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**SUPPORTING RESEARCH
INTO THE
THERAPEUTIC ROLE OF
MARIJUANA**

American College of Physicians
A Position Paper
2008

SUPPORTING RESEARCH INTO THE THERAPEUTIC ROLE OF MARIJUANA

A Position Paper of the
American College of Physicians

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. Also included with this paper is an addendum written by Tia Taylor, MPH, for the Health and Public Policy Committee; the addendum was approved by the Board of Regents in July 2008.

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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 (see Addendum): ACP urges an evidence-based review of marijuana's status as a Schedule I controlled substance to determine whether it should be reclassified to a different schedule. This review should consider the scientific findings regarding marijuana's safety and efficacy in some clinical conditions as well as evidence on the health risks associated with marijuana consumption, particularly in its crude smoked form.

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 chemo-therapy 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 an evidence-based review of marijuana's status as a Schedule I controlled substance to determine whether it should be reclassified to a different schedule. This review should consider the scientific findings regarding marijuana's safety and efficacy in some clinical conditions as well as evidence on the health risks associated with marijuana consumption, particularly in its crude smoked form.†

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.

†In response to questions about the intent of original Position 4, adopted by the ACP Board of Regents in January 2008, the Board of Regents approved a revised position 4 in July 2008. The original position 4 read as follows: "ACP urges review of marijuana status as a Schedule I controlled substance and reclassification into a more appropriate schedule, given the scientific evidence regarding marijuana's safety and efficacy in some clinical conditions." All references to ACP policy should use *only the revised position 4* as stated above. A more detailed explanation can be found in the addendum to this paper.

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.

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SUPPORTING RESEARCH INTO THE THERAPEUTIC ROLE OF MARIJUANA

An Addendum by the Health and Public Policy Committee

**A Position Paper of the
American College of Physicians**

Since the release of the *Supporting Research into the Therapeutic Role of Marijuana* position paper in February 2008, the American College of Physicians (ACP) has received responses from many organizations and individuals. ACP appreciates the thorough comments that have been provided to us from patients, physicians, and acknowledged experts in the field of drug abuse prevention and treatment. We have heard from many individuals who expressed strong views, both positive and negative, about the therapeutic role of marijuana. We also heard from individuals who suffered great personal losses from drug abuse by family members. We are appreciative of everyone who shared their perspectives.

The quantity and quality of the comments received by ACP suggest that this paper is accomplishing its principal goal—which is to initiate a renewed discussion, based on scientific evidence, of whether cannabinoids have a potential therapeutic value in the treatment of certain chronic medical conditions, and if so, whether federal policies relating to research and prescribing of cannabinoids need to be revisited to better serve the needs of patients who might benefit.

ACP's Health and Public Policy Committee (HPPC), on whose behalf the paper was commissioned, has carefully considered each of the comments received. **It has concluded that the recommendations made in the original paper are sound and supported by evidence, and should continue to be the basis of the College's recommendations, with one revision to address misunderstanding about the College's position on reclassification.** Acknowledging that some experts have differing views on the evidence, the HPPC decided that the College should provide additional explanation to address the most compelling issues that were raised about its recommendations. This addendum provides such explanation.

1. Legalization of Marijuana

Some commenters expressed concern that the College's positions could lead to legalization of marijuana for nonmedical purposes; others expressed support for such legalization. **ACP has taken no position on increasing, reducing, or eliminating existing state and federal prohibitions and restrictions on use of marijuana for general use, and any representation of the College's views to suggest otherwise is inaccurate.**

The objective of the paper is to review the science and make evidence-based recommendations for changes in public policy to support increased *research* into the therapeutic properties of marijuana and cannabinoids. The paper is not intended to address the issue of legalizing marijuana for medical or general use. Some interest groups on either side of the marijuana legalization debate, and some press accounts of the College's positions, may have erroneously interpreted or represented ACP's views to support a broader policy advocacy agenda relating to legalization of marijuana for medical or general use.

ACP believes that the scientific evidence suggesting that there may be therapeutic value in marijuana or cannabinoids should not be overshadowed by the controversy surrounding legalization of marijuana for general use. Our paper recognizes the issues surrounding the marijuana legalization debate, including marijuana dependence and marijuana as a gateway drug. The paper cites evidence that marijuana dependence is generally rare and less severe than for other controlled substances (1). Subsequently, the HPPC reviewed studies submitted by some commenters that suggest that long-term smoked marijuana use may be associated with increased incidences of mental illness; this merits further research (2).

