MEDICAL MARIJUANA: WHERE ARE WE NOW?

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Basics

Marijuana contains more than 460 different active chemicals and 60 different cannabinoids. It is derived from cannabis sativa and consists of the crushed leaves, stems and flowers of the plant. Hashish is produced by collecting and compressing trichromes, fine growths on the plant that produce a resin.

Marijuana has two major active ingredients, delta 9-tetrahydrocannabinol (THC) and cannabidiol. THC is the major psychoactive ingredient. Its potency varies depending on the particular derivative of the cannabis plant that is used. The average THC content of marijuana has increased over time with refinement in the cultivation process, increasing from 2% in 1980 to 5.5% in 2006. Thus, in general, the marijuana currently in use is considerably more potent than that available in the past. The THC content of the resin – and, thus, hashish – is much higher than that of products produced from other portions of the plant.

Cannabidiol is responsible for the more peripheral effects seen with the drug and may counteract some of the psychoactive effects of THC.

Political Considerations

There are records that indicate that marijuana was first used medically over 5,000 years ago in central Asia and China. In the 1830s, an Irish physician, W.B. O'Shaughnessy, wrote a paper advocating its use for conditions such as pain, vomiting, convulsions and spasticity. In 1854 the drug was listed on the US Dispensary. However, in 1937 the Marijuana Tax Act essentially eliminated its use from medical practice, and in 1942 it was removed from the US Dispensary. In 1970 the US Congress, bypassing the usual review process in the Controlled Substances Act, declared marijuana to have no medicinal value and designated it a Schedule 1 drug, i.e., one that has no medical application and a high potential for abuse.

Executive Summary *This article reviews the full spectrum of issues associated with marijuana and its use in the medical environment. Basic facts about the drug, its historical background, and the past and present political issues surrounding its use are discussed. The importance of the endocannabinoid system, the CB1 and CB2 receptors, and their location within the body are highlighted in explaining the physiologic effects of marijuana. The various forms of testing for the drug and their nuances are reviewed as are the basics of cannabis pharmacology, including variability of absorption by route of administration, the concepts of tolerance and withdrawal, and the risk for development of a dependence syndrome. The adverse effects of marijuana, including lung disease and lung cancer, adverse psychiatric effects, influence on brain development, cardiovascular effects and contribution to motor vehicle accidents, are discussed. Finally, the use of marijuana in medical treatment is reviewed, including the conditions for which it may be indicated, the profile of those most likely to use the drug in this manner and possible red flags for adverse outcomes with this type of therapy.*

Other drugs in this class include heroin, Quaaludes and LSD. In 1999 an Institute of Medicine review of the literature declared that the drug did have some potential benefit.

In 1996, with the passage of Proposition 215, California became the first state to permit medical use of marijuana. Since that time an additional 22 states and the District of Columbia (as of 1/29/15) have passed laws allowing the use of medical marijuana. These laws vary in structure. Most establish a patient registry, and some, but not all, allow dispensaries. Many of the laws are vague as to what conditions can

be treated with the drug, and many do not require an established relationship with or ongoing monitoring by a physician. Only a prescription is required. Four states – Colorado, Washington, Alaska and Oregon – have now passed laws that allow recreational use of the drug.

Despite its legalization to some degree in many states, marijuana is still a Schedule 1 drug under federal law. However, in August 2013, the Department of Justice modified its policies, adopting a "trust but verify" approach. This policy stated that, while reserving the right to enforce the Schedule 1 status of the drug, the federal government would not impinge on state laws if certain conditions were met. These conditions included prohibition of:

1. Distribution of marijuana to minors.
2. Revenue from sales going to criminal enterprises, gangs or cartels.
3. Diversion of marijuana to states where it is illegal.
4. Use of state-authorized marijuana sales to traffic in other drugs.
5. Use of firearms or violence in the cultivation or distribution of marijuana.
6. Drugged driving or other adverse public health consequences.
7. Growing of marijuana on public lands.
8. Marijuana possession or use on federal property.

One important consequence of its Schedule 1 status under federal law is that it makes study of the medical uses of marijuana very difficult. The only federally authorized source of cannabis for medical study is a strain grown at the University of Mississippi. Obtaining this material is difficult and it is only possible through an application to the National Institute of Drug Abuse.

