ORIGINAL ARTICLE

Medicinal use of cannabis in the United States: Historical perspectives, current trends, and future directions

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ABSTRACT

Cannabis (marijuana) has been used for medicinal purposes for millennia, said to be first noted by the Chinese in c. 2737 BCE. Medicinal cannabis arrived in the United States much later, burdened with a remarkably checkered, yet colorful, history. Despite early robust use, after the advent of opioids and aspirin, medicinal cannabis use faded. Cannabis was criminalized in the United States in 1937, against the advice of the American Medical Association submitted on record to Congress. The past few decades have seen renewed interest in medicinal cannabis, with the National Institutes of Health, the Institute of Medicine, and the American College of Physicians, all issuing statements of support for further research and development. The recently discovered endocannabinoid system has greatly increased our understanding of the actions of exogenous cannabis. Endocannabinoids appear to control pain, muscle tone, mood state, appetite, and inflammation, among other effects. Cannabis contains more than 100 different cannabinoids and has the capacity for analgesia through neuromodulation in ascending and descending pain pathways, neuroprotection, and anti-inflammatory mechanisms. This article reviews the current and emerging research on the physiological mechanisms of cannabinoids and their applications in managing chronic pain, muscle spasticity, cachexia, and other debilitating problems.

Key words: cannabinoids, cannabis, marijuana, chronic pain, opioids, opiates, botanical medicine

INTRODUCTION: AN OVERVIEW OF CANNABINOID MEDICINE IN THE UNITED STATES

Though disrupted by a post-1937 *Cannabis sativa* L. prohibition, the emerging field of cannabinoid medicine is growing in the United States (see Figure 1) as ever greater numbers of healthcare providers become educated about the physiologic importance of the endogenous cannabinoid system[1-3] and about the wide safety margins[4] and broad clinical efficacies[5-8] of cannabinoid drugs. Cannabinoid medicines are available in both purely botanical and purely chemical varieties and are useful for managing pain and other conditions in the growing chronically and critically ill patient population.[9] This article provides a current and historical perspective of the use of cannabinoid therapies in the United States.

The following is a brief overview of the various cannabinoid medicines currently utilized in the American healthcare sector. They fall into three categories: single molecule pharmaceuticals, cannabis-based liquid extracts, and phytocannabinoid-dense botanicals—the main focus of this article (Figure 2). The first category includes US Food and Drug Administration (FDA)-approved synthetic or semi-synthetic single molecule cannabinoid pharmaceuticals available by prescription. Currently, these are dronabinol, a Schedule III drug and nabilone, a Schedule II drug. Though both are also used off-label, dronabinol, a (-)*trans*-Δ9-tetrahydrocannabinol (THC) isomer found in natural cannabis, has been approved for two uses since 1985 and 1992,

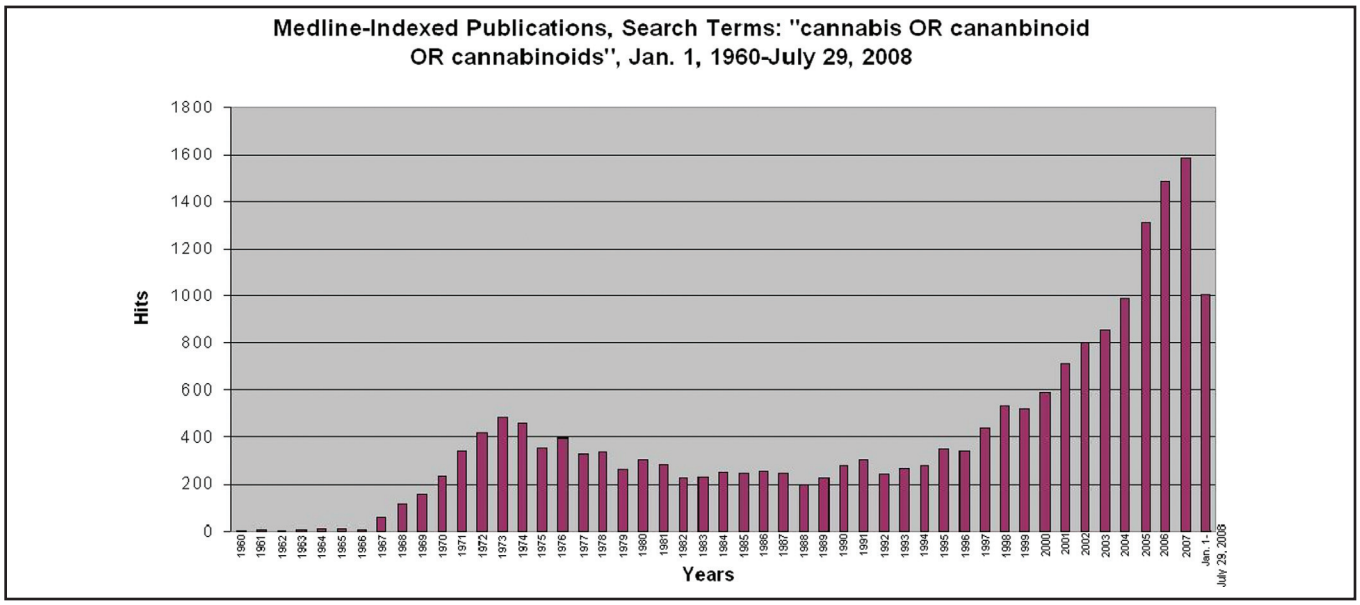

Figure 1. Medline-indexed publications on cannabis and cannabinoids are growing. It is estimated that there are now more than 15,000 articles on the chemistry and pharmacology of cannabis and cannabinoids and more than 2,000 articles on the endocannabinoids in the scientific literature.[1]

respectively: the treatment of nausea and vomiting associated with cancer chemotherapy in patients who have failed to respond adequately to conventional antiemetic treatments and the treatment of anorexia associated with weight loss in patients with AIDS.[10,11] Nabilone, a synthetic molecule shaped similarly to THC, has also been approved since 1985 for use in the treatment of nausea and vomiting associated with cancer chemotherapy.[12,13]

The second category of cannabinoid medicines being used in the United States includes a line of cannabis-based medicinal extracts developed by several companies. The industry leader is GW Pharmaceuticals, a UK-based biopharmaceutical company whose lead product is currently undergoing FDA-approved, multisite Phase IIb clinical trials for the treatment of opioid-refractory cancer pain in the United States[14] and has received prior approval for Phase III clinical trials in the United States. This botanical drug extract which goes by the nonproprietary name nabiximols has already secured approval in Canada for use in the treatment of central neuropathic pain in multiple sclerosis (in 2005) and in the treatment of intractable cancer pain (in 2007).[15] It is also available on a named patient basis in the United Kingdom and Catalonia,[16,17] a scheme which allows a doctor to prescribe an unlicensed drug to a particular "named patient," and has been exported to 22 countries to date. This phytocannabinoid natural product preparation, produced with permission from the British government, is made by formulating cold organic solvent ($CO_{2(l)}$) extracts of two strains of herbal *Cannabis sativa*—cultivated and ground-up in-house at an undisclosed location in the southern English countryside—into an oromucosal spray.