The paper readily acknowledges that there is evidence that general marijuana use for nonmedical purposes can pose substantial health risks to users, and that such risks are relevant to a broader discussion of legalization or decriminalization of marijuana use. We acknowledge concerns that marijuana may serve as a gateway drug. We believe, however, that such concerns, although legitimate and relevant to any decision on legalization, decriminalization, or reclassification pursuant to the Controlled Substance Act, should not preclude research to identify potential therapeutic value and leading to legitimate medical use of any controlled substance, consistent with other controlled substances presently in use for legitimate medical purposes..

Drawing on the experience with opiates as medicine, the Institute of Medicine (IOM) stated that:

"No evidence suggests that the use of opiates or cocaine for medical purposes has increased the perception that their illicit use is safe or acceptable. Clearly, there are risks that patients will abuse marijuana. . .and some likelihood of diversion of marijuana from legitimate medical channels into the illicit market. But those risks do not differentiate marijuana from many accepted medications that are abused by some patients or diverted from medical channels for nonmedical use (3)."

ACP maintains that the issues of marijuana dependence and the role it might play in leading to other illicit drug use are beyond the issues generally considered for medical uses of drugs and therefore should not be determining factors in evaluating the therapeutic potential of marijuana or cannabinoids.

2. Marijuana's Schedule in the Controlled Substance Act

Some commenters have stated incorrectly that ACP has recommended rescheduling marijuana from Schedule I to Schedule II of the Controlled Substance Act.

Instead, ACP believes that the evidence for the therapeutic value of cannabinoids for some patients is sufficiently strong to merit a *review* of marijuana's classification as a Schedule I controlled substance; any change in its classification would occur only if the evidence after such review was found to be sufficient to support such a change. Position 4, as originally stated in ACP's paper:

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

Because this statement has been misinterpreted as call for reclassification of marijuana from a Schedule I controlled substance to Schedule II, rather than as a call for review of the evidence, the HPPC has added the following clarifying language to Position 4:

ACP urges an evidence-based review of marijuana's status as a Schedule I controlled substance to determine whether it should be reclassified to a different schedule. This review should consider the scientific findings regarding marijuana's safety and efficacy in some clinical conditions as well as evidence on the health risks associated with marijuana consumption, particularly in its crude smoked form.

Schedule I substances, which include LSD and heroin, are those that have been determined to have no medicinal value and high potential for abuse (4). A review of the scientific evidence supports the therapeutic efficacy of marijuana and cannabinoids for certain conditions, such as HIV wasting and chemotherapy-induced nausea and vomiting (5–8). Cannabinoids have also been suggested to provide potential therapeutic benefit for other chronic conditions, but research evidence to support these claims is limited at this time.

Based on the evidence, the HPPC reaffirms ACP's view that the federal government should review the scientific evidence to determine whether marijuana and cannabinoids should be reclassified to a different schedule. Medications with abuse potential are placed in Schedule II of the Controlled Substances Act, which confirms evidence for therapeutic benefit but brings them under stricter control, including quotas on the amount that can be legally manufactured. Said scheduling also signals to physicians that a drug has abuse potential and that they should closely monitor its use by patients who could be at risk for drug abuse. Schedule II drugs 1) have high potential for abuse; 2) have accepted medical use for treatment in the United States or accepted medical use with severe restrictions; and 3) may lead to severe psychological or physical dependence if abused. Examples of Schedule II substances include morphine, cocaine, phencyclidine (PCP), methadone, and methamphetamine (9).

