WASHINGTON COUNTY
OREGON
Department of Health and Human Services

Marijuana and health:

A comprehensive review of 20 years of research

K.K. Repp, PhD, MPH
A.L. Raich, MS, MPH

October 20th, 2014

The views expressed in this report are those of the authors and do not necessarily reflect the position or policy of the Department of Health and Human Services or the Washington County government.

Table of Contents

List of figures and tables

I. Executive Summary

Recommended reading: Volkow 2014, Hall 2009 *IJDP*, Greydanus 2013

Introduction

Rarely has there been such a divide between science and public opinion as there is with medicinal and recreational use of marijuana. The purpose of this review is to summarize over 20 years of peer-reviewed publications from journals around the world, on the often complicated relationship between marijuana and health. With over 50 topics reviewed in detail throughout this report, please reference the specific review section for recommended reading and citation of the studies summarized below.

Prevalence of use

Marijuana is the most commonly used illicit drug both globally and nationally, with just under 19 million users in the US reporting marijuana use in the last month. Of recent marijuana initiates, most were younger than 18 years old when they first used marijuana. Recent use rates of marijuana in Washington County are similar to that of the Oregon state average with approximately 7% of 8th graders and 19% of 11th graders reporting current marijuana use. These numbers jump to 20% for first year US college students reporting marijuana use. The consequences of adolescent marijuana use can be quite severe. In many studies, adolescent marijuana use has been linked to lower educational attainment, early parenthood, increased reported use of other illicit drugs, lower income, greater welfare dependence and lower life satisfaction.

Addiction

There is controversy on the addictive potential of marijuana. Research clearly demonstrates that approximately 9% of those who experiment with marijuana will become addicted. This number goes up to 17% for those who start using marijuana as teenagers and up to 50% for those who smoke marijuana daily. The most recent version of The Diagnostic and Statistical Manual of Mental Disorders (DSM) V recognized Cannabis Use Disorder (CUD) and cannabis withdrawal syndrome as legitimate mental disorders requiring treatment. In 2004 and 2005, 1.7% of the US population met criteria for CUD for the previous 12 months, which is a substantially high prevalence of dependence, more than for any other illicit drug. Sixteen percent of substance abuse treatment admissions in the US were for cannabis-related disorders; this was second only to treatment admissions for alcohol-related disorders. The diagnosis of CUD is highly overrepresented in veterans with Post Traumatic Stress Disorder (PTSD) in Oregon and with college students at the national level. In addition to being addictive, there is considerable evidence that marijuana is a gateway drug to other illicit drugs and more recently a gateway drug to tobacco. Many studies support the notion that the earlier an individual uses marijuana, the more likely they are to later use illicit drugs and develop alcohol dependence. The potency of marijuana, as measured by THC concentration has greatly increased over time, which may contribute to CUD.

Social determinants

Social determinants and social context have a critical influence on marijuana use in a community. Neighborhood disorder, unemployment, and poverty inform the social norms for marijuana use and abuse. At an individual level, being from a socially disadvantaged group, having a lower socioeconomic position, or being a student or unemployed, are associated with increased use of marijuana. Legalizing marijuana for recreational or medicinal purposes also changes the social context for use of the drug.

Residents in states with medical marijuana laws have higher odds of marijuana use and lower perceived risk of use, than residents in states without such laws.

Neurocognitive effects

The neurocognitive effects of marijuana suggest that using marijuana while the brain is still developing causes more severe and sometimes irreversible damage to the brain. Neurocognitive effects associated with both early and adult use of marijuana include deficits in visual attention, verbal fluency, impulse control, short-term memory recall and other aspects of executive functioning. The neuropsychological effect of adolescent marijuana use is associated with depression and anxiety that is not fully restored with cessation of marijuana use. Although the long-term heavy use of marijuana does not produce anywhere near the debilitating impairment of chronic alcohol use, marijuana use is associated with neurocognitive impairments in memory, decision-making and attention that worsen with increasing years of regular use.

Psychosis

The acute symptoms most commonly associated with marijuana use are anxiety reactions and panic attacks. Marijuana is a causative agent of substance-induced psychosis, most commonly manifesting as schizophrenia-like psychosis. Marijuana can also induce the clinical onset of primary psychosis in vulnerable individuals in a dose-dependent manner, up to 7 years earlier than in those who do not use marijuana, with heavier users having the earliest onset of primary psychosis. It is estimated that 8–14% of schizophrenia cases are due to marijuana use. Additionally, for those who are already suffering from schizophrenia, marijuana can cause paranoia, higher hospitalization rates, and decreased brain volume over a 5-year period.

Smoke carcinogenicity

Marijuana smoke contains levels of ammonia, hydrogen cyanide, nitric oxide and aromatic amines at concentrations three to five times those found in tobacco smoke. Most importantly, the presence of polycyclic aromatic hydrocarbons, which are known carcinogens, have been documented in both mainstream and secondary smoke from marijuana. The impact of marijuana smoking on respiratory health has similarities to those of tobacco smoking. Regular and long-term marijuana use is associated with general airway inflammation, epithelial cell injury, pulmonary immune suppression leading to infection, decreased lung function, bronchitis, coughing on most days and phlegm production. Additionally, marijuana use has a larger negative effect on dental health status than tobacco, with increased dental caries, oral infections and periodontal disease.

Cancer

The study of marijuana use and cancer is still in its infancy, even with countries that have had legalized marijuana for decades. At this point, marijuana use is associated with prostate cancer, cervical cancer, nasopharyngeal, glioma, airways cancer, and nonseminoma germ cell tumors of the testis. The reported risk of lung cancer with marijuana use varies, with multiple types of epidemiologic studies showing increased risk. However, the general impression is that the risk of lung cancer associated with marijuana is much lower than the risk of lung cancer associated with tobacco.

Cardiovascular effects

The cardiovascular effects associated with marijuana are: increased blood pressure during intoxication, stroke, congestive heart failure, arrhythmias, myocardial infarction, lower limb arteritis, transient ischemic attack and sudden cardiac death. Within one hour of smoking marijuana, the risk of myocardial infarction increases to approximately five times the risk of that before smoking marijuana. In addition to the cardiovascular effects, chronic marijuana smoking is associated with increased visceral adiposity, adipose tissue insulin resistance, increased appetite and increased caloric intake from carbohydrates.

Maternal and child health

Prenatal marijuana exposure may produce long-term consequences for children. This exposure is associated with an increased risk for aggressive behavior and attention problem in girls. In both sexes, prenatal marijuana exposure is associated with birth defects, low birth weight, and lower reading scores on standardized tests. Postnatal marijuana exposure is associated with preterm labor, small for gestational age, admission to the neonatal intensive care unit, adverse birth outcomes and increased risk of stillbirth. These outcomes however, are not considered higher risk than those associated with tobacco use.

Motor vehicle crashes

Perhaps the greatest threat to public health from marijuana comes in the form of motor vehicle crashes. There is overwhelming evidence that marijuana use is associated with approximately twice the odds of both fatal and non-fatal motor vehicle collision. As time and legislation passes, more people are driving under the influence of marijuana. Nationally, marijuana-drugged drivers involved in fatal collisions significantly increased from 29% in 1993, to 37% in 2010. In Oregon, the percent of marijuana-drugged drivers involved in fatal crashes increased 49% pre-legalization to post legalization of medical marijuana. The drivers who are testing positive for THC are three to seven times more likely to be responsible for their crash as compared to drivers that had not used drugs or alcohol. Unfortunately, crash research demonstrates marijuana is rarely ingested without alcohol and when you combine the two, you get the worst of both worlds. With marijuana use alone, the odds of a fatal motor vehicle crash increase approximately two times and with alcohol ingestion alone the odds of a fatal crash increase approximately 14 times. Driving under the influence of both alcohol and drugs increases the odds of a fatal motor vehicle crash over 23 times relative to those drivers without drugs and alcohol in their system.

First responder hazards

Motor vehicle drivers are not the only people at risk for injury from hazardous incidents associated with marijuana. Studies of marijuana grow operations have revealed the dangers of this exposure to law enforcement and first responders. Law enforcement can have serious exposure to airborne fungal spores, volatile organic compounds, carbon dioxide, pesticides and fertilizers from these grow operations within the normal course of their duties. The airborne fungal spore concentration is high enough at most marijuana grow operations that respiratory protection may be suggested for the safety of these first responders.

Poisoning and overdoses

With the production of edible marijuana products including cookies, candies and brownies, unintentional marijuana poisoning is now a serious concern for both children and companion animals. Approximately

18% of marijuana poisonings reported to the National Poison Data System were for children under the age of 12 years. Oregon is second highest in the country for the rate of calls for unintentional marijuana pediatric exposures reported to poison centers. In terms of companion animals, dogs account for 96% of marijuana toxicity cases. Colorado has witnessed a significant correlation between the number of medical marijuana licenses and the number of marijuana toxicity cases seen in their veterinary hospitals. In the Portland metro area, DoveLewis has reported an increase in marijuana intoxication in pets from 79 cases in 2011 to 116 cases in 2013.

Clinical research and therapeutics

No review of the health effects of marijuana would be complete without reviewing the clinical research surrounding the medicinal use of marijuana. The Food and Drug Administration (FDA), which is responsible for approving drugs as safe and effective, has declined to approve smoked marijuana for any condition or disease. Medical marijuana differs significantly from other prescription medicine in the US because the evidence supporting its efficacy falls short of the standard required approval for other drugs by the FDA. To quote Yale psychiatric professor Samuel T. Wilkinson, "The evidence for medicinal marijuana use in PTSD, glaucoma, Crohn's disease, and Alzheimer's disease, relies largely on testimonials instead of adequately powered, double-blind, placebo-controlled randomized clinical trials…" According to the Institute of Medicine, the effects of marijuana on disease symptoms are modest and in most cases there are more effective FDA-approved medications. However, the study of isolated and purified compounds from the marijuana plant has yielded the development of multiple FDA-approved medications. There are clinical trials currently underway to explore several compounds or combinations of compounds, as the true pharmaceutical potential of this plant is only beginning to be clinically and scientifically explored.

Conclusion

In summary, across many studies in multiple countries, marijuana use has been significantly associated with a variety of acute and chronic health outcomes in the realms of physical health, mental health, injury and mortality.

II. Key questions and methods

Introduction

This report is provided to the Washington County Commissioners and the public to provide a review of the most recent scientific research on the health effects of marijuana in response to two issues: the potential placement of medical marijuana dispensaries within Washington County, Oregon and the upcoming statewide vote in November 2014 on legalizing recreational marijuana in Oregon.

Topics that this paper does not review include treatment or prevention of marijuana use and the use of synthetic cannabinoids, such as Spice or K2, or hookah use.

How to use this report

Each topic and subtopic in this report has its own clearly delineated section to allow the user to read only the topics of interest. However, as with any longitudinal data, there is overlap between certain subject areas, such as the effect of adolescent initiation of marijuana use and the long-term health effects, and the reader is encouraged to explore these potentially related areas. The major report sections contain recommended primary peer-reviewed literature for the specific subject matter.

Methods

Topic selection process

The final topic areas were selected by first cross-referencing a current systematic review on the health effects of marijuana [1] with older systematic reviews [2, 3] and a report issued by Clark County, Washington [4]. Washington County Health and Human Services Division leaders, including those in Mental Health Services, Environmental Health, and Animal Services, were consulted for additional topic areas. Additional topics were gleaned from non-peer-reviewed sources. Research results on the study questions below were included independent of the results being neutral, positive or negative.

Study questions

1. What are the acute and chronic mental health effects of marijuana use?
2. What are the acute and chronic physical health outcomes of marijuana use?
3. What are the health benefits of marijuana use?
4. What are the injury and violent death outcomes of marijuana use?
5. What are the prenatal, postnatal and reproductive health outcomes of marijuana use?
6. What are the antecedents of marijuana initiation and later initiation of other drug use?
7. Has marijuana potency changed over time?
8. How does placement of marijuana dispensaries affect the social determinants of health?
9. What are the social determinants of marijuana use?
10. What would be the effect of legalization on law enforcement, land use, economics, and policy?
11. What are the implications of State legalization vs. Federal laws?

Definition of marijuana use: exposure, outcome and dosage

Many international, national and local epidemiologic studies report the individual exposure of “ever” marijuana use. “Ever” use of marijuana means that the individual reported having ever used marijuana.

Except for studies involving blood/saliva/urine testing, this is largely a self-report of individuals using marijuana for any purpose, whether it is recreational or medicinal. Both medical and recreational marijuana use generally involve smoking portions of the intact *Cannabis sativa* plant. Thus differentiating the exposure between medical smoking and recreational smoking from an epidemiologic perspective is moot. Put another way, the health exposure of inhaling *C. sativa* smoke does not change whether you have a prescription to do so or are smoking for recreational purposes. However, the health status and outcomes of marijuana use for those using marijuana for medical reasons versus recreational reasons may be very different, as those with a medical prescription may be more likely to be ill and have severe medical conditions. Thus, there is generally no difference in exposure between recreational and medical smoking, but a difference in health co-morbidities and outcomes. In addition to exposure and outcome measurement, the studies referenced in this review also have a measurement for marijuana dosage. This is usually reported in joint-years, number of times smoking marijuana (daily, weekly, monthly use), or an actual measurement of THC concentration from bodily fluids. The phrase "medical marijuana" generally refers to smoking the *C. sativa* plant, rather than referring to the purified Food and Drug Administration-approved single or dual compound pharmaceuticals derived from the *C. sativa* plant.

Literature search

We searched electronic sources including PubMed, Google Scholar, *The Cochrane Library*, Centers for Disease Control and Prevention (CDC), CDC National Institute for Occupational Safety and Health (NIOSH), and the CDC Morbidity and Mortality Weekly Report (MMWR) for eligible, peer-reviewed studies. Bibliographies of key reviews and articles were fully considered. The search was restricted to English language articles with abstracts and full text available. We attempted to identify articles published in the preceding 10-year period, expanding beyond the 10-year publication period when necessary. The time range of literature cited in this study spans from 1990–2014, with over 30 studies published in 2014 alone. The databases were searched from April 1, 2014 through Sept 15, 2014.

We queried websites of non-peer reviewed sources, including the American Veterinary Medical Association, the American Society for the Prevention of Cruelty to Animals (ASPCA), and the Humane Society of the US. Various professional organizations' websites, including the Institute of Medicine of the National Academies (IOM), were also reviewed for any position statements on the use of marijuana for medical conditions.

We explored various government websites including the National Institute on Drug Abuse (NIDA), the Food and Drug Administration (FDA), the US Department of Agriculture (USDA), the US Drug Enforcement Administration (DEA), the Substance Abuse and Mental Health Services Administration (SAMHSA), the US Department of Labor Bureau for Labor Statistics (BLS), the National Highway Traffic Safety Administration, and the Agency for Healthcare Research and Quality (AHRQ).

Additional sources of information included personal interviews with subject matter experts. We successfully obtained interviews on the following topics: the effects of marijuana use on law enforcement, marijuana-related crime statistics for Washington County, companion animal poisoning, and issues surrounding food codes in relation to state versus federal law. We were unsuccessful in contacting a local fire and rescue group regarding risks to firefighters from marijuana grow operations.

Finally, we attempted contact with four national and state organizations of cannabis breeders, growers, and legal reform groups and requested information on economics, profitability, impacts on businesses resulting from the legalization of marijuana. We received no response from any of these organizations.

From a total of 2,066 peer-reviewed citations retrieved from PubMed and *The Cochrane Review*, 219 were evaluated for full-text review, and 151 peer-reviewed articles were considered for inclusion in this study. Fifty-six non-peer reviewed articles are also included in this study.

Review process

Washington County Health and Human Services Division leaders reviewed drafts of this paper, provided feedback, and suggested modifications.

Citation

Repp, K.K. and A.L. Raich (2014). Marijuana and health: A comprehensive review of 20 years of research. *Washington County Health and Human Services*. Hillsboro, OR: Washington County.

Contact

Marni Kuyl, MS, RN
Director
Washington County Department of Health and Human Services
155 N First Ave., MS 5
Hillsboro, OR 97124
503-846-4745
Marni_Kuyl@co.washington.or.us

III. Marijuana basics

Recommended reading: Greydanus 2013, National Institutes of Health 2012, El Sohly 2013, Mehmedic 2010

Marijuana basics and consumption

Marijuana is a product of the hemp plant, *Cannabis sativa*, and is grown worldwide [5]. The US Controlled Substances Act considers marijuana to be a Schedule I substance, meaning that it has a high potential for abuse, no currently accepted medical use as a treatment in the US, and a lack of accepted safety for use under medical supervision [6].

Marijuana is composed of a mixture of the dried and shredded leaves, stems, seeds, and flowers of the plant (Figure 1)[7]. It can be smoked in hand-rolled joints, pipes or bongs or combined with cigar tobacco (blunts) [7, 8].

Hashish, or cannabis resin, is collected from the trichomes or hairs of the plants [9] and, after drying, is compressed into cakes, balls, or sheets (Figure 2) [6]. It is smoked (by itself or mixed with tobacco) or ingested orally [1].

Hashish oil, also known as honey oil or butane hash oil, is produced by extracting the cannabinoids from the plant material or resin with a solvent, such as butane (Figure 3) [6, 9]. This oil can be vaporized and inhaled using a water pipe or a few drops can be put onto a cigarette and smoked [6].

