

Supporting Research into the Therapeutic Role of Marijuana

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This paper, written by Tia Taylor, MPH, was developed for the Health and Public Policy Committee of the American College of Physicians: J. Fred Ralston, MD, FACP, Chair; Molly Cooke, MD, FACP, Vice Chair; Andrew A. Chang, MA, Charles Cutler, MD, FACP; MA, David A. Fleming, MD, FACP; Brian P. Freeman, MD, FACP; Robert Gluckman, MD, FACP; Mark Liebow, MD, FACP; Kenneth Musana, MB, ChB; Robert McLean, MD, FACP; Mark Purtle, MD, FACP; P. Preston Reynolds; and Kathleen Weaver, MD, FACP. It was approved by the Board of Regents in January 2008.

Executive Summary

Marijuana has been smoked for its medicinal properties for centuries. Preclinical, clinical, and anecdotal reports suggest numerous potential medical uses for marijuana. Although the indications for some conditions (e.g., HIV wasting and chemotherapy-induced nausea and vomiting) have been well documented, less information is available about other potential medical uses. Additional research is needed to clarify marijuana's therapeutic properties and determine standard and optimal doses and routes of delivery. Unfortunately, research expansion has been hindered by a complicated federal approval process, limited availability of research-grade marijuana, and the debate over legalization. Marijuana's categorization as a Schedule I controlled substance raises significant concerns for researchers, physicians, and patients. As such, the College's policy positions on marijuana as medicine are as follows:

Position 1: ACP supports programs and funding for rigorous scientific evaluation of the potential therapeutic benefits of medical marijuana and the publication of such findings.

Position 1a: ACP supports increased research for conditions where the efficacy of marijuana has been established to determine optimal dosage and route of delivery.

Position 1b: Medical marijuana research should not only focus on determining drug efficacy and safety but also on determining efficacy in comparison with other available treatments.

Position 2: ACP encourages the use of nonsmoked forms of THC that have proven therapeutic value.

Position 3: ACP supports the current process for obtaining federal research-grade cannabis.

Position 4: ACP urges review of marijuana's status as a schedule I controlled substance and its reclassification into a more appropriate schedule, given the scientific evidence regarding marijuana's safety and efficacy in some clinical conditions.

Position 5: ACP strongly supports exemption from federal criminal prosecution; civil liability; or professional sanctioning, such as loss of licensure or credentialing, for physicians who prescribe or dispense medical marijuana in accordance with state law. Similarly, ACP strongly urges protection from criminal or civil penalties for patients who use medical marijuana as permitted under state laws.

Background

The marijuana plant, cannabis, contains more than 60 chemical compounds, known as cannabinoids. The main psychoactive element in marijuana is delta-9-tetrahydrocannabinol (THC). Cannabidiol (CBD) is the second most abundant cannabinoid, but it has no psychoactive effects. The concentration of THC and other cannabinoids in marijuana is highly variable, depending on growing condition, plant genetics, and processing after harvest (1). This variability in composition has hindered research on and evaluation of the drug's medical value.

Marijuana has been smoked for its medicinal properties for centuries. It was in the U.S. Pharmacopoeia until 1942 when it was removed because federal legislation made the drug illegal (2). The Controlled Substance Act of 1970 placed marijuana in the Schedule I category along with other substances deemed to have no medicinal value and high potential for abuse. Still, the overwhelming number of anecdotal reports on the therapeutic properties of marijuana sparks interest from scientists, health care providers, and patients. Over the past 20 years, researchers have discovered cannabinoid receptors: CB1, which mediates the central nervous system (CNS), and CB2, which occurs outside the CNS and is believed to have anti-inflammatory and immunosuppressive activity (3, 4). These scientific developments have revealed much information supporting expansion of research into the potential therapeutic properties of marijuana and its cannabinoids.

In 1997, the White House Office of National Drug Control Policy asked the Institute of Medicine (IOM) to review scientific evidence and assess the risks and benefits of marijuana. The IOM concluded that scientific developments indicate marijuana and its cannabinoids have therapeutic properties that could potentially treat many illnesses and conditions. The IOM recommended that cannabis research should focus on the development of rapid-onset, reliable, and safe delivery systems (5). Since the IOM report, the body of research on cannabinoids for symptom management has grown slightly.

