Further, lifetime users who began using at later ages (23–27) were less likely to develop nicotine dependence at wave III compared to those who began using at earlier ages ($t = -3.3$ $p < 0.01$, aOR, 0.82; 95% CI = 0.73 to −0.93).

Limitations associated with this study include self-reported data on substance use, and recall bias.

Agrawal and colleagues (2008), as described in the above section, studied women cannabis users and patterns of smoking and nicotine dependence. Survival analyses were used to examine whether women who smoked cannabis were at an increased risk of moving from regular smoker to nicotine dependent. After adjusting for covariates, the results indicate that women with a prior history of cannabis use were 2.8 times more likely (HR, 2.80; 95% CI = 1.84–4.26) to transition from regular smoking to nicotine dependence. Limitations associated with this study include the lack of generalizability to men, self-reported data on substance use, and recall bias.

Mixed Drug Use

Systematic Reviews The committee did not identify a good- or fair-quality systematic review that reported on the association between cannabis use and the development of substance dependence or substance abuse disorder.

Primary Literature In a longitudinal U.S. study of a nationally representative sample of 34,653 adults 18 years or older, Blanco and colleagues (2016) examined the association between cannabis use and the risk of developing substance abuse and other mental health disorders. This study investigated the potential association between cannabis use in the past year (Wave 1) with incident substance use disorders, alcohol abuse and dependence, other drug abuse and dependence, and nicotine dependence 3 years later (Wave 2). Both Wave 1 and Wave 2 adjusted for sociodemographic characteristics, a family history of substance use disorder, a disturbed family environment, childhood parental loss, low self-esteem, social deviance, education, recent trauma, past and present psychiatric disorders, and the respondent's history of divorce. The researchers found that, after adjusting for covariates, cannabis use in the 12 months preceding the interview was associated with an increased risk of developing any substance use disorders, including Cannabis Use Disorder (OR, 6.2; 95% CI = 4.1−9.4) (Blanco et al., 2016). The adjusted odds ratios for all incident psychiatric disorders in Wave 2 are presented in Table 14-1 below.

The frequency of cannabis use in Wave 1 was also associated with an incidence of any substance use disorder in Wave 2 (aOR, 1.9; 95% CI = 1.7−2.1), indicating a dose−response association between cannabis use and substance use disorder.[2] Some of the limitations of this study included the fact that substance use was ascertained by self-report, that there was a possibility of residual confounding, and that the follow-up period was limited to 3 years (Blanco et al., 2016).

[2] Frequency of cannabis use was measured as "no use," "some use but less than one use per month," and "one or more uses per month."

TABLE 14-1 Cannabis Use in the Past 12 Months and Incident Psychiatric Disorders in Wave 2

Incident Psychiatric Disorders in Wave 2	Adjusted OR (95% CI)
Any substance use disorder (includes cannabis use disorder)	6.2 (4.1–9.4)
Any alcohol use disorder	2.7 (1.9–3.8)
Alcohol abuse	1.5 (1.1–2.0)
Alcohol dependence	1.9 (1.4–2.7)
Other drug use disorder	2.6 (1.6–4.4)
Other drug abuse	3.4 (2.5–5.4)
Other drug dependence	2.7 (1.6–4.5)
Nicotine dependence	1.7 (1.2–2.4)

SOURCE: Adapted from Blanco et al., 2016.

Palmer and colleagues (2009) analyzed the substance use experiences of 1,733 individuals (ages 12–25) who participated in the Colorado Community Twin Study. Data on substance use experimentation and repeated-use were collected via self-reported questionnaires and psychiatric interviews in two waves about 5 years apart. Substance abuse and dependence were assessed using the Composite International Diagnostic Interview–Substance Abuse Module (CIDI–SAM) structured interview. With respect to substance use, experimentation was defined as "having used a substance one or more times in a person's lifetime," repeated marijuana use was defined as having used cannabis "six or more times in a respondent's lifetime," and cannabis abuse and dependence were defined based on the DSM-IV as having compulsive use without generally developing physiological dependence (APA, 1994, p. 216; Palmer et al., 2009, pp. 79–80).

Results show that the risks of alcohol abuse/dependence (OR, 3.44; 95% CI = 1.93–6.12) and tobacco dependence (OR, 4.12; 95% CI = 2.26–7.51) were greater in individuals who used cannabis more than once in their life time (without meeting a diagnosis of cannabis substance use disorder) compared to those who did not use cannabis (Palmer et al., 2009). Individuals diagnosed with cannabis use disorder had higher odds of being diagnosed with alcohol abuse/dependence (OR, 8.78; 95% CI = 3.15–24.53) and tobacco dependence (OR, 8.61; 95% CI = 3.15–23.56) than those who did not use cannabis. However, once the logistic regression models were adjusted for the individuals' involvement with alcohol and tobacco, the odds ratios no longer reached significance (Palmer et al., 2009).

The researchers found that individuals with cannabis use disorder were not at higher risk for alcohol abuse/dependence (OR, 1.77; 95% CI = 0.54–5.78) or tobacco dependence (OR, 2.61; 95% CI = 0.78–8.72) compared with those who had used cannabis more than once in their life time but did not have cannabis use disorder (Palmer et al., 2009). They note that the cannabis and other substance use results indicate "a model of generalized risk since substance use disorders on any substance in young adulthood could be predicted by involvement with any of the three substances in adolescence" (Palmer et al., 2009, p. 78). Study limitations include the difficulty capturing the more severe cases in the cohort, as they are generally not reported; questions about the reliability of self-reporting; of the fact that covariates of substance abuse were not included in the logistic regression models; and the failure of the authors to impose clustering criteria or the ability to distinguish between dependence with or without physiological symptoms (Palmer et al., 2009).

Using data from 1,265 participants of the Christchurch Health and Development longitudinal birth cohort study, Fergusson and colleagues (2008) explored factors associated with illicit drug use, abuse, or dependence among study participants at ages 16 to 25. Cannabis use data were collected for each year and were classified into four levels of frequency, "did not use cannabis," "used less than monthly on average (1–11 times)," "used at least monthly on average (12-50 times)," and "used at least weekly (>50 times)" (Fergusson et al., 2008, p. 169). Annual frequency of cannabis use was the strongest predictor of illicit drug use (β, 1.58; SE = 0.06, p <.0001) and drug abuse or dependence (β, 1.73; SE = 12, p <.0001) across age groups (Fergusson et al., 2008). The interaction between cannabis use and age was also explored and the association was found to diminish with increasing age. The adjusted odds ratios for the risk of illicit drug use and abuse/dependence for participants who used cannabis at least weekly are presented in Table 14-2 below. Study limitations include questions about the generalizability of the study and the fact that the assessments were based on self-reported data. The confidence intervals for some results are wide.

TABLE 14-2 Adjusted Odds Ratios (and 95% Confidence Intervals) for at Least Weekly Cannabis Use and Risk Factors for Cannabis Use and Illicit Drug Abuse/Dependence, at Ages 16–17, 20–21, and 24–25

Adjusted Odds Ratios for at Least Weekly Frequency of Use of Cannabis and the Risk of Illicit Drug Use at Specific Ages		
Age	OR	95% CI
16–17	92.20	46.53–182.72
20–21	26.31	17.50–39.69
24–25	7.53	4.48–12.43
Adjusted Odds Ratios for at Least Weekly Frequency of Use of Cannabis and Risk of Illicit Drug Abuse/Dependence		
16–17	117.92	26.31–523.74
20–21	27.61	11.24–67.90
24–25	6.49	2.19–19.20

SOURCE: Adapted from Fergusson et al., 2008.

Discussion of Findings

Most of the studies reviewed indicate an association between cannabis use and use of or dependence on other substances, with some data indicating this effect is more pronounced in younger individuals and is dependent on the dose or frequency of cannabis use. The strengths of some studies cited include the study designs (longitudinal cohort studies), the existence of large sample sizes, and the fact that adjustments were made for a variety of confounders. The magnitude of the associations appears in the moderate range. The limitations of the studies include, in most cases, the use of self-report for cannabis use, recall bias, and, in some cases, the limited duration of follow-up.

CONCLUSION 14-3 There is moderate evidence of a statistical association between cannabis use and the development of substance dependence and/or a substance abuse disorder for substances including, alcohol, tobacco, and other illicit drugs. The development of problem cannabis use is described in Chapter 13 of this report.

RESEARCH GAPS

To address the research gaps relevant to cannabis use and the abuse of other substances, the committee suggests the following:

- Additional studies are needed to determine whether cannabis use is an independent risk factor for, or causally contributes to, the initiation or use of and dependence on other drugs of abuse later in life.
- In states with legalized recreational cannabis, there need to be longitudinal studies that examine whether the prevalence of use of other drugs parallels the increase in prevalence of cannabis use.

SUMMARY

This chapter summarizes current research evidence on the association between cannabis use and the potential for abusing other substances. Several important research conclusions were reached (see Box 14-1); however, it is important that these conclusions are interpreted within the context of the limitations discussed in the Discussion of Findings sections above.

BOX 14-1
Summary of Chapter Conclusions*

There is moderate evidence of a statistical association between cannabis use and:

- The development of substance dependence and/or a substance abuse disorder for substances including, alcohol, tobacco, and other illicit drugs (14-3)

There is limited evidence of a statistical association between cannabis use and:

- The initiation of tobacco use (14-1)
- Changes in the rates and use patterns of other licit and illicit substances (14-2)

* Numbers in parentheses correspond to chapter conclusion numbers.

REFERENCES

Agrawal, A., P.A.F. Madden, K.K. Bucholz, A.C. Hewath, and M.T. Lynskey. 2008. Transitions to regular smoking and to nicotine dependence in women using cannbis. *Drug and Alcohol Dependence* 95(1–2):107–114.

Aharonovich, E., X. Liu, S. Samet, E. Nunes, R. Waxman, and D. Hasin. 2005. Postdischarge cannabis use and its relationship to cocaine, alcohol, and heroin use: A prospective study. *American Journal of Psychiatry* 162(8):1507–1514.

APA (American Psychiatric Association). 1994. *Statistical Manual of Mental Disorders, 4th Edition*. American Psychiatric Association, Washington, D.C.

Blanco, C., D. S. Hasin, M. M. Wall, L. Florez-Salamanca, N. Hoertel, S. Wang, B. T. Kerridge, and M. Olfson. 2016. Cannabis use and risk of psychiatric disorders: Prospective evidence from a U.S. national longitudinal study. *JAMA Psychiatry* 73(4):388–395.

Buu, A., A. Dabrowska, M. Mygrants, L. I. Puttler, J. M. Jester, and R. A. Zucker. 2014. Gender differences in the developmental risk of onset of alcohol, nicotine, and marijuana use and the effects of nicotine and marijuana use on alcohol outcomes. *Journal of Studies on Alcohol and Drugs* 75(5):850–858.

Buu, A., A. Dabrowska, J. E. Heinze, H. F. Hsieh, and M. A. Zimmerman. 2015. Gender differences in the developmental trajectories of multiple substance use and the effect of nicotine and marijuana use on heavy drinking in a high-risk sample. *Addictive Behaviors* 50:6–12.

CBHSQ (Center for Behavioral Health Statistics and Quality). 2015. *Behavioral health trends in the United States: Results from the 2014 National Survey on Drug Use and Health.* U.S. Department of Health and Human Services, Publication No. SMA 15-4927, NSDUH Series H-50. http://www.samhsa.gov/data/sites/default/files/NSDUH-FRR1-2014/NSDUH-FRR1-2014.pdf (accessed November 25, 2016).

Fergusson, D. M., J. M. Boden, and L. J. Horwood. 2008. The developmental antecedents of illicit drug use: Evidence from a 25-year longitudinal study. *Drug and Alcohol Dependence* 96(1–2):1–2.

IOM (Institute of Medicine). 1999. *Marijuana and medicine: Assessing the science base*. Washington, DC: National Academy Press.

Kandel, D. 1975. Stages in adolescent involvement in drug use. *Science* 190:912–914.

Mayet, A., S. Legleye, N. Chau, and B. Falissard. 2011. Transitions between tobacco and cannabis use among adolescents: A multi-state modeling of progression from onset to daily use. *Addictive Behaviors* 36(11):1101–1105.

Mayet, A., S. Legleye, F. Beck, B. Falissard, and N. Chau. 2016. The gateway hypothesis, common liability to addictions or the route of administration model: A modelling process linking the three theories. *European Addiction Research* 22(2):107–117.

Novins, D. K., and A. E. Barón. 2004. American Indian substance use: The hazards for substance use initiation and progression for adolescents aged 14 to 20 years. *Journal of the American Academy of Child & Adolescent Psychiatry* 43(3):316–324.

Palmer, R. H., S. E. Young, C. J. Hopfer, R. P. Corley, M. C. Stallings, T. J. Crowley, and J. K. Hewitt. 2009. Developmental epidemiology of drug use and abuse in adolescence and young adulthood: Evidence of generalized risk. *Drug and Alcohol Dependence* 102(1–3):1–3.

Panlilio, L.V., Justinova, Z., Mascia, P., Pistis, M., Luchicchi, A., Lecca, S., Barnes, C., Redhi, G.H., Adair, J., Heishman, S.J., Yasar, S., Aliczki, M., Haller, J., and Goldberg, S.R. 2012. Novel use of a lipid-lowering fibrate medication to prevent nicotine reward and relapse: preclinical findings. *Neuropsychopharmacology* 37:1838–1847.

Patton, G. C., C. Coffey, M. T. Lynskey, S. Reid, S. Hemphill, J. B. Carlin, and W. Hall. 2007. Trajectories of adolescent alcohol and cannabis use into young adulthood. *Addiction* 102(4):607–615.

Secades-Villa, R., Garcia-Rodriguez, O., Jin, C.J., Wang, S., and Blanco, C. (2015). Probability and predictors of the cannabis gateway effect: A national study. *Journal of Drug Policy* 26(2): 135–142.

Timberlake, D.S., Haberstick, B.C., Hopfer, C.J., Brickerm J., Sakai, J.R., Lessem, J.M., Hewitt, J.K. 2007. Progression from marijuana use to daily smoking and nicotine dependence in a national sample of U.S. adolescents. *Drug and Alcohol Dependence* 88(2–3): 272–281.

Vanyukov, M. M., R. E. Tarter, G. P. Kirillova, L. Kirisci, M. D. Reynolds, M. J. Kreek, K. P. Conway, B. S. Maher, W. G. Iacono, L. Bierut, M. C. Neale, D. B. Clark, and T. A. Ridenour. 2012. Common liability to addiction and "gateway hypothesis": Theoretical, empirical and evolutionary perspective. *Drug and Alcohol Dependence* 123(Suppl 1):S3–S17.

Whiteside, L. K., J. Russo, J. Wang, M. L. Ranney, V. Neam, and D. F. Zatzick. 2016. Predictors of sustained prescription opioid use after admission for trauma in adolescents. *Journal of Adolescent Health* 58(1):92–97.

Part IV
Research Barriers and Recommendations

15
Challenges and Barriers in Conducting Cannabis Research

Several states have legalized cannabis for medical or recreational use since the release of the 1999 Institute of Medicine (IOM)[1] report *Marijuana and Medicine: Assessing the Science Base* (IOM, 1999). As of October 2016, 25 states and the District of Columbia had legalized the medical use of cannabis, while four states and the District of Columbia had also legalized recreational cannabis use (NCSL, 2016; NORML, 2016a).[2] In November 2016, voters in California, Maine, Massachusetts, and Nevada approved ballot initiatives to legalize recreational cannabis, while voters in Arkansas, Florida, Montana, and North Dakota approved ballot initiatives to permit or expand the use of cannabis for medical purposes (NORML, 2016b).

Policy changes are associated with marked changes in patterns of cannabis use. In recent years, the number of U.S. adolescents and adults aged 12 and older who reported using cannabis increased by 35.0 percent and 20.0 percent for use in the past month and in the past year, respectively (Azofeifa et al., 2016). Revenue from the sale and taxation of cannabis can serve as a proxy measure for cannabis use and suggests that the scope of cannabis use in the United States is considerable. For example, the total estimated value of legal cannabis sales in the United States was $5.7 billion in 2015 and $7.1 billion in 2016 (Arcview Market Research and New Frontier Data, 2016). At the state level, the Colorado Department of Revenue reported that sales and excise taxes on recreational and medical cannabis sales totaled $88,239,323 in fiscal year 2015 (CDOR, 2016, p. 29),[3] and in Washington, state and local sales taxes and state business and occupation taxes on recreational and medical cannabis totaled $53,410,661 in fiscal year 2016 (WDOR, 2016ab).[4]

Despite these changes in state policy and the increasing prevalence of cannabis use and its implications for population health, the federal government has not legalized cannabis and continues to enforce restrictive policies and regulations on research into the health benefits or harms of cannabis products that are available to consumers in a majority of states. These policies and regulations may impose barriers to conducting research on the health effects of cannabis and cannabinoids has been limited in the United States, leaving patients, health care professionals, and policy makers without the evidence they need to make sound decisions regarding the use of

[1] As of March 2016, the Health and Medicine Division continues the task of producing consensus studies and convening activities previously undertaken by the Institute of Medicine.

[2] The count of states where cannabis is legalized for medical use includes Ohio and Pennsylvania, where medical cannabis laws were not operational as of October 2016 (NCSL, 2016).

[3] $22,225,750 (Marijuana Sales Tax (2.9%)) + $42,017,798 (Retail Marijuana Sales Tax [10%]) + $23,995,775 (Retail Marijuana Excise Tax [15%]) = $88,239,323.

[4] Medical Cannabis: $5,236,536 (State Retail Sales Tax) + $792,906 (State Business and Occupation Tax) + $ 2,084,323 (Local Retail Sales Tax) = $8,113,765. Recreational Cannabis: $30,017,823 (State Retail Sales Tax) + $4,050,212 (State Business & Occupation Tax) + $11,228,861 (Local Retail Sales Tax) = $45,296,896. $8,113,765 (Total Medical Cannabis Taxes) + $45,296,896 (Total Recreational Cannabis Taxes) = $53,410,661.

cannabis and cannabinoids. This lack of evidence-based information on the health effects of cannabis and cannabinoids poses a public health risk.

In order to promote research on cannabis and cannabinoids, the barriers to such research must first be identified and addressed. The committee identified several barriers to conducting basic, clinical, and population health research on cannabis and cannabinoids, including regulations and policies that restrict access to the cannabis products that are used by an increasing number of consumers and patients in state-regulated markets, funding limitations, and numerous methodological challenges. The following sections discuss these barriers in detail.

REGULATORY, SUPPLY, AND FINANCIAL BARRIERS

Regulatory Barriers

Investigators seeking to conduct research on cannabis or cannabinoids must navigate a series of review processes that may involve the National Institute on Drug Abuse (NIDA), the U.S. Food and Drug Administration (FDA), the U.S. Drug Enforcement Administration (DEA), institutional review boards, offices or departments in state government, state boards of medical examiners, the researcher's home institution, and potential funders. A brief overview of some of these review processes is discussed.

Researchers conducting clinical research on biological products such as cannabis must submit an investigational new drug (IND) application to the FDA. As a next step, the investigator may contact NIDA, an important source of research-grade cannabis, to obtain an administrative letter of authorization (LOA). A LOA describes the manufacture's facilities, as well as the availability and pertinent characteristics of the desired cannabis product (e.g., strains, quality, strength, pharmacology, toxicology). To safeguard against the acquisition of cannabis or cannabinoids for non-research purposes, investigators must also apply for a DEA registration and site licensure before conducting studies involving cannabis or any of its cannabinoid constituents, irrespective of their pharmacologic activity.[5] The investigator must submit the IND and LOA to the FDA and the DEA for review (FDA, 2015).

After submitting an IND application, researchers must wait at least 30 days before initiating research, during which period the FDA reviews the application to ensure that research participants will not be exposed to unreasonable risk (FDA, 2016b). If the FDA determines that the proposed research would expose study participants to unreasonable risk or that the IND application is in some other way deficient, a clinical hold postponing the research may be imposed. This hold is not lifted until and unless the sponsoring researchers have resolved the deficiencies (FDA, 2016a).

It is important to note that the Controlled Substances Act of 1970 classified cannabis as a Schedule I substance, the highest level of drug restriction.[6] As defined by the Act, Schedule I substance are those that: (1) have a high potential for abuse; (2) have no currently accepted medical use in treatment in the United States; and, (3) have a lack of accepted safety for their use

[5] Code of Federal Regulations, Registration of Manufacturers, Distributors, and Dispensers of Controlled Substances, Title 21, § 1301.11 and Code of Federal Regulations, Schedules of Controlled Substances, Title 21, § 1308.11.

[6] Code of Federal Regulations, Schedules of Controlled Substances, Title 21, § 1308.11; United States Code, Schedules of Controlled Substances, Title 21, § 812.

under medical supervision.[7] Other substances classified in Schedule I include heroin, LSD, mescaline, hallucinogenic amphetamine derivatives, fentanyl derivatives (synthetic opioid analgesics), and gammahydroxybutyrate (GHB).[8] By contrast, Schedule II substances, though they also have a high potential for abuse and may lead to severe psychological or physical dependence, are defined as having a currently accepted medical use and can be prescribed with a controlled substance prescription (DEA, 2006).[9]

In some states, researchers conducting clinical research on cannabis or cannabinoids products must also apply for and receive a controlled substance certificate from a state board of medical examiners or a controlled substance registration from a department of the state government in order to conduct clinical trials or any other activity involving Schedule I substances (Alabama Board of Medical Examiners, 2013; MDHSS, n.d.). Some state governments require additional approvals. For example, California requires that all trials involving Schedule I or II controlled substances to be registered with and approved by the Research Advisory Panel of California (CADOJ/OAG, 2016). When the necessary approvals are secured, only then can the investigator apply for a DEA registration and site licensure to conduct research on a Schedule I controlled substance.

Researchers conducting trials of Schedule I substances must additionally submit a research protocol to the DEA that includes details regarding the security provisions for storing and dispensing the substance.[10] Previously, non-federally funded studies on cannabis were also required to undergo an additional review process conducted by the Public Health Service. This review process was determined to unnecessarily duplicate the FDA's IND application process in several ways, and as of June 2015 is no longer required.[11]

To ensure that controlled substances obtained for research purposes will be stored and accessed in accordance with DEA security requirements, local DEA officials may perform a pre-registration inspection of the facility where the proposed research will take place (University of Colorado, 2016). DEA security requirements include storing cannabis in a safe, steel cabinet, or vault, and limiting access to the storage facility to "an absolute minimum number of specifically authorized employees.[12] The extent of the security measures required by DEA varies with the amount of cannabis being stored,[13] and among local DEA jurisdictions (Woodworth, 2011). Funders must bear the costs of meeting the necessary security requirements.