The types of marijuana listed above can also be consumed as tea or mixed with food (Figures 1-4) [7, 8]. Delta-9-tetrahydrocannabinol (THC) is one of over 480 constituents of marijuana and is believed to be the main component that produces the psychoactive effect experienced by marijuana users [6]. Potency of marijuana is generally measured by the percent of THC in the product.

Figure 1. Loose marijuana stems and leaves "Loose Marijuana (http://www.justice.gov/dea/pr/multimedia-library/image-gallery/images_marijuana.shtml)" by Drug Enforcement Administration US Department of Justice - public domain.

Figure 2. Low quality hashish "Low Quality Hashish (http://commons.wikimedia.org/wiki/File:Hashish-2.jpg)" by Erik Fenderson - public domain, via Wikimedia Commons.

Figure 3. Whipped butane honey oil "Whipped Butane Honey Oil (http://commons.wikimedia.org/wiki/File:Butane_honey_oil_after_being_whipped_2.JPG)" by Vjiced - CC-BY-SA-3.0 (http://creativecommons.org/licenses/by-sa/3.0), via Wikimedia Commons.

Figure 4. Edible marijuana "KCCS Cookie (http://commons.wikimedia.org/wiki/File:KCCS_Cookie.JPG)" by MjolnirPants - CC-BY-SA-3.0 (http://creativecommons.org/licenses/by-sa/3.0/deed.en), via Wikimedia Commons.

The endocannabinoid system and the effects of THC

The human body has a large communication network known as the endocannabinoid system, which plays a crucial role in brain development and function, including cognition, memory, reward, pain perception, motor coordination, and appetite [2, 7]. Two key components of this system are *cannabinoid receptors*, specific sites on the surface of nerve cells, and *endogenous cannabinoids*, naturally occurring chemicals that control many mental and physical functions [7]. When marijuana is smoked, THC passes from the lungs into the bloodstream, is carried to organs throughout the body, including the brain, and binds to cannabinoid receptors [7]. THC artificially stimulates the body's cannabinoid receptors, disrupting the normal function of the endogenous cannabinoids [7]. The artificial overstimulation of these receptors in key brain areas by the THC in marijuana is what produces the marijuana "high" and other mental processing effects [7]. If stimulated on a consistent basis over time, the normal function of the cannabinoid receptors can be changed and addiction can occur [7].

Other components of marijuana include over 60 other cannabinoids and various other chemicals. Some of these cannabinoids can have an additive or antagonistic effect with THC [10]. One cannabinoid of importance is cannabidiol (CBD), which is thought to offset some of the psychoactive effects of THC [10].

Marijuana potency and potency trends

Marijuana potency is usually measured by the percentage of THC content in the product [10]. The part of the plant used for consumption is one factor determining THC content. The highest THC levels are found in the sinsemilla, unfertilized flower heads [9]. The plant variety also determines the potency, with some cannabis grown specifically for its psychoactive effects [10]. Some preparation methods, such as producing hash oil, result in a higher THC content. Storage methods can also affect marijuana potency; storage in an airtight container helps prevent THC degradation. Marijuana grown indoors can have a higher THC content by facilitating the best growth conditions [10].

Hash oil usually has the highest THC potency, with an average THC concentration of 20%, followed by hashish with 5 – 15%, and marijuana with 1 – 5% THC (Figure 5) [11]. When considering THC

concentration, it is important to consider certain cannabinoids also present that may mitigate the effects of THC. One cannabinoid of importance is CBD, which is thought to offset some of the psychoactive effects of THC [10]. Although high levels of THC can be indicative of greater psychoactive properties, the percentage of CBD relative to that of THC might also be of importance due to the antipsychotic and anti-anxiety effects of CBD [10].

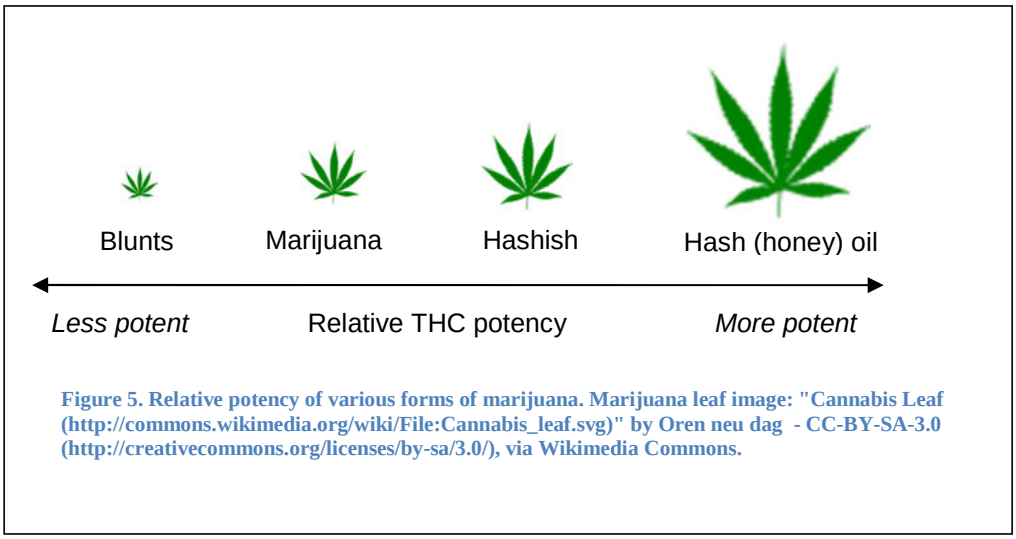

Figure 5. Relative potency of various forms of marijuana. Marijuana leaf image: "Cannabis Leaf (http://commons.wikimedia.org/wiki/File:Cannabis_leaf.svg)" by Oren neu dag - CC-BY-SA-3.0 (http://creativecommons.org/licenses/by-sa/3.0/), via Wikimedia Commons.

A meta-analysis of 21 case series studies suggested that there has been a recent and consistent increase in cannabis potency worldwide [10, 12, 13]. Cannabis samples tested in the US, the Netherlands, United Kingdom and Italy have shown increases in potency over the last 10 years [10]. Increased potency has been observed in some countries, but there is enormous variation between samples, meaning that cannabis users may be exposed to greater variation in a single year than over years or decades [10]. The potency of marijuana, as detected by THC content in confiscated samples, has been steadily increasing from about 3% in the 1980s to 12% in 2012 [1, 12]. This increase in THC content raises concerns that the consequences of marijuana use may be worse now than in the past and may account for the significant increases in emergency department visits by persons reporting marijuana use (Figure 6). Between the early 1990s and the early 2000s, the prevalence of marijuana use remained stable but more US adults had a marijuana use disorder [14]. The fact that marijuana use disorders have significantly increased in the absence of increased frequency and quantity of marijuana use, suggests that the concomitant increase in potency of THC may have contributed to the rising rates of marijuana use disorders [14].

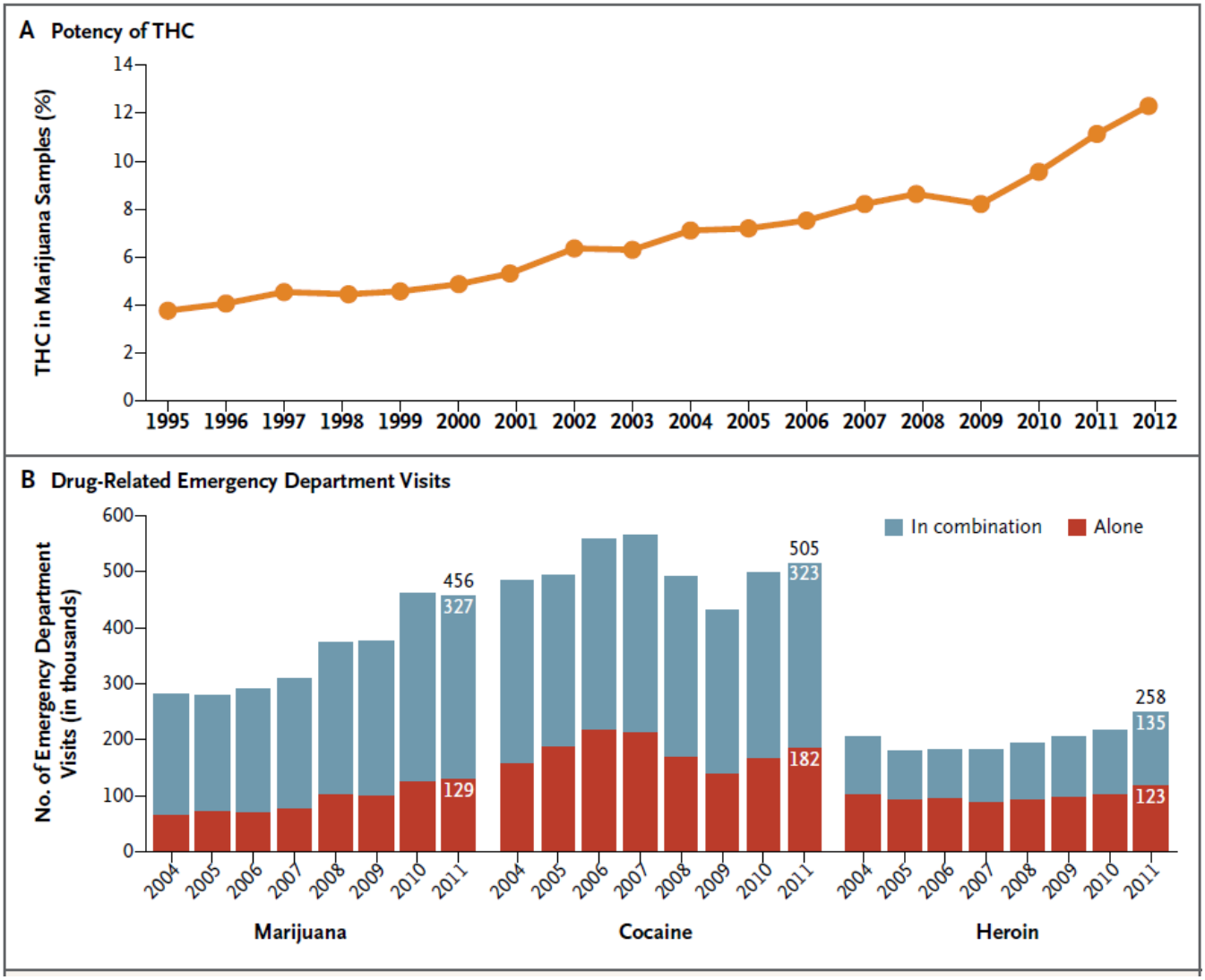

Figure 6. Increases over time in the potency of tetrahydrocannabinol (THC) in marijuana and the number of emergency department visits involving, marijuana, cocaine or heroin. From "Adverse effect of marijuana use," by Volkow et al., *The New England Journal of Medicine*, page 2223. Copyright 2014 by Massachusetts Medical Society. Reprinted with permission.

IV. Demographics, prevalence, and trends of marijuana use

Recommended reading: Oregon Public Health Division, CD Summary, June 17th, 2014

Global prevalence of marijuana use

Cannabis is the most commonly used illicit drug worldwide. It is difficult to obtain estimates of global marijuana use as not all countries conduct national surveys on drug use; of those that do, they conduct them only periodically, once every three to five years [15]. It is estimated that the prevalence of marijuana use globally is approximately 4% [15]. In Europe, approximately 5% of adults (15–64 years) and 11% of young adults (15–34 years) reported using marijuana in the past year [16].

United States prevalence of marijuana use

National

According to the 2012 US National Survey on Drug Use and Health (NSDUH) conducted by SAMHSA, marijuana was the most commonly used illicit drug in the US, with 18.9 million people aged 12 years or older reporting use of marijuana in the past month [17]. This reflects an increase in marijuana use from 6.2% of the population using in 2002 to 7.3% of the population using in 2012. Of the 2.7 million persons aged 12 or older who used illicit drugs for the first time within the past 12 months in 2007, the majority (56%) reported that their first drug was marijuana; this averages to approximately 6,000 initiates per day [18]. This estimate of past year initiates in 2007 was about the same as the number of initiates per year from 2002–2006 [18].

Local and State

Fewer residents of Washington County reported current marijuana use than the Oregon state resident average in a national survey conducted by the Substance Abuse and Mental Health Services Administration (SAMHSA) (Table 1) [19].

Region Years 2010–12	Prevalence of past month marijuana use	95% Confidence Interval
Washington County, Oregon	9.7 %	7.6% – 12.3%
Oregon	11.2%	9.7% – 12.8%
West	8.9%	9.4% – 9.3%
National	7.0%	6.8% – 7.2%

Table 1. Prevalence of marijuana use in the past month among persons aged 12 or older by state and sub-state regions (SAMSHA NSDUH).

Adolescents

Most (62%) of the 2.1 million recent marijuana initiates were younger than age 18 when they first used marijuana [18]. Among youths aged 12 to 17, an estimated 4.6% had used marijuana for the first time within the past year, similar to the rate in 2006 (4.7%) [18].

The Oregon Healthy Teens Survey of 2013 reported that in Washington County, Oregon 7% of 8th graders and 19% of 11th graders reported current marijuana use [20], which was lower than the Oregon average of 10% of 8th graders and 21% of 11th graders [21]. The Youth Risk Behavior Surveillance in the US reports that 23% of high school students had used marijuana during the 30 days prior to the survey [22]. The Monitoring the Future survey reported that marijuana use in the past month among adolescents in the 8th, 10th, and 12th grades declined from a peak use of 18% in 1997 to a low of 12% in 2007 [23]. Since 2007, however, marijuana use has been on the rise with approximately 16% of adolescents reporting marijuana use in 2013.

College students

Use in US college students (full- or part-time students one to four years past high school) has been increasing, from approximately 14% reported current marijuana use in 1991 to 21% in 2013 [24]. In a study of first year US college students, approximately 20% reported using marijuana and of these, 44% of males and 9% of females drove a motor vehicle after using marijuana [25].

Oregon Medical Marijuana Program

Medical marijuana is legal in Oregon. Since the program first began in 1999, the Oregon Medical Marijuana Program (OMMP) has served more than 45,000 registered patients [26]. As of October 2014, the OMMP reports there are 69,429 patients, 34,624 caregivers and 1,628 physicians with current OMMP patients. At the county level as of October 2014, Washington County has 4,670 medical marijuana patient registrants, Multnomah County has 11,718 registrants and Clackamas County has 4,919 registrants. A detailed breakdown of the state-level diagnosed medical conditions for OMMP patients is shown below (Table 2).

Diagnosed medical conditions of Oregon Medical Marijuana Program patients	Count
Agitation related to Alzheimer's disease	79
Cachexia (wasting syndrome)	1,134
Cancer	3,456
Glaucoma	1,087
HIV+/AIDS	744
Nausea	9,409
Posttraumatic Stress Disorder (PTSD)	2,433
Severe pain	**64,692**
Seizures, including but not limited to epilepsy	1,753
Persistent muscle spasms, including but not limited to those caused by Multiple Sclerosis	17,474

Table 2. List of diagnosed qualifying medical conditions for Oregon Medical Marijuana Program (OMMP) patients as of October 2014. (OMMP Statistics as of October 2014, accessed 10/17/14, http://public.health.oregon.gov/DiseasesConditions/ChronicDisease/MedicalMarijuanaProgram/Pages/data.aspx. Also OR PH DIV 2014)

Marijuana product demand: Colorado

Marijuana is legal for recreational and medicinal use in Colorado. The demand for marijuana in Colorado by adult residents is estimated to be 121.4 metric tons in 2014, with the demand by visitors to the state estimated to be 8.9 metric tons [27]. In Colorado, the 22% most frequent marijuana users account for two-thirds of the product demand [27]. In contrast, the entire population of rare users (less than once per month), a group that accounts for almost one-third of all users, represents less than 1% of total demand [27].

V. Therapeutic potential of cannabis and cannabinoids

Recommended reading: Wilkinson 2014, Kogan 2007, National Cancer Institute 2014, US Department of Justice 2014, Borgelt 2013, Grotenhermen 2012

Medicinal marijuana versus other prescription medications

The term "medical marijuana" is ambiguous in that it can refer to two of the three forms in which cannabinoids occur: 1) endocannabinoids, which are neuromodulatory lipids, 2) phytocannabinoids, the hundreds of compounds in the *C. sativa* plant; and 3) synthetic cannabinoids, which are laboratory produced and the foundation of the pharmaceutical industry [28]. As with opium poppies before it, study of a drug-containing plant has resulted in the discovery of an endogenous control system at the center of neurobiological function whose manipulation has significant implications for the development of novel pharmacotherapies [28].

As of May 2014, there were 237 researchers registered with the Drug Enforcement Agency (DEA) to perform studies with marijuana, marijuana extracts, and non-THC marijuana derivatives that exist in the plant, such as cannabidiol and cannabinol [29]. Of these 237 researchers, sixteen are approved to conduct research with smoked marijuana on human subjects [29]. Because of the health risks associated with smoking, smoked marijuana is generally not recommended for long-term medical use, except in the terminally ill [30]. Short-term use of smoked marijuana even for patients with debilitating symptoms, such as vomiting, *must* meet the condition of documented failure of all approved medications to provide relief before marijuana treatment begins [30]. Except for the harms associated with smoking, the adverse effects of marijuana use are within the range of effects tolerated for other medications [30].

