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REVIEW

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U.S. Policy Responses to Calls for the Medical Use of Cannabis

Wayne Hall, PhD

The Centre for Youth Substance Abuse Research, The University of Queensland and National Addiction Centre, Australia, and National Addiction Centre, Kings College London, United Kingdom

This paper discusses the evolution of U.S. policy responses to calls to allow patients to use cannabis for medical purposes. It first summarizes the research evidence on the safety and efficacy of cannabinoids for various medical uses. It then outlines the challenges in developing new pharmaceutical cannabinoids that are safe, effective, and acceptable to patients. It briefly describes the strengths and limitations of the different ways in which U.S. states have allowed patients to use cannabis for medical purposes. These include allowing access for research trials only, allowing medical necessity as a defense against prosecution, and allowing commercial medical dispensaries to provide cannabis to approved patients. It argues that liberal definitions of indications for medical cannabis use and the commercialization of medical cannabis supply in California have produced the *de facto* legalization of recreational cannabis use.

In the19th century, the medical profession used cannabis preparations to treat pain, convulsions, spasm, and nausea, and induce sleep [1-3]. Medical use of cannabis declined in the early 20th century with the advent of analgesics that could be delivered in better standardized doses than oral cannabis preparations [3]. This decline was accelerated by the signing of international drug control treaties in the 20th century that classed cannabis as a drug with no medical use.

There was renewed interest in the medical use of cannabis in the 1970s in the United States. This occurred in the midst of rising recreational cannabis use among young people, ensuring that the debate about the medical use of cannabis would become entangled in the debate about whether its recreational use should be permitted [4]. This entanglement has made it difficult to allow patients to use cannabis preparations, polarized expert and lay opinions on whether cannabis has any medical uses, and made it difficult to conduct clinical trials of the effectiveness and safety of cannabinoids and cannabis.

The purpose of this paper is to briefly describe U.S. policy responses to calls for patients to be allowed to use the prohibited drug cannabis for medical purposes. The U.S. medical cannabis debate has produced a variety of different medical cannabis schemes that have been implemented in around half of the states over the past 40 years. These schemes also have been internationally influential in prompting other countries (e.g., Canada, Israel, and the Netherlands) to allow access to cannabis for medical uses.

The paper begins by reviewing the evidence on the efficacy and safety of cannabis and its constituents when used for a variety of medical purposes (namely, controlling nausea and vomiting, stimulating appetite, controlling neuropathic pain and muscle spasm in multiple sclerosis, and treating intractable epilepsy). It then describes medical marijuana referenda and the schemes that these have produced in different states. I argue that states that have liberally defined criteria for medical cannabis use and allowed commercial supply of cannabis to approved patients, as exemplified in California, have created *de facto* legal access to cannabis for recreational use. I end by outlining the type of evidence that is required for better based policies toward the use of cannabis and its constituents for medical purposes.

To whom all correspondence should be addressed: Wayne Hall, The Centre for Youth Substance Abuse Research, The University of Queensland, Herston, Queensland 4029 Australia; Tele: +61 (07) 3365-5246; Fax: +61 (0)7 3365- 5488; Email: w.hall@uq.edu.au.

†Abbreviations: CBD, cannabidiol; IND, Investigational New Drug program; MS, multiple sclerosis; RCT, randomized controlled trial; TGA, Therapeutic Goods Administration; THC, tetrahydrocannabinol

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DO CANNABIS AND ITS CONSTITUENTS HAVE MEDICAL USES?

In this paper, ***cannabis*** refers to products of the *cannabis sativa* plant, such as marijuana (the flowering tops of the plant) and hash (compressed resin), which are usually smoked by both recreational and medical cannabis users [5]. The principal psychoactive ingredient of the cannabis plant is tetrahydrocannabinol (THC†), which acts on specific receptors in the brain, known as cannabinoid or CB1 receptors. These receptors also respond to a naturally occurring cannabinoid in the brain called anandamide [6].

The term ***cannabinoids*** is used to describe pharmaceutical drugs that act on the brain's cannabinoid system. These can be derived from the cannabis plant or chemically synthesized. If they produce similar psychoactive effects to THC, they are called cannabinoid agonists [6,7].

Medicinal cannabis extracts are standardized preparations of the cannabis plant that deliver defined standard doses of cannabinoids. For example, nabiximols (trade name Sativex) is a cannabis extract produced by combining equal amounts of extracts from two cloned cannabis plants that produce high levels of THC and cannabidiol (CBD), respectively. CBD is a cannabinoid that has few psychoactive effects, but it appears to moderate the psychoactive effects of THC that some patients find unpleasant [8]. Sativex is delivered as an oral sublingual spray to provide patients with defined doses of THC and CBD without the patients having to smoke cannabis [8].