Potential Medical Uses of Marijuana

Appetite Stimulation/Antiemetic

The research supporting THC as an effective appetite stimulant and antiemetic is abundant. In 1986, the U.S. Food and Drug Administration approved Marinol[®] (dronabinol), an oral synthetic form of THC, to treat severe weight loss associated with AIDS (HIV/AIDS wasting) and nausea and vomiting associated with chemotherapy for patients who fail to respond to other antiemetics. Clinical trials have demonstrated that both oral and smoked marijuana stimulate appetite, increase caloric intake, and result in weight gain among patients experiencing HIV wasting (6–9). Studies of chemotherapy patients with nausea and vomiting found THC to be equivalent or superior to other antiemetics (including prochlorperazine or metoclopramide) for symptom reduction (10). Research has also found that administration of THC along with another antiemetic was more effective than either drug alone, suggesting opportunities for combined therapy. The IOM concluded that cannabinoids are “modest” antiemetics but may be effective for

those who respond poorly to other available antiemetics. THC and other cannabinoids may offer relief not found in other drugs (11).

Glaucoma

High intraocular pressure (IOP) is a known risk factor for glaucoma. Cannabinoids have been shown to have neuroprotective properties and to reduce IOP, pupil restriction, and conjunctival hyperemia (12–14). Smoked or eaten marijuana and oral THC can reduce IOP by approximately 25% in people with normal IOP who have visual field changes, with similar results exhibited in healthy adults and glaucoma patients. However, the effects of cannabinoids on IOP are short-lived, and high doses are required to produce any effects at all. There is concern that long-term use of marijuana could reduce blood flow to the optic nerve because of its systemic hypotensive effects and its potential for interaction with other antiglaucoma drugs (15). In addition, the cardiovascular and psychoactive effects of smoked marijuana contraindicate its use in glaucoma patients, many of whom are elderly and have comorbidities. This led to the development and testing of a topical THC, but its effect on IOP was insignificant. As a result, the IOM and American Academy of Ophthalmology concluded that no scientific evidence has demonstrated increased benefits or diminished risks of marijuana use to treat glaucoma compared with the wide variety of pharmaceutical agents currently available (16, 17).

Neurological and Movement Disorders

Anecdotal, survey, and clinical trial data suggest that smoked marijuana and oral THC provide relief of spasticity, pain, and tremor in some patients with multiple sclerosis (MS), spinal cord injuries, or other trauma (18, 19). A recent study of patients with HIV-associated sensory neuropathy (HIV–SN) found that those who smoked marijuana 3 times a day reported a decrease of 34% in HIV–SN, compared with 17% in the placebo group. However, the psychoactive effects of THC impaired posture and balance among subjects (20). CBD has some anti-inflammatory properties and inhibits smooth muscle contractions, thus making it a potentially powerful anticonvulsant that does not contain the psychoactive effects of THC. CBD has been indicated as a treatment for several types of seizures and epilepsy, although human research is scant. Preclinical trials revealed that the anticonvulsant properties of cannabinoids differ widely by dose and between species. CBD has been shown to induce seizures in some species and to be strongly anticonvulsant in others (21).

Analgesic

Current research on the role of various forms of marijuana as an analgesic is promising. Oral doses of THC resulted in pain reductions similar to that from codeine among cancer patients (22). A randomized, double-blind trial of patients with rheumatoid arthritis found that Sativex[®], an oromucosal THC spray, significantly reduced pain on movement and at rest and improved quality of sleep (23). While studies indicate that THC has analgesic properties, there is a very narrow therapeutic window between doses that produce useful analgesia and those that produce unacceptable adverse effects. A recent study found that subjects who smoked 4% THC cigarettes reported reduced pain sensations after 45 minutes. On the other hand, subjects who smoked 8%

THC cigarettes reported an increased sensitivity to pain after 45 minutes (24). In another study, smoked marijuana increased sensitivity to electric shock among normal patients. The biphasic action of THC, stimulation followed by sedation, increases then decreases pain. These properties support the need for research to identify the specific kinds of pain that may be relieved by marijuana and the development of a synthetic cannabinoid with few actions other than analgesia.