Physiology

Marijuana produces its physiologic effects through the endocannabinoid system. This is a moderator system that regulates neurotransmitter release at the level of the synapse. In this capacity it functions in parallel with and in conjunction with the adrenergic, cholinergic and dopaminergic systems, and produces effects in the central and autonomic nervous systems. The endocannabinoid system operates through two different types of receptors, CB1 and CB2.

The CB1 receptors are located primarily in the central nervous system, are the primary binding site for THC and are, thus, responsible for the psychoactive effects of the drug. The concentration of these receptors in certain areas of the brain provides an explanation for many of the physical and cognitive effects seen with cannabis use. These locations and effects include:

1. Mesolimbic system – reinforcement of pleasurable activities.
2. Cerebellum and basal ganglia – effect on motor tone and coordinated movement.
3. Hippocampus – modulation of mood.
4. Hippocampus, prefrontal cortex – effects on short-term memory, concentration, attention and tracking behavior.
5. Hypothalamus – vegetative functions.
6. Food intake receptors – influence on appetite ("munchies").
7. Spinal cord – pain pathways, analgesia.
8. Central reward center – potential addictive behavior.

However, there is a near absence of CB1 receptors in the brainstem, which serves to negate the severity of adverse effects with excessive doses of the drug. As a consequence, a lethal outcome from a marijuana overdose has never been reported.

The CB2 receptors, on the other hand, are located only in the periphery, primarily in neurons and immune cells. Activation of these receptors leads to multiple outcomes including immunosuppression, anti-inflammatory effects and reduced pain sensation.

Testing

Marijuana is fat-soluble and, thus, tends to concentrate in adipose tissue, a fact that can be relevant to drug-testing protocols. The most commonly used format for detection of cannabis use is the analysis of urine for metabolites of THC. The time frame when such a test can be positive depends on the cutoff level used, the amount of drug absorbed and the frequency of use. Urine tests will usually be positive 1-3 days after acute intake, but can be abnormal up to a month or more in selected chronic users. This prolonged time frame for detection is related to the fat solubility of the drug and the resultant slow leaching of the material from its adipose stores.

Blood and oral fluid assays test for both the parent compound and its metabolites (blood) or THC alone (oral fluid). These tests are usually positive for only a few hours after intake, but can be positive for up to 1-2 days in heavy users. Hair analysis, which tests for metabolites, can be positive for up to 90 days in heavy regular users, but detection depends heavily on the length and amount of the hair sample that is tested.

Pharmacology

THC is rapidly absorbed when cannabis is smoked. Peak serum concentrations are usually reached in 10-20 minutes, with maximum clinical effects occurring in about 30 minutes. Heavy users tend to absorb the

drug more efficiently. Oral intake can produce similar physical effects, but the THC is absorbed more slowly and erratically. As a result, concentrations in the blood peak later, in 1-3 hours, and generally at levels lower than those seen with smoking. Consequently, because of the more rapid onset and easier titration of effects, most medical users prefer to smoke their marijuana.

As with alcohol and opioids, tolerance many develop with chronic use, so that increasing doses of THC are needed to produce comparable effects over time. Like the other drugs, a withdrawal syndrome also exists with cessation of regular marijuana use and is characterized by anxiety, irritability, depressed mood, restlessness, disturbed sleep, gastrointestinal symptoms and decreased appetite. These symptoms usually begin in the first few days after the onset of abstinence and persist for several weeks. However, the withdrawal syndrome is generally milder than that seen with the other noted substances. This is felt to be due to the slow leaching of the fat-soluble marijuana from adipose tissues, which results in low levels of THC persisting in the body, despite a lack of ongoing intake.

The existence of a dependence syndrome is recognized with cannabis and occurs in about 9% of regular users, a rate that is considerably lower than that seen with other drugs (Figure 1). It is characterized by the four C's; lack of Control over intake, Compulsive use, Craving for the drug and Continued use despite the occurrence of adverse physical or social consequences. However, dependence almost exclusively occurs in individuals who begin using marijuana in adolescence or early adulthood. There is essentially no risk for those who begin using the drug after age 25.

Figure 1

Lifetime Risk for Dependence

Percentage Risk for Dependence by Substance

Sechrist JM, Mayo Clin Proc, 2012; 87:172-186.

