Commentary

Medical Marijuana

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On November 5, 1996, California voters passed the Compassionate Use Act (Proposition 215) by a wide margin (56% to 44%). This law now permits "seriously ill" patients and their primary caregivers to cultivate and possess marijuana for the patients' personal medical use if they have the "written or oral recommendation or approval of a physician." Several diagnoses for which marijuana may have palliative benefit are listed in the proposition, but its use is not limited to these diagnoses, and there is no age limitation. Many physicians and the California Medical Association (CMA) opposed this proposition because it bypasses the pharmacologic safeguards of the US Food and Drug Administration and has a potential for abuse. But it is now the law, and its passage (and the proposal of similar laws in other states) has accelerated the societal debate on medical marijuana use and created a scientific and legal dilemma for physicians in California.

Legal Issues

Before the passage of Proposition 215, no one questioned that California physicians could discuss the use of marijuana with patients, including expressing an opinion on using it to alleviate symptoms, without being subject to prosecution under federal drug laws. Since the passage of the proposition, however, even a verbal "recommendation" has legal force and allows a patient to obtain marijuana. Because marijuana remains a schedule I substance under federal law, it is still illegal to prescribe (or distribute, possess, or cultivate), and therefore, such a recommendation could be viewed as an illegal act. On December 30, 1996, Barry R. McCaffrey, Director of the Office of National Drug Control Policy, announced possible federal sanctions against physicians who discuss or recommend the medical use of marijuana. These included the revocation of Drug Enforcement Administration registration, exclusion from Medicare and Medicaid programs, and criminal prosecution.[1]

This announcement was interpreted by many physicians as an attempt to intimidate them and to censor the free exchange of information between physicians and patients. The CMA and the American Medical Association strongly objected to this stance, and several California physicians brought a class-action suit in federal court seeking an injunction against federal threats to punish physicians for discussing or recommending the use of medical marijuana (*Conant v McCaffrey*). On April 30, 1997, the federal court issued a preliminary injunction enjoining the federal government from threatening or prosecuting physicians based on conduct relating to medical marijuana use so long as that conduct "does not rise to the level of a criminal offense"—that is, deliberately assisting in obtaining the substance. This injunction remains in effect until the class-action suit is decided at trial. It protects California physicians who, in the context of a bona fide physician-patient relationship, discuss or recommend the medical use of marijuana to patients with a specific list of diagnoses: the acquired immunodeficiency syndrome (AIDS) or human immunodeficiency virus (HIV) infection, cancer, glaucoma, seizures, or muscle spasms.[2]

For Which Conditions Do Patients Self-medicate With Marijuana?

A tabulation of categories of the *International Classification of Diseases, Ninth Revision*, assigned to more than 900 members of the Oakland Cannabis Buyer's Cooperative indicates that 62% have AIDS or are seropositive for HIV, 10% use marijuana for pain or arthritis, 8% for mood disorders, 6% for neurologic symptoms, 4% for cancer, 4% for glaucoma, and 6% for "other" conditions (T. Mikuriya, MD, written communication, October 1997). Information supplied by the Los Angeles Cannabis Buyer's Cooperative, with more than 600 registered patients, indicates that 70% of the patients have AIDS, 10% have cancer, and 20% have "other" diagnoses, including neurologic diseases and glaucoma but also a variety of conditions that are not ordinarily associated with marijuana therapy, such as hepatitis, heart disease, and renal failure (S. Imler, written communication, August 1997).

These data indicate that the major group now using medical marijuana is that of patients with AIDS, who use the drug for appetite stimulation and to alleviate

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ABBREVIATIONS USED IN TEXT
AIDS = acquired immunodeficiency syndrome
CMA = California Medical Association
HIV = human immunodeficiency virus
NIDA = National Institute on Drug Abuse
NIH = National Institutes of Health
THC = tetrahydrocannabinol

cachexia and neuropathic pain. These patients use smoked marijuana in preference to dronabinol, an oral preparation of tetrahydrocannabinol (THC), which can be prescribed. Possible reasons for this preference are discussed later.

