Current Medical and Legal Status for Smoked “Medical Marijuana” and Addiction
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IS MARIJUANA A MEDICINE?: FDA DRUG APPROVAL
“Medical marijuana” does not meet the legal definition of drug as defined by the Food and Drug Administration (FDA) in the US.1 The drug approval process for a medication is established by the Food and Drug Administration following the Federal Food, Drug, and Cosmetic Act officially recognized in 1938.2 An important responsibility of the FDA is to provide drug approval for prescription drugs sold in the marketplace for medical purposes in the US. To determine whether the smoked marijuana plant in its natural form qualifies as safe and effective by FDA standards, the drug must undergo investigation by the FDA.3,4

The most important factors in considering FDA approval of a drug are determining the safety and effectiveness of the drug. While the FDA does support clinical trials testing the significance of plant-derived marijuana in treating medical conditions, the FDA has yet to approve smoked marijuana for medical use. In many states, marijuana is prescribed outside of the usual doctor-patient relationship, and a doctor does not monitor nor evaluate the response to marijuana for the patient’s medical condition. Typically, to approve “medical marijuana,” a doctor possesses a special certification for its use as “medical marijuana.” Further, “medical marijuana” is not dispensed in pharmacies, does not undergo the typical physician prescribing route,5 and may be grown by caregivers who are not under any supervision or regulation. The marijuana that is sold in dispensaries is not tested by the FDA for effectiveness or safety.4 Distribution is loosely regulated by local ordinances and state law,6 mostly to control the numbers and locations of dispensaries.

The FDA requires 12 stages that a drug must pass to receive FDA approval.7 Stage 1 is animal testing; stage 2 is Investigational New Drug Application (IND). The FDA reviews the IND to ensure the proposed clinical trials do not place human subjects at “unreasonable risk of harm.”7 Stage 3 is clinical trial phase one focused on safety; stage 4 is clinical trial phase two focused on effectiveness; and stage 5 is clinical trial phase 3 testing on large groups of individuals. Stage 6 is FDA review after all the information is collected; stage 7 is a New Drug Application to the FDA for approval; and stages 8-9 are application reviewed. Stage 10 is drug labeling to ensure that the physician and consumer are well informed; stage 11 is facility inspection of where the drugs will be manufactured; and stage 12 is FDA drug approval after review.4,7 “Medical marijuana” does not participate in any of these stages.

STUDIES ON SMOKED MARIJUANA
Most of the studies that have claimed therapeutic benefit of marijuana-related chemicals were performed on cannabinoids, both...
naturally occurring and synthetic, not on smoked marijuana plant itself and not on tetrahydrocannabinol (THC), the psychoactive ingredient in marijuana.8 Those studies done on the smoked form of marijuana were short term, such as 5 days, or involved co-occurring use of multiple other addicting drugs.8,11 Marijuana has many side effects that may outweigh any perceived benefits, and the question is how good can a medication be or become if it has the ability to incapacitate and disable, as does smoked marijuana. Further, marijuana can be a gateway drug.12 It may not be the only gateway drug, and as use of one addicting drug can lead to use of another addicting drug, there is a generalized vulnerability to interchange, substitute, and complement addicting drugs.13

MEDICAL STATUS FOR SMOKED MARIJUANA PER ORGANIZED MEDICINE
The Drug Enforcement Administration and the federal government are not alone in viewing smoked marijuana as having no documented medical value. Medical organizations have also stated they do not accept smoked marijuana as medicine.14 The American Medical Association (AMA) endorses “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.”15 In November 2009, the AMA amended its policy, urging that marijuana’s status as a Schedule I controlled substance be reviewed “with the goal of facilitating the conduct of clinical research and development of cannabinoids-based medicines, and alternate delivery methods.”15 The AMA also stated that “this should not be viewed as an endorsement of state-based medical cannabis programs, the legalization of marijuana, or that scientific evidence on the therapeutic use of cannabis meets the current standards for a prescription drug product.”15

The American Society of Addiction Medicine’s (ASAM) Public Policy Statement on Medical Marijuana clearly rejects smoking marijuana as a means of drug delivery.16 ASAM further recommends that “cannabis, cannabis-based products, and cannabis delivery devices should be subject to the same standards that are applicable to other prescription medications and medical devices and...should not be distributed or otherwise provided to patients until such products or devices have received marketing approval from the Food and Drug Administration.”16 ASAM also “discourages state interference in the federal medication approval process.”16 ASAM continues to support these policies and has also stated that ASAM “does not support the legalization of marijuana.”15

The American Academy of Child and Adolescent Psychiatry (AACAP) “is concerned about the negative impact of medical marijuana on youth. Adolescents are especially vulnerable to the many adverse development, cognitive, medical, psychiatric, and addictive effects of marijuana.”17 Of greater concern to the AACAP is that “adolescent marijuana users are more likely than adult users to develop marijuana dependence, and their heavy use is associated with increased incidence and worsened course of psychotic, mood, and anxiety disorders.”17 The ‘medicalization’ of smoked marijuana has distorted the perception of the known risks and purported benefits of this drug.”17 Based upon these concerns, the “AACAP thus opposes medical marijuana dispensing to adolescents.”17