Adverse Effects

There has been noted an association with lung cancer in chronic marijuana smokers in some clinical studies, but not all. This association would not be surprising as there are 50% to 70% more carcinogens present in the inhaled material than that found in tobacco smoke, and there is one-third more retention of tar in the lungs. In addition, the marijuana smoke is usually more deeply inhaled and held in the lungs longer than what is seen with a typical cigarette smoker.

In one study, lifetime cannabis use totaling <20 joints was not associated with the development of lung cancer. However, heavy use, defined as >10.5 joint years (joint year = one joint per day for a year), had a relative risk for lung malignancy of 5.7. These authors estimated that one joint per day was roughly equivalent to one pack of cigarettes per day in terms of lung cancer risk.

Another study followed Swedish conscripts for 40 years. Of these army recruits, individuals who had used marijuana more than 50 times by age 18-20 had a hazard ratio (HR) for developing lung cancer that was 2.12 compared to never users, even when controlling for tobacco use. This risk was relatively equivalent to the risk seen with those smoking a half-pack of cigarettes per day. The HR for those who had used marijuana in the intermediate range of 11-50 times by age 18-20 was 1.68.

Although smoking marijuana may increase blood carboxyhemoglobin levels five-fold, short-term acute use may actually lead to bronchodilation. Ongoing use, on the other hand, is associated with an increased frequency of chronic bronchitis with increased inflammation of the airways. Interestingly, the risk of emphysema is not increased. Thus, the likelihood for developing chronic lung disease appears to be significantly less than that seen with tobacco use. In one study, the authors estimated that the chronic use of one pack per day of cigarettes was equivalent to approximately 7.9 joints per day of marijuana in terms of adverse lung effects.

There is an increased risk of adverse psychiatric effects with use of marijuana, with a clearly increased risk of schizophrenia and other psychoses and possibly an increased risk of bipolar disorder and depression. The drug appears to unmask a predisposition to these conditions in susceptible individuals and this risk appears to be dose dependent (Figure 2 next page). Of note, the risk appears to flow both ways, i.e., marijuana users have worse psychosis and psychotic individuals are more likely to use the drug.
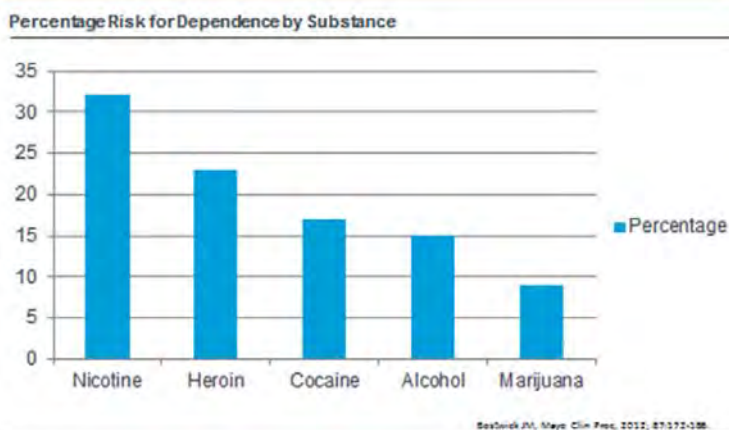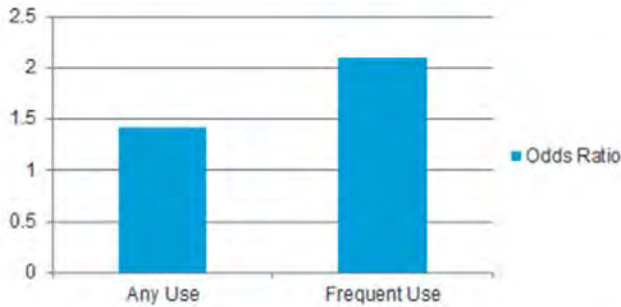
Figure 2

Risk of Psychosis with Marijuana Usage

Odds Ratio by Amount of Usage

BezGwisk JW, Mayo Clin Proc. 2012; 87:172-186.