Adverse Effects

Acutely, smoked marijuana increases heart rate and may decrease blood pressure on standing; however, some patients find the drug's psychoactive effects more disturbing. Undesired effects include impairment of short-term memory, attention, motor skills, reaction times, and the organization and integration of complex information (25). These effects are generally more severe for oral THC than for smoked marijuana (26).

The chronic effects of smoked marijuana are of much greater concern, as its gas and tar phases contain many of the same compounds as tobacco smoke. Chronic use of smoked marijuana is associated with increased risk of cancer, lung damage, bacterial pneumonia, and poor pregnancy outcomes. Chronic marijuana use has also been linked to the development of tolerance to some effects and the appearance of withdrawal symptoms (restlessness, irritability, mild agitation, insomnia, sleep disturbances, nausea, cramping) with the onset of abstinence. However, these withdrawal symptoms are mild compared with those experienced with opiates or benzodiazepines (27). Moreover, THC, while quite potent in comparison with other psychoactive drugs, has remarkably low lethal toxicity. This led the IOM to conclude that "except for harms associated with smoking, adverse effects of marijuana use are within the range of effects tolerated for other medications (28)."

Positions

As with any potential therapeutic drug, there are many factors that should be considered in evaluating its medicinal value. These include the drug's side effects, methods of administration, and availability and comparability of alternatives. However, marijuana's categorization as a Schedule I controlled substance creates additional concerns for researchers, physicians, and patients. As such, the College adopts the following positions on medical marijuana:

Position 1: ACP supports programs and funding for rigorous scientific evaluation of the potential therapeutic benefits of medical marijuana and the publication of such findings.

Preclinical and clinical research and anecdotal reports suggest numerous potential medical uses for marijuana. Unfortunately, the debate surrounding marijuana's legalization for general use has obscured scientific findings. Current available data suggest numerous indications for cannabinoids, especially antiemesis, appetite stimulation, and pain relief. For patients with AIDS or those undergoing chemotherapy, who suffer severe pain, nausea, and appetite loss, cannabinoid drugs may provide symptom relief not found in any other medication. The data supporting cannabinoid use for the relief of muscle spasticity and movement disorders is promising, but further research is needed to clarify the roles of cannabinoids in treating these

conditions. For epilepsy and glaucoma, the data is much less convincing, and many of the reports supporting marijuana use for these conditions remain anecdotal. In addition, while the therapeutic effects of THC are well established, less is known about the effects and potential indications of other cannabinoids. Additional research is needed to clarify both the therapeutic properties of cannabinoids and their effects on symptom management. The IOM recommended the following guidelines for clinical trials of marijuana for medical use:

- Clinical trials should involve only short-term use (less than 6 months);
- Clinical trials should be conducted in patients for whom there is a reasonable expectation of efficacy;
- Clinical trials should be approved by institutional review boards; and
- Clinical trials should collect efficacy data (29).

Position 1a: ACP supports increased research for conditions where the efficacy of marijuana has been established to determine optimal dosage and route of delivery.

To date, much of the research into the medicinal properties of marijuana has been on oral and smoked forms of THC. The pharmacokinetics of oral and smoked THC differ greatly and therefore have varying implications. The oral, synthetic THC has low and variable bioavailability (30). Oral THC is slow in onset of action but produces more pronounced, and often unfavorable, psychoactive effects that last much longer than those experienced with smoking (31). On the other hand, smoked THC is quickly absorbed into the blood and effects are experienced immediately. Studies have found that patients prefer the immediate effect on symptoms that occurs after smoking marijuana (32, 33). Therefore, there may be some patient populations (e.g., cancer patients who experience nausea and vomiting during chemotherapy) for whom the inhalation route might offer advantages over the currently available capsule formulation (34). Also, many cancer and HIV/AIDS patients may prefer smoking over swallowing a pill.

However, examining the effects of smoked marijuana can be difficult because the absorption and efficacy of THC on symptom relief is dependent on subject familiarity with smoking and inhaling. Experienced smokers are more competent at self-titrating to get the desired results. Thus, smoking behavior is not easily quantified or replicated (35). Other problems with smoked marijuana include difficulty in attempting to match placebo control against smoked marijuana (especially for those with previous marijuana experience) and the no-smoking policy of hospitals and public facilities. Overall, the clinical utility of smoked marijuana is limited by its short duration of action and accompanying side effects. Although the long-term effects of smoked marijuana may not be relevant for patients with terminal illnesses or debilitating symptoms, the residual effects of smoked marijuana are prohibitive for long-term medical use. The IOM concluded that clinical trials of smoked marijuana should be the first step toward the possible development of nonsmoked, rapid-onset cannabinoid delivery systems (36). Additional research is also needed to determine optimal dosage of cannabinoid drugs for symptom management.