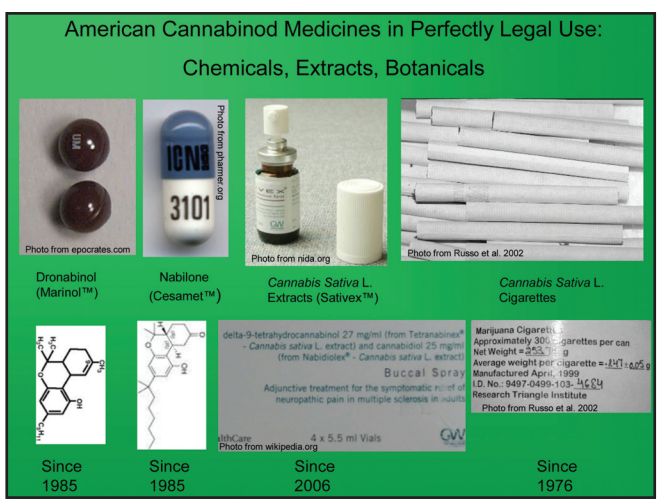

Figure 2. Four cannabinoid medicines that are currently in legal use in US patients.

The third category of cannabinoid medicines currently being used in the United States includes the Schedule I medicinal plant *Cannabis sativa* L. itself, which, while currently unavailable for general prescription use in the United States, is in use in the context of two active controlled clinical trials,[18,19] 33 completed controlled clinical trials,[20-52] and one on-going,

yet essentially defunct, three-decade investigational clinical study.[53,54] The few patients enrolled in American cannabis clinical studies are prescribed a cannabis strain or blend cultivated under contract at the federal research farm at the University of Mississippi at Oxford. The analytical chemist in charge of the farm (whom author SKA met at the 2005 International Cannabinoid Research society meeting) holds the patent on a rectal suppository formulation of dronabinol. This drug has heretofore been produced by total synthesis, but recently it and other cannabinoid formulations were approved for commercial extraction as natural products directly from the cannabinoid botanical supply grown in Oxford, Mississippi.[55] Since cultivation began, the federal cannabis herbal product has been inaccessible for general medical use, and since 1970, federal agencies have maintained the ideological hardliner position that cannabis, pejoratively termed "mari(h/j)uana" during the early 1900s, has "no currently accepted medical use in treatment in the United States."[56]

As the focus of this article is on cannabinoid botanicals, this overview of cannabinoid medicines in use in the United States would be incomplete without a brief overview of the clinical evidence base for their use. The contemporary era of American cannabinoid botanical medicine clinical research began in May 1998 when the first FDA-approved clinical study of cannabis use in a patient population in 15 years enrolled its first subject.[30,57] Overall, the 33 completed and published American controlled clinical trials with cannabis have studied its safety, routes of administration, and use in comparison with placebos, standard drugs, and in some cases dronabinol, in: appetite stimulation in healthy volunteers, the treatment of HIV neuropathy and other types of chronic and neuropathic pain, both pathological and experimentally induced, spasticity in multiple sclerosis, weight loss in wasting syndromes, intraocular pressure in glaucoma, dyspnea in asthma, both pathological and experimentally induced, and emesis, both secondary to cancer chemotherapy and experimentally induced. There has been only one long-term, prospective, federally funded cannabis clinical study that was jointly administered by National Institute on Drug Abuse (NIDA) and FDA. This technically is a study in name only as no clinical response data in the patient cohort have ever been systematically collected or disseminated. The study has been running for more than three decades without any documented follow-up aside from one independent comprehensive health assessment of four of the then seven enrolled patients in 2001 which showed no demonstrable adverse outcomes related to their chronic medicinal cannabis use.[54] Because of attrition, the program now has only these four chronically ill patients enrolled in total (three of whom author SKA has met). It was abruptly closed to new enrollees in 1992 with the explanation from the US Public Health Service that the program was undermining negative public perceptions about cannabis needed to sustain its illegality for the general population.[58]

Four reviews of modern human clinical studies with cannabis and cannabinoids in the United States and elsewhere have recently been published in the peer-reviewed literature.[5-8] Musty et al.'s[8] "Effects of smoked cannabis and oral Δ9-tetrahydrocannabinol on nausea and emesis after cancer chemotherapy: A review of state clinical trials" reviewed seven state health department-sponsored clinical trials with data from a total of 748 patients who received smoked cannabis and 345 patients who received oral THC for the treatment of nausea and vomiting following cancer chemotherapy in Tennessee (1983), Michigan (1982), Georgia (1983), New Mexico (1983 and 1984), California (1989), and New York (1990). To assess the evidence from these clinical trials, the authors systematically performed a meta-analysis of the individual studies, to assess possible beneficial effects. These trials were randomized, although it is not clear that they were truly blind. The authors found that patients who received smoked cannabis experienced 70-100 percent relief from nausea and vomiting, while those who used oral THC experienced 76-88 percent relief. Even judged in the bright light of modern day evidence-based medicine criteria, the evidence is fully convincing that cannabis does relieve nausea and vomiting in this setting.