Indications for Medical Cannabis Use

Advocates claim that cannabis and cannabinoids can be used to treat nausea and vomiting as side effects of cancer treatment; poor appetite in patients with AIDS-related wasting; chronic pain and painful spasms in multiple sclerosis; epileptic convulsions; and glaucoma [6-10]. In each of these indications, they are used as an adjunctive or second-line treatment. Adjunctive treatments are those used in combination with other medical treatments, while second-line treatments are those reserved for patients in whom standard treatments have proven ineffective or have been poorly tolerated because of side effects [7]. The following sections outline the medical indications for which there is some evidence from clinical trials and a biologically plausible rationale for medical use. The focus is on evidence from controlled clinical trials, independent systematic reviews where available from the Cochrane Collaboration, and the Institute of Medicine.

Cannabinoids as Antiemetics

In the 1970s and 1980s, controlled clinical trials found that THC was more effective in treating nausea produced by cancer chemotherapy and radiotherapy than either placebo or the antiemetic drugs in common use [3,7,11,12]. These studies were done decades ago, many of the trials were small, and there are now much more effective antiemetic agents than drugs with which cannabinoids were compared [7,13]. The antiemetic effects of cannabinoids and these newer drugs have not been directly compared, but indirect comparisons indicate that the newer agents achieve complete control of nausea in 90 percent of patients, whereas cannabinoids achieved complete control in only 30 percent of patients [7,13]. This evidence indicates that cannabinoids are not a first-line treatment for nausea and vomiting in cancer patients, but they still may be adjunctive or second-line treatments [7,9].

Appetite Stimulation

Dronabinol (Marinol) was registered in the United States as an appetite stimulant in patients with terminal cancer and AIDS-related wasting in the early 1990s on the basis of several small-scale clinical trials [11]. A Cochrane review of these studies concluded that the evidence was too weak to draw any conclusions about efficacy or safety [14]. The use of cannabinoids to stimulate appetite in AIDS patients largely has been obviated by the advent of highly effective anti-retroviral drugs that prevent most HIV-infected persons from developing AIDS-related wasting.

Neuropathic Pain and Spasticity in Multiple Sclerosis

Analgesia is one of the oldest reasons for medical cannabis use [15]. THC and other cannabinoid agonists act on similar pathways to the opioids but produce analgesia via distinct mechanisms. This suggests that the analgesic effects of combining opioids and cannabinoids could be larger than the sum of their individual analgesic effects [16]. In double-blind and placebo-controlled clinical trials, cannabinoids produce moderate analgesia equivalent to moderate doses of codeine [7,17].

The role of cannabinoids in controlling neuropathic pain has been evaluated in clinical trials in patients with multiple sclerosis (MS) [18]. In these trials, patients given Sativex reported greater subjective relief of painful muscle spasms than patients who received placebo. There were, however, only marginal reductions in observer ratings of muscle spasm after 3 weeks of treatment [19]. Larger reductions were reported in observer ratings and patient reports of spasticity and pain in a 12-month follow-up of the subset of these patients who continued to use cannabinoids for over a year [20]. A meta-analysis of the controlled trials (involving 298 patients) [21] found that Sativex produced a larger reduction in pain (1.5 versus 0.8 points on a 10-point rating scale) than placebo after 3 weeks of treatment [21]. This improvement was less than that defined as "clinically significant" (2 points).

A recent review of studies of nabiximols (Sativex) in MS [18] concluded that most have shown a greater reduction in symptoms of spasticity in patients receiving Sativex than in those on placebo. The adverse effects were also generally mild to moderate, with the most common being dizziness, diarrhea, fatigue, nausea, headache, and somnolence. Podda and Constaninescu emphasized that Sativex was added to more traditional anti-spasticity drugs rather than being used as a stand-alone treatment [18].

Epilepsy

Cannabidiol (CBD) has anti-convulsant effects in animal models of epilepsy [22]. Four small randomized, placebo-controlled trials of CBD have been conducted on patients whose epilepsy had not responded to first-line anti-convulsants. CBD was given in addition to their usual anti-convulsant drugs [23]. The studies were small, and, according to a Cochrane review, their results were inconclusive [24].

There has been recent clinical interest in using CBD to treat Dravet's syndrome, the childhood epilepsy syndrome. Epilepsy in Dravet's syndrome does not respond to conventional anti-convulsants and can produce severe intellectual disability and death if untreated. Some parents have reported that cannabis extracts with high levels of CBD have controlled or greatly improved their children's epilepsy. Randomized, controlled clinical trials are proposed to test the therapeutic effects of CBD [25,26].