The FDA, which is responsible for approving drugs as safe and effective medicine, has thus far declined to approve smoked marijuana for any condition or disease [29]. The FDA has noted that there is sound evidence that smoked marijuana is harmful and that no sound scientific studies support the medical use of marijuana for treatment in the US, and no animal or human data support the safety or efficacy of marijuana for general medical use [29]. No other prescription medication is smoked [31].

According to the National Institute on Drug Abuse (NIDA), study of cannabinoids has led to the development of two FDA-approved medications, and is leading to the development of new pharmaceuticals that harness the therapeutic benefits of cannabinoids while minimizing or eliminating the harmful side effects (including the "high") produced by eating or smoking the leaves [29].

As of 1999, the accumulated data indicate a potential therapeutic value for cannabinoid drugs, particularly for symptoms such as pain relief, control of nausea and vomiting, and appetite stimulation [30]. In clinical studies, the best-supported indications for cannabis are spasticity in multiple sclerosis and pain, but the evidence is limited and has not been repeatable [32]. The effects of cannabinoids on the symptoms studied are generally modest, and in most cases there are more effective medications [30]. Defined substances, such as purified cannabinoid compounds, are preferable to plant products, which are of variable and uncertain composition [30].

Medical marijuana differs significantly from other prescription medications in the US [31]. Evidence supporting its efficacy varies substantially and in general falls short of the standard required for approval of other drugs by the FDA. The evidence for medicinal marijuana use in PTSD, glaucoma, Crohn's

disease and Alzheimer's disease, relies largely on testimonials instead of adequately powered, double-blind, placebo-controlled randomized clinical trials [31]. For most of these conditions, medications that have been subjected to the rigorous approval process of the FDA already exist [31]. Furthermore, the many conditions for which medical marijuana is approved have no common etiology, pathophysiology, or phenomenology, raising skepticism about a common mechanism of action [31]. Unlike other prescription medications, marijuana contains more than 100 cannabinoids, terpenoids, and flavonoids that produce individual, interactive, and entourage effects [31].

The authoritative report by the Institute of Medicine, *Marijuana and Medicine* [30], acknowledges the potential benefits of smoking marijuana in stimulating appetite, particularly in patients with AIDS and the related wasting syndrome, and in combating chemotherapy-induced nausea and vomiting, severe pain, and some forms of spasticity [1]. The report, however, stresses the importance of focusing research efforts on the therapeutic potential of synthetic or pharmaceutically pure cannabinoids [1, 30].

Cannabis products manufactured by pharmaceutical companies

A medical role for specific cannabinoid compounds remains under active medical research [8]. The cannabinoid medicines currently utilized in the American healthcare sector fall into three categories: single molecule pharmaceuticals, cannabis-based liquid extracts, and phytocannabinoid-dense botanicals [33].

Synthetic or semi-synthetic single molecule cannabinoids

The first category includes US FDA approved synthetic or semi-synthetic single molecule cannabinoid pharmaceuticals available by prescription [33]. These include: Sativex®, Marinol®, and Cesamet® [8, 29]. Cesamet® and Marinol® have been approved for use in the anorexia-cachexia (wasting) syndrome as well as for nausea and vomiting [8]. Marinol® has been used to treat glaucoma by lowering intraocular pressure or relieve chemotherapy-induced emesis [8]. Marijuana has been used to treat the wasting syndrome associated with HIV/AIDS [8], but there is evidence suggesting marijuana use exacerbates HIV-associated cognitive deficits [1]. A newer tablet formulation of THC called Namisol® is in Phase II clinical trials, and has been studied to ameliorate pain and spasms in adults with multiple sclerosis as well as to relieve nausea, and vomiting in HIV or cancer patients [8]. Although it has not yet undergone clinical trials to establish its effectiveness and safety, a cannabidiol-based drug called Epidiolex® has recently been created to treat certain forms of childhood epilepsy [29].

Cannabis-based extracts

The second category of cannabinoid medicines being used in the US includes a line of cannabis-based extracts that are in Phase IIb clinical trials for the treatment of opioid-refractory cancer pain [33].

Cannabis sativa, the plant

The third category of cannabinoid medicine currently being used in the US includes the Schedule I plant *Cannabis sativa* itself [33]. As of 2009, the plant was under investigation in two active controlled clinical trials and 33 completed controlled clinical trials [33]. Overall, 33 completed and published US controlled clinical trials with cannabis have studied its safety, routes of administration and use in comparison with placebos, standard drugs, and in some cases dronabinol, in: appetite stimulation in healthy volunteers, the treatment of HIV neuropathy and other types of chronic and neuropathic pain, both pathological and experimentally induced, spasticity in multiple sclerosis, weight loss in wasting

syndromes, intraocular pressure in glaucoma, dyspnea (shortness of breath) in both pathological and experimentally induced asthma, and emesis, both secondary to cancer chemotherapy and experimentally induced [33]. It's of note that in the clinical trials using smoked cannabis for pain there was a range of 15–56 total people participating in the trials [33]. If there are encouraging results in these small clinical trials, in order to reach Phase III clinical trials to confirm drug effectiveness, evaluate side effects and compare to regularly used treatments to potentially receive FDA approval, large trials requiring between 1,000 and 3,000 people are needed. Research for this report was unable to yield a single report of smoked cannabis moving beyond a small US Phase II clinical trial for any health issue for any reason. Major medical organizations have called for the reclassification of cannabis to a Schedule II controlled substance so that more research can be rigorously conducted on marijuana as is done with other pharmaceuticals [28].

Cannabinoids and adverse events

The therapeutic use of cannabis and cannabis-based medicines raises safety concerns for patients, clinicians, policy-makers, insurers, researchers and regulators [34]. In a systematic review of safety studies of medical cannabinoids published over the past 40 years, a total of 4,779 adverse events were reported among participants with 4,615 (97%) of the events being nonserious [34]. Dizziness was the most commonly reported nonserious adverse event (16%) among people exposed to cannabinoids [34]. Short-term use of medical cannabinoids appears to increase the risk of nonserious adverse events [34]. Of the 164 serious adverse events, including 5 deaths, the most common was relapse of multiple sclerosis (21 events, 13%), vomiting (16 events, 10%), and urinary tract infection (15 events, 9%) [34].

Clinical trials

Several controlled clinical trials on cannabinoids have been performed and a meta-analysis of these support a beneficial effect of dronabinol and nabilone on chemotherapy induced nausea and vomiting [5]. There are no published data on the use of whole cannabis for other cancer-related or cancer treatment-related symptoms [5]. Thus, at present there is insufficient evidence to recommend inhaling cannabis as a treatment for cancer related symptoms or cancer treatment related side effects [5]. A full list of clinical trials with study design and outcomes involving cannabis can be found here: http://www.cannabis-med.org/studies/study.php. Below is a figure from a recent *New England Journal of Medicine* publication, listing current clinical conditions that may be relieved with marijuana treatment or cannabinoids (Figure 7).

Clinical Conditions with Symptoms That May Be Relieved by Treatment with Marijuana or Other Cannabinoids.*

Glaucoma

Early evidence of the benefits of marijuana in patients with glaucoma (a disease associated with increased pressure in the eye) may be consistent with its ability to effect a transient decrease in intraocular pressure,[53,54] but other, standard treatments are currently more effective. THC, cannabinol, and nabilone (a synthetic cannabinoid similar to THC), but not cannabidiol, were shown to lower intraocular pressure in rabbits.[55,56] More research is needed to establish whether molecules that modulate the endocannabinoid system may not only reduce intraocular pressure but also provide a neuroprotective benefit in patients with glaucoma.[57]

Nausea

Treatment of the nausea and vomiting associated with chemotherapy was one of the first medical uses of THC and other cannabinoids.[58] THC is an effective antiemetic agent in patients undergoing chemotherapy,[59] but patients often state that marijuana is more effective in suppressing nausea. Other, unidentified compounds in marijuana may enhance the effect of THC (as appears to be the case with THC and cannabidiol, which operate through different antiemetic mechanisms).[60] Paradoxically, increased vomiting (hyperemesis) has been reported with repeated marijuana use.

AIDS-associated anorexia and wasting syndrome

Reports have indicated that smoked or ingested cannabis improves appetite and leads to weight gain and improved mood and quality of life among patients with AIDS.[61] However, there is no long-term or rigorous evidence of a sustained effect of cannabis on AIDS-related morbidity and mortality, with an acceptable safety profile, that would justify its incorporation into current clinical practice for patients who are receiving effective antiretroviral therapy.[62] Data from the few studies that have explored the potential therapeutic value of cannabinoids for this patient population are inconclusive.[62]

Chronic pain

Marijuana has been used to relieve pain for centuries. Studies have shown that cannabinoids acting through central CB1 receptors, and possibly peripheral CB1 and CB2 receptors,[63] play important roles in modeling nociceptive responses in various models of pain. These findings are consistent with reports that marijuana may be effective in ameliorating neuropathic pain,[64,65] even at very low levels of THC (1.29%).[66] Both marijuana and dronabinol, a pharmaceutical formulation of THC, decrease pain, but dronabinol may lead to longer-lasting reductions in pain sensitivity and lower ratings of rewarding effects.[67]

Inflammation

Cannabinoids (e.g., THC and cannabidiol) have substantial antiinflammatory effects because of their ability to induce apoptosis, inhibit cell proliferation, and suppress cytokine production.[68] Cannabidiol has attracted particular interest as an antiinflammatory agent because of its lack of psychoactive effects.[58] Animal models have shown that cannabidiol is a promising candidate for the treatment of rheumatoid arthritis[58] and for inflammatory diseases of the gastrointestinal tract (e.g., ulcerative colitis and Crohn's disease).[69]

Multiple sclerosis

Nabiximols (Sativex, GW Pharmaceuticals), an oromucosal spray that delivers a mix of THC and cannabidiol, appears to be an effective treatment for neuropathic pain, disturbed sleep, and spasticity in patients with multiple sclerosis. Sativex is available in the United Kingdom, Canada, and several other countries[70,71] and is currently being reviewed in phase 3 trials in the United States in order to gain approval from the Food and Drug Administration.

Epilepsy

In a recent small survey of parents who use marijuana with a high cannabidiol content to treat epileptic seizures in their children,[72] 11% (2 families out of the 19 that met the inclusion criteria) reported complete freedom from seizures, 42% (8 families) reported a reduction of more than 80% in seizure frequency, and 32% (6 families) reported a reduction of 25 to 60% in seizure frequency. Although such reports are promising, insufficient safety and efficacy data are available on the use of cannabis botanicals for the treatment of epilepsy.[73] However, there is increasing evidence of the role of cannabidiol as an antiepileptic agent in animal models.[74]

* AIDS denotes acquired immunodeficiency syndrome, CB1 cannabinoid-1 receptor, and CB2 cannabinoid-2 receptor, HIV human immunodeficiency virus, and THC tetrahydrocannabinol.

Figure 7. List of clinical condition with symptoms that may be relieved by treatment with marijuana or other cannabinoids. From "Adverse effect of marijuana use," by Volkow et al., *The New England Journal of Medicine*, page 2223. Copyright 2014 by Massachusetts Medical Society. Reprinted with permission.

VI. Marijuana dependence and withdrawal

Recommended reading: SAMHSA reports

Cannabis abuse and dependence were considered substance related disorders in DSM-IV. As of DSM-V, cannabis abuse and dependence are now considered part of the same substance use disorder: cannabis use disorder (CUD). The criteria below are included to understand the research referencing cannabis dependence, occurring before designation of CUD.

DSM-IV criteria for substance dependence

A maladaptive pattern of substance use, leading to clinically significant impairment or distress, as manifested by three (or more) of the following, occurring at any time in the same 12-month period:

1. Tolerance, as defined by either of the following:
    a. A need for markedly increased amounts of the substance to achieve intoxication or desired effect
    or
    b. Markedly diminished effect with continued use of the same amount of the substance
2. Withdrawal, as manifested by either of the following:
    a. The characteristic withdrawal syndrome for the substance
    or
    b. The same (or a closely related) substance is taken to relieve or avoid withdrawal symptoms
3. The substance is often taken in larger amounts or over a longer period than was intended
4. There is a persistent desire or unsuccessful efforts to cut down or control substance use
5. A great deal of time is spent on activities necessary to obtain the substance (e.g., visiting multiple doctors or driving long distances), use the substance (e.g., chain-smoking), or recover from its effects
6. Important social, occupational, or recreational activities are given up or reduced because of substance use
7. The substance use is continued despite knowledge of having a persistent physical or psychological problem that is likely to have been caused or exacerbated by the substance (e.g., current cocaine use despite recognition of cocaine-induced depression, or continued drinking despite recognition that an ulcer was made worse by alcohol consumption)

Transition from cannabis use to dependence

In the US, cannabis dependence is among the most common forms of illicit-drug dependence in the population with about 1 in 10 of those who ever use cannabis becoming dependent on it [18, 35-37]. The number goes up to about 1 in 6 among those who start using marijuana as teenagers and to 1 in 2–4 among those who smoke marijuana daily [1]. In summary, a large body of evidence now demonstrates that cannabis dependence, both behavioral and physical, occurs in about 7–10% of regular users, and that early onset of use, and especially weekly or daily use, is a strong predictor of future dependence [38, 39].

Cannabis dependence demographics and trends

Estimates from 2004 and 2005 indicate that 1.7% of the US population met DSM-IV criteria for cannabis abuse or dependence during the past year, which is substantially more than for any other illicit

drug [37, 40]. The prevalence of DSM-IV marijuana abuse or dependence significantly increased between 1991 and 2002, with the greatest increases observed among young black men and women, and young Hispanic men [14].

Treatment admission for cannabis

The CUD research is supported by the treatment admissions for marijuana abuse. Approximately 16% (~300,000 people) of all substance abuse treatment admissions in the US were for cannabis-related disorders; second only to alcohol-related disorders [37]. In 2007, 936,000 people reported receiving treatment for marijuana use [18].

Cannabis dependence relative to other drugs

Animal research demonstrates the potential for cannabis dependence, but this potential is observed under a narrower range of conditions than with benzodiazepines, opiates, cocaine or nicotine [30]. Animals develop tolerance to the effects of repeated doses of THC, and studies suggest that cannabinoids may affect the same reward systems as alcohol, cocaine, and opioids [35]. In the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC), in which Oregon participates, the transition to cannabis dependence occurred faster than transition to nicotine or alcohol dependence [41]. Indeed, marijuana was the illicit drug that had the highest rate of past year dependence or abuse in 2007, followed by pain relievers and cocaine [18].

Risk factors for cannabis dependence

As compared with persons who begin marijuana use in adulthood, those who begin in adolescence are approximately 2–4 times more likely to have symptoms of cannabis dependence within two years after first use [1]. Social anxiety disorder is an independent risk factor for cannabis dependence [42]. A review of twin studies found a substantial genetic contribution to the likelihood of using, abusing and developing dependence on cannabis [43].

Cannabis Use Disorder (CUD)

Cannabis use disorders (CUD) encompass the two distinct diagnoses of abuse and dependence, defined in the DSM-IV by the same criteria as for other substance abuse disorders [44]. This disorder can be classified as mild, moderate or severe. By definition, individuals with CUD experience functional problems in their lives as a result of their cannabis use, such as loss of major role functions and repeated legal problems [44].

Co-substance use and CUD

Some evidence suggests differential neurocognitive effects of cannabis that depend on whether the individual also uses other substances [45]. Cannabis may exert neuroprotective effects among heavy alcohol using adolescents, alcohol-dependent adults and methamphetamine-dependent adults [45]. Relative to cannabis use only, co-occurring cannabis and tobacco use was associated with a greater likelihood of cannabis use disorders, more psychosocial problems, and poorer cannabis cessation outcomes [46].

Veterans, Posttraumatic Stress Disorder (PTSD) and CUD

In an investigation of the rates and trends of CUD diagnoses among patients of the Veterans Affairs (VA) Health Care System, results indicated that the prevalence of CUD diagnoses within the VA have

increased more than 50% over the past 7 years (2002–9), [47]. The prevalence of patients with a CUD diagnosis but no other illicit substance abuse diagnosis rose 115% during the same time period [47].

Posttraumatic stress disorder (PTSD) develops after a terrifying ordeal that involved physical harm or the threat of physical harm [48]. In an investigation of the rates and trends of CUD diagnoses among patients of the Veterans Affairs Health Care System, rates of PTSD were higher among patients with CUD but no other illicit substance abuse disorder, compared with other substance abuse disorder groups ($p<0.01$) [47]. In contrast, the CUDs at the US population-level have not significantly changed since 2002 [47]. Unfortunately, for all years of data available, Oregon has the highest percentage of individuals seen in VA hospitals with a CUD diagnosis without another illicit substance abuse diagnosis; a 50% increase from 2002 to 2009 [47]. National findings suggest that veterans are using cannabis at higher rates among states where medical use is legal (like Oregon), and a greater number of these individuals are suffering from abuse or dependence [47].