Bagshaw et al.'s[7] "Medical efficacy of cannabinoids and marijuana: A comprehensive review of the literature" reviewed 80 human studies of cannabis and cannabinoids, including 10 case reports, and found a preponderance of evidence in support of their use in the treatment of refractory nausea, refractory pain, and appetite loss. It is not possible to tell from this review or even from examining a sampling of the original studies exactly how well the individual studies were controlled, randomized, or blinded. Case reports can only be considered as anecdotal evidence. However, this review of

the literature does a good job at describing the pharmacology, therapeutics, adverse effects, and societal implications of the medical use of marijuana within the context of the data available in these trials and case reports. Safety is one key conclusion that can be derived from this summary. The most prominent effects of marijuana are mediated by receptors in the brain and acute intoxication is characterized by euphoria, transient short-term memory interruption, and stimulation of the senses. Actual intoxication is not a commonly seen effect in clinical trials since the doses are tightly controlled. Thus, outright adverse side effects such as depersonalization, panic attacks, and increased heart rate are rarely reported. Moreover, none of these studies noted any significant withdrawal symptoms. Thus one can conclude, on the basis of these studies, that cannabis shows clinical efficacy for the treatment of refractory nausea, pain, and appetite loss (cachexia).

Ben Amar's[6] "Cannabinoids in medicine: A review of their therapeutic potential" identified 72 controlled studies of the therapeutic effects of cannabis and cannabinoids. In this review, a meta-analysis was performed through Medline and PubMed up to July 1, 2005. The key words used were cannabis, marijuana, marihuana, hashish, hashich, haschich, cannabinoids, tetrahydrocannabinol, THC, dronabinol, nabilone, levonantradol, randomised, randomized, double-blind, simple blind, placebo-controlled, and human. The research also included reports and reviews published in English, French, and Spanish. For the final selection, the authors only included properly controlled clinical trials. Open-label studies were excluded. Seventy-two controlled studies evaluating the therapeutic effects of cannabis and cannabinoids were identified. For each clinical trial, the country where the project was held, the number of patients assessed, the type of study and comparisons done, the products and the dosages used, their efficacy, and adverse effects are described. The authors concluded that on the basis of the reviewed studies, cannabinoids present an "interesting" therapeutic potential as antiemetics, appetite stimulants in debilitating diseases (cancer and AIDS), analgesics, and in the treatment of multiple sclerosis, spinal cord injuries, Tourette's syndrome, epilepsy, and glaucoma.

Rocha et al.'s[5] "Therapeutic use of *Cannabis sativa* on chemotherapy-induced nausea and vomiting among cancer patients: Systematic review and meta-analysis" identified 30 randomized, controlled clinical trials that evaluated the antiemetic efficacy of cannabinoids in comparison with conventional drugs and placebo. A Cochrane-style meta-analysis of 18 studies, including 13 randomized, controlled clinical trials comparing cannabis to standard antiemetics for treatment of nausea and vomiting in cancer patients receiving chemotherapy, revealed a statistically significant patient preference for cannabis or its components versus a control drug, the latter being either placebo or an antiemetic drug such as prochlorperazine, domperidone, or alizapride ($n = 1138$; RR = 0.33; CI = 0.24-0.44; $p < 0.00001$; NNT = 1.8).

Although the aforementioned reviews and meta-analyses draw from both American and internationally conducted research, current and past clinical trials of cannabis—not cannabinoids—occurring specifically in the United States deserve some separate considerations due to historical and political reasons. Seven randomized, placebo-controlled or dronabinol-controlled clinical trials of cannabis from 2005 to 2008 conducted in patient populations in the United States—published after Ben Amar's[6] review cut-off date—which investigated indications such as HIV-related and other forms of painful neuropathy, spasticity in multiple sclerosis, and appetite stimulation in HIV patients, have consistently shown statistically significant improvements in pain relief, spasticity, and appetite in the cannabis-using groups compared with controls.[20-23,25-27] In fact, nearly all of the 33 published controlled clinical trials with cannabis conducted in the United States have shown significant and measurable benefits in subjects receiving the treatment, though it is important to note that there is a potential for a bias toward publication of positive results. Four notable negative results are from Chang et al.'s[42] randomized, placebo-controlled study involving eight patients receiving cancer chemotherapy which reported that smoked cannabis or oral THC had no antiemetic effect compared with placebo; the California state health department-sponsored study[34] in which smoked cannabis given to 98 patients was found to be inferior to oral THC given to 2,000 patients for nausea and vomiting associated with cancer chemotherapy; Greenberg et al.'s[32] randomized placebo-controlled trial in 10 patients with spastic multiple sclerosis and 10 healthy controls which showed a subjective feeling of clinical improvement in some patients, but greater impairment of posture and balance in the patient group; and Hill et al.'s[48] placebo-controlled study of cannabis in the treatment of electrically

induced experimental pain in 26 healthy male volunteers, six of whom received placebo and 20 of whom received cannabis, which showed decreased pain tolerance and increased sensitivity to pain in the cannabis using group.

In assessing the past literature *en bloc*, the primary limitations are the relatively small size of many of the trials, as well as the unclear degree to which some of the earlier studies were blinded. Indeed, as the clinical effects of cannabinoids are usually quite apparent, true blinding would be difficult under any circumstance. Further, given the variability in methodologies among the studies, it is not possible to combine all of the data and attempt to do a valid, statistical analysis comparing cannabis with placebo. Despite these limitations, it is our opinion that the majority of American cannabis clinical trials provide empirical evidence supporting the medical efficacy of cannabis.

CONTESTING CANNABIS AS MEDICINE

The rising prominence of phytocannabinoid-rich botanicals in healthcare is actually a rediscovery and not a novel medical practice since the medicinal use of the dried flowers of cannabis has an extensive ancient history cross-culturally, with the oldest documented references known today in the Chinese pharmacopoeia of Emperor Shen-Nung dated to 2737 BCE in the oral tradition, but written down in the first century CE.[59,60] The medical use of cannabis in the modern period was common in the United States from the mid-1850s to the early 1940s due to its introduction into Western medicine as "Indian Hemp" by Calcutta Medical College cofounder and professor, Dr. W.B. O'Shaughnessy (1809-1889), in a landmark 1839 journal article.[61]