National Institutes of Health Expert Panel

Although legal protections are currently in place for physicians discussing the use of marijuana, the medical and scientific dilemma remains whether marijuana is actually of therapeutic benefit and whether it poses important medical risks. Research on the medical effects of marijuana has been limited, and much of the evidence for its purported medical benefits is anecdotal. On February 19 and 20, 1997, the National Institutes of Health (NIH) convened an expert panel to discuss the medical use of marijuana. The report of this panel has now been released and may be helpful to physicians in discussing the medical use of marijuana with patients.[3]

Smoked Marijuana

Current debate centers on the claim that smoked marijuana is therapeutically superior to the approved oral form of its most active ingredient, THC. The idea of smoking crude plant material is troublesome to many physicians and unpleasant for many patients. The pharmacokinetics of THC from smoked marijuana, however, differ substantially from those of the oral form. When marijuana is smoked, THC in the form of an aerosol in the inhaled smoke is absorbed within seconds and delivered to the brain rapidly and efficiently, as would be expected of a highly lipid-soluble drug.[4] Maximum blood concentrations are reached about the time smoking is finished and then rapidly dissipate. Psychopharmacologic effects peak at 30 to 60 minutes. After the oral ingestion of THC or marijuana, plasma concentrations of THC rise slowly over 1 to 3 hours; the onset is slower, and subjective effects last for 5 to 12 hours without a clear peak.[4]

A possible advantage of smoking rather than ingesting marijuana is the rapid onset and dissipation of effects, because these allow patients to self-titrate the dose, much as with systems of patient-controlled analgesia. Furthermore, the plant contains many other compounds (including about 60 cannabinoids) that may produce some benefit.

There are obvious drawbacks to this route of administration. Pyrolytic by-products are inhaled directly, and the effects of long-term smoking are known to be damaging to the lungs. Although some users claim that marijuana can be heated without burning and the resulting vapor inhaled, this has never been substantiated. The NIH panel recommended strongly that resources be allocated to develop a safe and effective inhaled form of THC.

Medical Conditions for Which Marijuana Might Have Potential Use

The NIH panel identified five areas where there is at least a suggestion of therapeutic value for marijuana and for which further study is indicated.

Stimulate Appetite or Alleviate Cachexia

Loss of weight and decreased caloric intake are major concerns of patients with AIDS or cancer and their caregivers. Although these are the conditions for which most patients appear to self-medicate, there have been no controlled studies of the efficacy of smoked marijuana in the AIDS-wasting syndrome or cancer cachexia; likewise, there are no systematic studies of the risks of smoked marijuana in these immune-compromised patients. Data indicate that inhaled marijuana increases appetite and food intake in healthy persons.[5] The use of dronabinol has been shown to increase appetite and produce weight gain in patients with AIDS and is approved for this indication.[6,7] Because there are no current cost-effective treatments for the wasting of AIDS or cancer, this may be an area of appropriate medical use for marijuana if it is shown to be safe and effective.

Nausea and Vomiting Associated With Cancer Chemotherapy

Many reports have been published on the effects of cannabinoids on chemotherapy-induced nausea and vomiting. Most of the clinical trials were done in the 1970s or 1980s in which oral THC was used rather than smoked marijuana. They indicate that THC is superior to placebo, equivalent or superior to prochlorperazine, but inferior to metoclopramide as an antiemetic.[8,9] A few studies have also used smoked marijuana, with similar results.[10,11] Many patients, especially those not experienced in marijuana use, have unpleasant side effects both from smoked marijuana and oral THC, and this is a major reason for the discontinuation of use.[11,12] Since these studies, more effective antiemetics have been developed, such as the serotonin antagonists ondansetron and granisetron. No studies compare the use of marijuana or THC with these new-generation antiemetics, but a survey of clinical oncologists indicates that most think that marijuana is not nearly as effective as the serotonin antagonists.[13] Even with these highly effective drugs, some patients have no response to their use,[14] and marijuana may be useful for these patients or as an additive to current best therapy.

Glaucoma

Studies in the 1970s showed dramatic decreases in intraocular pressure with smoked marijuana in patients with glaucoma.[15,16] The effect is especially prominent in patients with poorly controlled glaucoma. The effect of marijuana on intraocular pressure was additive to the eyedrops available in the 1970s, but the additive effect has not been tested with newer categories of antiglaucoma eyedrops. If it is still additive, this would suggest a unique mechanism of action, the investigation of which may yield useful therapeutic agents.