Additionally, as with any human clinical trial, approval from an institutional review board must be sought.[14] Obtaining this approval confirms that an appropriate plan to protect the rights and welfare of human research subjects has been outlined in the proposed research efforts.

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[7] United States Code, Schedules of Controlled Substances, Title 21, § 812(b)(1).

[8] Code of Federal Regulations, Schedules of Controlled Substances, Title 21, § 1308.11.

[9] United States Code, Schedules of Controlled Substances, Title 21, § 812(b)(2).

[10] Code of Federal Regulations, Registration of Manufacturers, Distributors, and Dispensers of Controlled Substances, Title 21, § 1301.18.

[11] Office of the Secretary, Office of the Assistant Secretary for Health, Department of Health and Human Services. Notice. "Announcement of Revision to the Department of Health and Human Services Guidance on Procedures for the Provision of Marijuana for Medical Research as Published on May 21, 1999," Federal Register, 80, no. 120 (June 23, 2015): 35960, https://www.gpo.gov/fdsys/pkg/FR-2015-06-23/pdf/2015-15479.pdf.

[12] Code of Federal Regulations, Registration of Manufacturers, Distributors, and Dispensers of Controlled Substances, Title 21, § 1301.72 (a) and (d).

[13] Code of Federal Regulations, Registration of Manufacturers, Distributors, and Dispensers of Controlled Substances, Title 21, § 1301.71 (c).

[14] Code of Federal Regulations, Institutional Review Boards, Title 21, § 56.103.

If a study is being conducted in a clinical research center, a separate review may be required by this entity's medical or research advisory committee.

In summary, basic and clinical researchers seeking to obtain cannabis or cannabinoids from NIDA for research purposes, including efforts to determine the value of cannabis or cannabinoids for treating a medical condition or achieving a therapeutic end need, must obtain a number of approvals from a range of federal, state, or local agencies, institutions, or organizations. This process can be a daunting experience for researchers. The substantial layers of bureaucracy that emerge from cannabis's Schedule I categorization is reported to have discouraged a number of cannabis researchers from applying for grant funding or pursing additional research efforts (Nutt et al., 2013). Given the many gaps in the research of the health effects of cannabis and cannabinoids, there is need to address these regulatory barriers so that researchers will be better able to address key public health questions about the therapeutic and adverse effects of cannabis and cannabinoid use.

CONCLUSION 15-1 There are specific regulatory barriers, including the classification of cannabis as a Schedule I substance, that impede the advancement of cannabis and cannabinoid research.[15]

Barriers to Cannabis Supply

In the United States, cannabis for research purposes is only available through the NIDA Drug Supply Program (NIDA, 2016d). The mission of NIDA is to "advance science on the causes and consequences of drug use and addiction and to apply that knowledge to improve individual and public health", rather than to pursue or support research into the potential therapeutic uses of cannabis or any other drugs (NIDA, 2016c). As a result of this emphasis, less than one-fifth of cannabinoid research funded by NIDA in fiscal year 2015 concerns the therapeutic properties of cannabinoids (NIDA, 2016e).[16] Since NIDA funded the majority of all the National Institutes of Health (NIH)-sponsored cannabinoid research in fiscal year 2015 (NIDA, 2016e),[17] its focus on the consequences of drug use and addiction constitutes an impediment to research on the potential beneficial health effects of cannabis and cannabinoids.

All of the cannabis that NIDA provides to investigators is sourced from the University of Mississippi, which is currently the sole cultivator of the plant material and has been since 1968 (NIDA, 1998, 2016d).[18] In the past, the varieties of cannabis that were available to investigators

[15] The committee was specifically directed in its statement of task not to comment on cannabis policy issues, such as regulatory options for legalization, taxation, or distribution. While the committee has identified the Schedule 1 classification of cannabis as posing a significant barrier to the conduct of scientific research on the health effects of cannabis, the committee is aware that any decision on the regulation of cannabis involves many factors far outside the committees remit and expertise. Specifically, the committee did not comment on the abuse or dependency liability or accepted medical use of cannabis compared to other scheduled drugs.

[16] In fiscal year 2015, NIDA's investment in cannabinoid research totaled $66,078,314, of which $10,923,472 was allocated for therapeutic cannabinoid research (NIDA, 2016e).

[17] In fiscal year 2015, NIH's investment in cannabinoid research totaled $ $111,275,219, of which $66,078,314 was allocated to NIDA (NIDA, 2016e).

[18] NIDA contracts with the University of Mississippi through an open solicitation process. Although the University of Mississippi is currently NIDA's only supplier of research grade cannabis, other groups can compete for the contract (NIDA, 2015, 2016d).

through NIDA were limited in scope and were not of comparable potency to what patients could obtain at their dispensaries (Stith and Vigil, 2016). Because of restrictions on production and vicissitudes in supply and demand, federally produced cannabis may have been harvested years earlier, is stored in a freezer (a process that may affect the quality of the product) (Taschwer and Schmid, 2015; Thomas and Pollard, 2016), and often has a lower potency than cannabis sold in state-regulated markets (Reardon, 2015; Stith and Vigil, 2016). In addition, many products available in state-regulated markets (e.g., edibles, concentrates, oils, wax, topicals) are not commonly available through federal sources (NIDA, 2016b). Since the products available through the federal system do not sufficiently reflect the variety of products used by consumers, research conducted using cannabis provided by NIDA may lack external validity. In July 2016, NIDA posted a formal request for information on the varieties of cannabis and cannabis products of interest to researchers (NIDA, 2016f). Reflecting the perceived shortcomings of cannabis and cannabis products currently provided by NIDA, a summary of the comments received in response to this request states that "the most consistent recommendation was to provide marijuana strains and products that reflect the diversity of products available in state dispensaries" (NIDA, 2016f).

Naturally, it is difficult for a single facility at the University of Mississippi to replicate the array and potency of products available in dispensaries across the country. It is worth noting, however, that NIDA has been increasingly responsive to the needs of clinical investigators. For example, NIDA has contracted with the University of Mississippi to produce cannabis strains with varying concentrations of delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) (NIDA, 2016b), and NIDA has previously authorized development of cannabis extracts, tinctures, and other dosage formulations for research purposes (Thomas and Pollard, 2016). As mentioned above, NIDA has sought public comment on the needs of cannabis researchers in order to inform efforts to "expand access to diverse marijuana strains and products for research purposes" (NIDA, 2016f). In addition, cannabis is made available to research investigators funded by the National Institutes of Health at no cost.[19] Finally, the DEA has adopted a new policy that increases the number of entities that may be registered under the Controlled Substances Act (CSA) to grow (manufacture) marijuana to supply legitimate researchers in the United States.[20] Under this new policy, the DEA will facilitate cannabis research by increasing the number of private entities allowed to cultivate and distribute research-grade cannabis. As of December 2016, the University of Mississippi remains the sole cultivator of cannabis provided to researchers by NIDA (NIDA, 2016d).

Although new plans are being made to provide a wider array of more clinically relevant cannabis products for research, at present this issue is still a significant barrier for conducting comprehensive research on the health effects of cannabis use. How the proposed changes will affect cannabis research in the future remains to be seen.

[19] In December 2016, cannabis provided by NIDA was generally free for NIH-sponsored research. For research not funded by the federal government, the cost of non-placebo cannabis was $10.96 per cigarette and $1,133 per pound ($2,497 per kilogram) (NIDA, 2016b).

[20] DEA,U.S. Department of Justice. Policy Statement. "Applications to Become Registered Under the Controlled Substances Act to Manufacture Marijuana to Supply Researchers in the United States," Federal Register, 81, no. 156 (August 12, 2016): 53846, https://www.gpo.gov/fdsys/pkg/FR-2016-08-12/pdf/2016-17955.pdf (accessed January 7, 2017).

CONCLUSION 15-2 It is often difficult for researchers to gain access to the quantity, quality, and type of cannabis product necessary to address specific research questions on the health effects of cannabis use.

BOX 15-1
Illustrative Examples of the Current Research Barriers to Colorado Researchers

As a concrete example of the impact of the divide between federal and state policy, cannabis concentrate sales doubled in Colorado from 2015 to 2016, reaching $60.5 million in the first quarter of 2016 (Marijuana Business Daily Staff, 2016), and yet current federal law prevents chemists from examining the composition of those products as it may relate to safety, neuroscientists from testing the effects of those products on the brain or physiology in animal models, and clinical scientists from conducting research on how these products may help or harm patients. And while between 498,170 and 721,599 units of medical and recreational cannabis edibles were sold per month in Colorado in 2015 (CDOR, 2016b, p. 12), federal law also prohibits scientists from testing those products for contaminants, understanding the effects of these products in animal models, or investigating the effects in patient populations.

Funding

Funding for research is another key barrier; without adequate financial support, cannabis research will be unable to inform healthcare or public health practice or to keep pace with changes in cannabis policy and patterns of cannabis use. NIH is responsible for funding research across a number of health domains. In 2015, NIH spending on all cannabinoid research totaled $111,275,219 (NIDA, 2016e). NIDA, a member institute of NIH, has as its mission to study factors related to substance abuse and dependence and conducts research on the negative health effects and behavioral consequences associated with the abuse of cannabis and other drugs (NIDA, 2016c). Because cannabis was historically perceived to have only negative effects, the majority of cannabis research has been conducted under the auspices of NIDA.

In fiscal year 2015, studies supported by NIDA accounted for 59.3 percent ($66,078,314) of all NIH spending on cannabinoid research; however, only 16.5 percent ($10,923,472) of NIDA's spending on cannabinoid research supported studies investigating therapeutic properties of cannabinoids (NIDA, 2016e).[21,22] As demonstrated in Chapter 4 of this report, a growing body of evidence suggests that cannabis and cannabinoids also have therapeutic health effects. In light of these findings, a comprehensive research agenda that investigates both the potential adverse and therapeutic health effects of cannabis use is needed.

However, it may be unrealistic to expect NIDA to have the resources or interest to fund this broader research agenda, which could involve investigating the health effects of cannabis use on a diverse range of conditions (e.g., metabolic syndrome, cardiovascular disease, cancer,

[21] $66,078,314 (Total NIDA spending on cannabinoid research in fiscal year 2015) / $111,275,219 (Total NIH spending on cannabinoid research in fiscal year 2015) = 0.593. $10,923,472 (Total NIDA spending on therapeutic cannabinoid research in fiscal year 2015) / $66,078,314 (Total NIDA spending on cannabinoid research in fiscal year 2015) = 0.165.

[22] By contrast, NIH spending on tobacco research totaled $300 million in 2015, and spending on research related to the harms and benefits of alcohol use totaled $473 million in 2015 (NIH, 2016).

obesity and sedentary behavior, Alzheimer's disease) that are targeted by other institutes and centers of NIH. While it is not clear how these studies might be funded, almost assuredly the changing norms and the changing legal status of cannabis will have an impact on conditions that are targeted by institutes other than NIDA, and it will become increasingly important to have a funding mechanism to better understand the comprehensive health effects of cannabis so that consumers and policy makers can respond to changing trends accordingly.

CONCLUSION 15-3 A diverse network of funders is needed to support cannabis and cannabinoid research that explores the beneficial and harmful health effects of cannabis use.

METHODOLOGICAL CHALLENGES

Drug Delivery Challenges

Another challenge in investigating the potential health effects of cannabis and cannabinoids is the identification of a method of administering the drug that is accepted by study participants, that can be performed at most research sites, and that ensures standardized dosing. Smoking as a route of administration is particularly challenging, as some study participants may not view it as an acceptable method of drug administration, and academic medical centers or other locations where cannabis or cannabinoid research takes place may lack facilities where study participants can smoke under controlled conditions. Furthermore, variations among individuals in terms of their cannabis smoking techniques make it difficult to ensure that study participants reliably receive the targeted dose of the drug. Devices for providing a metered dose of cannabis via inhalation exist (Eisenberg et al., 2014), but the FDA has not approved such devices for use. Standardized smoking techniques have also been developed (Foltin et al., 1988), but can be difficult to perform correctly. These difficulties are due in part to differences among individuals in their tolerance of the potential psychoactive effects of the drug (D'Souza et al., 2008; Ramaekers et al., 2009), which may prevent the receipt of equal doses by all study participants.

Researchers have also explored vaporization as a method for administering cannabis (Abrams et al, 2007). Cannabinoids vaporize at lower temperatures than the temperature at which pyrolytic toxic compounds are created through combustion; as a result, levels of some carcinogenic compounds are lower in cannabis vapor than in cannabis smoke (Eisenberg et al., 2014). However, there is a paucity of research on the effectiveness of these devices as a mode of drug administration. For example, data on the plasma concentrations of cannabinoids achieved through use of vaporizers exists, but is limited (Abrams et al, 2007; Zuurman et al., 2008). In addition, even less is known about the long-term pulmonary effects of inhaling a vaporized liquid than about the effect of inhaling plant material. As vaporizing devices proliferate and evolve, researchers may benefit from advances in their portability and usability, but will also have to account for clinically relevant differences in the functioning and effectiveness of an increasingly wide range of models.

To circumvent the practical and methodological challenges involved in administration of cannabis through smoking or vaporization, investigators may choose to study the health effects of orally administered dronabinol or nabilone, which offer a more controlled method of drug delivery. However, the effects generated by these isolated cannabinoids might be at least in part

different from those produced by the use of the whole cannabis plant, which also contains cannabidiol (CBD) and other cannabinoids, as well as terpenoids and flavonoids. As a result, extrapolating from the observed health effects associated with use of an isolated cannabinoid such as dronabinol or nabilone in order to predict the health effects associated with the use of cannabis may lead to erroneous conclusions.

The Placebo Issue

The gold standard of drug development is the prospective, randomized, double-blind, placebo-controlled clinical trial. Placebo cannabis produced by solvent extraction is available from NIDA, and has a potency of 0.002 percent THC by weight and 0.001 percent CBD by weight (NIDA, 2016b).[23] The extraction process seems to retain the terpenoids and flavonoids so that the combusted placebo material smells similar to the true cannabis, thus helping to preserve the blinding to some extent. However, the psychoactive and vasoactive effects of cannabis pose a considerable challenge for effective blinding, since study participants who feel such effects will surmise that they are receiving cannabis or cannabinoids, and not a placebo.

Strategies to promote the effectiveness of blinding exist. For example, if the cannabis being studied has a very low THC content, study participants—especially those who, through regular use of more potent cannabis strains, are inured to the psychoactive effects of cannabis with low THC content—may not notice the psychoactive effects of the cannabis and therefore be unable to reliably determine whether they are using cannabis or a placebo. There is also a possibility that cannabis products with a lower ratio of the concentration of THC to the concentration of CBD may have less psychoactivity than products with a comparatively higher ratio of the concentration of THC to the concentration of CBD (Hindocha et al., 2015; Jacobs et al., 2016). Using these strains with diminished psychoactive effects could promote more effective blinding. Researchers may also try treating both study arms in a placebo-controlled cannabis trial with a mildly psychoactive or sedating drug, the effects of which may help to ensure that study participants are unable to determine whether they are receiving a placebo or cannabis. However, by introducing another active agent the investigators risk obfuscating the results of their study.

A potential method for assessing the effectiveness of blinding in a cannabis trial is to ask study participants to guess whether they are receiving true cannabis or placebo. If most or all of the participants correctly guess their assignment, it can be inferred that the blinding was ineffective. Whether or not such methods are employed, investigators risk undermining their study results. On the one hand, conducting the test carries the risk of discovering that attempts at blinding were ineffective, thereby rendering the study results invalid. On the other hand, not conducting the test may lead journal reviewers aware of the challenges of blinding in cannabis trials to assume that blinding was ineffective and to discount the study results accordingly. Thus, research to address the challenge of achieving reliably effective blinding in a cannabis trial is of marked importance.

[23] In December 2016, placebo cannabis provided by NIDA was generally free for NIH-sponsored research. For research not funded by the federal government, the cost of placebo cannabis was $13.94 per cigarette and $1,133 per pound ($2,497 per kilogram) (NIDA, 2016b).

Exposure Assessment

In order to arrive at valid and meaningful results, population studies on the health effects of cannabis require as detailed an ascertainment of exposure to cannabis as possible. However, obtaining such a detailed exposure history can be difficult. This is especially true for recreational cannabis use, due to the lack of a standardized dose and the existence of diverse routes of administration, including multiple modes of inhalation (Schauer et al., 2016). In addition, known pharmacological biomarkers of cannabis use may be unreliable in some circumstances, while population studies to identify novel pharmacological biomarkers of cannabis exposure are limited (Hartman et al., 2016; Schwope et al., 2011). Furthermore, the wide variety of different cannabis strains developed through a long and ongoing process of cultivation and the associated variation in the concentration of active substances in cannabis further complicates the characterization of cannabis exposure (ElSohly and Gul, 2014; Elsohly et al., 2016; Mehmedic et al., 2010). Finally, recreational cannabis may contain chemical contaminants or adulterants (Busse et al., 2008). Cannabis users may be unaware of the presence of these chemicals, making it unlikely that such chemicals would be identified through toxicological evaluation unless the user became involved in a forensic investigation.

Most observational studies, particularly case-control and cohort studies, depend on self-report in order to assess cannabis exposure. These reports may be incomplete, inaccurate, or imprecise due to failure on the part of investigators to ask cannabis users detailed questions about their cannabis exposure history, including the source of their cannabis exposure (e.g., smoking, edibles, vaping), or because users themselves may have limited knowledge of some aspects of their exposure or may be resistant to reporting some information. Personal recall of substance use may also be affected by other factors. For example, memory problems have been identified as a cause of inaccuracies in reporting drug use (Johnson and Fendrich, 2005; Pedersen, 1990). In other cases, study participants may not report illicit substance use in attempt to conform to perceived social norms (Johnson and Fendrich, 2005). Similarly, individuals with substance dependency syndromes may have psychiatric co-morbidity that affects the accuracy of reporting.

Finally, important information often missing from cannabis exposure histories is the extent of other substance use. As noted in Chapter 14, there is limited evidence that cannabis use is associated with the use of other licit or illicit substances. Despite this association and the confounding effect of polysubstance use on evaluations of the health effects of cannabis use, surveys used to characterize cannabis exposure histories do not always assess for the presence of other substance use. Since second-hand exposure to cannabis smoke can have minor health effects, there may also be value in assessing for such exposure as part of larger assessments of cannabis exposure (Herrmann et al., 2015).

Cannabis-Related Study Designs

In researching the health outcomes of cannabis use, the committee identified a number of studies, particularly cohort studies, of general health outcomes such as all-cause mortality or important chronic illnesses such as cancers or cardiovascular diseases. For both cohort and case-control studies, a better assessment of cannabis use would offer more valuable information, such as years of use and age at first use. Particularly for cohort studies, this would offer better ascertainment of the duration and net burden of use as well as more insight into period and age

effects. As discussed in the proceeding health outcomes chapters of the report, in many of the existing cohort studies cannabis use was often queried only at baseline, and thus there was little information on interval use over time or on the variation or cessation in that use. There was also very limited information on interval health events as the cohorts progressed, impeding a summarization of long-term use and the consequent health effects. Attention to these issues will likely improve the precision of study findings.

CONCLUSION 15-4 To develop conclusive evidence for the effects of cannabis use on short- and long-term health outcomes, improvements and standardization in research methodology (including those used in controlled trials and observational studies) are needed.

SUMMARY

The methodological challenges and the regulatory, financial, and access barriers described above markedly affect the ability to conduct comprehensive basic, clinical, and public health research on the health effects of cannabis use, with further consequences for the many potential beneficiaries of such research. In the absence of an appropriately funded and supported cannabis research agenda, patients may be unaware of viable treatment options, providers may be unable to prescribe effective treatments, policy makers may be hindered from developing evidence-based policies, and health care organizations and insurance providers lack a basis on which to revise their care and coverage policies. In short, such barriers represent a public health problem. See Box 15-2 for a summary of the chapter conclusions.

BOX 15-2
Summary of Chapter Conclusions*

There are several challenges and barriers in conducting cannabis and cannabinoid research, including:

- There are specific regulatory barriers, including the classification of cannabis as a Schedule I substance, that impede the advancement of cannabis and cannabinoid research (15-1)
- It is often difficult for researchers to gain access to the quantity, quality, and type of cannabis product necessary to address specific research questions on the health effects of cannabis use (15-2)
- A diverse network of funders is needed to support cannabis and cannabinoid research that explores the beneficial and harmful health effects of cannabis use (15-3)
- To develop conclusive evidence for the effects of cannabis use on short- and long-term health outcomes, improvements and standardization in research methodology (including those used in controlled trials and observational studies) are needed (15-4)

* Numbers in parentheses correspond to chapter conclusion numbers.

REFERENCES

Abrams, D. I., H. P. Vizoso, S. B. Shade, C. Jay, M. E. Kelly, and N. L. Benowitz. 2007. Vaporization as a smokeless cannabis delivery system: A pilot study. *Clinical Pharmacology & Therapeutics* 82(5):572–578.

Alabama Board of Medical Examiners. 2013. Chapter 540-X-4: Controlled Substances Certificate in *Alabama Board of Medical Examiners Administrative Code*. http://www.alabamaadministrativecode.state.al.us/docs/mexam/540-X-4.pdf (accessed December 29, 2016).

Arcview Market Research and New Frontier Data. 2016. *The State of Legal Marijuana Markets, 4th Edition: Executive Summary*. San Francisco, CA: The Arcview Group. http://mjardin.com/wp-content/uploads/2016/05/Executive-Summary-State-of-Legal-Marijuana-Markets-4th-Edition-1.pdf (accessed December 8, 2016).

Azofeifa, A., M. E. Mattson, G. Schauer, T. McAfee, A. Grant, and R. Lyerla. 2016. National estimates of marijuana use and related indicators—national survey on drug use and health, United States, 2002–2014. *The Morbidity and Mortality Weekly Report Surveillance Summaries* 65(11):1–28.

Busse, F., L. Omidi, K. Timper, A. Leichtle, M. Windgassen, E. Kluge, and M. Stumvoll. 2008. Lead poisoning due to adulterated marijuana. *New England Journal of Medicine* 358(15):1641–1642.

CADOJ/OAG (State of California Department of Justice/Office of the Attorney General). 2016. *Research Advisory Panel: Guidelines*. https://oag.ca.gov/research/guide (accessed November 3, 2016).

CDOR (Colorado Department of Revenue). 2016. *Annual Report 2015*. Denver, CO: Colorado Department of Revenue. https://www.colorado.gov/pacific/sites/default/files/2015%20Annual%20Report_1.pdf (accesssed December 8, 2016).

CDOR 2016b. *MED 2015 Annual Update*. Denver, CO: Colorado Department of Revenue. https://www.colorado.gov/pacific/sites/default/files/2015%20Annual%20Update%20FINAL%2009262016_1.pdf (accessed December 7, 2016).