Marijuana's current scheduling and the federal process for obtaining research-grade marijuana poses unique challenges for researchers. Currently, the National Institute on Drug Abuse (NIDA) is the only legal producer and distributor of marijuana and cannabinoids that can be used for federally approved research. In addition to applying for a DEA license and FDA approval, investigators who wish to study marijuana must also submit their protocols to NIDA, a review process that exists for no other drug. Although the FDA review process has a 30-day deadline, the NIDA Public Health Service review has no deadlines and no formal appeals process. This extra process has been imposed on medical marijuana research despite federal law requiring adequate competition in the production of pharmaceuticals, including Schedule I drugs (10). DEA regulations specify at 21 C.F.R. § 1301.33 (b), "In order to provide adequate competition, the Administrator shall not be required to limit the number of manufacturers in any basic class to a number less than that consistent with maintenance of effective controls against diversion solely because a smaller number is capable of producing an adequate and uninterrupted supply (11)." It is for this reason that researchers have requested that the DEA and NIDA allow privately funded, government-approved, research-grade marijuana production facilities. In February 2007, DEA administrative-law Judge Mary Allen Bittner recommended that the DEA and NIDA approve such a facility proposed by Professor Lyle Craker, Ph.D., director of the Medicinal Plant Program at the University of Massachusetts-Amherst Department of Plant,

Soil and Insect Sciences. "NIDA's system for evaluating requests for marijuana for research has resulted in some researchers who hold DEA registrations ...being unable to conduct their research because NIDA has refused to provide them with marijuana," Bittner said. Judge Bittner also ruled that there is an "inadequate" supply of marijuana available for research purposes (12). The DEA has no deadline on whether to accept Bittner's nonbinding ruling.

Review of marijuana's scheduling is not a new concept. In the 1980s, the Drug Enforcement Agency (DEA) held extensive hearings on the transfer of marijuana to Schedule II. In 1988, DEA administrative-law Judge Francis L. Young recommended that the DEA Administrator, "conclude that the marijuana plant considered as a whole has a currently accepted medical use in treatment in the United States, that there is no lack of accepted safety for use of it under medical supervision and that it may lawfully be transferred from Schedule I to Schedule II." (13) The DEA overruled the judge's order, and in 1992 issued a final rejection of all requests for reclassification (14). Since then, other petitions for rescheduling marijuana have also been denied (15). Considering the evidence available today about the potential therapeutic benefits and risks associated with marijuana and its cannabinoids, ACP believes that it is time to review the evidence to determine whether reclassification is appropriate.

3. Protection for Physicians and Patients due to Inconsistency in Federal and State Laws

Reclassification of marijuana from a Schedule I to a Schedule II controlled substance, should this occur based on a review of the evidence, would reduce the conflict that now occurs between federal laws on controlled substances and state laws designed to allow physicians to prescribe marijuana and its cannabinoids for therapeutic purposes consistent with the science. If an evidence-based review of the science on marijuana and its cannabinoids results in a determination that reclassification is appropriate, the substance should be rescheduled and regulated accordingly.

In the interim, marijuana's Schedule I status poses legal concerns for physicians and patients where state and federal controlled-substances laws are inconsistent. Medical marijuana use is permitted by law in Alaska, California, Colorado, Hawaii, Maine, Montana, Nevada, New Mexico, Oregon, Rhode Island, Vermont, and Washington. In addition, Maryland law allows a partial defense of medical necessity for patients who require the use of marijuana. Despite these state laws, possession of marijuana is a punishable federal offense. A ruling by the Ninth U.S. Circuit Court of Appeals reaffirmed, and the Supreme Court let stand, the right of physicians and patients to discuss the therapeutic potential of marijuana. However, 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 (16). In addition, patients who follow the advice of their physicians risk up to one year in federal prison for possession of marijuana and up to five years in federal prison for growing a marijuana plant; federal law does not make a distinction between medicinal and recreational use of marijuana.

The HPPC is concerned that the conflicts between federal and state laws put physicians and patients in an untenable situation of being at risk for federal prosecution for acting within the authority of state laws on the distribution and use of marijuana for purely therapeutic purposes in accordance with the scientific evidence. ACP's recommendation would not exempt physicians from federal or state laws or state disciplinary actions governing the misuse or abuse of prescriptive authority or drugs or patients from the misuse or abuse of prescribed medications.

The HPPC is also concerned that the conflicts between federal and state laws on the use of marijuana for therapeutic purposes can undermine the federal regulatory structure for approval of drugs for therapeutic purposes based on an assessment of safety and effectiveness. Rather than having such issues resolved by state ballot initiatives or state legislation, HPPC believes that it is the responsibility of federal regulatory agencies to take the steps necessary to conduct an evidence-based evaluation of the safety and effectiveness of marijuana and its cannabinoids for therapeutic purposes; to propose changes in its classification if appropriate based on the evidence; and then, if necessary, ask Congress to modify federal drug enforcement laws to distinguish between provision and use of marijuana and its cannabinoids for accepted therapeutic purposes as supported by such evidence versus provision and use of marijuana and its cannabinoids for nontherapeutic general purposes or for clinical conditions for which safety and efficacy have not been established.