In a prospective study evaluating cannabis use among veteran residential treatment for PTSD, symptom severity between treatment intake and discharge was incrementally predictive of cannabis use frequency at four months after discharge [49]. Specifically, veterans who experienced lower levels of change in PTSD symptom severity during the course of residential treatment for PTSD were more likely to use cannabis after discharge from treatment [49]. Most notably, these effects were specific to cannabis and were not found for other substances examined among this sample, including alcohol and opiates [49].

General population PTSD and cannabis use

In a representative US sample, PTSD diagnoses were associated with increased odds of lifetime history of cannabis use as well as past year daily cannabis use [50]. Consistent with US clinical literature, individuals with a substance use disorder (SUD) plus PTSD experience significantly poorer physical and mental health and greater disability than those with a SUD alone [51].

College students and CUD

The prevalence of CUD was 9.4% among all first-year college students and approximately 25% among past-year cannabis users [44]. Among college cannabis users, concentration problems (40%), driving while high (19%) and missing class (14%) were among the most prevalent cannabis-related problems, even among those who endorsed no CUD criteria [44]. Of cannabis-using college students, one in ten users met the clinical definition for dependence, and 14.5% met the definition for abuse [44].

Cannabis withdrawal syndrome

Cannabis withdrawal syndrome is now recognized in the DSM-V. Symptoms of cannabis withdrawal syndrome include irritability, sleeping difficulties, dysphoria, craving and anxiety, which makes cessation difficult and contributes to relapse [1]. Chronic cannabis users can develop psychological addiction and a withdrawal syndrome comparable to heroin addiction [8]. Cannabis withdrawal symptoms have been observed in humans who have been abruptly withdrawn after 20 days of high dose THC and in long-term cannabis users [3]. In a literature review spanning 50 years, cannabis withdrawal was found to be associated with stroke, myocardial infarction, and lower limb arteritis [52].

Gateway drug

Animal models show that THC can prime the brain for enhanced responses to other drugs [1]. A consistent finding in the US has been the regular sequence of initiation into drug use in which cannabis use has typically preceded involvement with "harder" illicit drugs, such as stimulants and opioids [35]. Cannabis use is more strongly associated with other illicit drug use than alcohol or tobacco use [3].

Earlier cannabis initiation predicts other illicit drug use

Almost all adolescents who tried cocaine and heroin had first used alcohol, tobacco and cannabis in that order; regular cannabis users were much more likely to later use heroin and cocaine; and the earlier the age at which cannabis was first used, the more likely the use of other illicit drugs [2, 43, 53]. In studies involving twins, individuals who used cannabis by age 17 years had odds of other drug use, alcohol dependence, and drug abuse/dependence that were 2.1 to 5.2 times higher than those of their co-twin who did not use cannabis before age 17 years [54, 55].

Cannabis use and initiation of tobacco use

Researchers discovered, and a US cohort study confirmed that weekly or more frequent cannabis use during the teens and young adulthood was associated with an increased risk of later initiation of tobacco use and progression to nicotine dependence, suggesting that cannabis might now be a "gateway" drug to tobacco use, rather than vice versa [43].

VII. Social determinants of marijuana use

Recommended reading: Macleod 2004, Lynskey 2000, Karriker-Jaffe 2013

Neighborhood influence on marijuana use

Neighborhood context can define social norms for substance use and abuse within a community. In an ethnically and geographically diverse sample of middle school students, perceived neighborhood disorder was significantly related to their use of marijuana ($p<0.001$) [56]. Marijuana initiation is more likely among adolescents living in neighborhoods with a higher unemployment rate [57]. For adults, neighborhood characteristics affect substance use along gender lines. Residence in an affluent neighborhood is associated with lower odds of marijuana use in women, but not in men [58]. Neighborhood urbanicity is significantly associated with both monthly and increased marijuana use in men, but not in women [58].

Individual antecedents of marijuana use

Both nationally and internationally, marijuana use is disproportionately frequent in adults who belong to disadvantaged social groups. After adjusting for individual and family factors, marijuana use and abuse is especially prevalent among individuals who experience a downward socioeconomic trajectory from childhood to adulthood [59]. In a large French cohort study, low socioeconomic position was significantly associated with marijuana use and marijuana abuse [60]. Heavy marijuana use has been linked to lower income, greater need for socioeconomic assistance, unemployment, criminal behavior, and lower satisfaction with life [1]. Consistent with these socioeconomic associations, students, the unemployed and those not in the labor force, have a higher prevalence of marijuana use than the employed, both domestically and internationally [58, 60]. Young people who become regular cannabis users are more likely than their peers to have a history of antisocial behavior; to be nonconformist,

rebellious and feel alienated; to perform poorly at school; to have low academic expectations; and to affiliate with drug-using peers [43]. Interestingly, agoraphobia, a panic disorder in which a person fears being in places where it is hard to escape, is significantly associated with a higher predisposition to cannabis use, regardless of anxiety condition and other confounding factors [42].

Adolescent use of marijuana

Individuals who start using alcohol, tobacco and marijuana in adolescence are more likely to continue this behavior as adults. Adolescents are more likely to initiate and use marijuana if they have a higher proportion of in-school friends who binge drink alcohol, if they no longer attend school, or have high rates of absenteeism [57]. Indeed, adults who report heavy drinking in their adolescent years, experience significantly increased and monthly adult marijuana use [58].

The influence of parental use of tobacco and marijuana

There are significant differences in perceptions, attitudes, and marijuana use between those who have parents that use or have used marijuana and those who have parents that have not used marijuana [61]. Compared with those who have parents who have *never* used marijuana, persons aged 18–25 who say that their parents *have* used marijuana are much more likely to think that: marijuana is not addictive, marijuana is not damaging to the brain, smoking marijuana is safer than alcohol, and smoking marijuana is safer than tobacco [61]. The presence of cannabis and nicotine use disorders in parents appears to increase the risk for major depressive disorder in their late adolescent offspring [8].

Consequences of adolescent marijuana use

The consequences of adolescent marijuana use could have considerable long-term implications. In a systematic review of 16 longitudinal population studies, youth marijuana use was consistently associated with both lower educational attainment, leaving the parental home early, early parenthood, and increased reported use of other illicit drugs [62]. High levels of cannabis use in late adolescence and early adulthood is related to poorer educational outcomes, lower income, greater welfare dependence and unemployment, and lower relationship and life satisfaction [63].

Changing the social context: legalization of marijuana use

In states participating in NESARC, which includes Oregon, states with medical marijuana laws had nearly double the odds of marijuana use than residents of states without such laws [64]. These results have been replicated in at least two other studies that have shown higher rates of marijuana use and lower perceived risk of use in states with medical marijuana laws [65]. However, marijuana dependence was not more prevalent among marijuana users in these states [64]. Medical marijuana laws increase marijuana arrests among adult males by about 15–20% and treatment admissions to rehabilitation facilities for marijuana increase among adult males by 10–20% after the passage of medical marijuana laws [66]. A study using Portland, Oregon data found the proportion of adult and juvenile arrestees testing positive for cannabis did not significantly change pre- and post-medical legalization of marijuana [67]. Using survey data from the Youth Risk Behavior Survey in which Oregon does not participate, national results suggest that state medical marijuana laws have not measurably affected adolescent marijuana use in the first few years after their enactment [68].

VIII. Neurocognitive effects of marijuana use

Recommended reading: Crane 2013, Crean 2011

Cannabis produces euphoria and relaxation, perceptual alterations, time distortion, and the intensification of ordinary sensory experiences, such as eating, watching films, and listening to music [35]. Short-term memory and attention, motor skills, reaction time, and skilled activities are impaired while a person is intoxicated [35].

Adolescent cannabis use and neurocognitive effects

In line with animal studies, accumulating evidence from studies with human subjects suggest initiation of cannabis use during early adolescence may be more detrimental to some aspects of neurocognition compared to later initiated use [45]. Unfortunately, this developmental stage also represents a peak period of time for use and experimentation with alcohol, cannabis and other illicit substances [69]. Those who initiate marijuana use before 15–17 years of age demonstrate more pronounced deficits in visual attention, verbal fluency, inhibition, short-term recall memory, consequence sensitivity, impulsivity and other aspects of executive functioning as compared to those who initiate use later [45, 70].

Heavy cannabis use in adolescence is associated with even more severe outcomes. Daily cannabis use in young women was associated with an over fivefold increase in the odds of reporting a state of depression and anxiety after adjustments for intercurrent use of other substances [71]. Neuropsychological impairment was concentrated among adolescent-onset cannabis users, with more persistent use associated with greater decline [72]. Further, cessation of cannabis use did not fully restore neuropsychological functioning among adolescent-onset cannabis users [72].

Sex differences and neurocognitive effects

There are sex differences in cannabis' influence on neurobehavioral functioning. Female total brain size peaks between 10 and 11 years of age while male total brain size peaks at 14 to 15 years of age [45]. Thus, if cannabis use is initiated in early to mid-adolescence, it is possible that males may be more vulnerable to neurobehavioral disturbances, compared to females [45]. Indeed, data suggest the potential for different behavioral, tolerance and metabolic effects that influence patterns of use and abuse between males and females [45]. These sex differences in neurocognitive functioning are more for the non-acute effects of cannabis, rather than acute effects [45].

Acute medical adverse effects

Acute marijuana use can lead to suppression of rapid eye movement and diffuse slowing of background electroencephalogram (EEG) activity [8]. The smoke of cannabis can be irritating to conjunctival, nasopharyngeal, and bronchial tissue leading to injected conjunctiva, chronic cough, sinusitis, pharyngitis and chronic bronchitis [8]. Acute effects of cannabis include increased heart rate along with an increased blood pressure and then decreased vascular resistance-induced orthostatic hypotension [8].

Acute effects of cannabis on neurocognitive function

A recent review of cannabis' effect on executive functioning suggests that THC administration adversely affects inhibition, impulsivity, abstract reasoning, and episodic memory, including immediate and delayed recall, procedural memory and associative learning among occasional and regular cannabis users as well as non-users [36, 45]. Most studies document impairments in attention and concentration

following administration of small and large doses of THC in cannabis users and non-users compared to placebo administration [45].

Long-term effects of cannabis on neurocognitive function

The long-term heavy use of cannabis does not produce the severe or grossly debilitating impairment of memory, attention, and cognitive function that is found with chronic heavy alcohol use [35]. However, marijuana exposure, even in young recreational users, is associated with exposure-dependent alterations of the neural matrix of core reward structures [73].

There is some evidence for a dose-dependent relationship between the amount of THC smoked and degree of cognitive impairment [45]. Long-term heavy cannabis users show impairments in memory and attention that endure beyond the period of intoxication and worsen with increasing years of regular cannabis use [74]. Persistent cannabis use was associated with neuropsychological decline broadly across domains of functioning, even after controlling for years of education [72]. Heavy cannabis users often demonstrate poorer decision-making and risk-taking, which have been reported alongside functional brain alterations that may persist even after 28 days of abstinence [36, 45]. The most enduring and detectable neurocognitive deficits are seen in heavy cannabis users in the realms of decision-making, and concept formation and planning [36].

IX. Anxiety, psychosis, and schizophrenia associated with cannabis

Recommended reading: Radhakrishnan 2014

Large doses of THC produce confusion, amnesia, delusions, hallucinations, anxiety, and agitation [35]. The psychiatric medical conditions associated with cannabis in DSM-V are: cannabis-induced psychotic disorder, cannabis intoxication delirium, cannabis-induced anxiety disorder, cannabis-induced sleep disorder, and unspecified cannabis-related disorder (http://emedicine.medscape.com/article/286661-clinical).

Anxiety

Anxiety reactions and panic attacks are the acute symptoms most frequently associated with cannabis use [35, 42]. Frequent cannabis users consistently have a high prevalence of anxiety disorders and patients with anxiety disorders have relatively high rates of cannabis use [42]. About 20–30% of users show brief acute anxiety reactions after smoking the drug [42].

Psychosis

The relationship between substance abuse and psychosis is complex, as alcohol, cannabis, amphetamines and many other drugs have been implicated as a causative factor for psychotic disorders [75]. However, in a recent retrospective study of substance-induced psychotic disorders, only cannabis and alcohol were implicated as causative agents of psychosis [75].

Substance-induced psychosis

Although challenging to do so prospectively, it's important to distinguish between a primary psychotic disorder and a substance-induced psychotic disorder. At initial presentation, substance-induced psychosis is almost indistinguishable from a primary psychotic disorder [69]. Substance-induced psychotic disorders are associated with the emergence of psychosis during the use of the substance and

subside following the withdrawal or abstinence from the offending drug [75]. The most common type of substance-induced psychosis in cannabis users was schizophrenia-like psychosis [75].

Primary psychotic disorder

Cannabis use has been identified as potential risk factor for the development of a primary psychotic illness in at-risk adolescents, and these data suggest that reduction or cessation of cannabis use should be recommended for all adolescents with psychotic symptoms to prevent further deterioration [69]. There is increased risk of developing psychotic symptoms with increased frequency and dose of cannabis used [69]. The clinical evidence of increased risk of psychosis ranges from 1.6 to 3.1 in multiple study types in four countries [76]. Transition to daily cannabis abuse has been linked with an increased risk of psychotic symptoms up to five times that of non-users [69]. It is likely that, in combination with predisposing risk factors (genetic vulnerability, environmental factors, obstetric insults, and social adversities), cannabis is an additive risk factor in those with increased vulnerability [43, 69]. Unfortunately, those with psychosis who use cannabis may not notice improved psychotic symptoms with cessation of their cannabis [8].

Onset of primary psychosis

One research group reports a mean time of 7.0 ± 4.3 years between onset of cannabis use and onset of psychosis [8]. Patients with a history of cannabis use presented with their first episode of psychosis at a younger age than those who never used cannabis [77]. Additionally, those who had started cannabis at age 15 or younger had an earlier onset of psychosis than those who had started after 15 years of age [77]. A meta-analysis of longitudinal studies of cannabis use and psychosis reported 1.4 times the odds of psychotic disorders among those who had ever used cannabis versus those who had never used cannabis [3]. An overview of systematic reviews on cannabis and psychosis found a consistent association between cannabis use and psychotic symptoms [78].

Cannabis dose and primary psychosis

Daily use, especially of high-potency cannabis, drives the earlier onset of psychosis in cannabis users [77]. Importantly, subjects who had been using high-potency cannabis every day had the earliest onset (6 years earlier) of psychosis compared to those who have never used cannabis [77]. Daily users of cannabis were almost twice as likely to have psychotic symptoms and the risk was proportionate to consumption [76].

Adolescents and psychosis

Young people who reported psychotic symptoms at baseline were much more likely to experience psychotic symptoms at follow-up if they used cannabis than cannabis-using peers without such a history [43]. Cannabis use predicts psychosis vulnerability in adolescents and vice versa, which suggests that there is a bidirectional causal association between the two [79].

Psychosis summary

All of the reviews mentioned in this section, draw the conclusion that cannabis is neither a necessary nor a sufficient cause of psychosis but that it could be a component cause that interacts with genetic and environmental factors in vulnerable individuals, [78, 80-82]. Heavier marijuana use, greater drug potency, and exposure at a younger age can all negatively affect the mental disease trajectory by advancing the time of a first psychotic episode by 2–6 years [1]. Cannabis use has been shown to be

both cross-sectionally and prospectively positively associated with psychotic spectrum disorders, such as schizophrenia, depressive symptoms and anxiety symptoms including panic disorder [47]. Additionally, anxiety and posttraumatic stress have been linked to frequent and problematic cannabis use [47].

Schizophrenia

Cannabis is commonly used by those with schizophrenia and can cause paranoia in approximately 40% of persons experimenting with this drug [8]. Patients with schizophrenia who consume cannabis are hospitalized at rates higher than those who do not use cannabis [8]. In adults with schizophrenia, cannabis use was associated with greater brain volume loss over a five-year period [69]. In a large Swedish study, there was a six-fold increased risk of schizophrenia with report of cannabis use on at least 50 occasions [76]. Chronic use of marijuana may precipitate schizophrenia in vulnerable individuals [35]. Meta-analytical studies have estimated that 8–14% cases of schizophrenia may be due to cannabis use [82].

X. Chronic physical health effects

Recommended reading: Greydanus 2013

Carcinogenicity of marijuana smoke

Methods of cannabis smoking may place more cannabis particulate matter into the lungs than noted with typical cigarette smoking [8]. Marijuana smoking is characterized by about two-thirds larger inhalation or "puff" volume, 40% deeper inhalation, and four times longer retention of hotter and unfiltered smoke in comparison to tobacco cigarettes [83].

In 2009 marijuana smoke was placed on California's Proposition 65 list of chemicals known to the state to cause cancer [84]. Cannabis smoke is mutagenic *in vitro* and *in vivo* [35].

Marijuana smoke versus tobacco smoke

Independent of THC content, cannabis smokers are typically exposed to more carbon monoxide and tar than cigarette smokers [8]. In a study of the chemical composition of marijuana smoke, ammonia was found in mainstream marijuana smoke at levels up to twenty-fold greater than found in tobacco [85]. Additionally, hydrogen cyanide, nitric oxide, and some aromatic amines were found in marijuana smoke at a concentration 3–5 times those found in tobacco smoke [8, 85]. Perhaps most importantly, polycyclic aromatic hydrocarbons, which are known carcinogens, were also identified in marijuana smoke [8, 85]. The confirmation of the presence of known carcinogens and other chemicals implicated in respiratory diseases in both mainstream and sidestream smoke of marijuana cigarettes is important information for the communication of the risk related to exposure [85].