DEA (U.S. Drug Enforcement Administration). 2006. Section V: Valid Prescription Requirements. iIn *Practitioner's Manual: An Informational Outline of the Controlled Substances Act.* Washington, DC: Drug Enforcement Administration. Pp. 18–22. https://www.deadiversion.usdoj.gov/pubs/manuals/pract/pract_manual012508.pdf (accessed December 28, 2016).

D'Souza, D. C., M. Ranganathan, G. Braley, R. Gueorguieva, Z. Zimolo, T. Cooper, E. Perry, and J. Krystal. 2008. Blunted psychotomimetic and amnestic effects of delta-9-tetrahydrocannabinol in frequent users of cannabis. *Neuropsychopharmacology* 33(10):2505–2516.

Eisenberg, E., M. Ogintz, and S. Almog. 2014. The pharmacokinetics, efficacy, safety, and ease of use of a novel portable metered-dose cannabis inhaler in patients with chronic neuropathic pain: A phase 1a study. *Journal of Pain & Palliativce Care Pharmacotherapy* 28(3):216–225.

ElSohly, M., and W. Gul. 2014. Chapter 5: The Chemical Phenotypes (Chemotypes) of Cannabis. In *Handbook of Cannabis,* edited by R. Pertwee. New York: Oxford University Press. Pp. 89–110.

ElSohly, M. A., Z. Mehmedic, S. Foster, C. Gon, S. Chandra, and J. C. Church. 2016. Changes in cannabis potency over the last 2 decades (1995–2014): Analysis of current data in the United States. *Biological Psychiatry* 79(7):613–619.

FDA (U.S. Food and Drug Administration). 2015. Marijuana Research with Human Subjects. http://www.fda.gov/NewsEvents/PublicHealthFocus/ucm421173.htm (accessed January 3, 2017).

FDA 2016a. IND Application Procedures: Clinical Hold. http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/ucm362971.htm (accessed December 8, 2016).

FDA 2016b. Investigational New Drug (IND) Application: Introduction. http://www.fda.gov/drugs/developmentapprovalprocess/howdrugsaredevelopedandapproved/approvalapplications/investigationalnewdrugindapplication/default.htm (accessed December 8, 2016).

Fischedick, J., F. Van Der Kooy, and R. Verpoorte. 2010. Cannabinoid receptor 1 binding activity and quantitative analysis of cannabis sativa l. Smoke and vapor. *Chemical and Pharmaceutical Bulletin* 58(2):201–207.

Foltin, R., M. Fischman, and M. Byrne. 1988. Effects of smoked marijuana on food intake and body weight of humans living in a residential laboratory. *Appetite* 25:577–582.

Hartman, R. L., T. L. Brown, G. Milavetz, A. Spurgin, D. A. Gorelick, G. R. Gaffney, and M. A. Huestis. 2016. Effect of blood collection time on measured delta9-tetrahydrocannabinol concentrations: Implications for driving interpretation and drug policy. *Clinical Chemistry* 62(2):367–377.

Herrmann, E. S., E. J. Cone, J. M. Mitchell, G. E. Bigelow, C. LoDico, R. Flegel, and R. Vandrey. 2015. Non-smoker exposure to secondhand cannabis smoke II: Effect of room ventilation on the physiological, subjective, and behavioral/cognitive effects. *Drug and Alcohol Dependence* 151:194–202.

Hindocha, C., T. P. Freeman, G. Schafer, C. Gardener, R. K. Das, C. J. Morgan, and H. V. Curran. 2015. Acute effects of delta-9-tetrahydrocannabinol, cannabidiol and their combination on facial emotion recognition: A randomised, double-blind, placebo-controlled study in cannabis users. *European Neuropsychopharmacology* 25(3):325–334.

IOM (Institute of Medicine). 1999. *Marijuana and medicine: Assessing the science base*. Washington, DC: National Academy Press.

Jacobs, D. S., S. J. Kohut, S. Jiang, S. P. Nikas, A. Makriyannis, and J. Bergman. 2016. Acute and chronic effects of cannabidiol on delta(9)-tetrahydrocannabinol (delta(9)-THC)-induced disruption in stop signal task performance. *Experimental and Clinical Psychopharmacology* 24(5):320–330.

Johnson, T., and M. Fendrich. 2005. Modeling sources of self-report bias in a survey of drug use epidemiology. *Annals of Epidemiology* 15(5):381–389.

Lanz, C., J. Mattsson, U. Soydaner, and R. Brenneisen. 2016. Medicinal cannabis: In vitro validation of vaporizers for the smoke-free inhalation of cannabis. *PLoS ONE* 11(1):e0147286.

Marijuana Business Daily Staff. 2016. Chart of the Week: Sales of Marijuana Concentrates, Edibles Surging in Colorado. Marijuan Business Daily, June 13. http://mjbizdaily.com/chart-of-the-week-sales-of-marijuana-concentrates-edibles-surging-in-colorado (accessed December 29, 2016).

Mehmedic, Z., S. Chandra, D. Slade, H. Denham, S. Foster, A. S. Patel, S. A. Ross, I. A. Khan, and M. A. ElSohly. 2010. Potency trends of delta9-THC and other cannabinoids in confiscated cannabis preparations from 1993 to 2008. *Journal of Forensic Science* 55(5):1209–1217.

MDHSS (Missourri Department of Health and Senior Services). n.d. *Frequently Asked Questions*. http://health.mo.gov/safety/bndd/faqs.php (accessed December 29, 2016).

NCSL (National Conference of State Legislatures). 2016. *State Medical Marijuana Laws*. http://www.ncsl.org/research/health/state-medical-marijuana-laws.aspx (accessed December 22, 2016).

NIDA (National Institute on Drug Abuse). 1998. *Provision of Marijuana and Other Compounds for Scientific Research—Recommendations of the National Institute on Drug Abuse National Advisory Council*. https://archives.drugabuse.gov/about/organization/nacda/MarijuanaStatement.html (accessed December 29, 2016).

NIDA. 2015. *Information on Marijuna Farm Contract*. https://www.drugabuse.gov/drugs-abuse/marijuana/nidas-role-in-providing-marijuana-research/information-marijuana-farm-contract (accessed December 29, 2016).

NIDA. 2016a. *Marijuana and cannabinoid research at NIDA*. https://www.drugabuse.gov/drugs-abuse/marijuana/marijuana-cannabinoid-research-nida (accessed November 3, 2016).

NIDA. 2016b. *Marijuana plant material available from the NIDA drug supply program*. https://www.drugabuse.gov/researchers/research-resources/nida-drug-supply-program-dsp/marijuana-plant-material-available-nida-drug-supply-program (accessed November 3, 2016).

NIDA. 2016c. *National Institute on Drug Abuse (NIDA): Mission*. https://www.nih.gov/about-nih/what-we-do/nih-almanac/national-institute-drug-abuse-nida (accessed December 9, 2016).
NIDA. 2016d. *NIDA's Role in Providing Marijuana for Research*. https://www.drugabuse.gov/drugs-abuse/marijuana/nidas-role-in-providing-marijuana-research (accessed December 8, 2016).
NIDA. 2016e. *NIH Research on Marijuana and Cannabinoids*. https://www.drugabuse.gov/drugs-abuse/marijuana/nih-research-marijuana-cannabinoids (accessed December 29, 2016).
NIDA. 2016f. *Summary of Request for Information (RFI) Regarding Varieties of Marijuana and Marijuana Products for Research*. https://www.drugabuse.gov/drugs-abuse/marijuana/nidas-role-in-providing-marijuana-research/summary-request-information-rfi-regarding-varieties-marijuana-marijuana-products-research (accessed November 3, 2016).
NIH (National Institutes of Health). 2016. *Estimates of Funding for Various Research, Condition, and Disease Categories (RCDC)*. https://report.nih.gov/categorical_spending.aspx#legend1 (accessed December 29, 2016).
NORML (National Organization for the Reform of Marijuana Laws). 2016a. *About Marijuana*. http://norml.org/marijuana (accessed December 22, 2016).
NORML 2016b. *Election 2016—Marijuana Ballot Results*. http://norml.org/election-2016 (accessed December 22, 2016).
Nutt, D. J., L. A. King, and D. E. Nichols. 2013. Effects of Schedule I drug laws on neuroscience research and treatment innovation. *Nature Reviews Neuroscience* 14(8):577–585
Pedersen, W. 1990. Reliability of drug use responses in a longitudinal study. *Scandinavian Journal of Psychology* 31(1):28–33.
Pomahacova, B., F. Van der Kooy, and R. Verpoorte. 2009. Cannabis smoke condensate III: The cannabinoid content of vaporised cannabis sativa. *Inhalation Toxicology* 21(13):1108–1112.
Ramaekers, J. G., G. Kauert, E. L. Theunissen, S. W. Toennes, and M. R. Moeller. 2009. Neurocognitive performance during acute thc intoxication in heavy and occasional cannabis users. *Journal of Psychopharmacology* 23(3):266–277.
Reardon, S. 2015. Marijuana gears up for production high in U.S. labs. *Nature* 519(7543): 269–270.
Schauer, G. L., B. A. King, R. E. Bunnell, G. Promoff, and T. A. McAfee. 2016. Toking, vaping, and eating for health or fun: Marijuana use patterns in adults, U.S., 2014. *American Journal of Preventative Medicine* 50(1):1–8.
Schwope, D. M., E. L. Karschner, D. A. Gorelick, and M. A. Huestis. 2011. Identification of recent cannabis use: Whole-blood and plasma free and glucuronidated cannabinoid pharmacokinetics following controlled smoked cannabis administration. *Clinical Chemistry* 57(10):1406–1414.
Solowij, N., S. J. Broyd, H. H. van Hell, and A. Hazekamp. 2014. A protocol for the delivery of cannabidiol (CBD) and combined CBD and 9-tetrahydrocannabinol (THC) by vaporisation. *BMC Pharmacology and Toxicology* 15:58.
Stith, S. S., and J. M. Vigil. 2016. Federal barriers to cannabis research. *Science* 352(6290): 1182.
Taschwer, M., and M. G. Schmid. 2015. Determination of the relative percentage distribution of THCA and Δ(9)-THC in herbal cannabis seized in Austria - Impact of different storage temperatures on stability. *Forensic Science International* 254:167–171.
Thomas, B. F., and G. T. Pollard. Preparation and distribution of cannabis and cannabis-derived dosage formulations for investigational and therapeutic use in the United States. *Frontiers in Pharmacology* 7:285.
University of Colorado. 2016. *Drug Enforcement Administration (DEA) Controlled Substances*. http://www.ucdenver.edu/research/EHS/hazmat/Pages/DEA.aspx (accessed December 22, 2016).
WDOR (Washington Department of Revenue). 2016a. *Medical Marijuana Taxes*. http://dor.wa.gov/Docs/Reports/2014/MMJTax.xlsx (accessed December 8, 2016).
_____. 2016b. *Recreational Marijuana Taxes*. http://dor.wa.gov/Docs/Reports/2014/RMJTax.xlsx (accessed December 8, 2016).

Woodworth, T. W. 2011. How Will DEA Affect Your Clinical Study? Journal of Clinical Research Best Practices 7(12). https://firstclinical.com/journal/2011/1112_DEA.pdf (accessed December 8, 2016).

Zuurman, L., C. Roy, R. C. Schoemaker, A. Hazekamp, J. den Hartigh, J. C. Bender, R. Verpoorte, J. L. Pinquier, A. F. Cohen, and J. M. van Gerven. 2008. Effect of intrapulmonary tetrahydrocannabinol administration in humans. *Journal of Psychopharmacology* 22(7):707–716.

16

Recommendations to Support and Improve the Cannabis Research Agenda

This is a pivotal time in the world of cannabis policy and research. Shifting public sentiment, conflicting and impeded scientific research, and legislative battles have fueled the debate about what, if any, harms or benefits can be attributed to the use of cannabis or its derivatives. The committee has put forth a substantial number of research conclusions on the health effects of cannabis or cannabinoid. Based on their research conclusions, the members of the committee formulated four specific recommendations to address research gaps, improve research quality, improve surveillance capacity, and address research barriers. The report's full recommendations are described below.

ADDRESS RESEARCH GAPS

To address the research gaps outlined throughout this report, a comprehensive national research agenda will be required. The aspirational goal and organizing principle of this agenda should be to maximize the population health impact of cannabis research. Achieving this objective will require coordination and collaboration among researchers and research groups; support from stakeholders at the local, state, and national levels; and, the concurrent pursuit of several distinct research streams, including clinical and observational research and research in the areas of health policy, health economics, public health, and public safety.

The research agenda should include basic science studies to help inform efforts to maximize benefits and minimize harms associated with the acute and chronic use of cannabis and cannabinoids, as well as health policy and public health research to examine the health effects of broader social and behavioral changes associated with the legalization of recreational and/or medical cannabis and other changes in cannabis policy. To support the statistical associations identified in epidemiological research, the research agenda should also include basic science research that identifies plausible mechanisms by which cannabis affects specific health endpoints. Furthermore, translational research should be embedded in each of these research streams to ensure that research findings will be of practical use to help inform health care practices, public health priorities, national and state policy, and public safety standards.

Recommendation 1: To develop a comprehensive evidence base on the short- and long-term health effects of cannabis use (both beneficial and harmful effects), public agencies,[1] philanthropic and professional organizations, private companies, and clinical and public

[1] Agencies may include the CDC, relevant agencies of the NIH, and the FDA.

health research groups should provide funding and support for a national cannabis research agenda that addresses key gaps in the evidence base. Prioritized research streams and objectives should include, but need not be limited to:

Clinical and Observational Research

- Examine the health effects of cannabis use in at-risk or under-researched populations, such as children and youth (often described as less than 18 years of age) and older populations (generally over 50 years of age), pregnant and breastfeeding women, and heavy cannabis users.
- Investigate the pharmacokinetic and pharmacodynamic properties of cannabis, modes of delivery, different concentrations, in various populations, including the dose–response relationships of cannabis and THC or other cannabinoids.
- Determine the benefits and harms associated with understudied cannabis products, such as edibles, concentrates, and topicals.
- Conduct well-controlled trials on the potential beneficial and harmful health effects of using different forms of cannabis, such as inhaled (smoked or vaporized) whole cannabis plant and oral cannabis.
- Characterize the health effects of cannabis on unstudied and understudied health endpoints, such as epilepsy in pediatric populations; symptoms of posttraumatic stress disorder; childhood and adult cancers; cannabis-related overdoses and poisonings; and other high-priority health endpoints.

Health Policy and Health Economics Research

- Identify models, including existing state cannabis policy models, for sustainable funding of national, state, and local public health surveillance systems.
- Investigate the economic impact of recreational and medical cannabis use on national and state public health and health care systems, health insurance providers, and patients.

Public Health and Public Safety Research

- Identify gaps in the cannabis-related knowledge and skills of health care and public health professionals, and assess the need for, and performance of, continuing education programs that address these gaps.
- Characterize public safety concerns related to recreational cannabis use and evaluate existing quality assurance, safety, and packaging standards for recreational cannabis products.

IMPROVE RESEARCH QUALITY

In order to effectively guide health care decisions and inform public policy, the proposed cannabis research agenda must produce conclusive, actionable evidence. This will require research studies to be carefully designed and rigorously conducted and to have their data results accurately and comprehensively reported.

Ensuring that cannabis research is of uniformly high quality will require the development of guidelines for data collection, standards for research design and reporting, standardized terminology, and a minimum dataset for clinical and epidemiological studies.

Data collection guidelines could prioritize alternate methods for assessing cannabis use, such as whole blood or urine analysis, over those based on self-report or prescriptions. Standards for research design and methodology could require that researchers attempt to account for the confounding effects of alcohol, tobacco, or other relevant substances of abuse. Standards for research reporting could require that authors of systematic reviews report the key demographic characteristics of the study population, as well as information related to cannabis dose, frequency of use, and route of administration. A universal, standardized terminology would help to create standard units for describing cannabis use. Because much of the existing epidemiological research on cannabis use fails to distinguish between cannabis that is smoked and cannabis that is administered orally, topically, or via other routes, health effects associated with cannabis use may be conflated with those associated with smoking per se. To correct this, future research will need to employ data collection methods that distinguish between different types of cannabis and different routes of cannabis administration.

Wherever possible, these efforts should adapt existing tools to the particular needs and constraints of cannabis research. For example, workshop participants could build on commonly used guidelines and standards for conducting and reporting research, including PRISMA, CONSORT, STROBE, and Cochrane guidelines for systematic reviews.

Adequately addressing these topics will require input from numerous stakeholders, including clinical and public health cannabis researchers, research methodologists, representatives from working groups that have developed research reporting guidelines, organizations engaged in standards development, representatives from scientific publications, and representatives from government agencies directly or indirectly involved in the research process, including CDC, NIH, the U.S. Department of Health and Human Services, and FDA.

Recommendation 2: To promote the development of conclusive evidence on the short- and long-term health effects of cannabis use (both beneficial and harmful effects), agencies of the United States Department of Health and Human Services, including the National Institutes of Health and the Centers for Disease Control and Prevention should jointly fund a workshop to develop a set of research standards and benchmarks to guide and ensure the production of high-quality cannabis research. Workshop objectives should include, but need not be limited to:

- The development of a minimum dataset for observational and clinical studies, standards for research methods and design, and guidelines for data collection methods.
- Adaptation of existing research-reporting standards to the needs of cannabis research.
- The development of uniform terminology for clinical and epidemiological cannabis research.
- The development of standardized and evidence-based question banks for clinical research and public health surveillance tools.

IMPROVE SURVEILLANCE CAPACITY

The development of a comprehensive and conclusive evidence base on the health effects of cannabis must begin with data collection. In turn, data collection on a scale sufficient to guide state and national policy will require a diverse array of powerful surveillance tools and technologies.

In many cases, existing surveillance tools can be adapted to further the cannabis research agenda. For example, a recurrent and comprehensive set of cannabis-related questions could be added to existing nation health surveys. Researchers could use the Behavioral Risk Factor Surveillance System to track changes in the prevalence of medical and recreational cannabis use, the Medical Expenditure Panel Survey to assess the impact of medical cannabis laws on healthcare treatments and costs, and the National Vital Statistics System to monitor changes in the incidence rate of cannabis-related overdose deaths.

In other cases, novel diagnostic technologies will need to be developed to aid data collection efforts. For example, the growing incidence of cannabis poisonings among children and the demonstrated risks associated with driving under the influence of cannabis, underscore the need for rapid and non-invasive methods of assessing for acute cannabis intoxication.

Multiple stakeholders can contribute to these efforts. CDC's Center for Surveillance, Epidemiology and Laboratory Services, the Questionnaire Design Research Laboratory at the National Center for Health Statistics, and the Center for Behavioral Health Statistics and Quality at the Substance Abuse and Mental Health Services Administration (SAMHSA) can aid in the design and evaluation of survey questions that accurately capture key data points relating to cannabis use. State public health departments can collaborate with Association of Public Health Laboratories (APHL) to use existing public health laboratories to provide diagnostic tools and other laboratory resources to meet the needs of clinical and public health professionals engaged in cannabis research. Because of differences in cannabis product type, availability, access, and regulation, for the time being, such surveillance efforts need to be state-based.

In their potential role as conveners, the National Association of County and City Health Officials (NACCHO) and the Association of State and Territorial Health Officials (ASTHO) can aid federal agencies and state and local health departments in assessing the capacity to expand the resources of public health surveillance systems, as well as articulating strategies and prioritizing the actions necessary to meet the needs of a comprehensive cannabis research agenda.

Recommendation 3: To ensure that sufficient data are available to inform research on the short- and long-term health effects of cannabis use (both beneficial and harmful effects), the Centers for Disease Control and Prevention, the Substance Abuse and Mental Health Services Administration, the Association of State and Territorial Health Officials, National Association of County and City Health Officials, the Association of Public Health Laboratories, and state and local public health departments should fund and support improvements to federal public health surveillance systems and state-based public health surveillance efforts. Potential efforts should include, but need not be limited to:

- The development of question banks on the beneficial and harmful health effects of therapeutic and recreational cannabis use and their incorporation into major public health surveys, including the National Health and Nutrition Examination Survey, National Health Interview Survey, Behavioral Risk Factor Surveillance System,

National Survey on Drug Use and Health, Youth Risk Behavior Surveillance System, National Vital Statistics System, Medical Expenditure Panel Survey, and the National Survey of Family Growth.

- Determining the capacity to collect and reliably interpret data from diagnostic classification codes in administrative data (e.g., *International Classification of Diseases-10*)
- The establishment and utilization of state-based testing facilities to analyze the chemical composition of cannabis and products containing cannabis, cannabinoids, or THC.
- The development of novel diagnostic technologies that allow for rapid, accurate, and non-invasive assessment of cannabis exposure and impairment.
- Strategies for surveillance of harmful effects of cannabis for therapeutic use.

ADDRESS RESEARCH BARRIERS

The designation of cannabis as a Schedule I substance imposes numerous regulatory barriers that limit access to the funding and material resources necessary to conduct cannabis research. Unless these barriers are directly addressed, or creative solutions are developed to circumvent the challenges they pose, a comprehensive national cannabis research agenda will remain an elusive goal.

The evidence discussed in this report suggests that cannabis has both therapeutic value and public health risks. The public health case for pursuing cannabis research, which is premised on this potential for benefit and harm, is sharpened by the increased prevalence of cannabis use in states where medical and recreational cannabis has been legalized.

To ensure that policy makers are better informed to make decisions on cannabis research and policy, and to explore and characterize the full scope of political and non-political strategies for resolving regulatory barriers to cannabis research, an objective and evidence-based analysis of cannabis policy is necessary.

Recommendation 4: **The Centers for Disease Control and Prevention, National Institutes of Health, Food and Drug Administration, industry groups, and nongovernmental organizations should fund the convening of a committee of experts tasked to produce an objective and evidence-based report that fully characterizes the impacts of regulatory barriers to cannabis research and that proposes strategies for supporting development of the resources and infrastructure necessary to conduct a comprehensive cannabis research agenda. Committee objectives should include, but need not be limited to:**

- Proposing strategies for expanding access to research-grade marijuana, through the creation and approval of new facilities for growing and storing cannabis.
- Identifying nontraditional funding sources and mechanisms to support a comprehensive national cannabis research agenda.
- Investigating strategies for improving the quality, diversity, and external validity of research-grade cannabis products.