Today, nearly one and three-quarter centuries later, the medical science of cannabinoid botanicals has greatly advanced due in large part to the elucidation of *in vivo* cannabinergic structure and function. The cannabinoid system helps regulate the function of major systems in the body, making it an integral part of the central homeostatic modulatory system—the check-and-balance molecular signaling network that keeps the human body at a healthy "98.6," as illustrated by the title of the May 2008 theme issue[2] of the *Journal of Neuroendocrinology*: "Here, there and everywhere: The endocannabinoid system." The discovery and elucidation of the endogenous cannabinoid signaling system with widespread cannabinoid receptors and ligands in human brain and peripheral tissues, and its known involvement in normal human physiology, specifically in the regulation of movement, pain, appetite, memory, immunity, mood, blood pressure, bone density, reproduction, and inflammation, among other actions, has led to the progression of our understanding of the therapeutic actions of cannabinoid botanical medicines from folklore to valid science.[3,53]

Cannabinoids, which are classically 21-carbon terpenophenolics, of which cannabis contains 108,[1] along with other bioactive compounds, have many distinct pharmacologic properties, including analgesic, antiemetic, antispasmodic, antioxidative, neuroprotective, antidepressant, anxiolytic, and anti-inflammatory properties, as well as the capacity for glial cell modulation and tumor growth regulation. Their application in pain management is especially promising as cannabinoids inhibit pain in "virtually every experimental pain paradigm" in supraspinal, spinal, and peripheral regions[62] and have no risk of accidental lethal overdose.

However, these properties are medically underutilized and scarcely recognized by regulatory bodies as a large translational gap currently exists in the field of cannabinoid medicine between research-driven scientific knowledge and patient-centered medicine. This translational gap is a legacy of the historical and on-going suppression and misrepresentation of the scientific data by the opponents of medicinal cannabis. Although allowing patients' access to medical cannabis use consistently enjoys widespread support in all public polling, physicians' knowledge base of this medicine lags behind the public's comfortability with its use. In our opinion, there is significant evidence indicating that the major reason for this translational gap is due to lack of knowledge on the part of medical practitioners. This continues to be perpetuated by intentionally misleading practitioners about the scientific basis of cannabinoid medicines and omitting education about cannabinoid medicines in medical schools, residencies, and postgraduate and continuing medical education, in general.

There remains a near complete absence of education about cannabinoid medicine in any level of medical training. This is certainly true at our institution, the University of Washington. This occurs despite the fact that the Institute of Medicine concluded after reviewing relevant scientific literature, including dozens of works documenting marijuana's therapeutic value, that "nausea, appetite loss, pain,

and anxiety are all afflictions of wasting, and all can be mitigated by marijuana."[63] Further, legal access to marijuana for specific medical purposes continues to be supported by numerous national and state medical organizations including the American College of Physicians, which has historically been quite conservative. Other major players on this list include the American Academy of Family Physicians, the American Psychiatric Association Assembly, the American Academy of Addiction Psychiatry, the Washington State Medical Association, the California Medical Association, the Medical Society of the State of New York, the Rhode Island Medical Society, the American Academy of HIV Medicine, the HIV Medicine Association, the Canadian Medical Association, the British Medical Association, and the Leukemia and Lymphoma Society, among others.[64,65] The American Medical Association (AMA)-Medical Student Section has already adopted a favorable position statement which the House of Delegates of the AMA is currently studying and considering for adoption. At the most recent AMA meeting (November 2008), support for this position was expressed by the Pacific Rim Caucus of state medical associations, which includes California, Hawaii, Alaska, and Guam. The House of Delegates opted to commission a study by the AMA's Council on Science and Public Health on whether the accumulated evidence supports the position that marijuana should be reclassified from a Schedule I controlled substance into a more appropriate schedule and on whether medical ethics demands that the AMA call for protection of both doctors and patients who act in accordance with state medical marijuana laws. The report is slated for release later this year.

Clearly, there is a growing acceptability of the therapeutic practice of medicinal cannabis use amongst organized medicine groups, yet it is still classified as a Schedule I drug in the United States. Federal agencies such as the Drug Enforcement Administration (DEA) and the Department of Health and Human Services (HHS) are required by law to make drug reclassifications based on scientific and medical considerations. However, federal agencies continue to insist[66] that marijuana "has no currently accepted medical use in treatment in the United States" and that "there is a lack of accepted safety for the use of" marijuana "under medical supervision"[56] as grounds for maintaining its prohibition. In supporting these positions which are neither based on thorough scientific review nor any cogent line of logical reasoning (eg, given the fact that the most psychoactive constituent of cannabis, THC, is available as a Schedule III drug), federal and state agencies could be accused, based on the international bill of rights, of shrinking their specific legal "obligation to refrain from prohibiting or impeding traditional preventive care, healing practices and medicines," engaging in the "deliberate withholding or misrepresentation of information vital to health protection or treatment," and aiming for "the suspension of legislation or the adoption of laws or policies that interfere with the enjoyment of any of the components of the right to health." These are all specifically enumerated violations of governmental obligations to respect the human right to health in international law.[67]

GEOGRAPHIC AND LEGAL ISSUES IN THE ACCESS AND DELIVERY OF MEDICINAL CANNABIS IN THE UNITED STATES

In moving toward the protection and fulfillment of the right to health, 13 American states—Alaska, California, Colorado, Hawaii, Maine, Michigan, Montana, Nevada, New Mexico, Oregon, Rhode Island, Vermont, Washington—containing approximately 23.5 percent of the national population and representing 41.5 percent of the total geographic area of United States—have passed laws granting physicians the authority to approve or recommend use of cannabinoid botanicals based on medical evaluation to qualifying chronically or critically ill patients, thereby freeing such patients from state-level prosecution and the worst consequences of the ongoing denial of cannabis's medical utility in federal law. A medical marijuana authorization is the means by which patients receive *access* to this healthcare resource. Although not a true prescription, it is a legally recognized doctor–patient clinical discussion viewed as protected speech according to a ruling by the Ninth US Circuit Court of Appeals that the Supreme Court of the United States let stand.[68] Estimates indicate that in 2008, approximately 7,000 American physicians have made such authorizations for a total of approximately 400,000 patients.*

*Currently available figures indicate that more than 1,500 physicians have recommended medical marijuana use for 350,000 patients in California,[69,70] 182 physicians for 2,051 patients in Colorado,[71] 124 physicians for 4,047 patients in Hawaii,[72] 145 physicians for 634 patients in Montana,[73] 145 physicians for 900 patients in Nevada,[74] 2,970 physicians for 19,646 patients in Oregon,[75] 149 physicians for 302 patients in Rhode Island,[76] and 2,000 physicians[53] for 25,000 patients in Washington.[77]

After receiving medical marijuana authorizations, patients procure cannabinoid botanical medicinal products, or medical cannabis, for their self-administered use under medical supervision from in-state channels and hence *delivery* of the treatment is effectuated—actions which continue to be harshly criminally sanctioned under federal law.[78,79] In such a sociopolitical environment, major medicine access and delivery problems certainly do remain for patients. Patients often depend on the knowledge base of their healthcare providers when exploring treatment options. Access to knowledgeable physicians who feel comfortable recommending medical cannabis is a challenge for patients. Following such recommendations and receiving a safe and adequate supply is a major hardship because of the lack of comprehensive laws at the state level.