Pulmonary effects

The impact of marijuana smoking on respiratory health has some significant similarities to that of tobacco smoking [86]. One cannabis joint has been noted to be equivalent to 2.5–5 cigarettes in terms of pulmonary dysfunction [8]. Chronic cannabis smokers show many of the pathological changes in lung cells that precede the development of cancer in tobacco smokers [3].

Regular or heavy cannabis consumption can result in generalized airway inflammation with evidence of respiratory epithelial cell injury and damage to alveolar macrophages, which can lead to pulmonary

infection [8]. The immunological competence of regular cannabis smokers is impaired, increasing rates of respiratory infections and pneumonia and their use of health services for these infections [1, 3]. Lung function is significantly poorer and there are significantly greater abnormalities in the large airways of marijuana smokers than in non-smokers [35]. In a nationally representative US survey, after controlling for age, gender and current asthma, marijuana use was significantly associated with respiratory symptoms of chronic bronchitis, coughing on most days, phlegm production, wheezing, and chest sounds without a cold [86]. However, in a 20-year cohort study, occasional and low cumulative marijuana use was not associated with adverse effects on pulmonary function [87] and there is no evidence to date that chronic cannabis smoking increases the risk of emphysema [3].

Beyond compromised immunity and airway damage, there are risks for pulmonary infectious disease associated with marijuana smoking. Sharing of cannabis water pipes has led to the development of pulmonary tuberculosis [8] and smoking cannabis that contains fungal spores can result in pulmonary aspergillosis in those who are immunocompromised [8].

Cardiovascular effects

Cannabis smoking or ingestion of THC increases the heart rate by 20–50% within a few minutes to a quarter of an hour; this effect lasts for up to 3 hours [35]. Blood pressure is increased while the person is sitting, and decreased while standing [35].

In a literature review spanning 50 years, cannabis use was found to be associated with stroke, congestive heart failure, arrhythmias, myocardial infarction, and lower limb arteritis [8, 52]. Temporal associations between marijuana use and serious adverse events including sudden cardiac death, cardiomyopathy, transient ischemic attack, and cannabis arteritis have been described [88].

Smoking marijuana is a rare trigger of acute myocardial infarction [89]. The risk of myocardial infarction increased 4.8 times over baseline compared with periods of non-use and onset occurred within one hour of smoking marijuana [52, 89].

Cancer

Prostate and cervical cancer

In a large Kaiser Permanente cohort study, males who had ever smoked cannabis had an over three-fold increased risk of prostate cancer, and current cannabis smokers had a nearly five-fold increased risk of prostate cancer [3]. In a meta-analysis of 16 studies, increased risks of prostate and cervical cancers due to marijuana smoking were observed [90].

Nasopharyngeal and oropharyngeal cancer

Compared with those who have never smoked marijuana, those who have smoked marijuana had an elevated risk of oropharyngeal cancer and a reduced risk of oral tongue cancer [91]. In a case-control study in North Africa, marijuana smoking had a significantly elevated nasopharyngeal carcinoma risk, independent of cigarette smoking [92].

Head and neck cancer

The result of head and neck cancer was not elevated in those who had ever smoked marijuana, and there was no increasing risk associated with increasing frequency, duration or cumulative consumption of marijuana smoking [93]. However, in a meta-analysis of 16 studies, increased risks of adult-onset glioma due to marijuana smoking were observed [90].

Airway cancer

Chronic inflammatory and precancerous changes in the airways have been identified in cannabis smokers and the most recent case-control study shows an increased risk of airways cancer that is proportional to the amount of cannabis use [38].

Lung cancer

Studies that examined lung cancer risk factors found an association of marijuana smoking with increased tar exposure, alveolar macrophage tumoricidal dysfunction, increased oxidative stress, and bronchial mucosal histopathologic abnormalities as compared to tobacco smokers or nonsmoking controls [94]. In a case-control study, the risk of lung cancer increased by about 8% for each joint-year of cannabis smoking, after adjusting for confounding variables [83]. Heavy cannabis smoking was significantly associated with more than a twofold risk of developing lung cancer over the 40-year follow-up period in a large cohort study [95]. However, a population based case-control study showed no significant risk of lung cancer with even long-term or heavy use of marijuana [96]. The risk for lung cancer in marijuana smokers is not certain [3], however, the accumulated weight of evidence implies far lower risks for pulmonary complications of even regular heavy use of marijuana compared with the grave pulmonary consequences of tobacco [97].

Nonseminoma germ cell tumors of the testis

In a Washington case-control study, there was a significant association between marijuana use and occurrence of nonseminoma germ cell tumors of the testis [98]. This finding was replicated in Los Angeles, California, when compared to those who have never smoked marijuana, those who have smoked marijuana had a two-fold increased risk of testicular germ cell tumors, specifically nonseminoma and mixed histology tumors [99]. Overall testicular germ cell tumor cases were more likely to be frequent marijuana users (daily or greater) than were controls [100]. This finding of an association between frequent marijuana use and testicular germ cell tumor, particularly among nonseminoma, is consistent with previous reports mentioned above [100].

Dental effects

Prevalence and severity of dental caries was significantly higher in those who had used marijuana than those who did not across eight years of research and controlling for gender, race/ethnicity, where they lived, and exposure to secondhand smoke [101]. Marijuana had the largest negative effect on dental health status and the effects were even more than tobacco [101]. Marijuana users tend to have increased risks for dental caries, oral infections, and periodontal disease [8]. Dysplastic changes and premalignant lesions can be identified in oral mucosa of cannabis users [8].

Weight gain and adiposity

Marijuana use has been associated with increased appetite, high caloric diet, and decreases in high-density lipoprotein cholesterol and triglycerides [102]. Chronic use of marijuana can lead to weight gain

from overeating and reduced physical activity [8]. Mothers who used marijuana had a statistically significant higher weight gain during pregnancy than non-users [103]. Adolescents with an increasing marijuana use trajectory were more likely to exhibit an increased obesity trajectory in young adulthood [104]. In clinical trials conducted in the 1980s that involved healthy control subjects, inhaling marijuana led to an increase in caloric intake, mainly in the form of between-meal snacks, with increased intakes of fatty and sweet foods [5]. Carbohydrate intake and percent calories from carbohydrates, but not total energy intake, were significantly higher in cannabis smokers in a US cross-sectional case-control study [105]. Chronic cannabis smoking was associated with visceral adiposity and adipose tissue insulin resistance, but not with hepatic steatosis, insulin insensitivity, impaired pancreatic β-cell function, or glucose intolerance [105].

XI. Effects of marijuana on prenatal, postnatal and breastfeeding outcomes

Effects of prenatal marijuana exposure

THC freely crosses the placental barrier and directly affects the fetus [106]. The development of the fetal endocannabinoid receptor system may be vulnerable to maternal cannabis use during pregnancy and may produce long-term consequences in children [107].

Pregnant women who use marijuana, tend to use marijuana at a higher rate during the first trimester, with many reporting a cessation of use or decreased use by the third trimester [103]. Second-trimester prenatal marijuana use was the best predictor of lower IQ scores [106].

Intrauterine exposure to cannabis was associated with an increased risk for aggressive behavior and attention problems as early as 18 months of age in girls, but not boys [107]. For those with marijuana-only prenatal exposure, birth defect rates were significantly higher than expected for 35% of the birth defects including obstructive genitourinary defect, polydactyly, syndactyly, and reduction deformity of upper limbs [108]. Birth weights for babies of women using cannabis in pregnancy were 90 grams or 0.20 pounds lighter than the offspring of other women [106].

First trimester prenatal marijuana exposure of one or more joints/day significantly predicted poorer scores on the composite score and reading score of the Wechsler Individual Achievement Test at 14 years of age [109]. Prenatal marijuana exposure is associated with adverse perinatal effects [110] and increased risk of adverse birth outcomes [111].

Effects of postnatal marijuana exposure

The current evidence suggests subtle effects of heavy marijuana use on developmental outcomes of children [103]. However, these effects are not sufficient to warrant concerns greater than those associated with tobacco use [103]. Postnatal exposure can result from maternal use of marijuana during lactation [110]. Marijuana exposure via the mother's milk during the first month postpartum appeared to be associated with a decrease in infant motor development at one year of age [110]. Controlling for the effects of tobacco smoking, alcohol consumption and use of other illicit drugs, cannabis use in pregnancy was associated with low birth weight, preterm labor, small for gestational age, and admission to the neonatal intensive care unit [111]. Cannabis use during pregnancy, alone or in combination with smoking tobacco or illicit drug use was associated with an increased risk of stillbirth [112].

Breastfeeding

Marijuana can be detected in breast milk after recent maternal use [103]. THC is excreted into human breast milk in moderate amounts and in one feeding the infant would intake 0.8% of the weight-adjusted maternal intake of one joint [113]. THC can accumulate in human breast milk to high concentrations, and infants exposed to marijuana through their mother's milk will excrete THC in their urine for 2 to 3 weeks [113]. Infants exposed to marijuana via breast milk show signs of sedation, reduced muscular tonus, and poor sucking [113].

Male fertility

Human studies consistently conclude that THC negatively affects male reproductive physiology [114]. In a recent literature review on the insults of illicit drug use on male fertility, marijuana use in males has been linked with oligospermia, decreased levels of luteinizing hormone, lower plasma testosterone and dose-dependent reduced sperm motility [114].

XII. Crashes, injury, violent death and poisonings associated with marijuana

Motor vehicle crashes

Recommended reading: Masten 2014 and Wilson 2014

Driving impairment

The effects of recreational doses of cannabis on driving performance in laboratory simulators and standardized driving courses have been reported by some researchers as being similar to the effects of blood alcohol concentrations between 0.07% and 0.10% [35]. Individuals driving under marijuana influence may experience distortion of on-coming vehicle headlights, resulting in motor vehicle crashes [8]. Cannabis smoking increases lane weaving and impaired cognitive function [115]. Evidence suggests recent smoking and/or blood THC concentrations of 2–5 ng/ml are associated with substantial driving impairment, particularly in occasional smokers [115, 116]. Regular cannabis smokers who had previously driven under the influence of cannabis emphasized that publicity campaigns would not deter them from future driving under the influence, but a high likelihood of punishment was found to be a deterrent [115].

Prevalence of drivers testing positive for THC

In a 2007 National Roadside Survey of Alcohol and Drug Use by Drivers, the most frequently encountered single drug in oral fluid in both daytime and nighttime drivers was THC [117]. In a study of first year US college students, approximately 20% of students reported using marijuana and of these, 44% of males and 9% of females drove after using marijuana [25]. Additionally, 51% of male and 35% of female students rode as a passenger with a marijuana-using driver [25]. Driving and riding after using marijuana is common among underage, marijuana-using college students [25].

Risk of motor vehicle collision

Nearly two thirds of US trauma center admissions are due to motor vehicle crashes, with almost 60% of such patients testing positive for drugs or alcohol [115]. In a systematic review and meta-analysis of nine studies, driving under the influence of cannabis was associated with nearly double the risk of motor vehicle collision compared with unimpaired driving (p=0.003) [115, 118]. In surveys, drivers who report

using cannabis are twice as likely to report being involved in crashes than drivers who do not [43]. A meta-analysis of two decades of crash studies yielded a summary odds ratio of marijuana use to crash risk of 2.66, 95% CI: 2.07–3.41 [119]. Driving while under the influence of marijuana at least doubles the odds of a motor vehicle collision.

Risk of fatal motor vehicle collision

Acute cannabis consumption is associated with an increased risk of a motor vehicle crash, especially for fatal collisions [118, 120, 121]. Surveys conducted in widely separated localities have generally revealed the presence of THC in 4–14% of drivers who sustained injury or death in traffic crashes [122]. Using Fatal Analysis Reporting System data, detection of cannabis in drugged drivers involved in fatal collisions increased from 29% in 1993 to 37% in 2010 ($p<0.001$) [123]. The most commonly detected non-alcohol drug was cannabinol, the prevalence of which tripled from approximately 4% in 1999 to 12% in 2010 in US drivers who died within one hour of a motor vehicle crash [124]. In 2010, for drivers involved in fatal motor vehicle crashes that drug tested positive for cannabis only, approximately 60% were between the ages of 16–29 years, 55% also had a positive blood alcohol concentration, and 73% were fatally injured [123]. Fatally injured drivers using both alcohol and cannabis had higher plasma concentrations of THC than drivers using cannabis alone [124].

Cannabis and culpability in motor vehicle collisions

Surveys that established recent use of cannabis by directly measuring THC in blood showed that THC positives, particularly at higher doses, are about three to seven times more likely to be responsible for their crash as compared to drivers that had not used drugs or alcohol [122]. Drivers whose blood contained only cannabis were 2.3 times more likely to be culpable than those without cannabis or alcohol [115].

Effect of marijuana legalization on cannabis-positive drivers

In Oregon, the average percent of fatal-crash involved drivers testing positive for cannabis went from 14% pre-legalization up to 21% post-legalization of medical marijuana, a 49% increase [125]. This is in contrast to a 2013 study by Guenzburger that found after adjustments were made for driver drug testing frequency and cannabinoid prevalence among states without medical marijuana laws, implementation of medical marijuana laws was not associated with increased cannabinoid prevalence fatal motor vehicle crashes in Oregon [126].

The finding by Masten et al. is supported by a California time series analysis that showed the prevalence of cannabinoids in drivers in fatal crashes in California increased 2.1 percentage points (a 196% increase) from pre-implementation to post-implementation of the medical marijuana law [124]. The increase in the prevalence of cannabinol was most pronounced among fatally injured drivers less than 25 years of age [124]. Recent studies coming out of Washington and Colorado support the same trend; the average yearly percentage of drivers positive for THC and carboxy-THC significantly increased after legalization of marijuana [117, 127]. Drivers who reported having a medical cannabis permit in California were significantly more likely to test positive for THC [128].

Motor vehicle collisions with cannabis and alcohol

Crash culpability can be determined by calculating a responsibility index. The responsibility index is the percentage of drivers responsible for the crash divided by the percentage not responsible [115]. The responsibility index for drivers with cannabis only in their blood was 2.3 and increased to 9.4 for those

with alcohol only in their blood, and to 14.1 with both alcohol and cannabis [115]. Thus, drivers with alcohol and cannabis in their blood are more than 14 times more likely to be responsible for causing the motor vehicle collision.

Cannabis intoxicated drivers' drive more slowly and take fewer risks than alcohol-intoxicated ones [3]. In fact, the attributable risk of cannabis to car crashes is much smaller than that of alcohol (2.5% vs. 29%) [3]. However, when you combine the effects of cannabis intoxication with alcohol intoxication, you get the worst of both worlds. Alcohol and cannabis are commonly identified together in motor vehicle crash victims [115]. Indeed, in multiple studies across several countries, a range of 30% and greater than 40% of THC positive individuals also had illegal levels of alcohol detected in their system [115]. This association works both ways: driving under the influence of cannabis is also more common among people who also drive drunk [115].

Drivers who tested positive for both alcohol and drugs have substantially heightened odds of motor vehicle crash relative to those using neither alcohol nor drugs (OR: 23.2, 95% CI: 17.8–30.3) (Li 2013).

Injury

Cannabis users had two times higher rates of injury from all causes, including self-inflicted injury, motor vehicle crashes and assaults than non-users [3]. The self-inflicted injury usually associated with cannabis consumption is self-mutilation with cannabis-induced psychosis [8]. Cannabis consumption is also associated with non-traffic injuries, especially falls in the older adult population [8].

Risks for law enforcement and first responders

Marijuana grow operations are potential sources of serious exposure to airborne fungal spores, volatile organic compounds, carbon dioxide, carbon monoxide, THC, pesticides and fertilizers [129]. Indeed, interviews with Washington County Sherriff's Office personnel have revealed documented exposures to numerous dangerous substances at marijuana grow operations in the process of performing their normal duties (personal interview, June 5th, 2014). A recent Colorado study evaluating exposure risks at marijuana grow operations to first responders found that THC was detectable on surfaces within the indoor grow operations and on the hands of scene investigators [129]. Significantly elevated fungal spore levels were detected, especially upon plant removal, to the point of detecting more than 50,000 spores/m^3 of either *Cladosporium spp.* for outdoor grow operations or *Penicillium spp.* for indoor grow operations [129]. The authors' concluded that the high fungal spore concentration associated with the standard investigation of a marijuana grow operation could expose responders to mold levels classifiable as Indoor Air Quality problems that could require respiratory protection for safety [129].

Poisonings

Toxicity

The acute toxicity of cannabinoids is very low because they do not produce respiratory depression like opioids [3]. The estimated fatal dose in humans is 15g, many times greater than the dose that heavy users could consume in a day [3]. However, marijuana may be contaminated with pesticides, herbicides, or fungi, the latter being especially dangerous to immunocompromised individuals such as patients with HIV/AIDS or cancer [31].