Appendix A
Glossary

adjusted odds ratio – an odds ratio that controls for confounding variables

Ashworth scale – a clinical measure of muscle spasticity based on an assessment of a patient's muscle tone in different muscle groups

association – the statistical relation between two or more events, characteristics, or other variables

cannabinoid – one of a class of chemical compounds that act on cannabinoid receptors, Cannabinoids can be naturally derived from the cannabis plant or manufactured

cannabis – a broad term that can be used to describe the various products and chemical compounds derived from the *Cannabis sativa* or *Cannabis indica* species

cannabis use disorder - according to the *DSM-V*, a problem-causing pattern of cannabis use leading to clinically significant impairment or distress, as manifested by at least two distinguishing symptoms (e.g., cannabis is taken in larger amounts or for longer periods than intended; experience of craving; continued cannabis use despite the experience of physical, social, or interpersonal problems caused by cannabis use) occurring within a 12-month period

case series – an analysis of series of people with the disease (there is no comparison group in case series). Case series studies provide weaker evidence than case-control studies.
case-control study- an observational analytic study that enrolls one group of persons with a certain disease, chronic condition, or type of injury (case-patients) and a group of persons without the health problem (control subjects) and compares differences in exposures, behaviors, and other characteristics to identify and quantify associations, test hypotheses, and identify causes

cohort study – an observational analytic study in which enrollment is based on one's status of exposure to a certain factor or membership in a certain group. Populations are followed, and disease, death, or other health-related outcomes are documented and compared. Cohort studies can be either prospective or retrospective.

comparator – the agent to which the experimental arm of a study is compared, e.g., placebo, usual care, active control

control – comparator against which the study treatment is evaluated (e.g., concurrent [placebo, no treatment, dose–response, active], and external [historical, published literature])"

cross-sectional study - a study in which a sample of persons from a population are enrolled and their exposures and health outcomes are measured simultaneously; a survey

cultivar – a plant variety that has been produced in cultivation by selective breeding

dose – the quantity of a drug that is used at one time or in fractional amounts during a given period of time

dronabinol – a synthetic cannabinoid for oral administration, similar to THC. It is the active ingredient in Marinol®

evidence – information on which a conclusion about a cause-effect relationship is based. The most direct evidence for health effects in humans is usually based on studies of health endpoints that are conducted in humans, including randomized trials and non-randomized epidemiologic studies. Additional evidence can be provided by studies of intermediate endpoints or markers in humans as well as by non-human studies. The committee has developed a strength-of-evidence table so that the level of evidence is expressed in uniform terms and calibrated throughout the report (see Appendix B).

exclusion criteria – a list of characteristics in a protocol, any one of which may exclude a potential subject from participation in a study

health effects – the positive and negative health outcomes resulting from exposure to cannabis or cannabis-derived products

incidence – the number of new cases of a condition, symptom, death, or injury that develop during a specified period of time

inclusion criteria – the criteria in a protocol that prospective subjects must meet to be eligible for participation in a study

marijuana- a *Cannabis sativa* plant-derived product typically composed from the plant's dried leaves, stems, seeds, and buds

meta-analysis – a statistical technique for combining (pooling) the results of a number of studies that address the same question and report on the same outcomes to produce a more precise summary estimate of the effect on a particular outcome. Meta-analyses are frequently used in systematic reviews

morbidity – any departure, subjective or objective, from a state of physiological or psychological health and well-being, e.g., disease, injury, disability

mortality – death or loss of life

nabilone – a synthetic cannabinoid for oral administration, similar to tetrahydrocannabinol (THC). It is the active ingredient in Cesemet®

narrative review – narrative reviews tend to be mainly descriptive, do not involve a systematic search of the literature, and thereby often focus on a subset of studies in an area chosen based on availability or author selection. Generally, a narrative review offer lower-quality evidence than systematic reviews. For this reason and for the purpose of the report, narrative reviews are classified as primary literature

observational study – a study in which the investigator observes rather than influences exposure and disease among participants. Case-control and cohort studies are examples of observational studies

odds ratio (OR) – one measure of treatment effectiveness. It is the odds of an event happening in the experimental group expressed as a proportion of the odds of an event happening in the control group. The closer the OR is to 1, the smaller the difference in effect is between the experimental intervention and the control intervention. If the OR is greater (or less) than 1, then the effects of the treatment are more (or less) than those of the control treatment. Note that the effects being measured may be adverse (e.g., death or disability) or desirable (e.g., survival). When events are rare, the OR is analogous to the relative risk (RR), but as event rates increase the OR and RR diverge

outcome – events or experiences that clinicians or investigators examining the impact of an intervention or exposure measure because they believe such events or experiences may be influenced by the intervention or exposure

pooled estimate – an average derived from multiple studies with varying data but with a common measurement. Typically found in systematic reviews and meta-analyses

potency – the amount of drug required to produce a specific level of effect

pre-clinical – research studies that use cell culture or animal models to test scientific hypotheses. These studies are performed prior to clinical studies that use human subjects

prevalence – the number or proportion of individuals within a given population that share a specific characteristic

primary literature – peer-reviewed accounts of original research that contribute new evidence to science. By comparison, systematic reviews and literature reviews analyze existing evidence. Examples of the types of primary literature used in the report are randomized controlled trials, cohort studies, cross-sectional studies, case-control studies, and case series

problem cannabis use – a symptom of cannabis use disorder. Problem cannabis use includes the experience of persistent or recurrent social, interpersonal, social, occupational, academic, recreational, psychological, or physical problems caused or exacerbated by cannabis use

randomized controlled trial – a trial in which participants are randomly assigned to one of two or more groups, at least one of which (the experimental group) receives an intervention that is being tested and another (the comparison or control group) receives an alternative treatment or placebo. This design allows assessment of the relative effects of interventions

route of administration – the path by which a drug is taken into the body

systematic review – research that summarizes the evidence on a clearly formulated question according to a predefined protocol. Systematic and explicit methods to identify, select and appraise relevant studies and to extract, collate, and report their findings are used. Statistical meta-analysis may or may not be used. Systematic reviews were the optimal data source for identifying associations between cannabis exposure and all the health endpoints discussed in this report

Appendix B
Study Approach

In response to its charge, the committee developed a process defined by discrete actions building towards an evidence base that would eventually inform the committee's findings and conclusions. This process is depicted in Figure B-1.

FIGURE B-1 Summary of the committee's process.

The following sections detail the process by which the committee came to its conclusions about the weight of evidence regarding the association between cannabis and specific health endpoints. The steps include the literature search, the refinement of the specific health endpoints of medical and public health importance to be assessed, the identification and assessment of relevant literature (including published systematic reviews and primary literature), and the development of consistent and specific language to describe the integration of the literature to reflect the weight of evidence.

LITERATURE SEARCH

A professional research librarian worked with the committee to conduct the literature searches used to identify relevant research. Six searches were conducted. An initial search (Search 1) of Medline, Embase, and the Cochrane Database of Systematic Reviews found 19,189 total articles reporting on associations between cannabis exposure and health endpoints. Search 1 included articles that were published between January 1999 and June 2016 and that included a cannabis search term and search terms relevant to health effects of interest in at least one of several search fields (e.g., title, abstract, subject heading). A partial review of the search results found a large number of irrelevant documents. For this reason, a second and more limited search strategy was developed. Search 2 involved the same databases as Search 1 but used different search terms to identify articles associated with specific health endpoints, and it excluded articles with specific terms (e.g., "animal," "spice") in the title or abstract. Search 2 produced 1,978 articles between 1999 and the 2016. The substantial reduction in articles indicated that the more

limited search strategy caused relevant research to be excluded; consequently, a third and broader search strategy was developed.

Search 3 of the same databases produced 7,198 total articles reporting on associations between cannabis exposure and any health endpoint. This search included articles published between 1999 and 2016, excluded articles with specific terms (e.g., "mice," "spice") in the title or abstract, and limited articles by study design (e.g., clinical trial, observational study, systematic review).

The results of Search 2 and Search 3 were combined, and three additional searches were conducted in order to address potential gaps in the overall search results. Search 4 identified 1,396 articles in the PsycINFO database, filling gaps in the committee's collection of literature on the effects of cannabis exposure on mental health and psychosocial endpoints. Using the search term "Nabilone" (a synthetic cannabinoid), Search 5 identified 33 articles in Medline, Embase, and the Cochrane Database of Systematic Reviews that previous searches had not included. Search 6 identified 389 articles and brought the literature up to date by extending the date of publication parameter to August 2, 2016, and including articles published electronically ahead of print. The terms and strategies used in these searches are provided on page B-12 of this appendix. In addition to these six searches, committee members also reviewed their personal libraries, and added potentially relevant articles from these collections to the combined search results.

The results from searches 2 through 6 were combined to create a master library containing 10,759 unique articles, including 1,488 articles initially categorized as systematic reviews. These articles were then sorted into seven major health endpoint topic areas: injury and mortality; cardiovascular and respiratory symptoms and conditions; cancer, immune function, and infections; mental health symptoms and conditions; prenatal, perinatal, and postnatal health effects; psychosocial health effects; and therapeutic health effects.[1] Upon further reflection and review of the available literature, the committee decided to separate the original cardiovascular and respiratory topic area into two individual research topics, as well as to separate out two additional research topics—problem cannabis use, and cannabis use and abuse of other substances from the original mental health topic area. This final list of topic areas was subsequently divided into the 11 health endpoint topic areas covered in the chapters that comprise parts II and III of the report. Within each of these topic areas the committee identified specific research questions relating to health endpoints of medical and public health importance that would be the focus of the report. They based this list on their public health and medical expertise, their knowledge of the cannabis literature, input from the sponsors at the first meeting, and other key reviews about the health effects of cannabis. This process, which reduced the total number of articles to be reviewed by the committee, was necessary to make the scope of the report manageable, but it may have resulted in the exclusion of certain health outcomes of interest to health professionals, researchers, policy makers, or the public. Below, Box B-1 lists the health topic areas and specific health endpoints selected for review by the committee.

[1] The organization of Search 2 results involved different search terms and tools than the organization of Search 3 results. Search 2 topic groups were developed using unique search terms, online databases (Medline, Embase, Cochrane Database of Systematic Reviews), and Ovid search functions. Search 3 topics groups were developed using unique search terms, the Search 3 EndNote library, and the EndNote full-text keyword search function.

BOX B-1
Health Topics and Prioritized Health Endpoints
(listed in the order in which they appear in the report)

Therapeutic effects
- Chronic pain; cancer, chemotherapy-induced nausea/vomiting; appetite and weight loss; irritable bowel syndrome; epilepsy; spasticity related to multiple sclerosis; Tourette syndrome; amyotrophic lateral sclerosis; Huntington's disease; Parkinson's disease; dystonia; Alzheimer's disease/dementia; glaucoma; traumatic brain injury/spinal cord injury; addiction; anxiety; depression; sleep disorders; posttraumatic stress disorder; schizophrenia

Cancer
- Lung cancer; oral cancer; esophageal cancer; testicular cancer; other cancer

Cardiometabolic risk
- Acute myocardial infarction; stroke; metabolic dysregulation, metabolic syndrome, prediabetes, and diabetes

Respiratory disease
- Pulmonary function; respiratory symptoms (including chronic bronchitis); chronic obstructive pulmonary disorder; asthma

Immunity
- Immune Function; infectious disease

Injury and death
- All-cause mortality; occupational injury; motor vehicle crash; overdose injury and death

Prenatal, perinatal, and postnatal exposure to cannabis
- Pregnancy complications for the mother; fetal growth and development; neonatal conditions; later outcomes for the infant

Psychosocial
- Cognition (learning, memory, attention, intelligence); academic achievement and educational outcomes; employment/income; social relationships and other social roles

Mental health
- Schizophrenia other psychotic disorders; bipolar disorders, depression; suicide; anxiety; posttraumatic stress disorder

Problem cannabis use
- Cannabis use disorder

Cannabis Use and abuse of other substances
- Abuse of other substances

After filtering the original search results for articles relevant to the health endpoints of interest, 6,540 primary literature articles and 288 systematic reviews were left to be reviewed by the committee. Given the large number of potentially relevant articles, the committee decided to begin by reviewing the identified systematic reviews. To accomplish this, the committee

modified previously developed approaches for evaluating the quality of the systematic reviews and primary literature. These approaches are described in the systematic review: identification and quality review, primary literature: identification and quality review, and data synthesis and strength of evidence assessment sections below.

The committee identified articles as possibly being systematic reviews based on abstracts or key word searches and then evaluated each of the identified articles for the presence of the key elements of a systematic review by asking the following questions:

1. Does the article describe a search involving at least two databases?
2. Does the article describe a search involving appropriate search terms?
3. Does the article describe a search involving pre-specified eligibility criteria?
4. Does the article include a risk-of-bias discussion and/or quality assessment?
5. Does the article include a meta-analysis or qualitative synthesis of findings?
6. Does the article report on one or more health effect of cannabis on humans?

Articles that were deemed true systematic reviews using the above questions as a guideline were then assessed for quality based on five attributes adapted from other sources (Higgins et al., 2011). In their assessment of the quality of a systematic review, committee members considered the study eligibility criteria, how studies were identified and considered for inclusion, how data were collected and appraised by the authors, the methods by which study findings were selected and synthesized, and whether any conflict of interests were addressed. Below, Box B-2 lists the specific questions committee members were asked to consider in the quality assessment.

BOX B-2
Quality Assessment Questions

QUESTION

Rate your level of concern (high or low) regarding study eligibility criteria. Your response should be informed by the following questions:

Study eligibility criteria

- Was an "a priori" design provided?
- Were study eligibility criteria clearly specified?
- Were restrictions in eligibility criteria appropriate?

Identification and collection of studies

- Was a comprehensive literature search performed?
- Were the terms and structure of the search strategy likely to retrieve as many eligible studies as possible?
- Were restrictions based on date, publication format, or language appropriate? Was selection bias avoided?

Data collection and study appraisal

- Were at least two individuals involved in study selection and data extraction?
- Were the characteristics of the included studies provided?

- Was the scientific quality of the included studies assessed and documented?

Synthesis and findings

- Was the scientific quality of the included studies used appropriately in formulating conclusions?
- Were the methods used to combine the findings of studies appropriate?
- Was between-study variation (heterogeneity) minimal or addressed in the synthesis?
- Was the likelihood of publication bias assessed?
- Are the stated conclusions supported by the data presented?

Conflict of interest

- Was the conflict of interest for the systematic review stated?

Overall quality

- Rate the overall quality of the systematic review

Based on the responses to these questions, the overall quality of the systematic review was rated as good, fair, or poor. To ensure the accuracy of quality assessments, all systematic reviews were rated independently by at least two committee members. Disagreements among committee members regarding the overall quality of a systematic review were resolved through deliberation or by the assessment of a third committee member. Only those systematic reviews rated as good- or fair- quality were used to inform the report's findings, conclusions, and recommendations.

PRIMARY LITERATURE: IDENTIFICATION AND QUALITY REVIEW

For those health endpoints addressed by more than one good- or fair-quality systematic review, the committee gave primacy to the most recently published systematic reviews (since 2011). Any deviations in this process are detailed in the chapter text. For every health endpoint with an associated good- or fair-quality systematic review, the committee also reviewed relevant primary literature published after the cutoff date of the literature search used in that systematic review. For endpoints not addressed by at least one good- or fair-quality systematic review, the committee reviewed all relevant primary literature published between January 1, 1999, and August 2, 2016.

Committee members first reviewed article abstracts to identify and remove editorials, opinion pieces, grey literature, and other documents that were not peer-reviewed cross-sectional studies, case-control studies, cohort studies, randomized controlled trials (RCTs), or non-systematic literature reviews. During this preliminary review, committee members also assessed the relevance of the article to the health endpoint question.

In their in-depth review of the primary literature, committee members were guided by the Cochrane Quality Assessment for randomized controlled trials and the Newcastle–Ottawa Scale for cohort and case-control studies.[2] For a depiction of the flow of articles through the search and selection process, see Figure B-2

[2] The Cochrane Risk Assessment Tool was designed to assess for a risk of bias consequent to flaws in the design, conduct, analysis, and reporting of randomized trials (Higgins, 2011). The Newcastle–Ottawa Scale (NOS)

DATA SYNTHESIS AND STRENGTH OF EVIDENCE ASSESSMENT

After completing the identification and quality-assessment process described above, the committee formulated its findings and conclusions. The committee employed two strategies to ensure that report conclusions and recommendations were based on the best available evidence and that the strength of the evidence informing the conclusions was explicitly articulated. First, the committee privileged evidence drawn from RCTs, followed by non-randomized controlled trials, prospective controlled studies, and case-control studies. Case series and case studies were referenced only in the absence of higher quality studies. Second, the committee developed a set of standardized terms to describe the strength of the evidence informing every conclusion. Informed by the reports of previous IOM committees, the committee developed standard language to categorize the weight of evidence regarding whether cannabis or cannabinoids use (for therapeutic purposes) are an effective or ineffective treatment for the prioritized health endpoints of interest, or whether cannabis or cannabinoid use (primarily for recreational purposes) are statistically associated with the prioritized health endpoints of interest. The weight of the evidence was determined during private deliberations of subgroups of the committee. This hierarchy of evidence does not imply the magnitude of the observed effect or the importance of the health effect from an individual or population standpoint. Instead these terms reflect the quality, quantity, and consistency of the evidence supporting a conclusion. See Box B-3, for the terms and their descriptions.

BOX B-3
Weight-of-Evidence Categories

CONCLUSIVE EVIDENCE

For therapeutic effects: There is strong evidence from randomized controlled trials to support the conclusion that cannabis or cannabinoids are an effective or ineffective treatment for the health endpoint of interest.

For other health effects: There is strong evidence from randomized controlled trials to support or refute a statistical association between cannabis or cannabinoid use and the health endpoint of interest.

For this level of evidence, there are many supportive findings from good-quality studies with no credible opposing findings. A firm conclusion can be made, and the limitations to the evidence, including chance, bias, and confounding factors, can be ruled out with reasonable confidence.

SUBSTANTIAL EVIDENCE

For therapeutic effects: There is strong evidence to support the conclusion that cannabis or cannabinoids are an effective or ineffective treatment for the health endpoint of interest.

For other health effects: There is strong evidence to support or refute a statistical association between cannabis or cannabinoid use and the health endpoint of interest.

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was designed to assess the quality of non-randomized trials to be included in a systematic review. The NOS assesses studies along three dimensions: selection of study groups, comparability of study groups, and determination of endpoints and exposures (Wells et al., 2011)

For this level of evidence, there are several supportive findings from good-quality studies with very few or no credible opposing findings. A firm conclusion can be made, but minor limitations, including chance, bias, and confounding factors, cannot be ruled out with reasonable confidence.

MODERATE EVIDENCE

For therapeutic effects: There is some evidence to support the conclusion that cannabis or cannabinoids are an effective or ineffective treatment for the health endpoint of interest.

For other health effects: There is some evidence to support or refute a statistical association between cannabis or cannabinoid use and the health endpoint of interest.

For this level of evidence, there are several supportive findings from good- to fair-quality studies with very few or no credible opposing findings. A general conclusion can be made, but limitations, including chance, bias, and confounding factors, cannot be ruled out with reasonable confidence.

LIMITED EVIDENCE

For therapeutic effects: There is weak evidence to support the conclusion that cannabis or cannabinoids are an effective or ineffective treatment for the health endpoint of interest.

For other health effects: There is weak evidence to support or refute a statistical association between cannabis or cannabinoid use and the health endpoint of interest.

For this level of evidence, there are supportive findings from fair-quality studies or mixed findings with most favoring one conclusion. A conclusion can be made, but there is significant uncertainty due to chance, bias, and confounding factors.

NO OR INSUFFICIENT EVIDENCE TO SUPPORT THE ASSOCIATION

For therapeutic effects: There is no or insufficient evidence to support the conclusion that cannabis or cannabinoids are an effective or ineffective treatment for the health endpoint of interest.

For other health effects: There is no or insufficient evidence to support or refute a statistical association between cannabis or cannabinoid use and the health endpoint of interest.

For this level of evidence, there are mixed findings, a single poor study, or health endpoint has not been studied at all. No conclusion can be made because of substantial uncertainty due to chance, bias, and confounding factors.

DISCUSSION

The search strategies and processes described above were developed and adopted by the committee in order to adequately address a broad statement of task in a limited time frame, while

adhering to the National Academies of Sciences, Engineering, and Medicine's high standards for the quality and rigor of committee reports. Some limitations to these strategies and processes are discussed below.

First, the committee was not tasked to conduct a systematic review, which would have required a lengthy and robust series of processes. The committee did, however, adopt key features of that process: a comprehensive literature search, assessments by more than one person of the quality (risk of bias) of key literature and the conclusions, pre-specification of the questions of interest before conclusions were formulated, standard language to allow comparisons between conclusions, and declarations of conflict of interest via the National Academies conflict of interest policies. Second, there is a possibility that some literature was missed because of the practical steps taken to narrow a very large literature to one that was manageable within the time-frame available to the committee. Furthermore, very good research may not be reflected in this report because it did not directly address the health endpoint questions that the committee formulated.

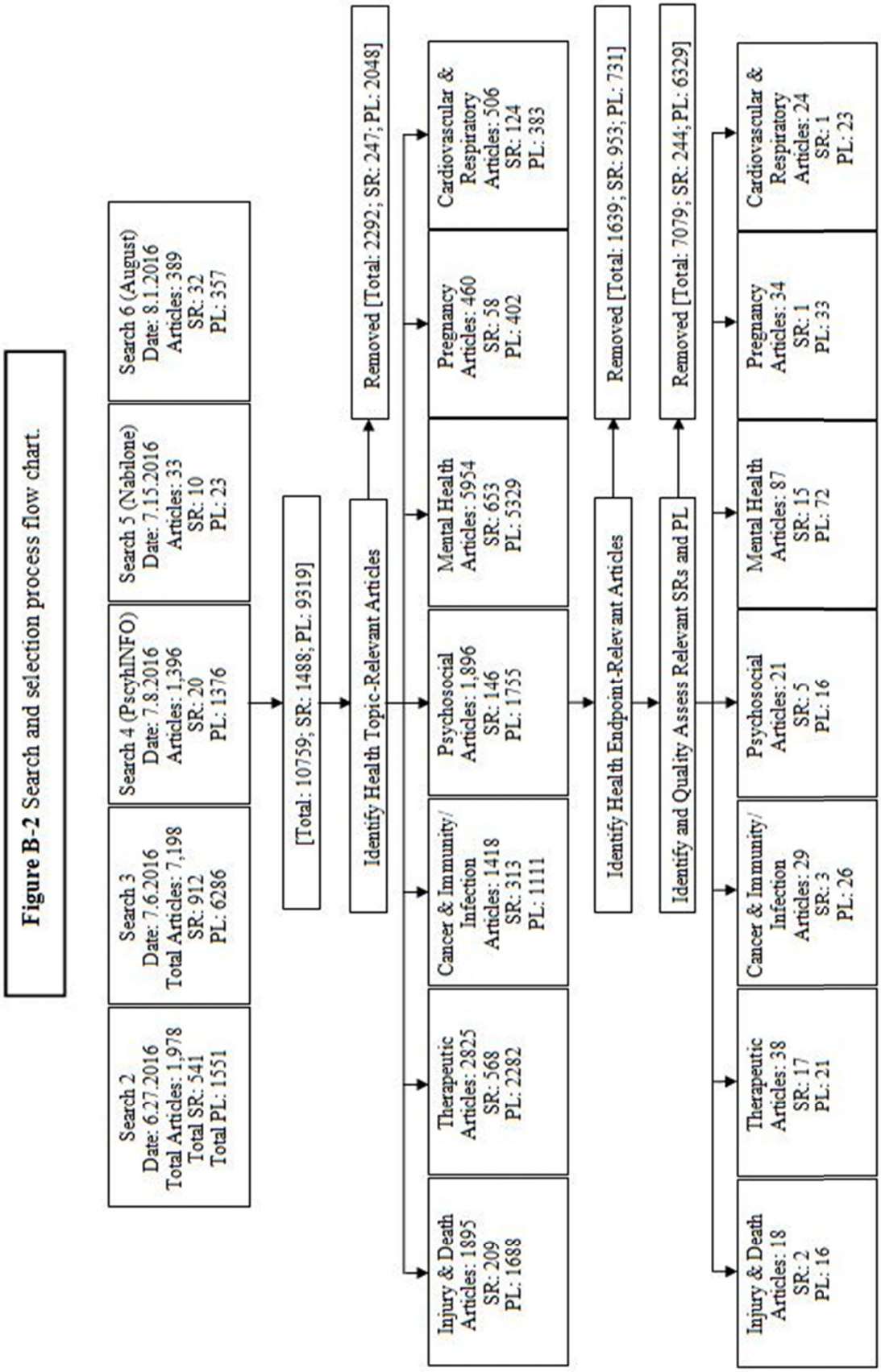

Figure B-2 Search and selection process flow chart.