🔑 The risk associated with cannabis use is particularly high in adolescence. Puberty is characterized by cerebral reorganization, especially in the frontal lobes. The developing brain is particularly vulnerable to the effects of cannabinoids, and significant adverse effects can be seen in daily and weekly users. These adverse effects include memory deficits, reduced attention span, reduced processing speed, abnormal social behavior, and increased susceptibility to anxiety and depressive disorders. The classic "stoner" character depicted in movies is representative of an individual who began heavy use of cannabis in his teen years. As noted previously, there is also a higher risk for developing dependence on marijuana, as well as possibly other drugs, in those who begin smoking it in adolescence.

Cannabis use can be associated with a variety of cardiovascular effects including sinus tachycardia, vasodilation, hypertension and arrhythmias. It has been associated with acute myocardial infarctions and worsened outcomes in those with known coronary disease. There have also been isolated reports of cerebral vasospasm and arteritis.

Marijuana use has been associated with significant bone loss and the development of osteoporosis.

🔑 One recent area of concern has been the effect of marijuana use on motor vehicle crashes. Cannabis use clearly affects some skills needed for safe driving. In addition, marijuana is associated with a greater chance of risk-taking behavior. Some studies show a significant association between marijuana use and decline in driving ability in a dose-related fashion. However, these results have been highly variable, possibly due to the effects of tolerance in heavy users. Another issue of concern in assessing the risk is the

difficulty in measuring acute intoxication with THC due to the limitations of the testing protocols

One recent study showed a significant association of marijuana use with motor vehicle crashes. Figure 3 summarizes the odds ratio for marijuana use being associated with an MV crash. It gives the overall risk in the first bar and then summarizes the results from eight different studies individually. On the X-axis is listed how the use of marijuana was documented. Four of the studies were based on self-reported use, two by urine testing, one by blood testing and one by urine and blood. Other studies have shown that the combination of cannabis plus alcohol (Figure 4) or opioids is especially bad. In the case of alcohol, the risk appears to be synergistic, i.e., the risk for use of both marijuana and alcohol together is greater than the sum of the risks for each alone.

Figure 3

Association of Marijuana with Motor Vehicle Crashes

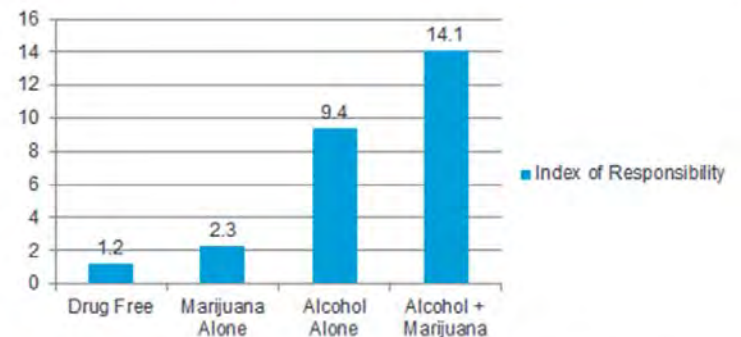Odds Ratio for Increased Crash Risk by Study and Indicator of Use
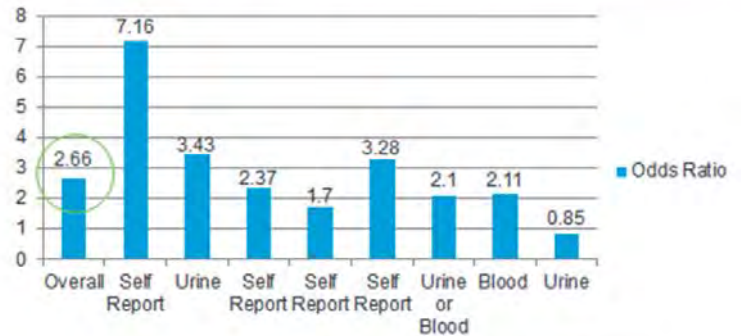
Li MC, Epidemiol Rev. 2012; 34:65-72.

Figure 4

Probability of Responsibility for a Motor Vehicle Accident

Responsibility by Substance

Bischdar MB, Traffic Inj Prev. 2008; 9:11-21.