The medical marijuana industry provides attractive and palatable marijuana-infused solid and liquid products, including cookies, candies, brownies and beverages [130]. Toxic reactions are usually mild after acute accidental ingestion but can cause significant sedation in children [130]. In older children, the stimulatory phase and hallucinations of marijuana intoxication can produce anxiety and panic episodes when not anticipated in an accidental ingestion [130]. Approximately 65% of marijuana poisonings reported to the National Poison Data System required treatment in a healthcare facility [131]. In 2012 there were 4,930 reports (1,440 single exposures) of poisoning by marijuana with 2 deaths, 5,225 reports of poisonings by THC homologs with 6 deaths, and 99 reports of poisoning by THC pharmaceuticals [131]. Approximately 18% of the reported marijuana poisonings were from children ages 12 or under [131]. Although the number of pediatric exposures to marijuana reported to the National Poison Data System was low, the rate of exposure increased from 2005 to 2011 in states that have passed recreational or medical marijuana legislation [132]. This finding was confirmed in Colorado, where a new appearance of unintentional marijuana ingestions by young children occurred after modification of drug enforcement laws for marijuana possession in Colorado [133]. Eight of the 14 cases of patients younger than 12 years old, involved medical marijuana, and 7 of these exposures were from food [133]. In Oregon from 2005–2011, there were 6.8 calls per 100,000 population for unintentional marijuana pediatric exposures reported to poison centers [132]. Oregon has the second highest call rate in the country to poison control centers for unintentional marijuana pediatric exposures [132].

Mortality

All-cause mortality

A systematic review of 18 years of publications revealed that there is insufficient evidence, particularly because of the low number of studies, to assess whether the all-cause mortality rate is elevated among cannabis users in the general population [134]. However, individual mortality studies hint at excess death for certain populations and manners of death.

Violent death

Violent and accidental death was the main contributor to excess mortality in marijuana smokers in a prospective 15-year Swedish study [35]. Nationally, of the percentage of violent deaths that were tested for alcohol and drugs whose results were positive, approximately 15% were positive for marijuana and 34% were positive for alcohol [135].

Homicide
Nationally, of homicide victims tested for alcohol and drugs, approximately 30% were positive for marijuana and 37% were positive for alcohol [135].

Suicide
Nationally, of suicide victims tested for alcohol and drugs, approximately 10% were positive for marijuana and 33% were positive for alcohol [135]. In a study measuring the association between legalization of medicinal marijuana and suicide, suicides among men aged 20–39 fell after marijuana legislation compared with those in states that did not legalize [136]. In Colorado, there was not a significant correlation between medical marijuana use, as assessed by the number of medical marijuana registrants and suicides per county [137].

Medical marijuana laws and opioid overdose deaths

States with medical cannabis laws (including Oregon) had a 25% lower mean annual opioid overdose mortality rate compared with states without medical cannabis laws (p=0.003) [138].

Physical violence

In a birth cohort study, individuals meeting diagnostic criteria for marijuana dependence were approximately four times more likely than control subjects to be violent [139]. The violence among marijuana-dependent individuals was best explained by a juvenile history of conduct disorder [139]. Increased rates of assault injuries were identified among men who were current marijuana users [140]. Marijuana use seems to have a protective effect on intimate partner violence (IPV). In married heterosexual couples, more frequent marijuana use by husbands and wives predicted less frequent intimate partner violence perpetration by husbands [141].

XIII. Companion animal poisoning

Recommended reading: Bodnar 2013, Meola 2012

The medical marijuana industry provides attractive and palatable marijuana-infused cookies, candies and brownies [130] that are as attractive to pets as they are children. Companion animals can be exposed to second-hand inhalation from marijuana smoke or can consume marijuana leaves or marijuana-infused baked goods [142, 143]. The American Society for the Prevention of Cruelty to Animals (ASPCA) Animal Poison Control Center has reported that dogs account for the vast majority (96%) of marijuana toxicity cases [144].

The onset of clinical symptoms in dogs usually occurs between one to three hours after ingestion of marijuana and can last from 30 minutes to 96 hours. Classic symptoms of intoxication in dogs include sedation, loss of body coordination, increased physical sensitivity to motion or sound, urinary incontinence, central nervous systems depression, hypersalivation, disorientation, pupil dilation, and slow heart rate [142, 143]. Approximately 30% of dog toxicity cases exhibit gastrointestinal symptoms, including vomiting. Large exposure to marijuana can result in stupor, hypothermia, and hypotension [142]. A definitive diagnosis of marijuana toxicity is usually confirmed through documentation of a known ingestion of marijuana [142] as there is currently no valid test for detecting THC in dogs [143].

Treatment of marijuana intoxication includes inducement of vomiting if possible, gastric lavage and enemas, IV fluids, activated charcoal, and intravenous lipid emulsion therapy [142]. The prognosis for recovery is excellent. The approximate cost to take one dog to the veterinarian to treat for accidental ingestion of medication is $791 (Veterinary pet insurance online quote).

It is difficult to ascertain the extent of pet marijuana toxicity cases in the US. Veterinarians at the ASPCA Animal Poison Control Center have consulted on more than 250 cases of marijuana toxicity from 1998 to 2002 [144]. In a study conducted in Colorado after medical marijuana was legalized but before recreational marijuana was legalized, 125 dogs were diagnosed with marijuana toxicity from 2005 through September 2010 [143]. Ingestion of baked goods made with medical grade THC butter resulted in two dog deaths [143]. A significant correlation was found between the number of medical marijuana licenses and the marijuana toxicity cases seen in two veterinary hospitals in Colorado [143].

Locally, marijuana-related cases treated at DoveLewis Emergency Animal Hospital increased from about 11% of all toxicity cases in 2011 to almost 20% in 2012 and the beginning of 2013 [145].

DoveLewis reported 79 cases of marijuana intoxication in 2011, 111 cases in 2012, and 116 cases in 2013 [146]. The majority of cases were dogs, who all had a positive treatment outcome [146].

XIV. Legalization issues

Recommended reading: Pacula 2014, Bostwick 2012

State versus Federal law

Marijuana is a Schedule I substance under the Controlled Substances Act of 1970, and the use of marijuana is an offense under federal law despite any state laws legalizing recreational or medical use [147].

The legalization of recreational marijuana in Colorado and Washington has revealed some important issues that need to be addressed regarding state and federal laws. Among these issues include the use of federal water for irrigating marijuana crops [148], whether lawyers will incur ethics sanctions for working with marijuana businesses [149], how and by whom edible marijuana will be regulated [150], and whether the banking industry will be able to legally serve the marijuana industry [151]. Legalization of marijuana for medical use brings additional issues. In states with legal medical marijuana there is no agreement among these states on physician authorization, patients' qualification for treatment, possession limits, and how the patients can purchase marijuana.

In response to state initiatives legalizing marijuana, a 2013 memo issued by Department of Justice (DOJ) Deputy Attorney General James Cole issued guidance for all federal enforcement activities concerning marijuana in all states. The DOJ expects that state and local governments with some form of legal marijuana will implement "strong and effective regulatory and enforcement systems" to address any threats to public safety, public health, and law enforcement.

State law cannot change federal law and in 1996 the US attorney general and the Drug Enforcement Agency (DEA) announced their intention to continue to enforce federal drug laws in states regardless of state law including prosecution of physicians [152]. Attorney General Janet Reno said: "Federal law still applies…US attorneys…will continue to review cases for prosecution and DEA officials will review cases as they have to determine whether to revoke the registration of any physician who recommends or prescribes so-called Schedule I controlled substances" [152].

In 2002, the Ninth Circuit Court of Appeals ruled that the First Amendment prohibits the government from punishing physicians "on the basis of the content (the potential usefulness of marijuana) of doctor-patient communications [152]." Once physicians move outside the physician-patient relationship and into the drug-trafficking arena, their speech and actions are not protected and the federal government may take action against them [152].

The most recent DOJ guidance to prosecutors suggest limiting criminal charges to "large-scale, for-profit commercial enterprises" and endorses four priorities for federal enforcement: preventing distribution of marijuana to minors, preventing revenue from going to a criminal enterprise, preventing trafficking of other illegal drugs and preventing drugged driving [152, 153]. Since states not only make their own laws, but also send senators and representatives to Washington to make federal law, the legalization trend will inevitably lead to changes in enforcement of federal law, even if Congress does not directly change federal marijuana laws [152].

XV. Medical marijuana dispensaries

Recommended reading: Morrison 2014, Freisthler 2013

The placement of medical marijuana dispensaries

Medical marijuana dispensaries tend to be located in census block groups with greater marijuana demand, high rates of poverty, greater density of alcohol outlets, and in unincorporated areas outside city boundaries [154]. Census block groups with higher household income are less likely to have a medical marijuana dispensary [154]. Medical marijuana dispensaries are more likely to be located in socially disadvantaged areas because more stable neighborhoods have the resources to resist dispensaries from being built [154].

The effect of medical marijuana dispensaries on local crime

Medical marijuana dispensaries with security cameras and signs requiring a prescription identification card have lower levels of violence within 100 and 250 feet of the dispensary relative to the dispensaries that do not have those security measures [155]. The density of medical marijuana dispensaries is not associated with violent or property crime rates based on population-level crime data [156]. In contrast, police report that medical marijuana dispensaries continue to be targeted because of the availability of larger quantities of drugs and cash [157]. Medical marijuana laws could still stimulate crime as newly opened medical marijuana dispensaries provide criminals with a highly attractive target with their repository of high quality marijuana and customers carrying large amounts of cash [158].

The effect of medical marijuana legislation on crime

When comparing FBI crime rates for states with medical marijuana laws (including Oregon) and states that do not, medical marijuana legislation does not appear to make crime worse [158].

Marijuana arrests

Between 2001 and 2010 there were over 8 million marijuana arrests in the US, 88% of which were for possession [159]. Marijuana arrests have increased between 2001 and 2010 and now account for over half (52%) of all drug arrests in the US, with marijuana possession arrests accounting for nearly half (46%) of all drug arrests [159]. In 2010, there was one marijuana arrest every 37 seconds and states spent combined over $3.6 billion enforcing marijuana possession laws [159]. On average nationally, a black person is 3.7 times more likely to be arrested for marijuana possession than a white person, even though black and whites use marijuana at similar rates [159]. In a preliminary report from the Seattle Police Department, observations suggest a correlation between arrest for public possession of marijuana and people of disadvantaged socioeconomic means [160]. Nationally, approximately $8.7 billion in savings would result from the legalization of marijuana in government expenditure of enforcement of marijuana prohibition [161]. In 2013 in Washington County, Oregon there were 1,505 marijuana-related arrests with the majority of arrests (88%) for less than one ounce of marijuana (Portland Police Data System, Table 3).

Product	Total	Possess for sale & Sale	Possess for use	Transport/ Manufacture/Cultivate	Other
Hashish	26	9	12	5	
Marijuana >1 oz.	154	81	40	26	1
Marijuana <1 oz.	1325	572	729	5	2
Total arrests	1501	662	780	36	3

Table 3. Washington County, Oregon, 2013 arrests related to marijuana. Data provided by the Washington County Sheriff's Office from the Portland Police Data System.

Marijuana dispensary summary

Medical marijuana dispensaries open in areas with high market potential. High housing value areas tend to exclude retail space, forcing medical marijuana dispensary placement in areas of social disadvantage [154]. Indeed, research demonstrates that medical marijuana dispensaries are placed in block groups with high proportions of people living under 150% of the poverty level, in unincorporated areas outside city boundaries, and in areas with a high density of alcohol outlets [154]. In fact, the density of alcohol outlets significantly predicts the density of medical marijuana dispensaries within a block group [154]. Presence of a medical marijuana dispensary exposes the local population to increased access to cannabis. If California is representative, it appears medical marijuana dispensaries are placed in the most vulnerable of all communities: neighborhoods with the highest marijuana demand that lack the social and economic resources to resist their establishment [154].

XVI. Organizations' position statements on the use of marijuana for medical conditions

The table below lists prominent medical and governmental organizations and their position statements on the use of marijuana. Of the 29 organizations listed below, 11 (38%) are explicitly against the medical use of marijuana. For the remainder, the majority of organizations that support medicinal marijuana are supporting the research development of purified cannabinoids through FDA trials and explicitly not supporting smoked marijuana as medicine.

Organization (Abbreviation, date)	Position
Alzheimer's Foundation of America	No guidelines/recommendations found.
Alzheimer's Society (UK)	No guidelines/recommendations found.

American Academy of Child and Adolescent Psychiatry (AACAP) (2014)	Because of the critical period of ongoing brain maturation during adolescence, AACAP: - Opposes efforts to legalize marijuana - Supports initiatives to increase awareness of adverse effects on adolescents - Supports improved access to evidence-based treatment rather than criminal charges for adolescents with cannabis use disorder - Supports careful monitoring of marijuana-related policy changes on child/adolescent mental health
American Academy of Family Physicians (AAFP, 2014)	The AAFP advocates that the medical use of marijuana be based on high quality, patient-centered, evidence-based research and advocates for further studies into the use of medical marijuana and related compounds.
American Academy of Neurology (AAN, 2014; Koppel, 2014)	Regarding Multiple Sclerosis (MS) and Parkinson's disease: there is not enough information to show if medical marijuana (including smoked medical marijuana) is safe or effective as treatment. For MS: certain forms of medical marijuana (pill or oral spray) can help treat some symptoms For Parkinson's disease: synthetic THC likely does not help relieve abnormal movements
American Academy of Ophthalmology (AAO, 2014)	The AAO Complementary Therapy Task Force found no scientific evidence demonstrating increased benefit and/or diminished risk of marijuana use in the treatment of glaucoma compared with the wide variety of pharmaceutical agents now available.
American Academy of Pediatrics (Joffe, 2004)	AAP opposes the legalization of marijuana but supports rigorous scientific research into the use of cannabinoids for relief of symptoms not currently ameliorated by existing legal drug formulations.

American Cancer Society (ACS, 2013)	ACS supports more research into benefits of cannabinoids but does not advocate use of inhaled marijuana or marijuana legalization. However, the ACS acknowledges there may benefits to cancer patients from the chemicals contained in marijuana to help alleviate nausea, vomiting, wasting, and muscle spasms caused by chemotherapy (based on IOM 1999 report).
American College of Physicians (ACP, 2008)	ACP encourages the use of non-smoked forms of THC that have proven therapeutic value and endorses the research supporting THC as an effective appetite stimulant and antiemetic.
American Epilepsy Society (AES, 2014)	Because of safety concerns and the lack of evidence of efficacy, AES does not support marijuana for the treatment of seizures. The AES recommends marijuana's status as DEA Schedule I controlled substance be reviewed in order to relieve restrictions on the use of marijuana in rigorous scientific studies.
American Glaucoma Society (Jampel, 2010)	There is no scientific basis for the use of marijuana agents in the treatment of glaucoma, unless a well-tolerated formulation of a marijuana-related compound with a much longer duration of action is shown in rigorous clinical testing to reduce damage to the optic nerve and preserve vision.
American Medical Association (AMA, n.d.) H-95.952 Cannabis for Medicinal Use	The AMA urges that marijuana's status as a DEA Schedule I controlled substance be reviewed. They clarify that this should not be viewed as an endorsement of state-based medical cannabis programs, or that scientific evidence on the therapeutic use of cannabis meets the current standards for a prescription drug product. The AMA supports further adequate and well-controlled studies of marijuana and related cannabinoids in patients who have serious conditions for which preclinical, anecdotal, or controlled evidence suggests possible efficacy and the application of such results to the understanding and treatment of disease.

American Nurses Association (ANA, 2008)	The ANA believes evidence demonstrates a connection between therapeutic use of marijuana and symptom relief. The ANA actively supports patients' rights to legally and safely utilize marijuana for symptom management and health care practitioners' efforts to promote quality of life for patients needing such therapy.
American Psychiatric Association (APA, 2013; APA, 2013 PTSD)	The APA believes there is no current scientific evidence that marijuana is in any way beneficial for the treatment of any psychiatric disorder, including posttraumatic stress disorder (PTSD).
American Public Health Association (APHA, 1995)	No specific endorsement of medical marijuana; encourages research on therapeutic properties and alternative methods of administration to smoking, and to make cannabis available as a legal medicine where shown to be safe/effective.
American Society of Addiction Medicine (ASAM, 2012)	ASAM recommends that any chemicals in marijuana shown to be effective and safe for use as treatment for illness should be made available as standardized and characterized products, approved by the FDA, and dispensed by professional pharmacies. ASAM recommends its members and other physician organizations/members reject responsibility for providing access to cannabis/cannabis-based products until these substances receive FDA approval ASAM rejects smoking as a means of drug delivery for safety reasons. ASAM does not support proposals to legalize marijuana in the US
American Society of Clinical Oncology	No guidelines found.
Association of Nurses in AIDS Care (ANAC, 2008)	No specific endorsement for use of medical marijuana

California Society of Addiction Medicine (CSAM, 2010)	All physicians recommending medical use of marijuana should be held to all accepted medical standards of practice for recommending/approving any medication. CSAM leaves the question of the medical value of cannabinoid-based medications to the FDA.
Canadian Agency for Drugs and Technologies in Health (CADTH, 2010)	No relevant evidence-based guidelines on the use of medical marijuana for specific medical conditions were identified.
Cleveland Clinic (2011)	No position statement. From their Alternative & Complimentary Therapies for MS guidance: Doctors do not recommend the use of marijuana to treat MS, as the drug is associated with serious long-term side effects such as heart attacks and memory loss.
Glaucoma Research Foundation (2012 and 2013)	In order to produce a short-term clinically relevant effect on intraocular pressure, constant marijuana inhalation is required (as much as every 3 hours). Thus, to be effective as a medication, marijuana would have to be ingested many times a day. A number of significant side effects from long-term oral use or inhalation make marijuana a poor choice for treatment of glaucoma. Up to now, no studies have shown that marijuana (or any chemical component of marijuana) can safely or effectively lower intraocular pressure better than medications currently available; more research is needed.
Hospice and Palliative Nurses Association (HPNA, 2014)	Nurses should be familiar with conditions for which medical marijuana might be beneficial, including nausea, vomiting, HIV cachexia/wasting, spasticity, MS, and glaucoma. Nurses should not practice out of their prescriptive authority as neither the FDA or DEA allow prescriptive privileges for medical marijuana.