Current data has shown that for some indications, particularly pain relief, there is a small margin between clinical benefit and unacceptable adverse events.

Position 1b: Medical marijuana research should not only focus on determining drug efficacy and safety but also on determining efficacy in comparison with other available treatments.

Most of the conditions for which efficacy of cannabinoid drugs has been determined already have well-established and effective treatments. However, little is known about how cannabinoids perform in comparison with these other treatments. Because of the availability of an oral form of THC, several studies have compared the effectiveness of both smoked THC and Marinol® to other antiemetic drugs (mainly prochlorperazine). Although the results from these studies varied, they all found that THC was as effective as prochlorperazine at controlling nausea and vomiting. Several studies also found that the combination of THC and other antiemetics was more effective than either drug alone. Research suggests that cannabinoids may have synergistic effects that may indicate its use as an adjunctive therapy to both antiemetics for nausea and vomiting and opioids for pain relief. Further research is needed to compare cannabinoids' efficacy and safety with current treatments and to examine their potential role in combination therapy for some conditions.

Position 2: ACP encourages the use of nonsmoked forms of THC that have proven therapeutic value.

The negative effects associated with long-term smoked marijuana use necessitate consideration of varying modes of cannabinoid delivery. Only 2 cannabinoid drugs are currently licensed for sale in the U.S. (dronabinol [Marinol®] and nabilone [Cesamet®]), and both are only available in oral form. While useful for some, these drugs have serious limitations. The oral route of administration hampers the effectiveness of THC because of slow absorption. In addition, swallowing a pill may not be feasible for patients with severe nausea and vomiting, for whom oral THC is indicated. To overcome the limitations of oral administration, researchers have focused on developing other nonsmoked, rapid-onset formulations.

Sativex®, an oromucosal spray of natural cannabis, was approved in June 2006 for prescription use in Canada to treat neuropathic pain in patients with MS. The manufacturer, GW Pharmaceuticals, received FDA approval to begin a U.S. clinical trial of Sativex for cancer patients in 2007.

The development of a vapor route for THC delivery offers promise for the future of medical marijuana research. A recent study found that THC administered through the Volcano® vaporizer resulted in higher plasma THC levels than smoked marijuana at both 30 and 60 minutes after administration. It also found that exhaled carbon monoxide increased very little after vapor compared with smoking (37). Those findings, along with patient preference for the vapor method, indicate opportunities for future clinical trials. Vaporization of THC offers the rapid onset of symptom relief without the negative effects from smoking. It allows patients to self-regulate their dosage immediately by ceasing inhalation when or if psychoactive effects become

unpleasant. Scientists are also developing a pulmonary dronabinol to be delivered with a pressurized metered-dosed inhaler. Preliminary studies show rapid absorption, but FDA approval remains distant.

Position 3: ACP supports the current process for obtaining federal research-grade medical marijuana.

Some scientists and physicians believe the procedures for obtaining marijuana for research and publishing research findings are particularly arduous because of the debate surrounding its legalization for general use (38). Marijuana’s designation as a Schedule I controlled substance does pose a unique challenge for researchers. The federal government is the only legal producer of marijuana for medical research; scientists must therefore apply for both an Investigational New Drug Application (IND) from the FDA and a Schedule I license from the Drug Enforcement Administration (DEA) to receive and dispense marijuana through a designated pharmacy. The marijuana is provided by the National Institute on Drug Abuse (NIDA) in the National Institutes of Health (NIH). Through the Drug Supply Program, NIDA arranges for marijuana to be grown and processed through contracts with the University of Mississippi and the Research Triangle Institute. The University grows, harvests, and dries marijuana, and the Institute processes it into cigarettes. Researchers can obtain marijuana free of charge from NIDA through an NIH-approved grant to investigate marijuana or through a separate protocol review.