NOTE: Numbers of systematic reviews and primary literature represent the quantity of unique articles of that type for a given search, or health topic area. Except in the bottom row, the total number of systematic reviews and primary literature for a given search or health topic area will not sum to the total articles for that search or health topic area, due to duplication of articles between systematic review and primary literature groups. Totals across searches and health topic areas will not sum due to duplication among searches and health topic areas.

SEARCH STRATEGIES

Search 2

Date: June 27, 2016

Total citations after eliminating duplicates:
Systematic reviews: 541
Primary literature: 1,551
Total: 1,978

Databases (search engine): Medline (Ovid); Embase (Ovid); Cochrane (Ovid)

Note: Ovid command-line syntax is provided below. Terms immediately followed by a forward slash (/) are Medical Subject Headings (MESH headings from MEDLINE) or EMTREE terms (from the EMBASE controlled vocabulary). The fields searched by a .mp in Embase and Medline include: title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, and unique identifier. The fields searched by a .mp in Cochrane include title, short title, abstract, full text, keywords, caption text.

Beneficial	
Search No.	**Search Syntax**
1	marijuana.mp. or cannabis/
2	cannabis.mp.
3	cannabinoids.mp. or cannabinoid/
4	tetrahydrocannabinol.mp. or tetrahydrocannabinol/
5	dronabinol.mp. or dronabinol/
6	cannabidiol.mp. or cannabidiol/
7	cannabinol.mp. or cannabinol/
8	THC.mp.
9	marinol.mp.
10	or/1-9
11	spice.ti,ab.
12	K2.ti,ab.
13	or/11–12
14	10 not 13
15	Rats/ or rats.ti,ab.
16	Mice/ or mice.ti,ab.
17	animals/ or animals.ti,ab.
18	or/15–17
19	14 not 18
20	Therapeutics/
21	“therapeutic use”.mp.
22	benefits.mp.
23	treatment.mp.
24	therapy.mp.
25	Palliative Care/ or palliation.mp.
26	“Quality of Life”/
27	or/20–26
28	19 and 27

29	Nausea/ or nausea.mp.
30	Vomiting/
31	vomiting.mp.
32	or/28–30
33	28 and 31
34	limit 32 to (abstracts and English language and humans and yr="1999–Current")
35	Analgesia/ or Analgesia.mp.
36	28 and 35
37	limit 36 to (English language and humans and yr="1999–Current")
38	Anxiety/ or anxiety relief.mp. or Anxiety Disorders/
39	28 and 38
40	limit 39 to (English language and humans and yr="1999–Current")
41	irritable bowel syndrome.mp. or Irritable Bowel Syndrome/
42	28 and 41
43	limit 42 to (English language and humans and yr="1999–Current")
44	improved sexual function.mp. or Sexual Behavior/
45	sexual function.mp.
46	or/44–45
47	28 and 46
48	limit 47 to (English language and humans and yr="1999–Current")
49	Interpersonal Relations/ or social relationships.mp.
50	28 and 57
51	limit 50 to (English language and humans and yr="1999–Current")
52	increased appetite.mp. or Appetite/ or Eating/
53	wasting.mp. or Wasting Syndrome/
54	or/52–53
54	28 and 54
55	limit 54 to (English language and humans and yr="1999–Current")
56	Substance-Related Disorders/ or addiction.mp.
57	28 and 56
58	limit 57 to (English language and humans and yr="1999–Current")
59	intraocular pressure.mp. or Intraocular Pressure/
60	28 and 59
61	limit 60 to (English language and humans and yr="1999–Current")
62	PTSD.mp. or Stress Disorders, posttraumatic/
63	trauma.mp.
64	or/62–63
65	28 and 64
66	limit 65 to (English language and humans and yr="1999–Current")
67	Premenstrual Syndrome/ or Premenstrual Dysphoric Disorder/ or premenstrual.mp.
68	28 and 67
69	limit 68 to (English language and humans and yr="1999–Current")
70	Epilepsy/ or seizure control.mp. or Seizures/
71	28 and 70
72	limit 71 to (English language and humans and yr="1999–Current")
73	sleep disorders.mp. or Sleep Wake Disorders/
74	insomnia.mp. or "Sleep Initiation and Maintenance Disorders"/
75	or/73–74
76	28 and 75

77	limit 76 to (English language and humans and yr="1999–Current")
78	Muscle Spasticity/ or Spasticity.mp.
79	Pain/
80	Multiple Sclerosis/
81	or/78–80
82	28 and 81
83	limit 82 to (English language and humans and yr="1999–Current")
84	cancer treatment.mp.
85	cancer prevention.mp.
86	or/84–85
87	28 and 86
88	limit 87 to (English language and humans and yr="1999–Current")
89	brain injury.mp. or Brain Injuries/
90	28 and 89
91	limit 90 to (English language and humans and yr="1999–Current")
92	34 or 37 or 40 or 43 or 48 or 51 or 55 or 58 or 61 or 66 or 69 or 72 or 77 or 83 or 88 or 91
93	limit 92 to (clinical study or clinical trial, all or clinical trial, phase I or clinical trial, phase II or clinical trial, phase III or clinical trial, phase IV or clinical trial or observational study or randomized controlled trial)
94	34 or 37 or 40 or 43 or 48 or 51 or 55 or 58 or 61 or 66 or 69 or 72 or 77 or 83 or 88 or 91
95	limit 94 to (meta-analysis or systematic reviews)
Cancer	
Search No.	**Search Syntax**
1	marijuana.mp. or cannabis/
2	cannabis.mp.
3	cannabinoids.mp. or cannabinoid/
4	tetrahydrocannabinol.mp. or tetrahydrocannabinol/
5	dronabinol.mp. or dronabinol/
6	cannabidiol.mp. or cannabidiol/
7	cannabinol.mp. or cannabinol/
8	THC.mp.
9	marinol.mp.
10	or/1–9
11	spice.ti,ab.
12	K2.ti,ab.
13	or/11–12
14	Rats/ or rats.ti,ab.
15	Mice/ or mice.ti,ab.
16	animals/ or animals.ti,ab.
17	or/14–16
18	10 not 13
19	cancer.mp. or Neoplasms/
20	lung cancer.mp. or Lung Neoplasms/
21	Esophageal Neoplasms/ or Pharyngeal Neoplasms/ or Laryngeal Neoplasms/ or "Head and Neck Neoplasms"/ or upper aerodigestive tract cancer.mp. or Mouth Neoplasms/
22	testicular cancer.mp. or Testicular Neoplasms/
23	childhood cancer.mp.

24	immune system.mp. or Immune System/
25	Immunity/
26	immunity.mp.
27	or/19–26
28	18 and 27
29	28 not 17
30	limit 29 to (human and English language and yr="1999–Current")
31	limit 30 to (clinical study or clinical trial, all or clinical trial, phase I or clinical trial, phase II or clinical trial, phase III or clinical trial, phase IV or clinical trial or observational study or randomized controlled trial)
32	limit 30 to (meta analysis or systematic reviews)
Cardiovascular	
Search No.	**Search Syntax**
1	marijuana.mp. or cannabis/
2	cannabis.mp.
3	cannabinoids.mp. or cannabinoid/
4	tetrahydrocannabinol.mp. or tetrahydrocannabinol/
5	dronabinol.mp. or dronabinol/
6	cannabidiol.mp. or cannabidiol/
7	cannabinol.mp. or cannabinol/
8	THC.mp.
9	marinol.mp.
10	or/1–9
11	Cardiovascular Abnormalities/ or Cardiovascular Diseases/ or cardiovascular.mp.
12	cerebrovascular.mp. or Cerebrovascular Disorders/
13	Peripheral Vascular Diseases/ or peripheral vascular.mp.
14	heart attack.mp. or Myocardial Infarction/
15	Stroke/ or stroke risk.mp.
16	thromboangiitis obliterans.mp. or Thromboangiitis Obliterans/
17	spice.ti,ab.
18	K2.ti,ab.
19	or/17–18
20	10 not 19
21	Rats/ or rats.ti,ab.
22	Mice/ or mice.ti,ab.
23	animals/ or animals.ti,ab.
24	or/21–23
25	or/11–16
26	20 and 25
27	26 not 24
28	27
29	limit 28 to (English language and humans and yr="1999–Current")
30	limit 29 to (clinical study or clinical trial, all or clinical trial, phase I or clinical trial, phase II or clinical trial, phase III or clinical trial, phase IV or clinical trial or observational study or randomized controlled trial)
31	limit 29 to (meta analysis or systematic reviews)

Injury	
Search No.	**Search Syntax**
1	marijuana.mp. or cannabis/
2	cannabis.mp.
3	cannabinoids.mp. or cannabinoid/
4	tetrahydrocannabinol.mp. or tetrahydrocannabinol/
5	dronabinol.mp. or dronabinol/
6	cannabidiol.mp. or cannabidiol/
7	cannabinol.mp. or cannabinol/
8	THC.mp.
9	marinol.mp.
10	or/1–9
11	spice.ti,ab.
12	K2.ti,ab.
13	or/11–12
14	Rats/ or rats.ti,ab.
15	Mice/ or mice.ti,ab.
16	animals/ or animals.ti,ab.
17	or/14–16
18	injury.mp. or “Wounds and Injuries”/
19	10 and 18
20	19 not 13
21	20 not 17
22	21
23	limit 22 to (English language and humans and yr=“1999–Current”)
24	Accidents, Traffic/ or motor vehicle accident.mp.
25	motor vehicle crash.mp.
26	or/24–25
27	10 and 26
28	27 not 13
29	28 not 17
30	29
31	limit 30 to (English language and humans and yr=“1999–Current”)
32	all-cause death.mp.
33	Death/
34	or/32–33
35	10 and 34
36	35 not 13
37	36 not 17
38	37
39	limit 38 to (English language and humans and yr=“1999–Current”)
40	Drug Overdose/
41	overdose death.mp.
42	or/40–41
43	10 and 42
44	43 not 13
45	44 not 17
46	45
47	limit 46 to (English language and humans and yr=“1999–Current”)

48	limit 23 to (clinical study or clinical trial, all or clinical trial, phase I or clinical trial, phase II or clinical trial, phase III or clinical trial, phase IV or clinical trial or observational study or randomized controlled trial)
49	limit 31 to (clinical study or clinical trial, all or clinical trial, phase I or clinical trial, phase II or clinical trial, phase III or clinical trial, phase IV or clinical trial or observational study or randomized controlled trial)
50	limit 39 to (clinical study or clinical trial, all or clinical trial, phase I or clinical trial, phase II or clinical trial, phase III or clinical trial, phase IV or clinical trial or observational study or randomized controlled trial)
51	limit 47 to (clinical study or clinical trial, all or clinical trial, phase I or clinical trial, phase II or clinical trial, phase III or clinical trial, phase IV or clinical trial or observational study or randomized controlled trial)
52	limit 23 to (meta analysis or systematic reviews)
53	limit 31 to (meta analysis or systematic reviews)
54	limit 39 to (meta analysis or systematic reviews)
55	limit 47 to (meta analysis or systematic reviews)
Mental Health	
Search No.	**Search Syntax**
1	marijuana.mp. or cannabis/
2	cannabis.mp.
3	cannabinoids.mp. or cannabinoid/
4	tetrahydrocannabinol.mp. or tetrahydrocannabinol/
5	dronabinol.mp. or dronabinol/
6	cannabidiol.mp. or cannabidiol/
7	cannabinol.mp. or cannabinol/
8	THC.mp.
9	marinol.mp.
10	or/1–9
11	spice.ti,ab.
12	K2.ti,ab.
13	or/11–12
14	Rats/ or rats.ti,ab.
15	Mice/ or mice.ti,ab.
16	animals/ or animals.ti,ab.
17	or/14–16
18	10 not 13
19	mental disease/ or mental health/
20	18 and 19
21	20 not 17
22	21
23	limit 22 to (human and English language and yr="1999–Current")
24	limit 23 to (clinical trial or randomized controlled trial or controlled clinical trial or multicenter study or phase 1 clinical trial or phase 2 clinical trial or phase 3 clinical trial or phase 4 clinical trial)
25	limit 24 to (journal and article)
26	limit 24 to (meta analysis or "systematic review")
27	limit 26 to (journal and (article or review))
28	cannabis addiction/
29	drug abuse/ or drug misuse/

30	cannabis dependence.mp.
31	or/28–30
32	18 and 31
33	32 not 17
34	33
35	limit 34 to (human and english language and yr="1999–Current")
36	limit 35 to (clinical trial or randomized controlled trial or controlled clinical trial or multicenter study or phase 1 clinical trial or phase 2 clinical trial or phase 3 clinical trial or phase 4 clinical trial)
37	limit 36 to (journal and article)
38	limit 35 to (meta analysis or "systematic review")
39	limit 38 to (journal and (article or review))
40	alcohol abuse/
41	tobacco dependence/ or tobacco consumption/
42	"tobacco use"/
43	drug abuse/
44	drug dependence/
45	or/40–44
46	18 and 45
47	46 not 17
48	47
49	limit 48 to (human and English language and yr="1999–Current")
50	limit 49 to (clinical trial or randomized controlled trial or controlled clinical trial or multicenter study or phase 1 clinical trial or phase 2 clinical trial or phase 3 clinical trial or phase 4 clinical trial)
51	limit 50 to (journal and article)
52	limit 49 to (meta analysis or "systematic review")
53	limit 52 to (journal and (article or review))
54	schizophrenia/
55	psychosis/
56	psychotic disorder.mp.
57	or/54–56
58	18 and 57
59	58 not 17
60	59
61	limit 60 to (human and English language and yr="1999–Current")
62	limit 61 to (clinical trial or randomized controlled trial or controlled clinical trial or multicenter study or phase 1 clinical trial or phase 2 clinical trial or phase 3 clinical trial or phase 4 clinical trial)
63	limit 62 to (journal and article)
64	limit 61 to (meta analysis or "systematic review")
65	limit 64 to (journal and (article or review))
66	depression/
67	18 and 66
68	67 not 17
69	68
70	limit 69 to (human and English language and yr="1999–Current")
71	limit 70 to (clinical trial or randomized controlled trial or controlled clinical trial or multicenter study or phase 1 clinical trial or phase 2 clinical trial or phase 3 clinical trial or

	phase 4 clinical trial)
72	limit 71 to (journal and article)
73	limit 70 to (meta analysis or "systematic review")
74	limit 73 to (journal and (article or review))
75	suicide/
76	18 and 75
77	76 not 17
78	77
79	limit 78 to (human and English language and yr="1999–Current")
80	limit 78 to (clinical trial or randomized controlled trial or controlled clinical trial or multicenter study or phase 1 clinical trial or phase 2 clinical trial or phase 3 clinical trial or phase 4 clinical trial)
81	limit 80 to (journal and article)
82	limit 79 to (meta analysis or "systematic review")
83	limit 82 to (journal and (article or review))
84	anxiety/
85	18 and 84
86	85 not 17
87	86
88	limit 87 to (human and English language and yr="1999–Current")
89	limit 88 to (clinical trial or randomized controlled trial or controlled clinical trial or multicenter study or phase 1 clinical trial or phase 2 clinical trial or phase 3 clinical trial or phase 4 clinical trial)
90	limit 89 to (journal and article)
91	limit 88 to (meta analysis or "systematic review")
92	limit 91 to (journal and (article or review))
Pregnancy	
Search. No	**Search Syntax**
1	marijuana.mp. or cannabis/
2	cannabis.mp.
3	cannabinoids.mp. or cannabinoid/
4	tetrahydrocannabinol.mp. or tetrahydrocannabinol/
5	dronabinol.mp. or dronabinol/
6	cannabidiol.mp. or cannabidiol/
7	cannabinol.mp. or cannabinol/
8	THC.mp.
9	marinol.mp.
10	or/1–9
11	spice.ti,ab.
12	K2.ti,ab.
13	or/11–12
14	Rats/ or rats.ti,ab.
15	Mice/ or mice.ti,ab.
16	animals/ or animals.ti,ab.
17	or/14–16
18	10 not 13
19	pregnancy outcomes.mp. or pregnancy outcome/
20	low birthweight.mp. or low birth weight/
21	premature labor/ or pre term delivery.mp.

22	birth defects.mp.
23	stillbirth/
24	miscarriage.mp. or spontaneous abortion/
25	neonatal mortality.mp. or newborn mortality/
26	physical growth.mp. or growth/
27	18 and 19
28	27 not 17
29	28
30	limit 29 to (human and english language)
31	18 and 20
32	31 not 17
33	32
34	limit 33 to (human and English language and yr="1999–Current")
35	18 and 21
36	35 not 17
37	36
38	limit 37 to (human and English language and yr="1999–Current")
39	18 and 22
40	39 not 17
41	40
42	limit 41 to (human and English language and yr="1999–Current")
43	or/23-25
44	18 and 43
45	18 and 43
46	45 not 17
47	46
48	46
49	limit 48 to (human and English language and yr="1999–Current")
50	18 and 26
51	50 not 17
52	51
53	limit 52 to (human and English language and yr="1999–Current")
54	limit 30 to (clinical study or clinical trial, all or clinical trial, phase I or clinical trial, phase II or clinical trial, phase III or clinical trial, phase IV or clinical trial or observational study or randomized controlled trial)
55	limit 30 to (meta analysis or systematic reviews)
56	limit 34 to (clinical study or clinical trial, all or clinical trial, phase I or clinical trial, phase II or clinical trial, phase III or clinical trial, phase IV or clinical trial or observational study or randomized controlled trial)
57	limit 34 to (meta analysis or systematic reviews)
58	limit 38 to (clinical study or clinical trial, all or clinical trial, phase I or clinical trial, phase II or clinical trial, phase III or clinical trial, phase IV or clinical trial or observational study or randomized controlled trial)
59	limit 38 to (meta analysis or systematic reviews)
60	limit 42 to (clinical study or clinical trial, all or clinical trial, phase I or clinical trial, phase II or clinical trial, phase III or clinical trial, phase IV or clinical trial or observational study or randomized controlled trial)
61	limit 42 to (meta analysis or systematic reviews)
62	limit 49 to (clinical study or clinical trial, all or clinical trial, phase I or clinical trial, phase

	II or clinical trial, phase III or clinical trial, phase IV or clinical trial or observational study or randomized controlled trial)
63	limit 49 to (meta analysis or systematic reviews)
64	limit 53 to (clinical study or clinical trial, all or clinical trial, phase I or clinical trial, phase II or clinical trial, phase III or clinical trial, phase IV or clinical trial or observational study or randomized controlled trial)
65	limit 53 to (meta analysis or systematic reviews)
66	breast feeding.mp. or Breast Feeding/
67	18 and 66
68	67 not 17
69	68
70	limit 69 to (English language and humans and yr="1999–Current")
71	Pregnancy/
72	71 and 18
73	72 not 17
74	73
75	limit 74 to (English language and humans and yr="1999–Current")
76	limit 70 to (clinical study or clinical trial, all or clinical trial, phase I or clinical trial, phase II or clinical trial, phase III or clinical trial, phase IV or clinical trial or observational study or randomized controlled trial)
78	limit 70 to (meta analysis or systematic reviews)
80	limit 75 to (clinical study or clinical trial, all or clinical trial, phase I or clinical trial, phase II or clinical trial, phase III or clinical trial, phase IV or clinical trial or observational study or randomized controlled trial)
82	limit 75 to (meta analysis or systematic reviews)
Psychosocial	
Search No.	**Search Syntax**
1	marijuana.mp. or cannabis/
2	cannabis.mp.
3	cannabinoids.mp. or cannabinoid/
4	tetrahydrocannabinol.mp. or tetrahydrocannabinol/
5	dronabinol.mp. or dronabinol/
6	cannabidiol.mp. or cannabidiol/
7	cannabinol.mp. or cannabinol/
8	THC.mp.
9	marinol.mp.
10	or/1–9
11	spice.ti,ab.
12	K2.ti,ab.
13	or/11–12
14	Rats/ or rats.ti,ab.
15	Mice/ or mice.ti,ab.
16	animals/ or animals.ti,ab.
17	or/14–16
18	10 not 13
19	psychosocial.mp. or Social Adjustment/
20	psychosocial effects.mp.
21	or/19–20
22	21 and 18

23	22 not 17
24	limit 23 to (English language and humans and yr="1999–Current")
25	cognitive development.mp.
26	Cognition/
27	Achievement/ or academic achievement.mp.
28	or/25–27
29	28 and 18
30	29 not 17
31	30
32	limit 31 to (English language and humans and yr="1999–Current")
33	cognitive impairment.mp. or Cognition Disorders/
34	33 and 18
35	34 not 17
36	limit 35 to (English language and humans and yr="1999–Current")
37	Employment/
38	Income/
39	or/37–38
40	39 and 18
41	40 not 17
42	limit 41 to (English language and humans and yr="1999–Current")
43	Interpersonal Relations/ or social relationships.mp.
44	43 and 18
45	44 not 17
46	45
47	limit 46 to (English language and humans and yr="1999–Current")
48	Social Behavior/ or social roles.mp.
49	48 and 18
50	49 not 17
51	limit 50 to (English language and humans and yr="1999–Current")
52	24 or 32 or 36 or 42 or 47 or 51
53	limit 52 to (clinical study or clinical trial, all or clinical trial, phase I or clinical trial, phase II or clinical trial, phase III or clinical trial, phase IV or clinical trial or observational study or randomized controlled trial)
54	24 or 32 or 36 or 42 or 47 or 51
55	limit 54 to (meta analysis or systematic reviews)
Respiratory	
Search No.	**Search Syntax**
1	marijuana.mp. or cannabis/
2	cannabis.mp.
3	cannabinoids.mp. or cannabinoid/
4	tetrahydrocannabinol.mp. or tetrahydrocannabinol/
5	dronabinol.mp. or dronabinol/
6	cannabidiol.mp. or cannabidiol/
7	cannabinol.mp. or cannabinol/
8	THC.mp.
9	marinol.mp.
10	or/1–9
11	spice.ti,ab.
12	K2.ti,ab.

