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Marijuana and cannabinoid research: Current status and future potential.

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Abstract

Unlike any other illegal drug of abuse, efforts undertaken by pro-marijuana advocates to legalize marijuana have attempted to exploit alleged medicinal applications to gain legal status and public acceptance. In the process, the accepted legal channels for bringing drugs to market have become trampled and circumvented, and it has been extremely difficult for the professional and lay public to sort the "wheat from the chaff."

A historical perspective will review the efforts to legitimize marijuana to date, the status of research involving cannabinoid and related substances will be examined, the legal status of cannabis will be reviewed, and the marijuana legalization campaign will be scrutinized.

Historical perspective

Ancient uses of marijuana (*cannabis sativa*) are considered by marijuana advocates as evidence to support medical and recreational uses today. The historical uses of marijuana cited by Grinspoon (1) include such cultures as India, Asia, the Middle East, South Africa, and South America and are considered by the medical excuse marijuana movement as evidence of appropriate medical uses of the drug. The Chinese allegedly used marijuana to "quicken the mind, induce sleep, cure dysentery, stimulate appetite, relieve headaches, and cure venereal disease." One reference from 1860 states marijuana provided beneficial medical effects "without interfering with the actions of the internal organs." Such folk medicine applications of marijuana from the 1700s and 1800s are referenced by Grinspoon as evidence justifying modern medical applications. The field of medicine in those earlier years was fraught with potions and herbal concoctions. Many of those were absolutely useless, or conversely were harmful to unsuspecting subjects.

The movement to legalize marijuana has existed in various forms since the 1970s. Throughout that time, the medical excuse for marijuana has become a centerpiece for the marijuana legalization movement. Several states have been forced to deal with full marijuana legalization campaigns along with numerous legal and ballot initiatives making marijuana accessible for alleged medical applications.

This author has previously reviewed the literature concerning the medicinal use of marijuana and contends that the medical excuse marijuana movement creates a medical "Pandora's box" creating numerous regulatory, medical, scientific, and ethical challenges (2,3). One previous work (2) has additionally traced the organization and financing of the medical excuse movement to a core of marijuana legalization advocates. This movement is funded largely by billionaire currency magnate, George Soros. Most notably, the medical excuse movement is responsible for fostering a "medicine by popular vote" mentality and undermining medical regulatory agencies (4). Ballot initiatives and legislative actions which bypass the FDA processes for consumer protection jeopardize the public and unwitting patients.

In 1997 the White House Office of National Drug Control Policy commissioned the National Academy of Science, Institute of Medicine (IOM) to evaluate the utility of marijuana for medicinal applications (5). One conclusion of the study determined that the challenge for future research will be to find cannabinoids which enhance therapeutic benefits while minimizing side effects such as intoxication and dysphoria. The future for medicinal applications of cannabinoids and whether cannabinoids are equal or superior to existing medicines remains to be determined, but the IOM evaluation is particularly clear on the smoking of marijuana:

"If there is any future for marijuana as a medicine, it lies in its isolated components, the cannabinoids and their synthetic derivatives. Isolated cannabinoids will provide more reliable effects than crude plant mixtures. Therefore, the purpose of clinical trials of smoked marijuana would not be to develop marijuana as a licensed drug, but such trials could be a first step towards the development of rapid-onset, non-smoked cannabinoid delivery system."

In its attempt to advance marijuana, the marijuana lobby has moved in the opposite direction of the IOM study. The medical excuse contingent now focuses on the allegedly superior benefits of the therapeutic whole plant uses. Of course, this means that patients would be exposed to 66 cannabinoids and over 400 other substances that exist in crude herbal marijuana (6). There exists a notable lack of research in the literature on beneficial effects of this therapeutic "witches brew" of substances as compared to isolated cannabinoids. This whole-plant strategy is pivotal to the advocates' arguments that there exist some unique properties of the aggregate plant products, yet this has never been substantiated in the medical literature.

Effects of marijuana use

The negative side effect profile of marijuana far exceeds most of the other effective agents available for symptoms such as nausea and appetite stimulation. Such side effects also pose danger to those who use marijuana for intoxication as well. Chronic, daily doses of the drug would be necessary to treat many of the proposed medical conditions.

Mental, affective, and behavioral effects are the most easily recognized consequences of acute and chronic marijuana use.