4. Smoked Marijuana as Medicine

Concerns have been raised that ACP has promoted smoked marijuana as medicine. **ACP has not advocated for the long-term use of smoked marijuana; rather, the paper explicitly discusses the harm associated with chronic use of smoked marijuana and stresses the need for development of nonsmoked forms of cannabinoid delivery systems strictly for therapeutic purposes supported by the evidence.**

The evidence suggests that some patients who have failed to respond to other treatments could be treated with cannabinoid drugs, including smoked marijuana (17–19). The IOM stated that there is "little future in smoked marijuana as a medically approved medication," but acknowledges that until a nonsmoked, rapid-onset cannabinoid drug delivery system becomes available, "there is no clear alternative for people suffering from chronic conditions that might be relieved by smoking marijuana." The IOM issued the following recommendation regarding short-term use of smoked marijuana:

Short-term use of smoked marijuana (less than six months) for patients with debilitating symptoms (such as intractable pain or vomiting) must meet the following conditions:

- failure of all approved medications to provide relief has been documented,
- the symptoms can reasonably be expected to be relieved by rapid-onset cannabinoid drugs,
- such treatment is administered under medical supervision in a manner that allows for assessment of treatment effectiveness, and
- involves an oversight strategy comparable to an institutional review board process that could provide guidance within 24 hours of a submission by a physician to provide marijuana to a patient for a specified use (20).

ACP agrees with the IOM recommendation that "clinical trials of cannabinoid drugs for symptom management should be conducted with the goal of developing rapid-onset, reliable, and safe delivery systems (21)."

Summary

It is evident that discussion of the therapeutic potential of cannabinoids invites strong views, both positive and negative. Some critics of the College's positions have expressed concerns about marijuana dependence, its potential as a "gateway" drug, and the effects of long-term use in its smoked form. HPPC understands such concerns, and ACP's paper expressly discusses these issues.

Regrettably, some have incorrectly concluded that ACP favors a broader agenda of decriminalization or legalization of smoked marijuana—a fundamental misunderstanding of the College's positions. ACP's paper does not address the broader issues of legalization or decriminalization of marijuana, and our call supporting increased research on the therapeutic value of cannabinoids should not be inferred to support a different agenda. The HPPC has clarified position #4 to address such misunderstandings of the College's recommendations.

The HPPC shares the concerns expressed by some about state ballot initiatives or legislation that can undermine the federal regulatory structure for assessing the safety and efficacy of new drugs before such drugs can be approved for therapeutic use. At the same time, however, the HPPC is concerned about the legal liabilities facing physicians and patients relating to marijuana use for therapeutic purposes when there is a conflict between state and federal laws. We believe that an evidence-based review by federal regulatory authorities on the safety and efficacy of marijuana and cannabinoids for therapeutic purposes will likely provide evidence to support both appropriate reclassification and adjustment of federal drug enforcement laws, reduce conflict between federal and state law, and strengthen public confidence in the federal regulatory structure.

The HPPC acknowledges and thanks all of those who expressed views on the College's recommendations, including those who shared deeply personal stories of family members who have been harmed by illegal drug usage as well as those who said they have personally benefited, or had a close friend or relative who benefited, from using marijuana and cannabinoids for therapeutic purposes. The issue of the medical value of these substances is complex. There are strong disagreements among acknowledged experts, and many people react emotionally to the issue based on personal experience, which can overshadow the evidence. Assessment of scientific evidence is also hindered when advocacy groups on either side of the issue use discussions about medical marijuana as platforms to push for broader policy changes relating to either legalizing or increasing penalties for marijuana use for general purposes.

The HPPC hopes that ACP's paper and this addendum will help clarify the issues and initiate a reasoned, evidence-based assessment of the potential therapeutic value of cannabinoids in treating certain medical conditions, and changes in federal and state law that may be needed to facilitate such assessment.

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