13	or/11–12
14	10 not 13
15	Rats/ or rats.ti,ab.
16	Mice/ or mice.ti,ab.
17	animals/ or animals.ti,ab.
18	or/15–17
19	pulmonary.mp. or Pulmonary Disease, Chronic Obstructive/
20	lung disease.mp. or Lung Diseases/ or Respiratory Tract Diseases/ or respiratory disease.mp. or COPD.mp.
21	or/19–20
22	21 and 14
23	22 not 18
24	23
25	limit 24 to (human and English language and yr="1999–Current")
26	limit 25 to (meta analysis or systematic reviews)
27	limit 25 to (clinical study or clinical trial, all or clinical trial, phase I or clinical trial, phase II or clinical trial, phase III or clinical trial, phase IV or clinical trial or observational study or randomized controlled trial)

Search 3

Date: July 6, 2016

Total citations after eliminating duplicates:
Systematic Reviews: 912
Primary Literature: 6,286
Total: 7,198

Databases (search engine): Medline (Ovid); Embase (Ovid); Cochrane (Ovid)

Note: Ovid command-line syntax is provided below. Terms immediately followed by a forward slash (/) are Medical Subject Headings (MESH headings from MEDLINE) or EMTREE terms (from the EMBASE controlled vocabulary). The fields searched by a .mp in Embase and Medline include: title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, and unique identifier. The fields searched by a .mp in Cochrane include title, short title, abstract, full text, keywords, caption text.

Search No.	Search Syntax
1	Cannabis/
2	Marijuana Smoking/
3	Marijuana Abuse/
4	Medical Marijuana/
5	Cannabinoids/
6	Dronabinol/
7	(cannabis or marijuana or cannabinoid or dronabinol or marinol).ti,ab.
8	THC.ti,ab
9	or/1–8
10	k2.ti,ab.
11	spice.ti,ab.

12	or/10-11
13	9 not 12
14	Mice/ or mice.ti,ab.
15	Rats/ or rats.ti,ab.
16	or/14–15
17	13 not 16
18	17
19	limit 18 to (English language and humans)
20	limit 19 to (classical article or clinical study or clinical trial, all or clinical trial, phase I or clinical trial, phase II or clinical trial, phase III or clinical trial, phase IV or clinical trial or comparative study or controlled clinical trial or evaluation studies or guideline or journal article or multicenter study or observational study or practice guideline or pragmatic clinical trial or randomized controlled trial or validation studies)
21	limit 19 to (addresses or autobiography or bibliography or biography or case reports or clinical conference or comment or congresses or consensus development conference or consensus development conference, NIH or "corrected and republished article" or dataset or dictionary or directory or duplicate publication or editorial or english abstract or festschrift or government publications or historical article or in vitro or interactive tutorial or interview or introductory journal article or lectures or legal cases or legislation or letter or meta analysis or news or newspaper article or overall or patient education handout or periodical index or personal narratives or portraits or published erratum or research support, non us gov't or retracted publication or "retraction of publication" or "review" or "scientific integrity review" or systematic reviews or technical report or video-audio media or webcasts)
22	20 not 21
23	limit 22 to yr=1999-current
24	limit 19 to (meta analysis or "review" or systematic reviews)
25	limit 19 to (addresses or autobiography or bibliography or biography or case reports or clinical conference or comment or congresses or consensus development conference or consensus development conference, NIH or "corrected and republished article" or dataset or dictionary or directory or duplicate publication or editorial or english abstract or festschrift or government publications or historical article or in vitro or interactive tutorial or interview or introductory journal article or lectures or legal cases or legislation or letter or news or newspaper article or overall or patient education handout or periodical index or personal narratives or portraits or published erratum or research support, non us gov't or retracted publication or "retraction of publication" or "scientific integrity review" or technical report or video-audio media or webcasts)
26	24 not 25
27	limit 26 to yr=1999-current

Search 4

Date: July 8, 2016

Total citations after eliminating duplicates:
Systematic Reviews: 20
Primary Literature: 1,376
Total: 1,396

Database (search engine): PsycINFO (ProQuest)

Note: Terms with SU in front of them are Subject Headings taken from the Thesaurus of Psychological Index Terms.

Search	Search Syntax
Systematic Reviews + Meta Analysis	((SU("Cannabinoids" OR "Cannabis" OR "Marijuana Usage" OR "Marijuana") OR TI,AB(cannabis OR marijuana OR cannabinoid OR dronabinol) NOT TI,AB("K-2" OR spice)) AND peer(yes) AND (la.exact("ENG"))) AND (me.exact(("Systematic Review" OR "Meta Analysis") NOT ("Empirical Study" OR "Quantitative Study" OR "Interview" OR "Longitudinal Study" OR "Followup Study" OR "Prospective Study" OR "Literature Review" OR "Treatment Outcome/Clinical Trial" OR "Qualitative Study" OR "Brain Imaging" OR "Clinical Case Study" OR "Retrospective Study" OR "Mathematical Model" OR "Twin Study" OR "Focus Group" OR "Field Study" OR "Experimental Replication" OR "Scientific Simulation" OR "Nonclinical Case Study")) AND rtype.exact(("Journal" OR "Peer-reviewed Journal" OR "Journal Article") NOT ("Comment/reply" OR "Editorial" OR "Letter" OR "Erratum/correction" OR "Review-book" OR "Column/opinion" OR "Abstract Collection" OR "Reprint" OR "Review-media" OR "Obituary")) AND po.exact(("Male" OR "Human" OR "Female" OR "Outpatient" OR "Inpatient") NOT "Animal") AND pd(19990101-20161231) AND PEER(yes))
Peer-reviewed Literature	(SU("Cannabinoids" OR "Cannabis" OR "Marijuana Usage" OR "Marijuana") OR TI(cannabis OR marijuana OR cannabinoid OR dronabinol) NOT TI,AB("K-2" OR spice)) AND peer(yes) AND (la.exact("ENG") AND me.exact(("Empirical Study" OR "Quantitative Study" OR "Longitudinal Study" OR "Followup Study" OR "Prospective Study" OR "Treatment Outcome/Clinical Trial" OR "Clinical Case Study" OR "Twin Study") NOT ("Interview" OR "Literature Review" OR "Qualitative Study" OR "Brain Imaging" OR "Mathematical Model" OR "Systematic Review" OR "Meta Analysis" OR "Field Study" OR "Focus Group")) AND rtype.exact(("Journal" OR "Peer-reviewed Journal" OR "Journal Article") NOT ("Comment/reply" OR "Editorial" OR "Letter" OR "Erratum/correction" OR "Review-book" OR "Column/opinion" OR "Abstract Collection" OR "Reprint" OR "Review-media" OR "Obituary"))) AND pd(19990101-20160601)

Search 5

Date: July 15, 2016

Total citations after eliminating duplicates:
Systematic Reviews: 10
Primary Literature: 23
Total: 33

Database (search engine): Medline (Ovid); Embase (Ovid); Cochrane (Ovid)

Note: Ovid command-line syntax is provided below. Terms immediately followed by a forward slash (/) are Medical Subject Headings (MESH headings from MEDLINE) or EMTREE terms (from the EMBASE controlled vocabulary). The fields searched by a .mp in Embase and Medline include: title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, and unique identifier. The fields searched by a .mp in Cochrane include title, short title, abstract, full text, keywords, caption text

Search No.	Search Syntax
1	nabilone.mp
2	spice.ti,ab.
3	K2.ti,ab.
4	or/2–3
5	1 not 4
6	Rats/ or rats.ti,ab.
7	Mice/ or mice.ti,ab.
8	animals/ or animals.ti,ab.
9	or/6–8
10	5 not 9
11	limit 10 to (English language and yr="1999-Current")
12	limit 11 to (clinical study or clinical trial, all or clinical trial, phase I or clinical trial, phase II or clinical trial, phase III or clinical trial, phase IV or clinical trial or observational study or randomized controlled trial)
13	limit 11 to (meta-analysis or systematic reviews)

Search 6

Date: August 2, 2016

Search Parameters: Published June 30, 2016–August 2, 2016

Total citations after eliminating duplicates:
Systematic Reviews: 32
Primary Literature: 357
Total: 389

Database (search engine): Embase (Ovid)

Note: The Medline search was duplicated in PubMed to ensure all e-pub and non-indexed / in-process citations were captured.

Epub Ahead of Print, In-Process and Other Non-Indexed Citations, Ovid MEDLINE(R) Daily, and Ovid MEDLINE(R), 1946 to Present	
Search No.	**Search Syntax**
1	Cannabis/
2	Marijuana Smoking/
3	Marijuana Abuse/
4	Medical Marijuana/
5	Cannabinoids/
6	Dronabinol/
7	(cannabis or marijuana or cannabinoid or dronabinol or marinol).ti,ab.
8	nabilone.ti,ab.
9	or/1–8
10	k2.ti,ab.
11	spice.ti,ab.

12	or/10–11
13	9 not 12
14	Mice/ or mice.ti,ab.
15	Rats/ or rats.ti,ab.
16	or/14–15
17	13 not 16
18	17
19	limit 18 to (English language and humans)
20	limit 19 to (classical article or clinical study or clinical trial, all or clinical trial, phase I or clinical trial, phase II or clinical trial, phase III or clinical trial, phase IV or clinical trial or comparative study or controlled clinical trial or evaluation studies or guideline or journal article or multicenter study or observational study or practice guideline or pragmatic clinical trial or randomized controlled trial or validation studies)
21	limit 19 to (addresses or autobiography or bibliography or biography or case reports or clinical conference or comment or congresses or consensus development conference or consensus development conference, NIH or "corrected and republished article" or dataset or dictionary or directory or duplicate publication or editorial or english abstract or festschrift or government publications or historical article or in vitro or interactive tutorial or interview or introductory journal article or lectures or legal cases or legislation or letter or meta analysis or news or newspaper article or overall or patient education handout or periodical index or personal narratives or portraits or published erratum or research support, non us gov't or retracted publication or "retraction of publication" or "review" or "scientific integrity review" or systematic reviews or technical report or video-audio media or webcasts)
22	20 not 21
23	limit 22 to ed=20160630-20160901
24	limit 19 to (meta-analysis or "review" or systematic reviews)
25	limit 19 to (addresses or autobiography or bibliography or biography or case reports or clinical conference or comment or congresses or consensus development conference or consensus development conference, NIH or "corrected and republished article" or dataset or dictionary or directory or duplicate publication or editorial or english abstract or festschrift or government publications or historical article or in vitro or interactive tutorial or interview or introductory journal article or lectures or legal cases or legislation or letter or news or newspaper article or overall or patient education handout or periodical index or personal narratives or portraits or published erratum or research support, non us gov't or retracted publication or "retraction of publication" or "scientific integrity review" or technical report or video-audio media or webcasts)
26	24 not 25
27	limit 26 to ed=20160630-20160901
Embase (Ovid)	
Search No.	**Search Syntax**
1	major clinical study/
2	clinical article/
3	case report/
4	clinical trial/
5	controlled clinical trial/
6	phase 1 clinical trial/
7	phase 2 clinical trial/
8	phase 3 clinical trial/
9	phase 4 clinical trial/

10	randomized controlled trial/
11	double blind procedure/
12	single blind procedure/
13	crossover procedure/
14	multicenter study/
15	controlled study/
16	“clinical trial (topic)”/
17	“controlled clinical trial (topic)”/
18	“phase 1 clinical trial (topic)”/
19	“phase 2 clinical trial (topic)”/
20	“phase 3 clinical trial (topic)”/
21	“phase 4 clinical trial (topic)”/
22	“randomized controlled trial (topic)”/
23	“multicenter study (topic)”/
24	cannabis/
25	cannabis addiction/ or medical cannabis/ or “cannabis use”/ or cannabis smoking/ or cannabis derivative/
26	cannabinoid/
27	dronabinol/
28	nabilone/
29	(Cannabis or marijuana or cannabinoid or dronabinol or nabilone or marinol).ti,ab.
30	or/24–29
31	k2.ti,ab.
32	spice.ti,ab.
33	or/31–32
34	30 not 33
35	Mice/ or mice.ti,ab.
36	Rats/ or rats.ti,ab.
37	or/35–36
38	34 not 37
39	or/1–23
40	38 and 39
41	limit 40 to (journal and article)
42	limit 40 to (book or book series or chapter or conference abstract or conference paper or conference proceeding or “conference review” or editorial or erratum or letter or note or “review” or short survey or trade journal)
43	41 not 42
44	case report/
45	43 not 44
46	45
47	limit 46 to (human and English language)
48	limit 47 to yr=“2016–Current”
49	limit 48 to dd=20160630-20161231
50	meta analysis/
51	“meta analysis (topic)”/
52	“meta analysis (topic)”/
53	“systematic review (topic)”/
54	or/50–53
55	38 and 54

56	limit 55 to (journal and (article or review))
57	56
58	limit 57 to (human and English language)
59	58
60	limit 59 to yr="2016–Current"
61	limit 60 to dd=20160630-20161231

REFERENCES

Higgins, J. P. T., D. G. Altman, P. C. Gøtzsche, P. Jüni, D. Moher, A. D. Oxman, J. Savovic, K. F. Schulz, L. Weeks, J. A. Sterne, the Cochrane Bias Methods Group, and the Cochrane Statistical Methods Group. 2011. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 343:d5928. doi:10.1136/bmj.d5928.

Wells, G. A., B. Shea, D. O'Connell, J. Peterson, V. Welch, M. Losos, P. Tugwell. 2011. The Newcastle–Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. http:// www. ohri.ca/programs/clinical_ epidemiology/oxford.asp (accessed November 28, 2016).

Appendix C
Systematic Reviews

THERAPEUTIC EFFECTS OF CANNABIS AND CANNABINOIDS

Chronic Pain

Andreae, M. H., G. M. Carter, N. Shaparin, K. Suslov, R. J. Ellis, M. A. Ware, D. I. Abrams, H. Prasad, B. Wilsey, D. Indyk, M. Johnson, and H. S. Sacks. 2015. Inhaled cannabis for chronic neuropathic pain: A meta-analysis of individual patient data. *Journal of Pain* 16(12):1121–1232.

Fitzcharles, M. A., P. A. Ste-Marie, W. Hauser, D. J. Clauw, S. Jamal, J. Karsh, T. Landry, S. LeClercq, J. J. McDougall, Y. Shir, K. Shojania, and Z. Walsh. 2016. Efficacy, tolerability, and safety of cannabinoid treatments in the rheumatic diseases: A systematic review of randomized controlled trials. *Arthritis Care and Research* 68(5):681–688.

Richards, B. L., S. L. Whittle, D. M. Van Der Heijde, and R. Buchbinder. 2012. Efficacy and safety of neuromodulators in inflammatory arthritis: A Cochrane systematic review. *Journal of Rheumatology* 39(Suppl 90):28–33.

Snedecor, S. J., L. Sudharshan, J. C. Cappelleri, A. Sadosky, P. Desai, Y. J. Jalundhwala, and M. Botteman. 2013. Systematic review and comparison of pharmacologic therapies for neuropathic pain associated with spinal cord injury. *Journal of Pain Research* 6:539–547.

Whiting, P. F., R. F. Wolff, S. Deshpande, M. Di Nisio, S. Duffy, A. V. Hernandez, J. C. Keurentjes, S. Lang, K. Misso, S. Ryder, S. Schmidlkofer, M. Westwood, and J. Kleijnen. 2015. Cannabinoids for medical use: A systematic review and meta-analysis. *JAMA* 313(24):2456–2473.

Cancer

Rocha, F., J. dos Santos Junior, S. Stefano, and D. da Silveira. 2014. Systematic review of the literature on clinical and experimental trials on the antitumor effects of cannabinoids in gliomas. *Journal of Neuro-Oncology* 116(1):11–24.

Chemotherapy-Induced Nausea and Vomiting

Phillips, R. S., A. J. Friend, F. Gibson, E. Houghton, S. Gopaul, J. V. Craig, and B. Pizer. 2016. Antiemetic medication for prevention and treatment of chemotherapy-induced nausea and vomiting in childhood. *Cochrane Database of Systematic Reviews* 2:CD007786.

Smith, L. A., F. Azariah, T. C. V. Lavender, N. S. Stoner, and S. Bettiol. 2015. Cannabinoids for nausea and vomiting in adults with cancer receiving chemotherapy. *Cochrane Database of Systematic Reviews* 11:CD009464.

Whiting, P. F., R. F. Wolff, S. Deshpande, M. Di Nisio, S. Duffy, A. V. Hernandez, J. C. Keurentjes, S. Lang, K. Misso, S. Ryder, S. Schmidlkofer, M. Westwood, and J. Kleijnen. 2015. Cannabinoids for medical use: A systematic review and meta-analysis. *JAMA* 313(24):2456–2473.

Anorexia and Weight Loss

Lutge, E. E., A. Gray, and N. Siegfried. 2013. The medical use of cannabis for reducing morbidity and mortality in patients with HIV/AIDS. *Cochrane Database of Systematic Reviews* 4:CD005175.

Whiting, P. F., R. F. Wolff, S. Deshpande, M. Di Nisio, S. Duffy, A. V. Hernandez, J. C. Keurentjes, S. Lang, K. Misso, S. Ryder, S. Schmidlkofer, M. Westwood, and J. Kleijnen. 2015. Cannabinoids for medical use: A systematic review and meta-analysis. *JAMA* 313(24):2456–2473.

Irritable Bowel Syndrome (IBS)

The committee did not identify any good- or fair-quality systematic reviews that reported on IBS.

Epilepsy

Gloss, D., and B. Vickrey. 2014. Cannabinoids for epilepsy. *Cochrane Database of Systematic Reviews* 3:CD009270.

Koppel, B. S., J. C. Brust, T. Fife, J. Bronstein, S. Youssof, G. Gronseth, and D. Gloss. 2014. Systematic review: Efficacy and safety of medical marijuana in selected neurologic disorders: Report of the Guideline Development Subcommittee of the American Academy of Neurology. *Neurology* 82(17):1556–1563.

Spasticity Associated with Multiple Sclerosis and Paraplegia Caused by Spinal Cord Injury

Koppel, B. S., J. C. Brust, T. Fife, J. Bronstein, S. Youssof, G. Gronseth, and D. Gloss. 2014. Systematic review: Efficacy and safety of medical marijuana in selected neurologic disorders: Report of the Guideline Development Subcommittee of the American Academy of Neurology. *Neurology* 82(17):1556–1563.

Whiting, P. F., R. F. Wolff, S. Deshpande, M. Di Nisio, S. Duffy, A. V. Hernandez, J. C. Keurentjes, S. Lang, K. Misso, S. Ryder, S. Schmidlkofer, M. Westwood, and J. Kleijnen. 2015. Cannabinoids for medical use: A systematic review and meta-analysis. *JAMA* 313(24):2456–2473.

Tourette Syndrome

Koppel, B. S., J. C. Brust, T. Fife, J. Bronstein, S. Youssof, G. Gronseth, and D. Gloss. 2014. Systematic review: Efficacy and safety of medical marijuana in selected neurologic disorders: Report of the Guideline Development Subcommittee of the American Academy of Neurology. *Neurology* 82(17):1556–1563.

Whiting, P. F., R. F. Wolff, S. Deshpande, M. Di Nisio, S. Duffy, A. V. Hernandez, J. C. Keurentjes, S. Lang, K. Misso, S. Ryder, S. Schmidlkofer, M. Westwood, and J. Kleijnen. 2015. Cannabinoids for medical use: A systematic review and meta-analysis. *JAMA* 313(24):2456–2473.

Amyotrophic Lateral Sclerosis (ALS)

The committee did not identify any good- or fair-quality systematic reviews that reported on ALS.

Huntington's Disease

Koppel, B. S., J. C. Brust, T. Fife, J. Bronstein, S. Youssof, G. Gronseth, and D. Gloss. 2014. Systematic review: Efficacy and safety of medical marijuana in selected neurologic disorders: Report of the Guideline Development Subcommittee of the American Academy of Neurology. *Neurology* 82(17):1556–1563.

Parkinson's Disease

Koppel, B. S., J. C. Brust, T. Fife, J. Bronstein, S. Youssof, G. Gronseth, and D. Gloss. 2014. Systematic review: Efficacy and safety of medical marijuana in selected neurologic disorders: Report of the Guideline Development Subcommittee of the American Academy of Neurology. *Neurology* 82(17):1556–1563.

Dystonia

Koppel, B. S., J. C. Brust, T. Fife, J. Bronstein, S. Youssof, G. Gronseth, and D. Gloss. 2014. Systematic review: Efficacy and safety of medical marijuana in selected neurologic disorders: Report of the Guideline Development Subcommittee of the American Academy of Neurology. *Neurology* 82(17):1556–1563.

Dementia

Krishnan, S., R. Cairns, and R. Howard. 2009. Cannabinoids for the treatment of dementia. *Cochrane Database of Systematic Reviews* 2:CD007204.

van den Elsen, G. A. H., A. I. A. Ahmed, M. Lammers, C. Kramers, R. J. Verkes, M. A. van der Marck, and M. G. M. O. Rikkert. 2014. Efficacy and safety of medical cannabinoids in older subjects: A systematic review. *Ageing Research Reviews* 14(1):56–64.

Glaucoma

Whiting, P. F., R. F. Wolff, S. Deshpande, M. Di Nisio, S. Duffy, A. V. Hernandez, J. C. Keurentjes, S. Lang, K. Misso, S. Ryder, S. Schmidlkofer, M. Westwood, and J. Kleijnen. 2015. Cannabinoids for medical use: A systematic review and meta-analysis. *JAMA* 313(24):2456–2473.