Concentration, motor coordination, and memory (7-11) are all adversely impacted. In an examination of college students (12), daily use of marijuana was associated with cognitive impairment of "executive functions" such as learning of lists, perseveration, and attention. In certain medical applications such as terminal cancer patients, such impairment may be less of a concern than in the daily functioning of high school and college students.

Pathologic behavior such as psychosis is also associated with marijuana use (13-15). Not surprisingly, an upsurge in marijuana-induced psychosis has been discovered in England since the marijuana laws were relaxed. This has resulted in substantial political conflict as well as a serious reconsideration of the legal status to "class B" by the Home Secretary Charles Clarke (16). Solowij and coworkers reported that the ability to focus attention and filter out irrelevant information was progressively impaired with the number of years of use but was not related to the frequency of use (17). Solowij also determined in a separate report that even among ex-cannabis smokers, the inability to reject complex irrelevant information persisted despite a mean abstinence of two years from marijuana use (18).

Chronic marijuana use is associated with increased cerebrovascular resistance through changes mediated, in part, in blood vessels or in the brain parenchyma (19). These findings might provide a partial explanation for the cognitive deficits observed in a similar group of marijuana users. Pulsatility index, a measure of cerebrovascular resistance, and systolic velocity were significantly increased in the marijuana users vs. control subjects. These increases persisted in the heavy marijuana users after a month of monitored abstinence.

Positron scanning (20) of subjects whose mean use of marijuana was 17 times per week for the last 2 years found lower blood flow in a large region of the posterior cerebellum. Not only does this have implications on motor coordination and function but also cognition, timing, processing sensory information, and attention.

The ability to perform complex tasks, such as flying (21-22) is impaired even 24 hours after the acute intoxication phase. The association of marijuana use with trauma and intoxicated motor vehicle operation is also well established (23-28). Evaluations of the effect of marijuana on driving (29) have determined that the combination of blood alcohol concentrations (BAC) of 0.07 and marijuana at 100ug/kg gave effects similar to BAC alone of 0.09. Blood alcohol concentrations of 0.07 and marijuana levels of 200ug/kg demonstrated effects similar to a BAC alone of 0.14 when measuring reaction time, on-road performance, and vehicle following. A second, related study found that a BAC of .05 combined with moderate marijuana use caused a significant drop in the visual search frequency.

In young smokers, the consequences of acute cardiovascular effects may be minimal. On the other hand, Mittleman et al found that risk of a myocardial infarction (MI) within one hour of use is increased by 4.8 times compared to periods of non-use. This type of effect along with the tachycardia caused by marijuana would limit use in elderly individuals or those suffering cardiac disease (30).

Despite arguments from the marijuana advocates to the contrary, marijuana is a dependence-producing drug. This dependence and associated "addictive" behaviors have been well described in the marijuana literature (31-36). Marijuana dependence consists of both a physical dependence (tolerance and subsequent withdrawal) and a psychological dependence. Justinova et al (37)

characterizes marijuana as highly reinforcing with a pronounced abuse potential. This is likely due at least in part to the rapid uptake of the smoked drug and may also explain the relative lack of abuse seen with oral preparations such as dronabinol (Marinol).

Withdrawal from marijuana has been induced by blockade of the CB1 receptor by rimonabant in animals (38) and has been characterized in humans (39). Marijuana withdrawal in human patients is often subtle and may be fairly benign because of the long half life and slow elimination.

The gateway effect of marijuana along with tobacco and alcohol is also well established in research (40,41). The use of cocaine and heroin is virtually always preceded by marijuana. Kandel and co-workers have pioneered research in this area and continue to find clear evidence of a gateway phenomenon (42,43). Golub contends that the importance of marijuana as a gateway drug has actually increased in recent years (44).

Respiratory difficulties associated with marijuana use preclude the inhaled route of administration as a medicine. Smoking marijuana is associated with higher concentrations of tar, carbon monoxide, and carcinogens than are found in cigarette smoking (45). Marijuana adversely impairs some aspects of lung function and causes abnormalities in the respiratory cell lines from large airways to the alveoli (46-54). Marijuana smoke causes inflammatory changes in the airways of young people that are similar to the effects of tobacco (55). In addition to these cellular abnormalities and consequences, contaminants of marijuana smoke are known to include various pathogenic bacteria and fungi (56-58). Those with impaired immunity are at particular risk for the development of disease and infection when these substances are inhaled.