At present, several highly effective eyedrops are available to treat glaucoma (including new β-blockers and prostaglandins), and surgical procedures are effective for refractory cases. The need for parenteral administration and long-term use and the systemic and psychotropic effects severely limit the practical utility of smoked marijuana for glaucoma.[16]

Analgesia

Considerable progress has been made in understanding how cannabinoids exert their cellular effects. Two kinds of cannabinoid receptors have been identified: CB_1 and CB_2. CB_1 receptors are present widely in the brain. An endogenous ligand for this receptor system is the arachidonic acid derivative, anandamide,[17] and there is some evidence that the cannabinoid-receptor system is part of a natural pain control system distinct from the endogenous opioid system.[3,4] Small clinical studies indicate that THC has some analgesic activity in patients with cancer pain, but there is a narrow therapeutic window between doses that produce useful analgesia and those that produce unacceptable central nervous system effects.[18] Defining the naturally occurring cannabinoid-receptor system is a good reason to pursue research into selective analogues that may enhance therapeutic effects and minimize adverse effects. In addition, the development of an inhaled form may allow some of the advantages of patient-controlled analgesia.

Cannabinoids have been shown to be possibly analgesic in animal models of neuropathic pain.[19] The NIH panel concluded that neuropathic pain represents a treatment problem for which currently available analgesics are, at best, marginally effective. Because cannabinoids do not act by the same mechanism as either opioids or nonsteroidal anti-inflammatory drugs, they may prove to be a useful adjunct in pain therapy.

Neurologic and Movement Disorders

There are anecdotal reports that the spasticity and nocturnal spasms produced by multiple sclerosis and partial spinal cord injury have been relieved by smoked marijuana and to some extent by the use of oral THC. A study of smoked marijuana in ten patients with spastic multiple sclerosis showed, however, that smoking marijuana further impairs posture and balance in these patients.[20] An anticonvulsant effect has been shown in animal models of epilepsy. Nevertheless, no large-scale controlled clinical studies have been reported.

Other Issues

Research

Given the high level of societal interest, we might ask why there have been relatively few controlled clinical trials of the medical effects of marijuana. To some extent, the interest in marijuana has been reduced by the development of new and highly effective antiemetics and glaucoma medications. The possible value of marijuana as an appetite stimulant and anticachexia agent, however, should be sufficient to stimulate study. Furthermore, even when good medications for a given condition exist, an additional agent might be useful to help occasional nonresponders or in conjunction with other medications.

The classification of marijuana as a schedule I substance has probably been a major hindrance to its study. The only legal and controlled source of marijuana for research in the United States is the National Institute on Drug Abuse (NIDA), whose farm in Mississippi produces marijuana. Federal marijuana is made available only after NIH peer review and also NIDA approval, and this has proved difficult to obtain.[21] These problems were recognized by the NIH panel, which noted recommendations by others that the current regulatory system should be modified to remove barriers to clinical research with controlled substances. Since the release of the NIH report, one proposal to study the effects and toxicity of marijuana in patients with AIDS has been approved and funded (S. Russell, "S.F. Study of Marijuana, AIDS Patients Is Approved," *San Francisco Chronicle*, October 9, 1997, p 1).

Distributing Marijuana to Patients

The concentration of cannabinoids in marijuana varies greatly, depending on growing conditions and plant genetics.[4] The presence of contaminants is of major concern for patients who may be immune compromised, such as those with cancer or AIDS. Because marijuana remains an illegal substance, patients obtain it from illegal—or at least uncontrolled—sources. Unlike the pharmacy system used for all other drugs, there is no governmental control of its strength or purity. This is a major concern of physicians who are contemplating whether or not to "recommend" marijuana use and can be solved only by research and a subsequent change in classification, if appropriate, to allow prescribing through controlled and regulated channels.

Summary

Although many clinical studies suggest the medical utility of marijuana for some conditions, the scientific evidence is weak. Many patients in California are self-medicating with marijuana, and physicians need data to assess the risks and benefits. The only reasonable solution to this problem is to encourage research on the medical effects of marijuana. The current regulatory system should be modified to remove barriers to clinical research with marijuana.

The NIH panel has identified several conditions for which there may be therapeutic benefit from marijuana use and that merit further research. Marijuana should be held to the same evaluation standards of safety and efficacy as other drugs (a major flaw in Proposition 215) but should not have to be proved better than current medications for its use to be adopted.

The therapeutic window for marijuana and THC between desired effect and unpleasant side effects is narrow and is a major reason for discontinuing use. Although the inhaled route of administration has the benefit of allowing patients to self-titrate the dose, the smoking of crude plant material is problematic. The NIH panel recommended that a high priority be given to the development of a controlled inhaled form of THC. The presence of a naturally occurring cannabinoid-receptor system in the brain suggests that research on selective analogues of THC may be useful to enhance its therapeutic effects and minimize adverse effects.

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