Traumatic Brain Injury/Intracranial Hemorrhage

The committee did not identify any good- or fair-quality systematic reviews that reported on traumatic brain injury/intracranial hemorrhage.

Addiction

Marshall, K., L. Gowing, R. Ali, and B. Le Foll. 2014. Pharmacotherapies for cannabis dependence. *Cochrane Database of Systematic Reviews* 12:CD008940

Prud'Homme, M., R. Cata, and D. Jutras-Aswad. 2015. Cannabidiol as an intervention for addictive behaviors: A systematic review of the evidence. *Substance Abuse: Research and Treatment* 9:33–38.

Anxiety

Whiting, P. F., R. F. Wolff, S. Deshpande, M. Di Nisio, S. Duffy, A. V. Hernandez, J. C. Keurentjes, S. Lang, K. Misso, S. Ryder, S. Schmidlkofer, M. Westwood, and J. Kleijnen. 2015. Cannabinoids for medical use: A systematic review and meta-analysis. *JAMA* 313(24):2456–2473.

Depression

Whiting, P. F., R. F. Wolff, S. Deshpande, M. Di Nisio, S. Duffy, A. V. Hernandez, J. C. Keurentjes, S. Lang, K. Misso, S. Ryder, S. Schmidlkofer, M. Westwood, and J. Kleijnen. 2015. Cannabinoids for medical use: A systematic review and meta-analysis. *JAMA* 313(24):2456–2473.

Sleep Disorders

Whiting, P. F., R. F. Wolff, S. Deshpande, M. Di Nisio, S. Duffy, A. V. Hernandez, J. C. Keurentjes, S. Lang, K. Misso, S. Ryder, S. Schmidlkofer, M. Westwood, and J. Kleijnen. 2015. Cannabinoids for medical use: A systematic review and meta-analysis. *JAMA* 313(24):2456–2473.

Posttraumatic Stress Disorder (PTSD)

The committee did not identify any good- or fair-quality systematic reviews that reported on PTSD.

Schizophrenia and Other Psychoses

McLoughlin, B. C., J. A. Pushpa-Rajah, D. Gillies, J. Rathbone, H. Variend, E. Kalakouti, and K. Kyprianou. 2014. Cannabis and schizophrenia. *Cochrane Database of Systematic Reviews* 10:CD004837.

Whiting, P. F., R. F. Wolff, S. Deshpande, M. Di Nisio, S. Duffy, A. V. Hernandez, J. C. Keurentjes, S. Lang, K. Misso, S. Ryder, S. Schmidlkofer, M. Westwood, and J. Kleijnen. 2015. Cannabinoids for medical use: A systematic review and meta-analysis. *JAMA* 313(24):2456–2473.

CANCER INCIDENCE

Lung Cancer

Zhang, L. R., H. Morgenstern, S. Greenland, S.-C. Chang, P. Lazarus, M. D. Teare, P. J. Woll, I. Orlow, and B. Cox, on behalf of the Cannabis and Respiratory Disease Group of New Zealand, Y. Brhane, G. Liu, and R. J. Hung. 2015. Cannabis smoking and lung cancer risk: Pooled analysis in the International Lung Cancer Consortium. *International Journal of Cancer* 136(4):894–903.

Head and Neck Cancers

de Carvalho, M. F., M. R. Dourado, I. B. Fernandes, C. T. Araujo, A. T. Mesquita, and M. L. Ramos-Jorge. 2015. Head and neck cancer among marijuana users: A meta-analysis of matched case-control studies. *Archives of Oral Biology* 60(12):1750–1755.

Testicular Cancer

Gurney, J., C. Shaw, J. Stanley, V. Signal, and D. Sarfati. 2015. Cannabis exposure and risk of testicular cancer: A systematic review and meta-analysis. *BMC Cancer* 15:897.

Esophageal Cancer

The committee did not identify any good- or fair-quality systematic reviews that reported on esophageal cancer.

Other Cancers in Adults

The committee did not identify any good- or fair-quality systematic reviews that reported on other cancers in adults.

Childhood Cancers

The committee did not identify any good- or fair-quality systematic reviews that reported on childhood cancers.

CARDIOMETABOLIC RISK

The committee did not identify any good- or fair-quality systematic reviews that reported on the health endpoints addressed in this chapter.

RESPIRATORY DISEASE

Pulmonary Function

Tetrault, J. M., K. Crothers, B.A. Moore, R. Mehra, J. Concato, and D.A. Fiellin. 2007. Effects of marijuana smoking on pulmonary function and respiratory complications: A systematic review. *Archives of Internal Medicine* 167:221–228.

Chronic Obstructive Pulmonary Disease

The committee did not identify any good- or fair-quality systematic reviews that reported on chronic obstructive pulmonary disease.

Respiratory Symptoms Including Chronic Bronchitis

Tetrault, J. M., K. Crothers, B. A. Moore, R. Mehra, J. Concato, and D. A. Fiellin. 2007. Effects of marijuana smoking on pulmonary function and respiratory complications: A systematic review. *Archives of Internal Medicine* 167:221–228.

Asthma

Tetrault, J. M., K. Crothers, B. A. Moore, R. Mehra, J. Concato, and D. A. Fiellin. 2007. Effects of marijuana smoking on pulmonary function and respiratory complications: A systematic review. *Archives of Internal Medicine* 167:221–228.

IMMUNITY

The committee did not identify any good- or fair-quality systematic reviews that reported on the health endpoints addressed in this chapter.

INJURY AND DEATH

All-Cause Mortality

Calabria, B., L. Degenhardt, W. Hall, and M. Lynskey. 2010. Does cannabis use increase the risk of death? Systematic review of epidemiological evidence on adverse effects of cannabis use. *Drug and Alcohol Review* 29(3):318–330.

Occupational Injury

The committee did not identify any good- or fair-quality systematic reviews that reported on occupational injury.

Motor Vehicle Crashes

Asbridge, M., J. A. Hayden, and J. L. Cartwright. 2012. Acute cannabis consumption and motor vehicle collision risk: Systematic review of observational studies and meta-analysis. BMJ 344:e536.

Calabria, B., L. Degenhardt, W. Hall, and M. Lynskey. 2010. Does cannabis use increase the risk of death? Systematic review of epidemiological evidence on adverse effects of cannabis use. Drug and Alcohol Review 29(3):318–330.

Elvik, R. 2013. Risk of road accident associated with the use of drugs: A systematic review and meta-analysis of evidence from epidemiological studies. Accident Analysis & Prevention 60:254–267.

Hartman, R. L., and M. A. Huestis. 2013. Cannabis effects on driving skills. Clinical Chemistry 59(3):478-492.

Li, M. C., J. E. Brady, C. J. DiMaggio, A. R. Lusardi, K. Y. Tzong, and G. Li. 2012. Marijuana use and motor vehicle crashes. Epidemiologic Reviews 34:65–72.

Rogeberg, O., and R. Elvik. 2016. The effects of cannabis intoxication on motor vehicle collision revisited and revised. *Addiction* 111:1348–1359.

Overdose Injuries and Death

The committee did not identify any good- or fair-quality systematic reviews that reported on overdose injuries and death.

PRENATAL PERINATAL AND NEONATAL EXPOSURE TO CANNABIS

Pregnancy Complications for the Mother

Gunn, J. K. L., Rosales, C.B., Center, K.E., Nunez, A., Gibson, S.J., Christ, C., and Ehiri, J.E. (2016). Prenatal Exposure to Cannabis and Maternal and Child Health Outcomes: A Systematic Review and Meta-Analysis. *BMJ Open, 6 (4) (no pagination)*(009986).

Fetal Growth and Development

Gunn, J. K. L., C. B. Rosales, K. E. Center, A. Nunez, S. J. Gibson, C. Christ, and J. E. Ehiri. 2016. Prenatal exposure to cannabis and maternal and child health outcomes: A systematic review and meta-analysis. *BMJ Open* 6(4):e009986.

Neonatal Conditions

Gunn, J. K. L., C. B. Rosales, K. E. Center, A. Nunez, S. J. Gibson, C. Christ, and J. E. Ehiri. 2016. Prenatal exposure to cannabis and maternal and child health outcomes: A systematic review and meta-analysis. *BMJ Open* 6(4):e009986.

Later Outcomes

The committee did not identify any good- or fair-quality systematic reviews that reported on later outcomes.

PSYCHOSOCIAL

Cognition

Batalla, A., S. Bhattacharyya, M. Yucel, P. Fusar-Poli, J. A. Crippa, S. Nogue, M. Torrens, J. Pujol, M. Farre, and R. Martin-Santos. 2013. Structural and functional imaging studies in chronic cannabis users: A systematic review of adolescent and adult findings. PLoS *ONE* 8(2):e55821.

Broyd, S. J., H. H. Van Hell, C. Beale, M. Yucel, and N. Solowij. 2016. Acute and chronic effects of cannabinoids on human cognition—A systematic review. *Biological Psychiatry* 79(7):557–567.

Grant, I., R. Gonzalez, C. L. Carey, L. Natarajan, and T. Wolfson. 2003. Non-acute (residual) neurocognitive effects of cannabis use: A meta-analytic study. Journal of the International Neuropsychological Society 9:679–689.

Martin-Santos, R., A. B. Fagundo, J. A. Crippa, Z. Atakan, S. Bhattacharyya, P. Allen, P. Fusar-Poli, S. Borgwardt, M. Seal, G. F. Busatto, and P. McGuire. 2010. Neuroimaging in Cannabis Use: A Systematic Review of the Literature. *Psychological Medicine* 40(3):383–398.

Schreiner, A. M., and M. E. Dunn. 2012. Residual effects of cannabis use on neurocognitive performance after prolonged abstinence: A meta-analysis. *Experimental and Clinical Psychopharmacology* 20(5):420–429.

Academic Achievement

Macleod, J., R. Oakes,A. Copello, I. Crome, M. Egger, M. Hickman, T. Oppenkowski, H. Stokes-Lampard, and G. Davey Smith. 2004. Psychological and social sequelae of cannabis

and other illicit drug use by young people: A systematic review of longitudinal, general population studies. *Lancet* 363(9421):1579–1588.

Employment and Income

The committee did not identify any good- or fair-quality systematic reviews that reported on employment and income.

Social Relationships and Other Social Roles

Macleod, J., R. Oakes,A. Copello, I. Crome, M. Egger, M. Hickman, T. Oppenkowski, H. Stokes-Lampard, and G. Davey Smith. 2004. Psychological and social sequelae of cannabis and other illicit drug use by young people: A systematic review of longitudinal, general population studies. *Lancet* 363(9421):1579–1588.

MENTAL HEALTH

Schizophrenia and Other Psychoses

Donoghue, K., and G. A. Doody. 2012. Effect of illegal substance use on cognitive function in individuals with a psychotic disorder: A review and meta-analysis. *Neuropsychology* 26(6):785–801.

Large, M., S. Sharma, M. T. Compton, T. Slade, and O. Nielssen. 2011. Cannabis use and earlier onset of psychosis: A systematic meta-analysis. *Archives of General Psychiatry* 68(6):555–561.

Marconi, A., M. Di Forti, C. M. Lewis, R. M. Murray, and E. Vassos. 2016. Meta-analysis of the association between the level of cannabis use and risk of psychosis. *Schizophrenia Bulletin* 42(5):1262–1269

Moore, T. H., S. Zammit, A. Lingford-Hughes, T. R. Barnes, P. B. Jones, M. Burke, and G. Lewis. 2007. Cannabis use and risk of psychotic or affective mental health outcomes: A systematic review. *Lancet* 370(9584):319–328.

Myles, N., H. Newall, O. Nielssen, and M. Large. 2012. The association between cannabis use and earlier age at onset of schizophrenia and other psychoses: Meta-analysis of possible confounding factors. *Current Pharmaceutical Design* 18(32):5055–5069.

Rabin, R. A., K. K. Zakzanis, and T. P. George. 2011. The effects of cannabis use on neurocognition in schizophrenia: A meta-analysis. *Schizophrenia Research* 128(1–3):111–116.

Szoke, A., A. M. Galliot, J. R. Richard, A. Ferchiou, G. Baudin, M. Leboyer, and F. Schurhoff. 2014. Association between cannabis use and schizotypal dimensions—A meta-analysis of cross-sectional studies. *Psychiatry Research* 219(1):58–66.

van der Meer, F. J., E. Velthorst, C. J. Meijer, M. W. Machielsen, and L. de Haan. 2012. Cannabis use in patients at clinical high risk of psychosis: Impact on prodromal symptoms and transition to psychosis. *Current Pharmaceutical Design* 18(32):5036–5044.

Yucel, M., E. Bora, D. I. Lubman, N. Solowij, W. J. Brewer, S. M. Cotton, P. Conus, M. J. Takagi, A. Fornito, S. J. Wood, P. D. McGorry, and C. Pantelis. 2012. The impact of

cannabis use on cognitive functioning in patients with schizophrenia: A meta-analysis of existing findings and new data in a first-episode sample. *Schizophrenia Bulletin* 38(2):316–330.

Zammit, S., T. H. Moore, A. Lingford-Hughes, T. R. Barnes, P. B. Jones, M., Burke, and G. Lewis. 2008. Effects of cannabis use on outcomes of psychotic disorders: Systematic review. *British Journal of Psychiatry* 193(5):357–363.

Bipolar Disorder

Gibbs, M., C. Winsper, S. Marwaha, E. Gilbert, M. Broome, and S. P. Singh. 2015. Cannabis use and mania symptoms: A systematic review and meta-analysis. *Journal of Affective Disorders* 171:39–47.

Depression

Lev-Ran, S., B. Le Foll, K. McKenzie, T. P. George, and J. Rehm. 2013. Bipolar disorder and co-occurring cannabis use disorders: Characteristics, co-morbidities and clinical correlates. *Psychiatry Research* 209(3):459–465.

Moore, T. H., S. Zammit, A. Lingford-Hughes, T. R. Barnes, P. B. Jones, M. Burke, and G. Lewis. 2007. Cannabis use and risk of psychotic or affective mental health outcomes: A systematic review. *Lancet* 370(9584):319–328.

Suicide

Borges, G., C. L. Bagge, and R. Orozco. 2016. A literature review and meta-analyses of cannabis use and suicidality. *Journal of Affective Disorders* 195:63–74.

Moore, T. H., S. Zammit, A. Lingford-Hughes, T. R. Barnes, P. B. Jones, M. Burke, and G. Lewis. 2007. Cannabis use and risk of psychotic or affective mental health outcomes: A systematic review. *Lancet* 370(9584):319–328.

Anxiety

Kedzior, K. K., and L. T. Laeber. 2014. A positive association between anxiety disorders and cannabis use or cannabis use disorders in the general population—A meta-analysis of 31 studies. *BMC Psychiatry* 14:136.

Posttraumatic Stress Disorder (PTSD)

The committee did not identify any good- or fair-quality systematic reviews that reported on PTSD.

PROBLEM CANNABIS USE

Development of Problem Cannabis Use

The committee did not identify any good- or fair-quality systematic reviews that reported on the development of problem cannabis use.

Risk and Protective Factors for Developing Problem Cannabis Use

Humphreys, K. L., T. Eng, and S. S. Lee. 2013. Stimulant medication and substance use outcomes: Ameta-analysis. *JAMA Psychiatry* 70(7):740–749.

Kedzior, K. K., and L. T. Laeber. 2014. A positive association between anxiety disorders and cannabis use or cannabis use disorders in the general population—A meta-analysis of 31 studies. *BMC Psychiatry* 14:136.

Risk and Protective Factors for Severity and Persistence of Problem Cannabis Use

The committee did not identify any good- or fair-quality systematic reviews that reported on the risk and protective factors for severity and persistence of problem cannabis use.

ABUSE OF OTHER SUBSTANCES

The committee did not identify any good- or fair-quality systematic reviews that reported on abuse of other substances.

Appendix D

Public Session Agendas

COMMITTEE MEETING 1
June 23-24, 2016

Meeting Location
The National Academies' Keck Center
Room 106
500 5th Street, NW
Washington, DC 20001

Open Session Agenda

The National Academies of Sciences, Engineering, and Medicine has been charged to appoint an ad hoc committee of experts to develop a comprehensive, in-depth review of existing evidence regarding the health effects of using marijuana and/or its constituents, as well as to identify both a short- and long-term research agenda focused on improving our understanding of the association of marijuana uses relevant to health outcomes.

Thank you for joining us at this meeting. If you have a continued interest in the progress of this study, please feel free to subscribe to our listserv, which can be accessed through our study's webpage: http://nationalacademies.org/hmd/activities/publichealth/marijuanahealtheffects.aspx

1:15 Welcome, Introductions, and Opening Remarks
Marie McCormick, Committee Chair

1:30 Sponsor Briefing on the Statement of Task
- Remarks from Sponsor Organizations
  - Steve Gust, Ph.D.
    National Institute of Drug Abuse
  - Debbie Winn, Ph.D.
    National Cancer Institute
  - Amy Cohn, Ph.D. (via WebEx)
    Truth Initiative
- Question and Answer Session with Committee and Sponsors

2:30 Adjourn Open Session

COMMITTEE MEETING 3
August 18, 2016
1:00-4:00pm (EDT)

Meeting Location
The National Academies' Keck Center
Room 106
500 5th Street, NW
Washington, DC
20001

Registration for in-person or webcast attendance:
http://www.surveygizmo.com/s3/2943914/Open-Session-Health-Effects-of-Marijuana
Please note that in-person seating is limited

Open Session Agenda

The National Academies of Sciences, Engineering, and Medicine has been charged to appoint an ad hoc committee of experts to develop a comprehensive, in-depth review of existing evidence regarding the health effects of using marijuana and/or its constituents, as well as to identify both a short- and long-term research agenda focused on improving our understanding of the association of marijuana uses relevant to health outcomes.

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1:00 p.m. Welcome, Introductions, and Opening Remarks
Marie McCormick, Committee Chair

1:15 p.m. Panel Discussions:

Health Effects of Cannabis

Speakers:

- Dr. Leslie R. Walker-Harding (Chair, Department of Pediatrics, Penn State Health Milton S. Hershey Medical Center; Medical Director, Penn State Children's Hospital)
- Dr. Sheryl Ryan (Professor of Pediatrics, Yale School of Medicine; Chief, Section of Adolescent Medicine, Yale School of Medicine)
- Dr. Michael Van Dyke (Section Chief, Environmental Epidemiology and Occupational Health, Colorado Department of Public Health and Environment)
- Dr. Peggy van der Pol (Senior Researcher, The Trimbos Institute, Netherlands Institute for Mental Health and

Addiction)

Health Impact of Interest: The Role of Cannabis Use in Motor Vehicle Accidents

- Speaker: Dr. Richard Compton (Director, National Highway Traffic Safety Administration, Office of Behavioral Safety Research)

Therapeutic Effects of Cannabis

Speakers:

- Dr. Igor Grant (Professor and Chair of the Department of Psychiatry at the University of California, San Diego School of Medicine; Director, HIV Neurobehavioral Research Program)
- Dr. Sheryl Ryan (Professor of Pediatrics, Yale School of Medicine; Chief, Section of Adolescent Medicine, Yale School of Medicine)

3:45 p.m. Question and Answer Session

4:00 p.m. Adjourn Open Session

Appendix E

Biographical Sketches for Committee Members, Staff, Fellow, and Advisor

COMMITTEE MEMBERS

Marie McCormick, M.D., Sc.D. (Chair), is a currently the Sumner and Esther Feldberg Professor of Maternal and Child Health in the Department of Social and Behavioral Sciences at the Harvard T.H. Chan School of Public Health and a professor of pediatrics at the Harvard Medical School, and she is also a senior associate for academic affairs in the Department of Neonatology at the Beth Israel Deaconess Medical Center. Dr. McCormick is a pediatrician with a second doctorate in health services research, with all of her postgraduate training done at Johns Hopkins. In 1987 she joined the faculty of the Department of Pediatrics at Harvard Medical School, and in 1991 she became a professor and the chair of the Department of Maternal and Child Health at the Harvard School of Public Health and a professor of pediatrics. Her research has focused on the effectiveness of perinatal and neonatal health services on the health of women and children with a particular concern in the outcomes of very premature infants. She has been a senior investigator on the evaluations of two national demonstration programs (the Robert Wood Johnson Foundation National Perinatal Regionalization Program and, currently, the federal Healthy Start Program). In addition, she has provided significant scientific input, in a variety of roles, to the design and conduct of Infant Health and Development Project, the largest multi-site, randomized trial of early childhood educational intervention, in particular, serving as the principal investigator of the follow-up done at 18 years of age. She is a member of the National Academy of Medicine, among other organizations. Her work on several committees, most notably the Immunization Safety Review Committee, has earned her the David Rall Medal for exceptional service.

Donald I. Abrams, M.D., is chief of the Hematology-Oncology Division at Zuckerberg San Francisco General Hospital and a Professor of Clinical Medicine at the University of California San Francisco. He was one the original clinician/investigators to recognize and define many early AIDS-related conditions. He has long been interested in clinical trials of complementary medicine interventions for human immunodeficiency virus infection and acquired immune deficiency syndrome (HIV/AIDS) and cancer, including evaluations of medicinal cannabis. In 1997 he received funding from the National Institute on Drug Abuse to conduct a clinical trial of the short-term safety of cannabinoids in HIV infection. Subsequently he was granted funds by the University of California Center for Medicinal Cannabis Research to conduct studies of the effectiveness of cannabis in a number of clinical conditions. He completed a placebo-controlled study of smoked cannabis in patients with painful HIV-related peripheral neuropathy as well as a study evaluating vaporization as a smokeless delivery system for medicinal cannabis. His last

National Institute on Drug Abuse-funded trial investigated the safety and pharmacokinetic interaction between vaporized cannabis and sustained-release opioid analgesics in patients with chronic pain. He is currently conducting a translational National Heart, Lung, and Blood Institute -funded trial investigating vaporized cannabis in patients with sickle cell disease. He received an A.B. in Molecular Biology from Brown University in 1972 and graduated from the Stanford University School of Medicine in 1977. After completing an Internal Medicine residency at the Kaiser Foundation Hospital in San Francisco, he became a fellow in Hematology-Oncology at the University of California San Francisco before joining the faculty. In 2004, he completed a distance learning fellowship in Integrative Medicine from the University of Arizona and has since been providing Integrative Oncology consultations at the UCSF Osher Center for Integrative Medicine.

Margarita Alegría, Ph.D., is the director of the Center for Multicultural Mental Health Research and a professor of psychology in the Department of Psychiatry at Harvard Medical School. Dr. Alegría researches mental health services for Latinos and other ethnic populations. She is currently the principal investigator of the Advanced Center for Mental Health Disparities and the Latino arm of the National Latino and Asian American Study as well as the co-principal investigator of the Cambridge Health Alliance/University of Puerto Rico Excellence in Partnerships for Community Outreach, Research on Health Disparities and Training (EXPORT) Center. Her published works focus on mental health services research, conceptual and methodological issues with minority populations, risk behaviors, and disparities in service delivery. Dr. Alegría received her Ph.D. from Temple University.