Figure 5

Trends in Alcohol and Drugs in Fatallly Injured Drivers in the US
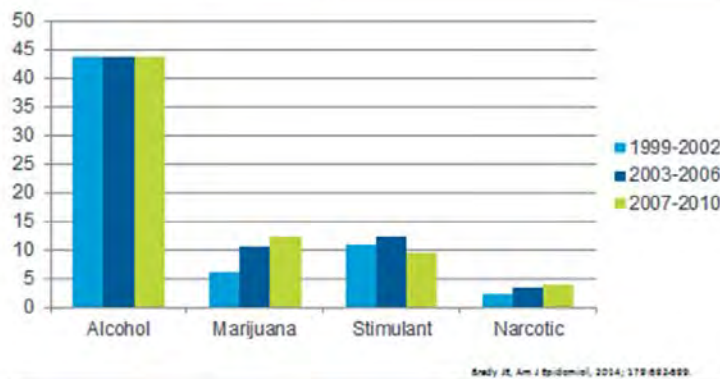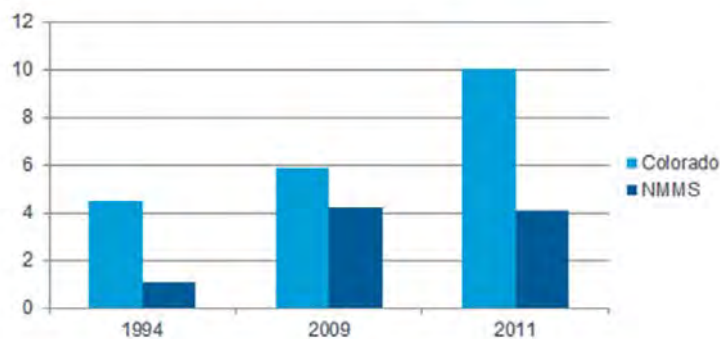1999-2010

Males who died within 1 hour of accident

Legend: 1999-2002, 2003-2006, 2007-2010

Brady JE, Am J Epidemiol, 2014; 179:692-699.

Figure 6

Trends in Fatal MV Crashes After MJ Commercialization
% Testing Positive for Marijuana

Colorado vs non-medical marijuana states (NMMS)

Legend: Colorado, NMMS

The effects on accident rates were mixed in early studies but recent papers have shown a disturbing trend. In one study, the percentage of fatally injured drivers who tested positive for marijuana had increased significantly in recent years (Figure 5). In another paper from Colorado, the proportion of fatally injured drivers who tested positive had increased substantially since the advent of commercialization of cannabis use in that state (Figure 6).

Medical Use

Marijuana is not the drug of first choice for any medical condition. Although research is limited due to its Schedule 1 status, efficacy has been shown for five major conditions. These include:

1. Severe nausea and vomiting - usually due to cancer chemotherapy or other conditions.
2. Weight loss and cachexia - most often due to cancer or HIV disease.
3. Spasticity - associated with neurologic diseases such as multiple sclerosis or spinal cord injuries.
4. Pain syndromes.
5. Glaucoma.

There are a number of idiosyncrasies associated with medical marijuana and the legislation that enables it. Many laws are vague as to what conditions are best treated with the drug. A significant number of states only require a prescription and no ongoing relationship with a physician to obtain it. Only two cannabinoid drugs are available orally and these are for the treatment of nausea and vomiting (dronabinol and nabilone). Most users smoke the "medication" because of the more rapid onset and easier titration to physical effects. As a result, the precise dose cannot be measured. Furthermore, there is no standardization of purity, which is unique among medical treatments.

Most current users of medical marijuana were heavy, regular recreational users prior to starting the medication. For example, one study of individuals applying for permits in California showed that 90% had tried the drug before age 20, 90% had admitted daily use prior to application and 85% had tried other illegal drugs (Figure 7). There has been four-fold increase in the use of cocaine and methamphetamine in pain patients using marijuana. On the other hand, many novice users find the psychoactive effects of THC difficult to tolerate.