In 1999, The Institute of Medicine (IOM), now known as the National Academy of Medicine, released a landmark report reviewing the supposed medical properties of marijuana.18 In the IOM report, the authors noted that the active compounds in marijuana may have medicinal potential and therefore should be researched further.18 However, the report concluded that there is little future in smoked marijuana as a medically approved medication.18

The IOM report explained that “smoked marijuana...is a crude THC delivery system that also delivers harmful substances.”18 In addition, “plants contain a variable mixture of biologically active compounds and cannot be expected to provide a precisely defined drug effect.”18 The authors explicitly stated that using smoked marijuana in clinical trials should not be designed to develop it as a licensed drug, but should be a stepping stone to the development of new, safe, delivery systems of cannabinoids.18 “Thus, even scientists and researchers who believe that certain active ingredients in marijuana may have poten-
tial medicinal value openly discount the notion that smoked marijuana is or can become "medicine."\textsuperscript{14}

**CURRENT POLICY FOR "MEDICAL MARIJUANA"

We believe an objective, scientific analysis of the medical facts to date would reveal that policy for "medical marijuana" seems to be based primarily on profit and addiction. State-approved "medical marijuana" is largely a political action arising outside of traditional medical practice and not based on usual medical scrutiny and standards. In addition, the public may want to expand availability of marijuana to recreational users; however, it is doubtful that the public understands that many marijuana users are heavy users, not recreational users.\textsuperscript{7} From experience with opioid medications, the public may have limited understand of drug addiction, the adverse consequences of addictive drug use, and that recreational or medicinal use of a drug with addiction potential often becomes particularly harmful and dangerous.\textsuperscript{19}

If marijuana is legalized, we envision commercial interests will likely expand to and target the addicted users as they do for alcohol and nicotine currently. While nearly 90\% of the population drinks alcohol,\textsuperscript{20} 80\% of the alcohol sold in the US is consumed by 20\% of those who consume alcohol.\textsuperscript{21} As the published rate for alcohol use disorder is about 6\%,\textsuperscript{20} those likely to consume alcohol regularly may be addicted. The same statement can be made for those who smoke cigarettes (15\% of US adults\textsuperscript{22}) and are addicted to nicotine (9\%).\textsuperscript{23} The addiction potential for marijuana is similar to alcohol and nicotine, and assuming legalization would lead to increased availability, the rate of addiction to marijuana could also increase correspondingly, similar to alcohol and nicotine, along with their comparable legal and health risks and costs.

The risk is that special groups and self-serving entrepreneurs will be common and will compete to manufacture and distribute marijuana, as do big tobacco and alcohol manufacturers. The questions are whether "big marijuana companies" would mislead marijuana users as big tobacco companies fraudulently claimed nicotine was not addicting and try to "pitch" that marijuana is safe without harmful health effects.

**MARIJUANA ADDICTION**

Substance-Related and Addictive Disorders, which includes Cannabis Use Disorder, occupy a major section of the *Diagnostic and Statistical Manual of Mental Disorders*, 5th edition (*DSM-5*).\textsuperscript{24} The *DSM-5* was based on extensive scientific studies performed in collaboration by many investigators over years, reviewed by multiple professionals, and subjected to controlled field trials for its validity and reliability. The *DSM-5* has a designated section and 11 criteria for Cannabis (marijuana) Use Disorder.\textsuperscript{24}

The basis for marijuana’s chemical addictive action is located in various portions of the brain,\textsuperscript{25} and its addiction potential is subserved in the mesolimbic system, similar to how other addicting drugs work.\textsuperscript{26} Cannabinoid receptors and endogenous cannabinoids have been isolated, and marijuana is believed to act at the cannabis receptors, similar to endogenous opioids.

Marijuana as a drug when smoked is subjectively claimed to produce euphoria and relaxation, release of tension, and outer world experiences; however, these are generally initial acute effects. Chronic use or large doses of smoked marijuana are more apt to result in negative effects, which are often harmful and unpleasant.\textsuperscript{27,28}

There may also be significant risk for exposure of marijuana for intentional use by teenagers\textsuperscript{29} and unintentional use by children.\textsuperscript{5} Marijuana is associated with other drug use.\textsuperscript{30} There are documented physical health problems, including cardiac, pulmonary, cancers, and mental effects.\textsuperscript{31} Of importance is that addictive or heavy use, not recreational use, drives legalization and its popularity.\textsuperscript{32-36} Daily or near-daily users “represent a minority of users yet are responsible for the majority of past-month use-days.”\textsuperscript{37}