William Checkley, M.D., Ph.D., is an associate professor of medicine at the Johns Hopkins University School of Medicine and has a joint appointment in the Department of International Health at the Bloomberg School of Public Health. His areas of clinical expertise include epidemiology, pulmonary disease, and critical care medicine. Dr. Checkley also serves as the medical director for Johns Hopkins International.Dr. Checkley earned his M.D. from Northwestern University and received his Ph.D. from Johns Hopkins University. He completed his internal medicine residency training at Emory University and his fellowship training in pulmonary and critical care medicine at Johns Hopkins School of Medicine. His research interests include international lung health, epidemiology, mechanical ventilation, and acute lung injury. Dr. Checkley has been recognized by the National Institutes of Health with the 2007 Postdoctoral National Research Service Award and the 2009 Pathway to Independence Career Award. He is certified in pulmonary disease and internal medicine by the American Board of Internal Medicine.

R. Lorraine Collins, Ph.D., is a psychologist and professor of community health and health behavior and the associate dean for research at the State University of New York at Buffalo (UB) School of Public Health and Health Professions (SPHHP). For two decades she conducted research as a senior scientist at UB's Research Institute on Addictions before joining the SPHHP as associate dean for research in 2008. Dr. Collins's research interests include cognitive and behavioral approaches to the conceptualization, prevention, and treatment of addictive behaviors, particularly among emerging and young adults. Examples of her projects funded by the National Institutes of Health include a study to examine the combined use of alcohol and marijuana and a study of the use of technology in interventions to reduce marijuana use.

Ziva Cooper, Ph.D., is an assistant professor of clinical neurobiology in the Department of Psychiatry at the College of Physicians and Surgeons of Columbia University. She received her Ph.D in biopsychology from the University of Michigan, where she studied the abuse liability of drugs in laboratory animals, specifically focusing on how different states of opioid dependence alter operant behavior maintained by various reinforcers. In 2009 she completed a postdoctoral fellowship under the mentorship of Drs. Margaret Haney and Sandra Comer in the Division on Substance Abuse at Columbia University studying human behavioral pharmacology of cannabinoids and opioids. Her general research interest involves understanding the neurobiological, environmental, and behavioral variables that influence the reinforcing effects of drugs. To that end she is currently concentrating on human laboratory models of polysubstance abuse in order to determine how multiple receptor systems contribute to the abuse liability of psychoactive drugs, including cannabinoids, opioids, and cocaine.

Adre J. Du Plessis, M.D., M.P.H., M.B.Ch.B., is the director of the Fetal Medicine Institute, the division chief of fetal and transitional medicine, and director of the Fetal Brain Program at Children's National Health System. In addition, Dr. Du Plessis is a professor of pediatrics and neurology at George Washington University School of Medicine. Dr. Du Plessis is a leading international expert in the normal and abnormal development of the brain as well as the mechanisms of injury to the immature brain. His career-long research focus has been on the nervous system of the fetus and newborn, the hazards and mechanisms of injury, and the potential prevention of insult to the brain. Under his leadership, the Fetal Medicine Institute provides individualized and specialized care to patients during and after the baby's birth. Dr. Du Plessis received his M.B.Ch.B. from the University of Cape Town, South Africa. He trained in pediatrics at the University of Cape Town, South Africa, and at Penn State University. In addition, he trained in child neurology at the St. Louis and Boston Children's Hospitals.

Sarah Feldstein Ewing, Ph.D., is a professor at the Oregon Health and Science University. Dr. Feldstein Ewing is a licensed clinical child psychologist with over a decade of experience using a variety of evidence-based approaches to prevent and intervene with adolescent health risk behavior, including alcohol use, cannabis use, and human immunodeficiency virus infection and acquired immune deficiency syndrome (HIV/AIDS) risk behavior. At this time, her lab has enrolled more than 1,000 youth within large-scale clinical trials to evaluate the developmental fit and treatment outcomes for motivational interviewing, behavioral skills training, cognitive behavioral approaches, mindfulness, and contingency management. She has published widely regarding the developmental fit, neurocognitive mechanisms, gender differences, and cross-cultural adaptation of these prevention and intervention approaches for this developmental stage. She has also developed a highly-innovative National Institutes of Health–funded line of translational research, evaluating the connection between basic biological mechanisms (e.g., functional brain activation, brain structure, genetic factors) and youth health risk behavior (e.g., clinical symptoms, HIV risk behaviors, treatment outcomes). She has conducted this work with alcohol-abusing adolescents, cannabis-abusing adolescents, adolescents engaged in risky sex, and youths with a high body mass index. Ultimately, the goal of her laboratory is to employ translational studies to (1) determine the driving factors underlying successful treatment outcomes, (2) develop more efficacious interventions, and (3) evaluate the efficacy of interventions in order to improve health outcomes and reduce the current disparities for high-risk

adolescents of all backgrounds.

Sean Hennessy, Pharm.D., Ph.D., is a professor of biostatistics and epidemiology and a professor of pharmacology at the Perelman School of Medicine, University of Pennsylvania. Dr. Hennessy's primary field of interest is pharmacoepidemiology, which is the study of the use and effects of medications in populations. Within pharmacoepidemiology, he has a particular interest in studying the clinical importance of drug–drug interactions. Dr. Hennessy's research has been funded by the Agency for Healthcare Research and Quality, the National Institutes of Health (NIH), pharmaceutical companies, and private foundations. He is currently leading an NIH-funded study on the clinical importance of drug–drug interactions. In addition to his research, Dr. Hennessy teaches clinical epidemiology to medical and graduate students and is active in promoting evidence-based practice at Penn, co-chairing its Drug Use and Effects Committee, and serving on its Pharmacy and Therapeutics Committee. Dr. Hennessy's clinical program has received two Quality and Safety Awards from the University of Pennsylvania Health System. Dr. Hennessy received the 2005 Young Alumnus Award from the University of the Sciences in Philadelphia, the 2007 Lean I. Goldberg Young Investigator Award from Pharmacology and Therapeutics, and the 2013 Samuel Martin Health Evaluation Sciences Research Award from the University of Pennsylvania Perelman School of Medicine.

Kent Hutchison, Ph.D., is a professor of psychology and neuroscience and the director of clinical training at the University of Colorado Boulder. He completed his Ph.D. in clinical psychology at Oklahoma State University and then subsequently completed an internship at Brown University, where he stayed as a postdoctoral fellow specializing in research on addiction from 1995 to 1998. After leaving Brown University, Dr. Hutchison accepted a faculty position at the University of Colorado Boulder. He was promoted to associate professor in 2002 and full professor in 2007. Dr. Hutchison moved to the Mind Research Network (MRN) in Albuquerque, New Mexico, to pursue a program of research combining neuroimaging, clinical outcomes, and genetics in 2007, where served as the chief science officer for two years. In 2011 he returned to the University of Colorado to help set up the Intermountain Neuroimaging Consortium, which involves the operation of two identical magnetic resonance scanners, one in Albuquerque at MRN and one in Boulder at the University of Colorado. He continues to serve as a liaison between the two organizations. Dr. Hutchison has a long track record of funding from the National Institutes of Health and publications. His research combines neuroimaging, epigenetic, pharmacological, and clinical perspectives. Recently he has focused on how inflammatory processes that result from alcohol abuse may damage important executive control circuits in the brain, ultimately contributing to loss of control over alcohol use. In large part because of the change in Colorado law legalizing cannabis, he has also become very interested in cannabinoids and has launched several studies to gather data about the effects of cannabis with different ratios of tetrahydrocannabinol to cannabidiol on a variety of measures, including measures related to cognitive function and immune system inflammation.

Norbert E. Kaminski, Ph.D., is the director of the Institute for Integrative Toxicology and a professor of pharamcology and toxicology in the Cell and Molecular Biology Program at Michigan State University. Research being conducted in his laboratory is in the general areas of immunopharmacology and immunotoxicology and encompasses a number of extramurally funded projects. A major emphasis of all of these projects is the elucidation of the molecular

mechanisms for the impairment of signal transduction cascades and gene expression during lymphocyte activation by drugs and chemicals. One major research focus is to characterize the mechanism for immune modulation by cannabinoid compounds. This effort has led to the first characterization of cannabinoid receptors within the immune system. Current goals include elucidation of signal transduction events initiated through—as well as independently of—cannabinoid receptors, including the peroxisome proliferator activated receptor (PPARy), leading to aberrant cytokine gene expression by T lymphocytes. A second major research focus is the characterization of the molecular mechanism responsible for altered B cell function produced by halogenated aromatic hydrocarbons, including dioxins and polychlorinated biphenols. This research, which resulted in the first characterization of the aryl hydrocarbon (AH) receptor and aryl hydrocarbon receptor nuclear translocator in B cells, has lead to testing of the hypothesis that dioxin and dioxin-like compounds suppress antibody responses by impairing B cell differentiation in an AH receptor-dependent manner. A third area of his research concerns studies aimed at characterizing the role of cytokine expression patterns in airway remodeling induced by chemical and protein respiratory allergens as well as by respiratory pathogens.

Sachin Patel, M.D., Ph.D., is an associate professor of psychiatry and of molecular physiology and biophysics at the Vanderbilt University School of Medicine. Dr. Patel's overall research goal is to understand the role of neuronal cannabinoid signaling in brain function relevant to psychiatric disorders. His lab has recently focused specifically on the role of the cannabinoid system in the regulation of stress response physiologyand the subsequent development of anxiety and depressive phenotypes relevant to affective disorders. The lab is using animal models to examine the effects of adolescent stress exposure on the cannabinoid system and cannabinoid-mediated synaptic plasticity in the amygdala, a key brain region implicated in affective disorders and developmental disorders, including autism. His lab is also interested in the role of cannabinoid signaling in modulating behavioral and synaptic alterations induced by very early life stress. Given that stress, especially early life stress, is associated with significantly higher rates of psychiatric disorders, including depression and post-traumatic stress disorder, understanding the cellular and molecular adaptations induced by stress exposure could provide opportunities for the development of novel therapeutic interventions for stress-related psychiatric disorders in children and adults. Another major focus of Dr. Patel's research is understanding the fundamental mechanisms of cannabinoid-mediated synaptic plasticity in the amygdala and how these forms of plasticity change during development. Understanding how the cannabinoid system modulates synaptic efficacy within emotional centers of the brain could provide mechanistic insight into developmental alterations induced by cannabis use during adolescence, which has been shown to be a risk factor for the development of psychiatric disorders, including schizophrenia. His lab is interested in understanding the mechanisms by which cannabis exposure early in life leads to an increased risk for the development of psychiatric disorders during adulthood.

Daniele Piomelli, Ph.D., is a professor of anatomy and neurobiology, has a joint appointment in biological chemistry and pharmacology, and holds the Lousie Turner Arnold Chair in Neurosciences at the University of California, Irvine (UCI), School of Medicine. Dr. Piomelli was trained in neuroscience and pharmacology. Research in his lab is focused on the function of lipid-derived messengers, with particular emphasis on the endogenous cannabinoids anandamide and 2-arachidonoylglycerol. Current research efforts converge on three areas: the formation and

deactivation of anandamide and 2-arachidonylglycerol; physiological roles of the endogenous cannabinoid system; and development of therapeutic agents that target anandamide and 2-arachidonylglycerol metabolism. Primary neural cell cultures and state-of-the-art analytical techniques such as liquid chromatography/mass-spectrometry are used to investigate the formation and deactivation of anandamide and 2-arachidonoylglycerol in brain cells. Protein purification and cloning approaches are employed to characterize the molecular mechanisms underlying these processes. Cellular pharmacology and medicinal chemistry, in collaboration with leading international labs, are used to identify pharmacological agents that interfere with various aspects of endogenous cannabinoid function, and their therapeutic potential is explored in vitro and in vivo. Dr. Piomelli is also the director of the UCI Department of Pharmacology National Institute on Drug Abuse Training Grant and the Center for Drug Discovery.

Stephen Sidney, M.D., M.P.H., is the director of research clinics and a senior research scientist at the Kaiser Permanente Northern California Division of Research, where he has been conducting epidemiological studies since 1982. He is certified by the American Board of Internal Medicine and is a fellow of the American Heart Association Council on Epidemiology and Prevention. Dr. Sidney's research interests include cardiovascular diseases including stroke, physical activity and fitness, cognitive function, and obesity, with an emphasis on health disparities. He conducted a National Institute on Drug Abuse–funded study from 1991 to 1994 on health outcomes associated with marijuana use utilizing survey and health outcome data from Kaiser Permanente Northern California, a large integrated health care system. He is the principal investigator of the Oakland field center of National Heart, Lung, and Blood Institute–funded Cardiovascular Risk Development in Young Adults (CARDIA) study, an ongoing 30-year longitudinal study of cardiovascular risk and disease development in individuals who were 18–30 years old at baseline, which includes marijuana use data collected throughout the study period. Dr. Sidney has authored or co-authored more than 350 peer-reviewed scientific publications covering a diverse range of topics, primarily in the area of cardiovascular epidemiology and also including more than 20 articles regarding epidemiological aspects of cannabis use and health outcomes. He received a B.A. in mathematics from Yale University, an M.D. from the Stanford University School of Medicine, and an M.P.H. in epidemiology from the University of California Berkeley School of Public Health.

Robert B. Wallace, M.Sc., M.D., is the Irene Ensminger Stecher Professor of epidemiology and internal medicine at the University of Iowa Colleges of Public Health and Medicine and is the director of the University's Center on Aging. He has been a member of the U.S. Preventive Services Task Force and the National Advisory Council on Aging of the National Institutes of Health. He is an elected member of the National Academy of Medicine, past chair of the National Academies of Sciences, Engineering, and Medicine's (The National Academies) Board on Health Promotion and Disease Prevention, and current chair of the Board on Select Populations. He recently received the Walsh McDermott award for distinguished service to the Academy. He is the author or co-author of more than 350 publications and 22 book chapters and has been the editor of four books, including the current edition of Maxcy-Rosenau-Last's *Public Health and Preventive Medicine*. Dr. Wallace's research interests are in clinical and population epidemiology, with a focus on the causes and prevention of disabling conditions among older people. He has had substantial experience in the conduct of both observational cohort studies of older people and clinical trials, including preventive interventions related to fracture, cancer,

coronary disease, and women's health. For more than 17 years he was the site principal investigator for the Women's Health Initiative, a set of national intervention trials exploring the prevention of breast and colon cancer and coronary disease. He is a co-principal investigator of the Health and Retirement Study, a national cohort study of the health and economic status of older Americans. He has been a co-investigator and collaborator in several national and international studies of the causes and prevention of chronic illness in older people. Dr. Wallace does clinical trial safety monitoring for Novartis Pharmaceuticals and Merck and Co. in the area of bone health, for which he receives honoraria.

John Wiley Williams, M.D., M.H.S., is a professor of medicine at Duke University Medical Center and a past recipient of the Veterans Affairs (VA) Health Services Career Development Award and a Robert Wood Johnson Foundation Generalist Faculty Scholar Award. He received his bachelor and M.D. degrees from the University of North Carolina. Dr. Williams completed residency training at the University of Iowa and a research fellowship at Duke University. He is a primary care internist who is trained in epidemiology, biostatistics, and literature synthesis. Dr. Williams' topical interests include depression, mental health services, dementia, and the implementation of best practices. He is scientific editor for the *NC Medical Journal* and a medical editor for the Foundation for Informed Medical Decision Making. Dr. Williams directs the Durham VA Evidence Synthesis Program and has led numerous systematic reviews, many focusing on mental health services. Dr. Williams is board certified in internal medicine and active in clinical practice and resident physician education at the Durham VA Medical Center.

PROJECT STAFF, FELLOW, AND ADVISOR

Jennifer A. Cohen, M.P.H., is a program officer in the Health and Medicine Division of the National Academies of Sciences, Engineering, and Medicine on the Board on Population Health and Public Health Practice. She received her undergraduate degree and her M.P.H. from the University of Maryland. Ms. Cohen has been involved with the National Academies committees that produced O*rgan Procurement and Transplantation, Clearing the Air: Asthma and Indoor Air Exposures, Veterans and Agent Orange: Herbicide/Dioxin Exposure and Type 2 Diabetes, Veterans and Agent Orange: Update 2000, Veterans and Agent Orange: Herbicide/Dioxin Exposure and Acute Myelogenous Leukemia in the Children of Vietnam Veterans, Veterans and Agent Orange: Update 2004, Veterans and Agent Orange: Update 2006, Veterans and Agent Orange: Update 2008, Veterans and Agent Orange: Update 2010, Veterans and Agent Orange: Update 2012, Post-Vietnam Dioxin Exposure in Agent Orange-Contaminated C-123 Aircraft,* and *Veterans and Agent Orange: Update 2014.* She was also rapporteur for *Challenges and Successes in Reducing Health Disparities*.

Brownsyne Tucker Edmonds, **M.D., M.S., M.PH**., (*Norman F. Grant/American Board of Obstetrics and Gynecology Fellow*) is an Assistant Professor in the Department of Obstetrics and Gynecology at the Indiana University School of Medicine. Originally from Atlanta, GA, she received her undergraduate degree in Community Health and African American Studies at Brown University. She went on to receive her medical degree from Brown Medical School, and, concurrently, completed a Master's in Public Health at the Harvard School of Public Health with a concentration in Quantitative Methods. Dr. Tucker Edmonds trained in Obstetrics and

Gynecology at Duke University Medical Center where she served as an Administrative Chief Resident in her final year. She then entered the Robert Wood Johnson Foundation Clinical Scholars Program fellowship at the University of Pennsylvania, where she received health services research training and a Masters in Health Policy Research. Most recently, she completed a Clinical Ethics Fellowship through the Indiana University Health Fairbanks Center for Medical Ethics. Her work currently focuses on communication and decision-making in the management of periviable deliveries--when end-of-life decisions are made at the very beginning of life.

Kelsey Geiser, M.A., is a research associate with the Health and Medicine Division's Board on Population Health and Public Health Practice. Previously, she worked in the Division of Behavioral and Social Sciences and Education with the Board on Children, Youth, and Families on two consensus studies titled *Parenting Matters: Supporting Parents of Children Ages 08* and *Preventing Bullying Through Science, Policy, and Practice*. Prior to her work at the Academies, Ms. Geiser wrote for the Stanford News Service and worked in the Palo Alto district office of Congresswoman Anna Eshoo. She has a B.A. and an M.A. in history from Stanford University with a focus on the historical treatment of women's and family health issues.

Hope R. Hare, M.F.A., is the administrative assistant for the Board on Population Health. She keeps the board information updated, administers the twice yearly board meeting, and provides support for the board director and staff. Ms. Hare has worked for the National Academies of Sciences, Engineering, and Medicine since 2001. She holds an M.F.A. from Cornell University.

Leigh Miles Jackson, Ph.D. (*Study Director*), is a senior program officer in the Health and Medicine Division of the National Academies of Sciences, Engineering, and Medicine Board on the Board on Population Health and Public Health Practice. Previously, she worked in the Division of Behavioral and Social Sciences and Education with the Board on Children, Youth, and Families. She has served as the study director for the Committee on the Use of Economic Evidence to Inform Investments in Children, Youth, and Families and as the program officer for the Roundtable on the Communication and Use of Social and Behavioral Sciences. Prior to joining the National Academies, she was a developmental psychopathology and neurogenomics research fellow at Vanderbilt University, where she investigated the role of chronic sleep disturbance and specific epigenetic modifications on the health outcomes of adolescents. She has a bachelor's degree in chemistry from Wake Forest University and a Ph.D. in molecular and systems pharmacology from Emory University.

Rose Marie Martinez, Sc.D. (*Senior Board Director*), has been the director of the Health and Medicine Division's Board on Population Health and Public Health Practice since 1999. Prior to joining the National Academies of Sciences, Engineering, and Medicine, Dr. Martinez was a senior health researcher at Mathematica Policy Research (1995–1999), where she conducted research on the impact of health system change on the public health infrastructure, access to care for vulnerable populations, managed care, and the health care workforce. She is a former assistant director for health financing and policy with the U.S. General Accounting Office and served for 6 years directing research studies for the Regional Health Ministry of Madrid, Spain.

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Marjorie Pichon, B.A., is a senior program assistant for the Health and Medicine Division's Board on Population Health and Public Health Practice. While at the National Academies of Sciences, Engineering, and Medicine she has contributed to projects such as a National Strategy for the Elimination of Hepatitis B and C, Public Health Approaches to Reduce Vision Impairment and Promote Eye Health, and a workshop on Strategies to Improve Cardiac Arrest Survival. Prior to joining the National Academies, Ms. Pinchon served as a Community Health Corps volunteer for MedStar PromptCare, assisting underserved members of the community gain access to medical care. She graduated from Lewis & Clark College in May 2014 with a B.A. in psychology and a minor in rhetoric and media studies. During this time she collaborated on research in the colleges Human Computer Interaction Lab studying how the structure of play influences creativity in children.

Kathleen Stratton, Ph.D. (*Advisor*), began her career at the National Academies of Sciences, Engineering and Medicine in 1990 in what was known at the time as the Institute of Medicine (IOM). She has spent most of her time with the Board on Population Health and Public Health Practice. She has staffed committees addressing vaccine safety and development, pandemic preparedness, environmental and occupational health, drug safety, Medicare payment programs, and tobacco control. She was given the IOM Cecil Research Award in 2002 for sustained contributions to vaccine safety and was made a staff scholar in 2005. After 2 years at The Pew Charitable Trusts working on Food and Drug Administration reform, she returned to the National Academies in Fall 2013. She received a B.A. in natural sciences from Johns Hopkins University and a Ph.D. in pharmacology and toxicology at the University of Maryland at Baltimore. She conducted postdoctoral research in the Department of Neuroscience at the Johns Hopkins School of Medicine.

Sara Tharakan, B.A., was a research associate in the Health and Medicine Division's Board on Population Health and Public Health Practice. While at the National Academies of Sciences, Engineering, and Medicine, she worked on a number of projects, including Comprehensive Cancer Care for Children and Their Families: Summary of a Joint Workshop, Policy Issues in the Development and Adoption of Biomarkers for Molecularly Targeted Cancer Therapies: Workshop Summary, and Speech and Language Disorders in Children: Implications for the Social Security Administration's Supplemental Security Income Program. Prior to joining the National Academies she worked as an assistant researcher for the EKAM Foundation. Ms. Tharakan has a B.A. in political science and government from the University of North Carolina at Chapel Hill and is pursuing an M.Sc. at the London School of Economics and Political Science.

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