Work in the field of medical geography which has a specialization in assessing spatial perspectives on healthcare access and delivery systems focuses on the key question: what is the impact of geographic factors on the acquisition of various medical services? Given the current state of conflicting policies that regulate cannabinoid botanical medical systems in the United States, federal courts have mandated that the medical geography of cannabinoid botanicals access and delivery be necessarily bipolar, with patients receiving *access to* treatment at one set of locations and *delivery of* treatments at other locations. Note that the terms *access* and *delivery* here carry specific meanings with respect to cannabinoid botanical medical systems in the United States; they should not be thought of in terms of their general usages in the field of medical geography.

Generally speaking, according to key experts in the field,

> access to healthcare, is the product of four sets of variables: the availability of services, the possession of the means of access (money or insurance, transportation), the nondiscriminatory attitudes of health care providers, and the failure of the ill themselves to cope with their situation, such as their ability to recognize symptoms, communicate with health professionals, and navigate the health care system.
>
> Meade and Earickson[80(p 381)]

For accessing healthcare with cannabinoid botanicals, the critical variable is availability of the service. This is contingent on the legality of the practice in a given region and its acceptability within the medical profession. In this healthcare delivery system, the authorizing physician "acts as a gatekeeper for the individual entering the formal health care delivery system."[81(p 182)] For Joseph and Phillips,[82] people's "socio-economic accessibility" of a healthcare service includes consideration of "whether they are permitted to use it (organizational and institutional restrictions on accessibility)"(p. 2). However, proof of access or accessibility is not simply the mere presence or legality of a service or practitioner who provides it. It is only through *utilization* of healthcare resources that accessibility is revealed. The medical cannabis healthcare system, which is now functionally available in 13 states, is most certainly under-utilized due in large part to a lack of understanding about the workings of such programs on the part of clinicians and patients alike and to a lack of basic knowledge on the science underpinning cannabinoid therapeutics on the part of clinicians who often operate as if cannabinoid medicines or the cannabinoid signaling system simply do not exist or are of only minor and insignificant importance. In addition, lingering social stigmas such as the flippant connotations which cannabis use often carries likely create aversion to its use on behalf of doctors and patients alike.

ONE STATE'S EXPERIENCE: AUTHORIZING THE MEDICAL USE OF CANNABIS IN WASHINGTON STATE

Washington State voters originally passed the Medical Use of Marijuana Act in 1998 as a ballot initiative (I-692). The Washington State Legislature subsequently amended the Act in 2007 with Engrossed Senate Substitute Bill 6032. In early 2008, the Washington Department of Health further clarified the law by adopting a rule defining a "60-day supply" of medical marijuana. Two of the authors of this article (SKA, GTC) lobbied against these revisions on a number of grounds, not the least of which was that the supply limitations are not based on the known pharmacology of cannabis. Rather, these were amounts arrived at through an arbitrary, nonscientific process. The entire act can be found on-line (*www.doh.wa.gov/hsqa/medical-marijuana/*), codified in Chapter 69.51A of the Revised Code of Washington and at Chapter 246-275 of the Washington Administrative Code. A readable guide to the law created by the American Civil Liberties Union of Washington State, from which some

detailed legal information in the following sections is freely drawn, can be found on-line as well (*www.aclu-wa.org/detail.cfm?id = 182*).

The University of Washington School of Medicine, which is the only medical school in a five-state region (Washington, Alaska, Idaho, Wyoming, Montana) subsequently adopted policy guidelines for physicians regarding medical marijuana in March 2002.[83] The medical marijuana law amendment process, which occurred primarily in the 2007 state Legislative session[84] was allotted $94,000. This money was allocated to the Washington State Department of Health (WA DOH) to formally study medical marijuana dosing and supply needs. Despite this, WA DOH summarily ignored the only peer-reviewed studies done on the actual dosing of medicinal cannabis,[33,53] and chose instead to listen extensively to law enforcement representatives who presented their own anecdotal opinions on what they believed would be appropriate amounts of cannabis to be allowed for medical uses. Ultimately the WA DOH defined a 60-day supply of medical marijuana as not more than 24 ounces of usable marijuana and not more than 15 cannabis plants. Usable marijuana is defined as "the dried leaves and flowers of the Cannabis plant Moraceae[sic]" and does not include "stems, stalks, seeds and roots" (WAC 246-75-010 (2)(d)). A plant is defined as "any marijuana plant in any stage of growth" (WAC 246-75-010 (2)(b)). Patients maintain the right to present evidence in court that their necessary medical use exceeds the presumptive amount (WAC 246-75-010 (3)(c)). Patients who possess not more than this amount will be presumed to be in compliance with the law, whereas patients who require more than this amount still maintain the right to present evidence of their personal, actual medical need in court.

As of February 2009, valid documentation for medical marijuana has been provided to an estimated 25,000 qualifying patients by approximately 1,000-2,000 Washington-licensed physicians across the state.[53,77] The list of state-approved qualifying conditions includes cancer, human immunodeficiency virus (HIV), multiple sclerosis, epilepsy or other seizure disorder, spasticity disorders; intractable pain, defined as pain unrelieved by standard medical treatments and medications; glaucoma, either acute or chronic, limited to mean increased intraocular pressure unrelieved by standard treatments and medications; Crohn's Disease with debilitating symptoms unrelieved by standard treatments or medications; Hepatitis C with debilitating nausea and/or intractable pain unrelieved by standard treatments or medication; or any disease, including anorexia, which results in nausea, vomiting, wasting, appetite loss, cramping, seizures, muscle spasms, and/or spasticity, when these symptoms are unrelieved by standard treatments or medications. A process exists whereby additional conditions may be added to this list.