Because of the high biovariability in cannabis plants, obtaining research-grade cannabis is critical to conducting well-designed clinical trials on the safety and efficacy of marijuana and its cannabinoids. In addition, because of the drug’s widespread general use and high potential for abuse, it is imperative that the federal process is followed for obtaining research-grade marijuana and conducting clinical trials.

Position 4: ACP urges review of marijuana’s status as a Schedule I controlled substance and its reclassification into a more appropriate schedule, given the scientific evidence regarding marijuana’s safety and efficacy in some clinical conditions.

Currently, marijuana is a Schedule I controlled substance, meaning it has no medicinal value and high potential for abuse. An evaluation by several Department of Health and Human Services agencies, including the FDA and NIDA, concluded that no sound scientific studies supported medical use of marijuana for treatment in the United States (39). This conflicts with a review by the IOM, which declared that “for patients such as those with AIDS or who are undergoing chemotherapy and who suffer simultaneously from severe pain, scientific studies support medical use of marijuana for treatment in the United States.” The IOM also concluded that compared with other licit and illicit drugs, including alcohol, tobacco, and cocaine, “dependence among marijuana users is relatively rare and dependence appears to be less severe than dependence on other drugs.” (40) A clear discord exists between the scientific community and federal legal and regulatory agencies over the medicinal value of marijuana, which impedes the expansion of research.

The concern that marijuana is a “gateway” drug also hinders opportunities to evaluate its potential therapeutic benefits. However, the IOM concluded that marijuana is a gateway drug only in the sense that its use normally precedes, rather than follows, initiation of other illicit drugs. Marijuana has not been proven to be the cause or even the most serious predictor of serious drug abuse. It is also important to note that the data on marijuana’s role in illicit drug use progression only pertains to its nonmedical use (41).

Dronabinol, oral THC, is classified as a Schedule III substance. Recently, the DEA proposed a rule that would allow for classification of both synthetic and natural (derived from the cannabis plant) dronabinol products in Schedule III. Opiates are highly addictive yet medically effective substances and are classified as Schedule II substances. There is no evidence to suggest that medical use of opiates has increased perception that their illicit use is safe or acceptable (42). Given marijuana’s proven efficacy at treating certain symptoms and its relatively low toxicity, reclassification would reduce barriers to research and increase availability of cannabinoid drugs to patients who have failed to respond to other treatments.

Position 5: ACP strongly supports exemption from federal criminal prosecution; civil liability; or professional sanctioning, such as loss of licensure or credentialing, for physicians who prescribe or dispense medical marijuana in accordance with state law. Similarly, ACP strongly urges protection from criminal or civil penalties for patients who use medical marijuana as permitted under state laws.

Reclassification of marijuana into a more appropriate schedule would remove the legal stresses that can affect the physician–patient relationship. Although marijuana is a Schedule I drug, 12 states currently have legislation permitting its use for medicinal purposes. Similar legislation is pending in New York and support has been shown for legislation in Minnesota and New Hampshire. The movement among states to permit the use of marijuana for certain conditions was spearheaded by California's Proposition 215, which received the support of 56% of state voters in 1996. This led to the establishment of a \$3 million state-funded Center for Medicinal Cannabis Research (CMCR) at the University of California’s San Diego and San Francisco campuses. CMCR receives the marijuana for its research from NIDA.

Despite these state laws and initiatives, possession of marijuana is a punishable federal offense. In 2005, the Supreme Court ruled that state laws confer no immunity from prosecution under federal law, which does not include a medical exemption to the prohibition on marijuana possession. This creates additional concerns for researchers, physicians, and patients. Physicians must be selective in their wording (when discussing the substance) so as not to appear that they are aiding or abetting patients in obtaining cannabis. In addition to the legalities, the lack of availability and standards on dose and route of delivery present medical concerns. Physicians cannot supervise and have very little control over their patient’s behavior. Also, the quality of the drug is usually undeterminable.

Conclusion

Evidence not only supports the use of medical marijuana in certain conditions but also suggests numerous indications for cannabinoids. Additional research is needed to further clarify the therapeutic value of cannabinoids and determine optimal routes of administration. The science on medical marijuana should not be obscured or hindered by the debate surrounding the legalization of marijuana for general use.

Notes

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