**RELATIONSHIPS BETWEEN PERCEIVED RISK OF MARIJUANA AND HARMFUL EFFECTS**

There is a clear inverse relationship between the perception of risk and marijuana use, particularly among youth.\textsuperscript{29} Currently, reports indicate that the perceived risk by the public for marijuana use is low\textsuperscript{38} (a misrepresentation that may be perpetuated among users). Additionally, the popularity of legalizing marijuana—60\% of the public endorses it\textsuperscript{39} —and the low perceived risk of use of marijuana to health and the individual in society, and
even beneficial use, are contrary to data and expense.\textsuperscript{40} 

Historically, marijuana use often starts in youth,\textsuperscript{36} and youth may be exposed to misconceptions that marijuana is not addicting and is harmless. Further, references to “medical marijuana” may send the message that it is also beneficial. However, clinical studies suggest otherwise— that smoked marijuana is associated with poor social outcomes and employment, lower income, lower levels of life satisfaction, and relationship satisfaction.\textsuperscript{41,42}

**TOXIC PSYCHIATRIC AND MEDICAL EFFECTS OF MARIJUANA**

Marijuana impairs mental and physical coordination, alters perception of time and surroundings, distorts comprehension of information and cognition, and interferes with insight and judgment.\textsuperscript{6} These changes may be transient or persistent.\textsuperscript{13} Marijuana causes users to become “stoned,” a perceptual distortion of time, and can induce psychotic symptoms consisting of hallucinations, paranoia, and delusions.\textsuperscript{27} In patients with preexisting schizophrenia, it can worsen the course of illness,\textsuperscript{42} and in bipolar disease, it can precipitate a manic episode with or without preexisting bipolar disease.\textsuperscript{44} Marijuana use may increase the likelihood of violent behaviors, which can lead to self-destructive and criminal behaviors.\textsuperscript{45,46} Furthermore, marijuana can cause anxiety and depression in users,\textsuperscript{6} which might be brief panic reactions, but long-lasting psychiatric effects have been described.\textsuperscript{13,27,47} Marijuana impairs the capacity for users to properly operate machinery and vehicles, and under the influence of cannabis, high rates of traffic accidents and deaths have been reported.\textsuperscript{48}

Regular use of marijuana can lead to a reduced quality of life compared to non-users.\textsuperscript{49} In users with preexisting mental conditions, the decline in quality of life may be even more severe.\textsuperscript{5} Marijuana’s negative effects on attention, memory, and learning may persist for days, weeks, or months after the acute effects subside.\textsuperscript{50} Consequently, someone who smokes marijuana daily may be functioning at a reduced intellectual level on a chronic basis.\textsuperscript{42} Heavy marijuana use has been linked to “lower income, greater welfare dependence, unemployment, criminal behavior, and lower life satisfaction.”\textsuperscript{50}

In adolescents, the use of marijuana has been associated with various mental health conditions, causes higher dropout rates in schools, and may increase the likelihood of using other illicit substances as well as licit substances like alcohol and opiates.\textsuperscript{29}

**RELATIONSHIP BETWEEN STATE MEDICAL MARIJUANA LAWS AND CANNABIS USE DISORDERS**

States have passed laws to legalize marijuana for both medical and recreational use, which has evolved rapidly. In this context, a key question has been whether the legal changes are influencing the rates of marijuana use. In answer to this critical question, Hasin et al.\textsuperscript{51} compared changes for states with and without medical marijuana legalization across three surveys conducted in 1991-1992, 2001-2002, and 2012-2013. They found a main effect of medical marijuana laws being associated with differential increases in cannabis use in states passing those laws.\textsuperscript{51,52}

Thus, state medical marijuana laws appear to have contributed to increased prevalence of illicit cannabis use and cannabis use disorders (addictive disorders). State-specific policy changes may also have played a role. Importantly, cannabis-related health consequences associated with changes in state marijuana laws should receive consideration by health care professionals and the public.\textsuperscript{51,52}

It is essential that psychiatrists understand the effect of marijuana laws because of the potential adverse effect of cannabis on mental health. Individuals with mental illness are more likely to use marijuana, and both acute intoxication and chronic use can exacerbate and induce psychiatric symptoms.\textsuperscript{44} Also, early cannabis use has been associated with onset of psychosis and risk for suicidality, and cannabis use can interfere with the treatment of mental disorders.\textsuperscript{44} Understanding the potential effect of cannabis use on mental illness is advanced by careful population studies, such as the work by Hasin et al.,\textsuperscript{51} as well as fast advances in neuroscience.

**CONCLUSION**

“Medical marijuana” is a gray market, “quasi-legal” in some states, despite state “medical marijuana” laws being in direct conflict with US federal law. Generally, federal law trumps state law in other legal matters (Supremacy Clause of the
US Constitution; however, in the case of “medical marijuana,” federal law passively gives way to state law by not enforcing federal law where marijuana industry is compliant with state law.6 “Medical marijuana” is not FDA approved as are other medications, even though the FDA’s main job is to ensure the efficacy and safety of medicinal drugs sold in the US.3 So far, based on the objective medical data and legal requirements for medications, health policy for “medical marijuana” should be held to the same standards as other medications for efficacy and potential for toxic and detrimental health effects.

REFERENCES