As with any state law, Washington's law does not change federal marijuana laws. Therefore, anybody who manufactures, distributes, dispenses, or possesses marijuana for any purpose still may be prosecuted under federal law (Title 21, Chapter 13, sections 841 and 844 of the United States Code). Fortunately, due to more pressing criminal justice priorities, very few medical marijuana patients or providers have warranted the attention of Washington's federal law enforcement agents and US Attorneys. The Medical Use of Marijuana Act does not legalize marijuana for recreational or any other use that is not specifically covered by the law. The law applies to only the medical conditions listed in the statute and others that may be approved by the Washington State Medical Quality Assurance Commission and Board of Osteopathic Medicine and Surgery. All other uses of marijuana remain illegal. Originally, the law protected qualifying patients and their designated providers from conviction by allowing them a medical marijuana "affirmative defense" but did not technically protect them from arrest or prosecution. In 2007, the Legislature added the following language which outlines an encounter process that law enforcement officers *may* choose to follow, but are technically not legally obligated to carry out: "If a law enforcement officer determines that marijuana is being possessed lawfully under the medical marijuana law, the officer may document the amount of marijuana, take a representative sample that is large enough to test, but not seize the marijuana."

ASSESSING A PATIENT FOR THE MEDICINAL USE OF CANNABIS

Who is a protected "qualifying patient" and how does a physician assess this patient for appropriateness? Washington's law protects patients suffering from specified terminal or debilitating medical conditions who have been diagnosed by, and received a qualifying statement from, a Washington state physician licensed under RCW 18.71 (M.D.) or RCW 18.57 (osteopath). The patient must be a resident of

Washington State at the time he or she is diagnosed by that physician with a covered illness, and he or she must be advised by the physician (1) about the "risks and benefits" of medical marijuana and (2) that he or she "may benefit from the medical use of marijuana." The Washington State Medical Association has developed a standard form for physicians to use. Interestingly, there is no specification as to how often the patient needs to be seen or exactly for how long the authorization is good.

For medical cannabis recommendations to be considered a standard, quality medical treatment, they should be accompanied by health information regarding cannabis usage, including patient education about auto-titration dosing schedules and harm reduction approaches that emphasize the least hazardous means of pharmacological delivery of cannabinoid botanicals (such as vaporization and oral administration). Patients should be provided treatment management over time, if feasible, and their authorizing physicians should be willing to submit medical testimony should patients encounter legal or administrative problems related to their possession or use of the botanical medicine. Patients should also be counseled that they do not necessarily have to be "high" to obtain a medical effect from the treatment. The American Academy of Cannabinoid Medicine, of which two coauthors (SKA, GTC) are founding members, is in the process of formation and intends to accredit physicians in this area of medicine and provide much-needed practice standards, ethics, and continuing medical education.

Oddly, the medical marijuana law of Washington State does not cover all terminal or debilitating medical conditions—only those illnesses and categories of illnesses currently listed in the statute or subsequently approved by the Medical Quality Assurance Commission (MQAC) and Board of Osteopathic Medicine and Surgery. However, the law does allow for anyone to petition the MQAC and the Board of Osteopathic Medicine and Surgery to add other terminal or debilitating conditions to the list. Qualifying patients must carry their "valid documentation" with them whenever they possess or use medical marijuana. Valid documentation consists of two items: (1) their physician's authorization and (2) proof of their identity, such as a Washington State driver's license or identity card. A qualifying patient must present both of these items to any law enforcement officer who questions the patient regarding his or her use of medical marijuana.

WHO IS A PROTECTED "DESIGNATED PROVIDER"?

Some qualifying patients need help growing, obtaining, storing, or using medical marijuana, so the law allows them to appoint a "designated provider" who will also be protected under the Medical Use of Marijuana Act. A designated provider is defined as a person who: (a) is 18 years of age or older; (b) has been designated in writing by a patient to serve as a designated provider; (c) is prohibited from consuming marijuana obtained for the personal, medical use of the patient for whom the individual is acting as a designated provider (though this does not preclude a designated provider from her/himself being a qualifying patient); and (d) is the designated provider to only one patient at any one time. This wording effectively eliminates medicinal cannabis cooperatives; however, the leaders of individual counties such as King County, the most populous county in Washington, have adopted written policies expressing their wish to not prosecute medical marijuana cooperatives whose patient-members are individually acting in accordance with state law.

Many patients using medicinal cannabis in Washington State are severely disabled and would not be able to physically perform the tasks necessary to cultivate cannabis, nor would they necessarily have access to just one individual to assign as their cannabis provider. Many have long argued that the WA DOH could certify growers through a formal licensure program that would also allow for state taxation of the produced cannabis. The DOH was amendable to this initially but could not do this due to a conflict with the federal laws. Nevertheless, a formal licensure process has begun in other regions such as New Mexico and numerous California municipalities. The qualifying patient must designate the provider in writing before the provider assumes responsibility for the patient's medical marijuana, and the designated provider must carry (1) a copy of the patient's designation, (2) a copy of the patient's physician authorization, and (3) proof of identity whenever he or she is growing, obtaining, or in possession of medical marijuana, to be presented to law enforcement on request.

DO STATE MEDICAL MARIJUANA LAWS PROTECT PHYSICIANS?

Our Washington law states specifically that licensed physicians "shall not be penalized in any