Institute of Medicine (Joy, 1999)	"Scientific data indicate the potential therapeutic value of cannabinoid drugs, primarily 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 are probably important determinants of their potential therapeutic value. They can influence symptoms indirectly which could create false impressions of the drug effect or be beneficial as a form of adjunctive therapy." "If there is any future for marijuana as a medicine, it lies in its isolated components, the cannabinoids and their synthetic derivatives."
Mayo Clinic (2013)	Ranking the scientific evidence on marijuana use for medical reasons, the Mayo clinic states: There is no strong scientific evidence for marijuana use in any medical condition. There is good scientific evidence for marijuana use in chronic pain and MS. There is unclear scientific evidence for marijuana use in amyotrophic lateral sclerosis, appetite stimulant, atopic dermatitis, brain injuries, dementia, chemotherapy side effects, epilepsy, glaucoma, and many others.
National Alliance on Mental Illness (NAMI)	No position statement found. On Marijuana and Mental Illness Fact Sheet, it states "there is an overwhelming consensus that marijuana is not helpful and is potentially dangerous for people with mental illness."
National Association of School Nurses (2014)	Marijuana should remain as a Schedule I drug under the Controlled Substances Act as there is not sufficient scientific evidence for the FDA to approve smoked marijuana for medical use, including in the student age group. The legal availability of marijuana allows more access to the student population and "puts students at higher risk of use and health consequences."

National Cancer Institute at the National Institutes of Health	No guidelines/recommendations found.
National Institute on Aging	No guidelines/recommendations found.
National Multiple Sclerosis Society (NMSS) (n.d.)	NMMS supports the rights of people with MS to work with "health care providers to access marijuana for medical purposes in accordance with legal regulations in those states where such use has been approved." Generally agreed that better treatments are needed for some symptoms of MS (pain, tremor, spasticity) that are not sufficiently relieved by available treatments. There are uncertainties about benefits of marijuana versus side effects. NMMS supports research to "better understand benefits and potential risks of marijuana and its derivatives as a treatment for MS."
US Food and Drug Administration (FDA, 2014)	Marijuana is not approved as a safe and effective drug for any indication

Table 4. List of organizations' position statement on the use of marijuana for medical conditions.

XVII. Limitations and gaps

Limitations of the evidence

Interpretation of the results of the studies included in this report must take into account limitations of the studies, including various potential biases, other factors that might influence risks or outcomes from marijuana use, how the studies were conducted, how marijuana use or impairment was assessed, and how outcomes from marijuana use were measured.

Measurement of marijuana use in these studies often relied on self-report via surveys or questionnaires, accurate recall of marijuana use, and subjects' honesty in reporting use of a drug that is illegal in most states in the US [86, 87, 90, 107]. Studies assessing marijuana use in school children are often conducted at school and might have failed to include some students who are truant or ill [162]. Other facets of marijuana use are also difficult to assess, including the frequency, dose, duration of use, and mode of administration (smoking or eating) [86, 87, 163]; whether the user titrates (adjusting the interval between puffs or holding smoke in the lung for a shorter period of time) [10]; and inability to report use accurately due to cognitive impairment from substance use [41].

Additionally, it appears that the potency of THC has been increasing over time in the US [1]. This can create difficulties in assessing the dose of THC a person receives [10] and might limit our ability to apply the results of older studies to our current situation [1]. However, how much THC potency has

increased is unknown because the THC concentration depends upon a number of factors including the source of the marijuana (domestic or foreign), the freshness, the part(s) of the plant, the method of preparation, and the growing technique [10, 12, 164].

Some factors influencing the assessment of marijuana outcomes include the frequent use of marijuana in combination with other drugs [1, 119]. Motor vehicle driving impairment due to marijuana use is measured in different ways across the country, sobriety tests [118], self-report, driving behavior (such as reaction time, monitoring of the speedometer, and increased braking time) [116], the presence of inactive THC metabolites in the urine, and the presence of THC in whole blood or serum analysis [118]. Each of these methods can have varying levels of validity and reliability [119]. Additionally, the effect of any drug on driving performance can vary by the drug type, dosage, and driver's physiological response and tolerance level [124].

Currently, little is known about the presence of genetic factors that might interact with environmental stressors to predispose a person to a later psychotic illness [80] or to increased risk of early initiation to marijuana use or drug use and dependence [54]. Many studies are conducted with a short duration of follow-up, limiting observation of potential long-term health effects [111]. Most studies were not able to determine causality due to the nature and volume of the research.

Gaps in knowledge

There are numerous gaps in our knowledge of the health effects of marijuana. Long-term effects of prenatal exposure to marijuana are poorly understood [1]. We do not have reliable information about the concentration of THC and other cannabinoids in commonly used marijuana products [2]. More research needs to be done to improve our knowledge of potential therapeutic benefits of marijuana [1], including the method of administration that provides the most benefit [8]. Few studies analyze other cannabinoids in marijuana samples even though some of these cannabinoids might have the potential to offset the effects of THC [10]. We know very little about the effects of second-hand exposure to marijuana smoke and other cannabinoids [1]. Finally, research is needed on how government policies on marijuana can affect public health outcomes [1].

XVIII. Literature cited

1. Volkow, N.D., et al., *Adverse health effects of marijuana use.* N Engl J Med, 2014. **370**(23): p. 2219-27.
2. Hall, W. and L. Degenhardt, *Adverse health effects of non-medical cannabis use.* Lancet, 2009. **374**(9698): p. 1383-91.
3. Hall, W., *The adverse health effects of cannabis use: what are they, and what are their implications for policy?* Int J Drug Policy, 2009. **20**(6): p. 458-66.
4. Ali, A., *Marijuana health review*. 2013, Clark County Public Health: Vancouver, WA.
5. National Cancer Institute. *Cannabis and Cannabinoids (PDQ®), Health Professional Version.* 2014 6/18/2014]; Available from: http://www.cancer.gov/cancertopics/pdq/cam/cannabis/healthprofessional/.
6. U.S. Department of Justice, Drug Enforcement Administration, *Drugs of Abuse, a DEA resource guide*. 2011.
7. National Institutes of Health, National Institute on Drug Abuse, *Research Report Series: Marijuana*. 2012, GPO: Washington.
8. Greydanus, D.E., et al., *Marijuana: current concepts.* Front Public Health, 2013. **1**: p. 42.

9. United Nations Office on Drugs and Crime (UNODC), Laboratory and Scientific Section, *Recommended methods for the identification and analysis of cannabis and cannabis products (revised and updated)*. 2009, Laboratory and Scientific Section: Vienna, Austria.
10. McLaren, J., et al., *Cannabis potency and contamination: a review of the literature.* Addiction, 2008. **103**(7): p. 1100-9.
11. National Highway Traffic Safety Administration. *Cannabis/Marijuana (delta 9-Tetrahydrocannabinol, THC).* 2004 21 August 2014].
12. Mehmedic, Z., et al., *Potency trends of Delta 9-THC and other cannabinoids in confiscated cannabis preparations from 1993 to 2008.* J Forensic Sci, 2010. **55**(5): p. 1209-17.
13. Cascini, F., C. Aiello, and G. Di Tanna, *Increasing delta-9-tetrahydrocannabinol (Delta-9-THC) content in herbal cannabis over time: systematic review and meta-analysis.* Curr Drug Abuse Rev, 2012. **5**(1): p. 32-40.
14. Compton, W.M., et al., *Prevalence of marijuana use disorders in the United States: 1991-1992 and 2001-2002.* Jama, 2004. **291**(17): p. 2114-21.
15. United Nations Office on Drugs and Crime (UNODC), Laboratory and Scientific Section, *World Drug Report 2014*. 2014, UNODC Laboratory and Scientific Section: Vienna, Austria.
16. Addiction, E.M.C.f.D.a.D., *European Drug Report: Trends and developments*. 2014: Luxembourg:. p. 80.
17. Substance Abuse and Mental Health Services Administration, *Results from the 2012 National Survey on Drug Use and Health: Summary of National Findings*. 2013, Substance Abuse and Mental Health Services Administration: Rockville, MD.
18. Substance Abuse and Mental Health Services Administration, *Results from the 2006 National Survey on Drug Use and Health: National Findings*. 2007, Substance Abuse and Mental Health Services Administration: Rockville, MD.
19. Substance Abuse and Mental Health Services Administration, National Surveys on Drug Use and Health, *Substate Estimates of Substance Use and Mental Illness from the 2010-2012 National Surveys on Drug Use and Health: Results and Detailed Tables, Table 3. Marijuana Use in the Past Month*. 2014.
20. Oregon Health Authority, Public Health Division, *2013 Oregon Healthy Teens Survey, Washington County,*. March 2014, Public Health Division.
21. Oregon Health Authority, Public Health Division, *2013 Oregon Healthy Teens Survey, OHT State Report,*. March 2014, Public Health Division.
22. Kann, L., et al., *Youth risk behavior surveillance--United States, 2013.* MMWR Surveill Summ, 2014. **63 Suppl 4**: p. 1-168.
23. Johnston, L.D., et al., *Monitoring the Future national results on drug use: 1975-2013: Overview, Key Findings on Adolescent Drug Use.* 2013, Institute for Social Research, The University of Michigan: Ann Arbor, MI.
24. Johnston, L.D., et al., *Monitoring the Future national results on drug use: 1975-2013: Volume 2, College Students & Adults Ages 19-55*. 2013, Institute for Social Research, The University of Michigan: Ann Arbor, MI.
25. Whitehill, J.M., F.P. Rivara, and M.A. Moreno, *Marijuana-using drivers, alcohol-using drivers, and their passengers: prevalence and risk factors among underage college students.* JAMA Pediatr, 2014. **168**(7): p. 618-24.
26. Oregon Health Authority, Public Health Division, Oregon Medical Marijuana Program, *The Oregon Medical Marijuana Program*. Nov. 2011, Oregon Medical Marijuana Program.

27. Light, M.K., et al., *Market Size and Demand for Marijuana in Colorado: Prepared for the Colorado Department of Revenue*. 2014, Marijuana Policy Group: Denver, CO.
28. Bostwick, J.M., *Blurred boundaries: the therapeutics and politics of medical marijuana.* Mayo Clin Proc, 2012. **87**(2): p. 172-86.
29. U.S. Department of Justice, Drug Enforcement Administration, Demand Reduction Section, *The Dangers and Consequences of Marijuana Abuse*. Jan. 2014.
30. Joy, J.E., S.J. Watson Jr, and J.A. Benson Jr, *Marijuana and Medicine: Assessing the Science Base, Institute of Medicine,*, ed. Institute of Medicine. 1999, Washington, D.C.: National Academy Press.
31. Wilkinson, S.T. and D.C. D'Souza, *Problems with the medicalization of marijuana.* Jama, 2014. **311**(23): p. 2377-8.
32. Baker, D., et al., *The therapeutic potential of cannabis.* Lancet Neurol, 2003. **2**(5): p. 291-8.
33. Aggarwal, S.K., et al., *Medicinal use of cannabis in the United States: historical perspectives, current trends, and future directions.* J Opioid Manag, 2009. **5**(3): p. 153-68.
34. Wang, T., et al., *Adverse effects of medical cannabinoids: a systematic review.* CMAJ, 2008. **178**(13): p. 1669-78.
35. Hall, W. and N. Solowij, *Adverse effects of cannabis.* Lancet, 1998. **352**(9140): p. 1611-6.
36. Crean, R.D., N.A. Crane, and B.J. Mason, *An evidence based review of acute and long-term effects of cannabis use on executive cognitive functions.* J Addict Med, 2011. **5**(1): p. 1-8.
37. Substance Abuse and Mental Health Services Administration, *Results from the 2005 National Survey on Drug Use and Health: National Findings*. 2006, Substance Abuse and Mental Health Services Administration: Rockville, MD.
38. Kalant, H., *Adverse effects of cannabis on health: an update of the literature since 1996.* Prog Neuropsychopharmacol Biol Psychiatry, 2004. **28**(5): p. 849-63.
39. California Society of Addiction Medicine. *Marijuana's Addictive Potential (for healthcare professionals)*. 2011 25 June 2014].
40. Gonzalez, R., *Acute and non-acute effects of cannabis on brain functioning and neuropsychological performance.* Neuropsychol Rev, 2007. **17**(3): p. 347-61.
41. Lopez-Quintero, C., 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): p. 120-30.
42. Crippa, J.A., et al., *Cannabis and anxiety: a critical review of the evidence.* Hum Psychopharmacol, 2009. **24**(7): p. 515-23.
43. Hall, W. and L. Degenhardt, *Prevalence and correlates of cannabis use in developed and developing countries.* Curr Opin Psychiatry, 2007. **20**(4): p. 393-7.
44. Caldeira, K.M., et al., *The occurrence of cannabis use disorders and other cannabis-related problems among first-year college students.* Addict Behav, 2008. **33**(3): p. 397-411.
45. Crane, N.A., et al., *Effects of cannabis on neurocognitive functioning: recent advances, neurodevelopmental influences, and sex differences.* Neuropsychol Rev, 2013. **23**(2): p. 117-37.
46. Peters, E.N., A.J. Budney, and K.M. Carroll, *Clinical correlates of co-occurring cannabis and tobacco use: a systematic review.* Addiction, 2012. **107**(8): p. 1404-17.
47. Bonn-Miller, M.O., A.H. Harris, and J.A. Trafton, *Prevalence of cannabis use disorder diagnoses among veterans in 2002, 2008, and 2009.* Psychol Serv, 2012. **9**(4): p. 404-16.
48. National Institute of Mental Health. *Post-Traumatic Stress Disorder (PTSD)*. n.d. 28 May 2014].

49. Bonn-Miller, M.O., A.A. Vujanovic, and K.D. Drescher, *Cannabis use among military veterans after residential treatment for posttraumatic stress disorder.* Psychol Addict Behav, 2011. **25**(3): p. 485-91.
50. Cougle, J.R., et al., *Posttraumatic stress disorder and cannabis use in a nationally representative sample.* Psychol Addict Behav, 2011. **25**(3): p. 554-8.
51. Mills, K.L., et al., *Trauma, PTSD, and substance use disorders: findings from the Australian National Survey of Mental Health and Well-Being.* Am J Psychiatry, 2006. **163**(4): p. 652-8.
52. Desbois, A.C. and P. Cacoub, *Cannabis-associated arterial disease.* Ann Vasc Surg, 2013. **27**(7): p. 996-1005.
53. Fergusson, D.M., J.M. Boden, and L.J. Horwood, *The developmental antecedents of illicit drug use: evidence from a 25-year longitudinal study.* Drug Alcohol Depend, 2008. **96**(1-2): p. 165-77.
54. Lynskey, M.T., et al., *Escalation of drug use in early-onset cannabis users vs co-twin controls.* JAMA, 2003. **289**(4): p. 427-33.
55. Agrawal, A., et al., *A twin study of early cannabis use and subsequent use and abuse/dependence of other illicit drugs.* Psychological Medicine, 2004. **34**(7): p. 1227-1237.
56. Wilson, N., et al., *Adolescent alcohol, tobacco and marijuana use: the influence of neighborhood disorder and hope.* Am J Health Promot, 2005. **20**(1): p. 11-19.
57. Tucker, J.S., et al., *Neighborhood characteristics and the initiation of marijuana use and binge drinking.* Drug Alcohol Depend, 2013. **128**(1-2): p. 83-9.
58. Karriker-Jaffe, K.J., *Neighborhood socioeconomic status and substance use by U.S. adults.* Drug Alcohol Depend, 2013. **133**(1): p. 212-21.
59. Bowes, L., et al., *Lifecourse SEP and tobacco and cannabis use.* Eur J Public Health, 2013. **23**(2): p. 322-7.
60. Redonnet, B., et al., *Tobacco, alcohol, cannabis and other illegal drug use among young adults: the socioeconomic context.* Drug Alcohol Depend, 2012. **121**(3): p. 231-9.
61. Hazelden and QMarketResearch, *Attitudes on Marijuana Survey: Young Adults Aged 18 to 25*. 2014: n.p.
62. Macleod, J., et al., *Psychological and social sequelae of cannabis and other illicit drug use by young people: a systematic review of longitudinal, general population studies.* The Lancet, 2004. **363**(9421): p. 1579-1588.
63. Fergusson, D.M. and J.M. Boden, *Cannabis use and later life outcomes.* Addiction, 2008. **103**(6): p. 969-76; discussion 977-8.
64. Cerda, M., et al., *Medical marijuana laws in 50 states: investigating the relationship between state legalization of medical marijuana and marijuana use, abuse and dependence.* Drug Alcohol Depend, 2012. **120**(1-3): p. 22-7.
65. Harper, S., E.C. Strumpf, and J.S. Kaufman, *Do medical marijuana laws increase marijuana use? Replication study and extension.* Ann Epidemiol, 2012. **22**(3): p. 207-12.
66. Chu, Y.W., *The effects of medical marijuana laws on illegal marijuana use.* J Health Econ, 2014.
67. Gorman, D.M. and J. Charles Huber, Jr., *Do medical cannabis laws encourage cannabis use?* Int J Drug Policy, 2007. **18**(3): p. 160-7.
68. Lynne-Landsman, S.D., M.D. Livingston, and A.C. Wagenaar, *Effects of state medical marijuana laws on adolescent marijuana use.* Am J Public Health, 2013. **103**(8): p. 1500-6.
69. Goerke, D. and S. Kumra, *Substance abuse and psychosis.* Child Adolesc Psychiatr Clin N Am, 2013. **22**(4): p. 643-54.