Exposure to marijuana during pregnancy (59-64) is associated with changes in size, weight, and neurologic abnormalities in the newborn. Additionally, hormonal function in both males and females is disrupted (65-69).

Substantial concern exists around what delayed and persistent effect marijuana may have on the unborn. Day and colleagues have identified a negative effect on intelligence parameters among 3 year olds when mothers used marijuana during the first and second trimesters of pregnancy (70). Dahl and coworkers have discovered sleep disruption among three year olds when exposed during pregnancy (71). Consistent with the reports of delayed performance, Fried (72) reported that children exposed in utero demonstrate increased behavioral problems, impaired language comprehension, and sustained attention and memory problems at age 4.

One of the earliest findings in marijuana research was the effect on various immune functions, which is evidenced by an inability to fight herpes infections and the discovery of a blunted response to therapy for genital warts during cannabis consumption (73,74). Evaluation of the effect of THC on NK- κ B has suggested a possible effect on the HIV genome (75).

Future directions

Useful delivery systems for isolated or synthetic cannabinoids could include nasal sprays, metered dose inhalers, transdermal patches, and suppositories. The problem with whole plant extracts, and certainly with smoking marijuana therapeutically, remains a relative "shotgun" effect of 66 cannabinoids and a plethora of other toxic substances.

As it relates to the potential for future medicinal applications, we suggest that there exists no compelling data to begin to suggest that plant marijuana for medicinal applications provides an advantage over individual cannabinoids or other existing medicine. For the most part, positive or negative physiological effects of cannabinoids are the result of the stimulation of cannabinoid receptors CB1 (76) and CB2 (77). CB1 receptors are most prevalent in the hippocampus, amygdala, cortex, basal ganglia, and cerebellum. Thus, they have association with effects on memory, emotion, cognition, and movement. They are also present in the periaqueductal gray matter of the dorsal horn of the spinal cord responsible for pain perception (78). CB2 receptors are mostly present in peripheral tissue. CB1 receptors are present in the brainstem which may explain the lack of respiratory suppression seen with narcotic analgesics. Refining and isolating the natural cannabinoids, synthesizing substances which target specific CB1 or CB2 receptor groups, or selective receptor inhibition, appear to represent the future for cannabinoid research.

The cannabis plant is relatively nonselective in its stimulation of cannabinoid receptors, and thus acute use results in a variety of side effects beyond the targeted therapeutic effects, limiting potential uses (78). Yet, it is likely the CB1 receptors that mediate marijuana dependence (38).

The identification of the cannabinoid receptors has opened the door to both the development of specific agonists for use on nausea, pain, and antagonists such as the new agent Rimonabant. There still exists potential for the development of cannabinoids which have enhanced therapeutic benefits with little intoxication or toxicity such as Delta-8-THC.

The most salient response to the marijuana lobby exists in the Food and Drug Administration processes which have been developed to protect the public and should continue to do so. Keeping to their mandate, proceeding to assure both efficacy and safety is paramount without manipulation or lobbying pressure from the legalization and medical excuse advocates. As a practicing physician, this author contends that we should demand the best quality and consistency of medicine for our patients. One must then realize that with marijuana the patient is exposed to a veritable "witches brew" of substances, most of which have never been examined for harmful effects. The medical literature lacks any clear documentation of a significant body of patients who have failed all other therapies for whom marijuana actually provides the only relief.

Ballot initiatives or legislative actions which support either medical excuse marijuana or outright legalization efforts create a huge conundrum for law enforcement and medical regulatory agencies. If physicians choose to recommend marijuana for patients, they should be aware that a minimum standard of care exists (79) for care providers. Informed consent should include the myriad of medical side effects and consequences of use. Failure to inform is actionable to the same degree as lack of informed consent for other dangerous medications or procedures.

Finally, the motivation of the medical excuse marijuana movement is suspect. While it masquerades as altruism, it is a Trojan Horse which the marijuana advocates themselves have identified as a "camel's nose under the tent" to gain acceptance of marijuana. The marijuana lobby has effectively influenced the public and exploited compassion and sympathy for suffering patients to advance the cause of legal marijuana. By framing the issue so simplistically, the pro-marijuana lobby has set the stage for a cultural and social shift to ultimately achieve the legalization of marijuana and, for that matter, other illicit drugs.

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