manner, or denied any right or privilege" for: (1) Advising patients about the risks and benefits of medical marijuana; or (2) Providing a qualifying patient with valid documentation that the medical use of marijuana may benefit that particular patient. Physicians and their prescription licenses are also protected under federal law. In *Conant v Walters*,[68] a ruling that the US Supreme Court has let stand, the Ninth Circuit Court of Appeals ruled that threats from the federal government to revoke physicians' DEA registrations or initiate investigations based solely on physicians' recommendations of medical marijuana to their patients violated the core privacy and First Amendment rights contained in the doctor-patient relationship.[85] It is important to note that physicians still cannot formally prescribe or provide marijuana to their patients as that would violate federal laws banning generalized prescription of schedule I drugs. Only patients and their designated providers may possess marijuana for the patient's medical use. In our experience, patients will often ask where they can obtain marijuana for medical use. Even though a physician can certainly tell a patient where to obtain prescribed drugs, it is technically illegal for a physician to instruct a patient on where to obtain cannabinoid botanicals that they have been medically authorized to use. However, the WA state law also states: "no one can be punished solely for being in the presence or vicinity of medical marijuana or its use" (RCW 69.51A.050). As long as they are not in actual possession of the patient's medical marijuana or actively participating in the growing, obtaining, delivering, or administering of the patient's medical marijuana, then family members, friends, roommates, healthcare providers, social workers, and anyone else may be around medical marijuana users and their designated providers without fear of prosecution under the state law. Additional stipulations in the law include: (1) No health insurer can be required to pay for the medical use of marijuana and (2) Places of employment, school buses, school grounds, youth centers, and correctional facilities are not required to accommodate the on-site use of medical marijuana. This definitely puts constraints on the use of medicinal cannabis since dosages for adequate pain relief can be quite costly. The WA State Department of Corrections (DOC) specifically prohibits the use of medicinal cannabis by anyone who is incarcerated, no matter what the diagnosis or how well-documented the medical need is.

CLINICAL APPLICATIONS: USING CANNABIS FOR PAIN MANAGEMENT

With regards to the medical use of cannabinoid botanicals specifically for pain management, several considerations should be noted in the risk-benefit ratio. In general, the three properties that make cannabinoids well-suited for analgesia are their established safety, remarkably low toxicity, and documented efficacy for relieving a wide range of pain states, from neuropathic pain to myofascial pain, to migrainous pain. Botanical cannabinoid medicines, with their 108 cannabinoids, have these three properties. With other natural and synthetic single-molecule cannabinoid therapeutic options, such as dronabinol, nabilone, and experimentally-used cannabinoid drugs such as levonantradol, and ajumelic acid, these properties of safety, low toxicity, and efficacy also apply. However, intolerable side effects such as drowsiness, dysphoria, and increased toxicity are occasionally reported in preclinical and clinical data with these compounds.[33,86] A recent review of 31 clinical studies on the adverse effects of medical cannabinoids by Wang et al.[4] showed that the vast majority of adverse events reported were not serious (96.6 percent). With respect to the "164 serious adverse events" that did occur, the authors reported that "there was no evidence of a higher incidence of serious adverse events following medical cannabis use compared with control [drugs] (rate ratio [RR] 1.04, 95% CI 0.78-1.39)."[4(p 1672)] The same held true for medical cannabinoids usage generally.[4(p 1676)] In addition, serious adverse events were not evenly reported in the literature. The authors note: "The fact that 99 percent of the serious adverse events from randomized controlled trials were reported in only two trials suggests that more studies with long-term exposure are required to further characterize safety issues."[4(p 1676)]

SAFETY PROFILE OF CANNABIS

In its 4,000+ years of documented use, there is no report of death from overdose with cannabis. In contrast, as little as 2 grams of dried opium poppy sap can be a lethal dose in humans as a result of severe respiratory depression. This fact about opium is borne out today in the unintentional deaths from prescribed opioids that continue to escalate.[87] If a very large dose of cannabis is consumed ("over dose"), which typically occurs via oral ingestion of a concentrated preparation of cannabis

flowers' resin (eg, in the form of an alcohol tincture or lipophillic extract), agitation and confusion, progressing to sedation, is generally the result.[88] This is time limited and disappears entirely once the cannabis and its psychoactive components are fully metabolized and excreted. This usually occurs within 3-4 hours, although oral ingestion may prolong the duration of these effects.[33] Some have even called this an "acute cannabis psychosis," and this exacerbates fears that cannabis consumption, in the long-term, might lead to schizotypy such as chronic, debilitating psychosis. Review of the current epidemiological data shows that such fears are unfounded.[89-92] No studies have established that cannabis contributes to psychosis. After careful and extensive consideration of the published data, the United Kingdom's Advisory Council on the Misuse of Drugs made these comments:

> In the last year, over three million people appear to have used cannabis but very few will ever develop this distressing and disabling condition. And many people who develop schizophrenia have never consumed cannabis. Based on the available data the use of cannabis makes (at worst) only a small contribution to an individual's risk for developing schizophrenia.[93(p 15)]

> For individuals, the current evidence suggests, at worst, that using cannabis increases the lifetime risk of developing schizophrenia by 1%.[93(p 11)]

The ACMD is a statutory and nonexecutive, nondepartmental, independent public body of experts that advises the UK government on drug-related issues. The ACMD revisited the issue in 2008, and after another thorough review that incorporated data that had been published since its prior review, they concluded:

> since the Council's previous review the evidence has become more, rather than less, confused. Although there is a consistent (though weak) association, from longitudinal studies, between cannabis use and the development of psychotic illness, this is not reflected in the available evidence on the incidence of psychotic conditions. The most likely (but not the only) explanation is that cannabis – in the population as a whole – plays only a modest role in the development of these conditions. The possibility that the greater use of cannabis preparations with a higher THC content might increase the harmfulness of cannabis to mental health cannot be denied; but the behaviour of cannabis users, in the face of stronger products – as well as the magnitude of a causal association with psychotic illnesses – is uncertain.[94(p 33)]

There is some documentation of a syndrome of acute schizoprhreniform reactions to cannabis that may occur in young adults who are under stress and have other vulnerabilities to schizophreniform illness. However, there are no evidence-based studies demonstrating that chronic cannabis use can cause or exacerbate schizophrenia or bipolar disorder. Nonetheless, medicinal cannabis use should be closely monitored in early teens or preteens who have preexisting symptoms of mental illness.

It should also be noted that cannabis use, when delivered via combustion-and-inhalation, does not have similar health hazards to nicotine-rich tobacco smoking, aside from the potential for bronchial irritation and bronchitis. A recent large, population-based retrospective case-control study involving 1,212 incident cancer cases and 1,040 cancer-free controls in the Los Angeles area matched to cases by age and gender demonstrated significant, strongly positive, dose dependant associations between tobacco smoking and the incidence of head, neck, and lung cancers but failed to demonstrate any significant positive associations or dose dependence with cannabis smoking and the incidence of those same cancers. In fact, a significant, albeit small, protective effect was demonstrated in one group of combusted cannabis consumers.[95] Other reviews, such as Melamede's,[96] offer physiological and pharmacological evidence to account for these significant differences between cannabis and tobacco smoke.