70. Dougherty, D.M., et al., *Impulsivity, attention, memory, and decision-making among adolescent marijuana users.* Psychopharmacology (Berl), 2013. **226**(2): p. 307-19.
71. Patton, G.C., et al., *Cannabis use and mental health in young people: cohort study.* BMJ, 2002. **325**(7374): p. 1195-8.
72. Meier, M.H., et al., *Persistent cannabis users show neuropsychological decline from childhood to midlife.* Proc Natl Acad Sci U S A, 2012. **109**(40): p. E2657-64.
73. Gilman, J.M., et al., *Cannabis use is quantitatively associated with nucleus accumbens and amygdala abnormalities in young adult recreational users.* J Neurosci, 2014. **34**(16): p. 5529-38.
74. Solowij, N., et al., *Cognitive functioning of long-term heavy cannabis users seeking treatment.* JAMA, 2002. **287**(9): p. 1123-31.
75. Aggarwal, M., et al., *Substance-induced psychotic disorders: 13-year data from a de-addiction centre and their clinical implications.* Asian J Psychiatr, 2012. **5**(3): p. 220-4.
76. Gururajan, A., et al., *Drugs of abuse and increased risk of psychosis development.* Aust N Z J Psychiatry, 2012. **46**(12): p. 1120-35.
77. Di Forti, M., et al., *Daily Use, Especially of High-Potency Cannabis, Drives the Earlier Onset of Psychosis in Cannabis Users.* Schizophr Bull, 2014.
78. Minozzi, S., et al., *An overview of systematic reviews on cannabis and psychosis: discussing apparently conflicting results.* Drug Alcohol Rev, 2010. **29**(3): p. 304-17.
79. Griffith-Lendering, M.F., et al., *Cannabis use and vulnerability for psychosis in early adolescence--a TRAILS study.* Addiction, 2013. **108**(4): p. 733-40.
80. Semple, D.M., *Book Review: Cannabis as a risk factor for psychosis: systematic review.* Journal of Psychopharmacology, 2005. **19**(2): p. 187-194.
81. Moore, T.H.M., et al., *Cannabis use and risk of psychotic or affective mental health outcomes: a systematic review.* The Lancet, 2007. **370**(9584): p. 319-328.
82. Radhakrishnan, R., S.T. Wilkinson, and D.C. D'Souza, *Gone to Pot - A Review of the Association between Cannabis and Psychosis.* Front Psychiatry, 2014. **5**: p. 54.
83. Mégarbane, B. and L. Chevillard, *The large spectrum of pulmonary complications following illicit drug use: features and mechanisms.* Chem Biol Interact, 2013. **206**(3): p. 444-51.
84. Tomar, R.S., J. Beaumont, and J.C.Y. Hsieh, *Evidence on the Carcinogenicity of Marijuana Smoke*. Aug. 2009, California Environmental Protection Agency, Reproductive and Cancer Hazard Assessment Branch, Office of Environmental Health Hazard Assessment.
85. Moir, D., 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): p. 494-502.
86. Moore, B.A., et al., *Respiratory effects of marijuana and tobacco use in a U.S. sample.* J Gen Intern Med, 2005. **20**(1): p. 33-7.
87. Pletcher, M.J., et al., *Association between marijuana exposure and pulmonary function over 20 years.* JAMA, 2012. **307**(2): p. 173-81.
88. Thomas, G., R.A. Kloner, and S. Rezkalla, *Adverse cardiovascular, cerebrovascular, and peripheral vascular effects of marijuana inhalation: what cardiologists need to know.* Am J Cardiol, 2014. **113**(1): p. 187-90.
89. Mittleman, M.A., et al., *Triggering Myocardial Infarction by Marijuana.* Circulation, 2001. **103**(23): p. 2805-2809.
90. Hashibe, M., et al., *Epidemiologic review of marijuana use and cancer risk.* Alcohol, 2005. **35**(3): p. 265-75.

91. Marks, M.A., et al., *Association of marijuana smoking with oropharyngeal and oral tongue cancers: pooled analysis from the INHANCE consortium.* Cancer Epidemiol Biomarkers Prev, 2014. **23**(1): p. 160-71.
92. Feng, B.J., et al., *Cannabis, tobacco and domestic fumes intake are associated with nasopharyngeal carcinoma in North Africa.* Br J Cancer, 2009. **101**(7): p. 1207-12.
93. Berthiller, J., et al., *Marijuana smoking and the risk of head and neck cancer: pooled analysis in the INHANCE consortium.* Cancer Epidemiol Biomarkers Prev, 2009. **18**(5): p. 1544-51.
94. Mehra, R., et al., *The association between marijuana smoking and lung cancer: a systematic review.* Arch Intern Med, 2006. **166**(13): p. 1359-67.
95. Callaghan, R.C., P. Allebeck, and A. Sidorchuk, *Marijuana use and risk of lung cancer: a 40-year cohort study.* Cancer Cause Control, 2013. **24**: p. 1811-1820.
96. Hashibe, M., 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): p. 1829-34.
97. Tashkin, D.P., *Effects of marijuana smoking on the lung.* Ann Am Thorac Soc, 2013. **10**(3): p. 239-47.
98. Daling, J.R., et al., *Association of marijuana use and the incidence of testicular germ cell tumors.* Cancer, 2009. **115**(6): p. 1215-23.
99. Lacson, J.C., et al., *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): p. 5374-83.
100. Trabert, B., et al., *Marijuana use and testicular germ cell tumors.* Cancer, 2011. **117**(4): p. 848-53.
101. Ditmyer, M., et al., *The effect of tobacco and marijuana use on dental health status in Nevada adolescents: a trend analysis.* J Adolesc Health, 2013. **52**(5): p. 641-8.
102. Rodondi, N., et al., *Marijuana use, diet, body mass index, and cardiovascular risk factors (from the CARDIA study).* Am J Cardiol, 2006. **98**(4): p. 478-84.
103. Hill, M. and K. Reed, *Pregnancy, Breast-feeding, and Marijuana: A Review Article.* Obstet Gynecol Surv, 2013. **68**(10): p. 710-8.
104. Huang, D.Y., H.I. Lanza, and M.D. Anglin, *Association between adolescent substance use and obesity in young adulthood: a group-based dual trajectory analysis.* Addict Behav, 2013. **38**(11): p. 2653-60.
105. Muniyappa, R., et al., *Metabolic effects of chronic cannabis smoking.* Diabetes Care, 2013. **36**(8): p. 2415-22.
106. Brown, H.L. and C.R. Graves, *Smoking and marijuana use in pregnancy.* Clin Obstet Gynecol, 2013. **56**(1): p. 107-13.
107. El Marroun, 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): p. 470-4.
108. Forrester, M.B. and R.D. Merz, *Risk of selected birth defects with prenatal illicit drug use, Hawaii, 1986-2002.* J Toxicol Environ Health A, 2007. **70**(1): p. 7-18.
109. Goldschmidt, L., et al., *School achievement in 14-year-old youths prenatally exposed to marijuana.* Neurotoxicol Teratol, 2012. **34**(1): p. 161-7.
110. Astley, S.J. and R.E. Little, *Maternal marijuana use during lactation and infant development at one year.* Neurotoxicol Teratol, 1990. **12**(2): p. 161-8.
111. Hayatbakhsh, M.R., et al., *Birth outcomes associated with cannabis use before and during pregnancy.* Pediatr Res, 2012. **71**(2): p. 215-9.

112. Varner, M.W., et al., *Association between stillbirth and illicit drug use and smoking during pregnancy.* Obstet Gynecol, 2014. **123**(1): p. 113-25.
113. Garry, A., et al., *Cannabis and breastfeeding.* J Toxicol, 2009. **2009**: p. 596149.
114. Fronczak, C.M., E.D. Kim, and A.B. Barqawi, *The insults of illicit drug use on male fertility.* J Androl, 2012. **33**(4): p. 515-28.
115. Hartman, R.L. and M.A. Huestis, *Cannabis effects on driving skills.* Clin Chem, 2013. **59**(3): p. 478-92.
116. Sewell, R.A., J. Poling, and M. Sofuoglu, *The effect of cannabis compared with alcohol on driving.* Am J Addict, 2009. **18**(3): p. 185-93.
117. Couper, F.J. and B.L. Peterson, *The prevalence of marijuana in suspected impaired driving cases in washington statedagger.* J Anal Toxicol, 2014. **38**(8): p. 569-74.
118. Asbridge, M., J.A. Hayden, and J.L. Cartwright, *Acute cannabis consumption and motor vehicle collision risk: systematic review of observational studies and meta-analysis.* BMJ, 2012. **344**: p. e536.
119. Li, M.C., et al., *Marijuana use and motor vehicle crashes.* Epidemiol Rev, 2012. **34**(1): p. 65-72.
120. Laumon, B., et al., *Cannabis intoxication and fatal road crashes in France: population based case-control study.* BMJ, 2005. **331**(7529): p. 1371.
121. Li, G., J.E. Brady, and Q. Chen, *Drug use and fatal motor vehicle crashes: a case-control study.* Accid Anal Prev, 2013. **60**: p. 205-10.
122. Ramaekers, J.G., et al., *Dose related risk of motor vehicle crashes after cannabis use.* Drug and Alcohol Dependence, 2004. **73**(2): p. 109-119.
123. Wilson, F.A., J.P. Stimpson, and J.A. Pagan, *Fatal crashes from drivers testing positive for drugs in the U.S., 1993-2010.* Public Health Rep, 2014. **129**(4): p. 342-50.
124. Brady, J.E. and G. Li, *Trends in alcohol and other drugs detected in fatally injured drivers in the United States, 1999-2010.* Am J Epidemiol, 2014. **179**(6): p. 692-9.
125. Masten, S.V. and G.V. Guenzburger, *Changes in driver cannabinoid prevalence in 12 U.S. states after implementing medical marijuana laws.* J Safety Res, 2014. **50**: p. 35-52.
126. Guenzburger, G. and S. Mastenj, *Changes in driver cannabinoid prevalence associated with implementing medical marijuana laws in 14 U.S. states*. 2013, California Office of Traffic Safety: Elk Grove, CA.
127. Salomonsen-Sautel, S., et al., *Trends in fatal motor vehicle crashes before and after marijuana commercialization in Colorado.* Drug Alcohol Depend, 2014. **140**: p. 137-44.
128. Johnson, M.B., et al., *The prevalence of cannabis-involved driving in California.* Drug Alcohol Depend, 2012. **123**(1-3): p. 105-9.
129. Martyny, J.W., et al., *Potential exposures associated with indoor marijuana growing operations.* J Occup Environ Hyg, 2013. **10**(11): p. 622-39.
130. Hurley, W. and S. Mazor, *Anticipated medical effects on children from legalization of marijuana in Colorado and Washington State: a poison center perspective.* JAMA Pediatr, 2013. **167**(7): p. 602-3.
131. Mowry, J.B., et al., *2012 Annual Report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 30th Annual Report.* Clinical Toxicology, 2013. **51**(10): p. 949-1229.
132. Wang, G.S., et al., *Association of unintentional pediatric exposures with decriminalization of marijuana in the United States.* Ann Emerg Med, 2014. **63**(6): p. 684-9.
133. Wang, G.S., G. Roosevelt, and K. Heard, *Pediatric marijuana exposures in a medical marijuana state.* JAMA Pediatr, 2013. **167**(7): p. 630-3.

134. Calabria, B., et al., *Does cannabis use increase the risk of death? Systematic review of epidemiological evidence on adverse effects of cannabis use.* Drug Alcohol Rev, 2010. **29**(3): p. 318-30.
135. Parks, S.E., et al., *Surveillance for violent deaths - National Violent Death Reporting System, 16 states, 2010.* MMWR Surveill Summ, 2014. **63**(1): p. 1-33.
136. Anderson, D.M., D.I. Rees, and J.J. Sabia, *Medical Marijuana Laws and Suicides by Gender and Age.* Am J Public Health, 2014.
137. Rylander, M., C. Valdez, and A.M. Nussbaum, *Does the legalization of medical marijuana increase completed suicide?* Am J Drug Alcohol Abuse, 2014. **40**(4): p. 269-73.
138. Bachhuber, M.A., et al., *Medical Cannabis Laws and Opioid Analgesic Overdose Mortality in the United States, 1999-2010.* JAMA Intern Med, 2014.
139. Arseneault, L., et al., *Mental disorders and violence in a total birth cohort.* Arch Gen Pshychiatry, 2000. **57**: p. 979-86.
140. Gerberich, S.G., et al., *Marijuana use and injury events resulting in hospitalization.* Ann Epidemiol, 2003. **13**(4): p. 230-7.
141. Smith, P.H., et al., *Couples' Marijuana Use Is Inversely Related to Their Intimate Partner Violence Over the First 9 Years of Marriage.* Psychol Addict Behav, 2014.
142. Bodnar, N. *Don't Fear the Reefer*. DoveLewis VetWrap, 2013. **Spring 2013**.
143. Meola, S.D., et al., *Evaluation of trends in marijuana toxicosis in dogs living in a state with legalized medical marijuana: 125 dogs (2005-2010).* J Vet Emerg Crit Care (San Antonio), 2012. **22**(6): p. 690-6.
144. Donaldson, C.W., *Marijuana exposure in animals.* Vet Med, 2002. **97**(6): p. 437-439.
145. Balas, M. *Pet Talk: Veterinarians report higher numbers of cases of pets ingesting pot*. The Oregonian, 2014. **5 April 2013**.
146. Prom, N. and DoveLewis Emergency Animal Hospital.
147. Executive Office of the President of the United States, O.o.N.D.C.P. *Marijuana Resource Center: State Laws Related to Marijuana*. n.d. 28 July 2014].
148. Ba, O. *Feds say Colorado pot growers can't use government-owned water*. HNGN Headlines & Global News. **21 May 2014**.
149. Colorado National Organization for the Reform of Marijuana Laws (NORML) *Colorado lawyers get official OK to work with pot businesses*. **24 Mar. 2014**.
150. Biros, A. *Marijuana Edibles: A Regulatory Nightmare*. FoodSafetyTech. **29 July 2014**.
151. Migoya, D. *Colorado, Washington governors ask feds for promised pot bank guidance*. The Denver Post. **27 May 2014**.
152. Annas, G.J., *Medical marijuana, physicians, and state law*. N Engl J Med, 2014. **371**(11): p. 983-5.
153. Cole, J.M., *Memorandum for all United States Attorneys: Guidance Regarding Marijuana Enforcement*. 2013.
154. Morrison, C., et al., *The economic geography of medical cannabis dispensaries in California.* Int J Drug Policy, 2014. **25**: p. 505-515.
155. Freisthler, B., et al., *Evaluating medical marijuana dispensary policies: spatial methods for the study of environmentally-based interventions.* Am J Community Psychol, 2013. **51**(1-2): p. 278-88.
156. Kepple, N.J. and B. Freisthler, *Exploring the ecological association between crime and medical marijuana dispensaries.* J Stud Alcohol Drugs, 2012. **73**(4): p. 523-30.

157. California Police Chiefs' Association, *White paper on marijuana dispensaries*. 2009, California Police Chiefs' Association: Sacramento: California.
158. Morris, R.G., et al., *The effect of medical marijuana laws on crime: evidence from state panel data, 1990-2006.* PLoS One, 2014. **9**(3): p. e92816.
159. American Civil Liberties Union, *The War on Marijuana in Black and White*. June, 2013, American Civil Liberties Union: New York, NY.
160. Atherley, L.T. and M. Baird, *Public Possession of Legal Marijuana: Research Note*. 2014, Seattle Police Department: Seattle, WA.
161. Miron, J.A. and K. Waldock, *The Budgetary Impact of Ending Drug Prohibition*. 2010, CATO Institute: Washington, D.C.
162. Monshouwer, K., et al., *Cannabis use and mental health in secondary school children. Findings from a Dutch survey.* Br J Psychiatry, 2006. **188**: p. 148-53.
163. van Amsterdam, J., et al., *Physical harm due to chronic substance use.* Regul Toxicol Pharmacol, 2013. **66**(1): p. 83-7.
164. King, L.A., C. Carpentier, and P. Griffiths, *Cannabis potency in Europe.* Addiction, 2005. **100**(7): p. 884-6.