Figure 7

Percentage Trying Illegal Drugs Among Medical Marijuana Applicants

Percentage by Drug Males and Females

Legend: Females, Males

*O'Connell TJ, Harm Reduct J. 2007; 4:16.*
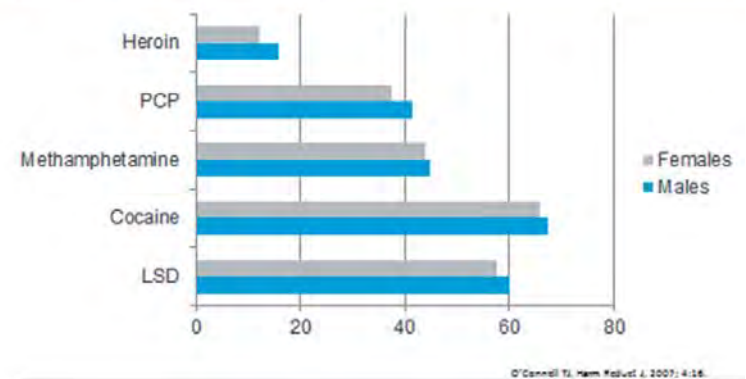
Medical marijuana can be problematic in individuals using opioid pain medication. These individuals are more likely to abuse or misuse opioids and more likely to use other illicit drugs. They are also more likely to be involved with the diversion of narcotics to the secondary market. In addition, the combination of cannabis and opioids has significant adverse effects on driving behavior and the risk of fatal accidents. Finally, the concurrent presence of the marijuana abuse disorder significantly increases the likelihood of a fatal drug overdose (Figure 8, next page).

Figure 8

Medication Related Accidental Overdose Death

Hazard Ratios by Psychiatric Condition

Behnet ASS, Am J Psych, 2012; 169:64-70.
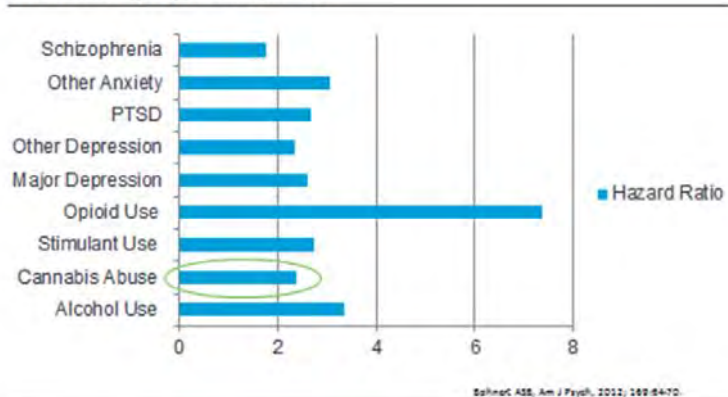
Summary

In summary, most medical marijuana patients were heavy, regular cannabis users before they started treatment. Most of these individuals prefer to smoke the drug. Due to the effects on lung function, lung cancer risks and vascular effects of inhaled marijuana, the baseline mortality risk of regular, heavy medical or non-medical users is likely closer to that of tobacco users than non-smokers. The available evidence would suggest that only the occasional user of marijuana would likely not have these smoker-like effects. The main issue, from a practical standpoint, in differentiating these latter groups is documenting the actual amount of drug that is being used. Use in adolescents is particularly problematic for the reasons detailed previously.

In terms of underwriting the use of medical marijuana, it is important to remember that the mortality risk is not from the drug itself, but rather the company it keeps — the medical conditions that are being treated and the social and behavioral issues associated with chronic heavy use. Key points to keep in mind in reviewing these cases include:

1. Many of the conditions best treated with medical marijuana are high-risk conditions from a life underwriting perspective. The exceptions are chronic pain and glaucoma.
2. Ideally the applicant should be under the regular care of a physician. If not, one is more likely dealing with recreational use.
3. There should be no indication or suspicion of misuse or abuse of marijuana and no indication of withdrawal symptoms in the records.
4. Use in individuals under the age of 18 is very high risk.
5. Caution should be exercised in individuals with any significant psychiatric illness, but especially psychosis, recently or in the past.
6. Beware of any evidence of or suspicion for significant alcohol or other substance abuse recently or in the past.
7. Current regular use of opioids is a red flag. The risk is especially high if there is any use of sedatives such as benzodiazepines as well.
8. Be alert to any significant driving criticism, especially with any history of a DWI or concurrent use of opioids.
9. Be cautious regarding other medical conditions where smoking medical marijuana could pose a significant extra risk. These would include conditions such as COPD, coronary artery disease, poorly controlled asthma and a history of tobacco-related cancers.

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