It is clear that, as an analgesic, cannabis is extremely safe with minimal toxicity. Unlike opioids, cannabinoid medicines do not promote appetite loss, wasting, and constipation, but instead can be used therapeutically to treat these symptoms. The synergistic effect of administering multiple active plant constituents and an entourage effect involving endocannabinoid signaling molecules and cannabinioid receptors CB1 and CB2 probably results in the superior analgesia of whole plant cannabis. Carter et al.[97] summarize this as follows: "Cannabinoids produce analgesia by modulating rostral ventromedial medulla neuronal activity in a

manner similar—but pharmacologically distinct from—that of morphine. This analgesic effect is also exerted by some endogenous cannabinoids...."[97(p 949)] Second, terpenoids, flavonoids, and essential oils present in cannabinoid botanical preparations have been shown to have therapeutic effects on mood, inflammation, and pain.[86,98-102] Third, cannabinoids are known to have antinociceptive effects in descending pain pathways, such as those mediated by the periaqueductal gray. Finally, cannabinoid-rich cannabis has anti-inflammatory properties (acting through prostaglandin synthesis inhibition and other cytokine-mediated mechanisms) and via retrograde signaling can presynaptically modulate the release of dopamine, serotonin, and glutamate—neurotransmitters involved in migraine, nausea, and many other noxious symptomatologies.

FUTURE TRENDS AND CONCLUSIONS

The future will likely see an ever-growing number of strategies for separating sought after therapeutic effects of cannabinoid receptor agonists from any potential unwanted effects. However, further progress in the clinical development of selective agonists and antagonists for CB1 and CB2 receptors may prove difficult. Progress in producing selective medications could be hindered by the fact that natural cannabis appears to work best when all of the naturally occurring cannabinoids as found in the plant, which have a multiplicity of empirically demonstrated medicinal properties, are allowed to work in concert with each other and with the other compounds in cannabis. This "orchestration" of effects, which has been best characterized in the case of the added anxiolytic effect of combining cannabidiol (CBD) with Δ9-THC versus THC alone,[98,103] appears to improve the efficacy and safety of the whole cannabis plant for medicinal use. This orchestration of effects is also reflective of the differing medicinal properties of various strains of the cannabis plant. Even among the same genotypic plants (ie, strains) there may be considerable differences in medicinal effect, as clinical effects are dependent not only on the genetic strain of the plant but also the conditions under which it was cultivated. These factors will ultimately determine the percentages of the various cannabinoids. A future promising area of research will be the identification and development of cannabis strains that are better suited to particular therapeutic ends. Although refinement of cannabinoids with high therapeutic potential may facilitate the production of cleaner, maximally therapeutic drugs, there may also be unwanted consequences.[100] For example, patients with amyotrophic lateral sclerosis (ALS) report that dronabinol, which is nearly 100 percent THC by weight, is too sedating and does not alleviate symptoms as well as natural cannabis.[101,102]

Effective delivery systems are also needed and will continue to be developed. Because the cannabinoids are volatile, they will vaporize at a temperature much lower than actual combustion of plant matter. Thus, heated air can be drawn through marijuana and the active compounds will vaporize into a fine mist, which can then be dosed and inhaled without the generation of smoke.[24,104] As noted previously, pharmacologically active, aerosolized and sublingual forms of cannabinoid-based medicinal extracts have recently been developed[15] and marketed, but these approvals should not be allowed to exclude or impede medicinal access to the class of organic botanicals from which such preparations are derived.

Arguably cannabis is neither a miracle compound nor the answer to everyone's ills. Yet it is not a plant that deserves the tremendous legal and societal commotion that has occurred over it. Over the past 30 years, the United States has spent hundreds of billions in an effort to stem the use of illicit drugs, including cannabis, with limited success. Because of this climate, unfortunately some very ill people have had to fight and, in many cases, lose long court battles to defend themselves for the use of a medicinal preparation that has helped them. Nonetheless, the purpose of this article is not to discuss the pros and cons of medicinal versus recreational marijuana use. That is a totally separate and altogether different issue. Yet, at the very least, it should be noted that there is no evidence that recreational cannabis use is any higher in states that allow for its medicinal use. Gorman et al. examined whether the introduction of laws allowing for the medical use of cannabis affected the level of cannabis use among arrestees and emergency department patients.[105] Using the Arrestee Drug Abuse Monitoring (ADAM) system, data from adult arrestees for the period 1995-2002 were examined in three cities in California (Los Angeles, San Diego, San Jose), one city in Colorado (Denver), and one city in Oregon (Portland). Data were also analyzed for juvenile arrestees in two of the California cities and Portland. Data on emergency

department patients from the Drug Abuse Warning Network (DAWN) for the period 1994-2002 were examined in three metropolitan areas in California (Los Angeles, San Diego, San Francisco), one in Colorado (Denver), and one in Washington State (Seattle). The analysis followed an interrupted time-series design. There was no statistically significant pre-medical marijuana law versus post-medical marijuana law differences found in any of the ADAM or DAWN sites. Thus, consistent with other studies of the liberalization of cannabis laws, medical cannabis laws do not appear to increase use of the drug. The authors theorized that the use of medical cannabis by "sick" patients might "de-glamorize" its use and thereby actually discourage use among others.

The scientific process continues to evaluate the therapeutic effects of marijuana through ongoing research and assessment of available data. With regard to the medicinal use of marijuana, our legal system should take a similar approach, using amassed scientific evidence and logic as the basis of policy-making rather than political views and societal trends that are more reflective of the ongoing debate over any potential harmful effects of recreational marijuana use. At the same time, physicians and medical students should make extra efforts to fill in the gaps in their training and knowledge base by educating themselves in the art and science of cannabinoid medicine.

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ACKNOWLEDGMENTS

This research was done in fulfillment of the doctoral dissertation of Dr. Sunil K. Aggarwal. Dr. Aggarwal is currently enrolled in the Medical Scientist Training Program at the University of Washington. The authors would like to acknowledge Dr. Ethan Russo for his help in preparing this manuscript. Supported indirectly by funding from the National Institute of General Medical Sciences of the NIH45 Center Drive MSC 6200 Bethesda, MD 20892-6200 and the National Science Foundation 4201 Wilson Boulevard, Arlington, Virginia 22230.

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