WHAT ARE THE RISKS OF MEDICAL CANNABINOID USE?

Risks of Short-Term Use

Wang et al. [27] conducted a meta-analytic review of the adverse effects in randomized controlled trials (RCT) of cannabinoids and cannabis extracts. They found that 97 percent of the adverse effects in the clinical trials were minor, with dizziness (20 percent) being the most common. They did not find a higher rate of serious adverse events in patients given cannabinoid drugs (either as plant extracts or THC preparations) than in those given placebo. Wang et al.'s conclusions agree with the Institute of Medicine [7], which concluded that the acute adverse effects of cannabinoids were "within the risks tolerated for many medications" and patients would develop tolerance to these effects with continued use.

The Risks of Longer-Term Use in Chronic Diseases

Wang et al. [27] were unable to evaluate the risks of longer-term medical use of cannabinoids (e.g., used to treat multiple sclerosis) because the clinical trials have all been short-term (from 8 hours to 12 months).

A small number of studies have been done on the emotional and cognitive effects of long-term Sativex use in patients with MS. In one study, patients who received Sativex for 50 weeks reported no statistically significant differences from placebo on cognitive and mood tests [28]. Participants in another RCT did not show any performance differences in the Paced Auditory Serial Addition Test or score differences in the Beck Depression Inventory [29]. Larger studies of this type need to be conducted over periods of years to assess the safety of long-term medical use of cannabinoids.

Population-based studies of recreational cannabis users provide indications of the possible adverse effects of long-term cannabis use that should be examined in longer-term clinical studies. These studies have examined the effects in adolescence and early adulthood of regular (usually daily) and sustained cannabis smoking by young people and, less commonly, the risks of long-term health harms, such as cancers, that may arise from exposure to carcinogens in cannabis smoke over decades [5,30].

Recreational users who use daily can become dependent on cannabis [31]. The risk is higher if they begin smoking cannabis in adolescence and smoke the most potent cannabis products daily during young adulthood [32]. A substantial minority of cannabis-dependent persons seek help to stop using cannabis [5]. The risks of dependence are probably higher in recreational users who smoke potent forms of cannabis multiple times per day than they are in older adults who use smaller oral doses of cannabinoids for symptomatic relief [4]. There is nonetheless some evidence that patients taking Sativex daily over a period of months experience withdrawal symptoms when they cease using the drug [33]. It is uncertain how many of these patients will develop a full dependence syndrome or experience difficulty in ceasing their use. We need studies of the risks and consequences of cannabis dependence in long-term medical cannabis or cannabinoid users to see if this is the case.

Longitudinal studies of young adults also suggest that daily cannabis can precipitate psychotic symptoms and disorders in individuals with a personal or family history of these disorders [34,35]. Again, this evidence comes from studies of young adults who started daily cannabis use in adolescence and used regularly throughout young adulthood, the period when the risk of developing psychotic disorders is at its highest. The Australian Therapeutic Goods Administration (TGA) has noted with concern reports of acute psychotic syndromes in patients given Sativex [33], as well as the abovementioned evidence that some patients develop dependence [33]. Given these reports, it would be prudent to advise persons with a personal or family history of psychosis to either avoid using cannabis for medical purposes or use it with care and monitor adverse psychological effects [36].

The cardiovascular risks of cannabinoid use are of greater potential concern to medical cannabis users. The risks of cardiovascular disease are higher among older adults than among younger recreational users [37], and there are epidemiological studies suggesting that cannabis smoking can precipitate myocardial infarction in older adults [5]. There are also a number of case reports of serious cardiovascular complications, including cardiac deaths, in young recreational cannabis users [38,39]. It would be prudent for older patients to avoid smoking cannabis and use oral cannabinoids or cannabis extracts.

The cancer risks of long-term cannabis smoking are unclear because studies have produced inconsistent findings, and in many of these studies, it has been difficult to separate the effects of cannabis smoking from those of tobacco smoking because most cannabis smokers have also smoked tobacco [5,40]. The cancer risks of cannabis use

may be of little concern to older patients with a limited life expectancy, such as those with terminal cancer. They may be of more concern in patients with MS or chronic pain, who may use cannabis daily over years and possibly decades. Again, it would be prudent for long-term medical cannabis users to avoid smoking cannabis and use oral cannabinoids or cannabis extracts.

HOW CAN WE MAKE PHARMACEUTICAL CANNABINOIDS AVAILABLE FOR MEDICAL USE?

A synthetic form of THC, dronabinol, was registered for medical use as an antiemetic and appetite stimulant in the United States in 1985. Nabilone, a synthetic cannabinoid with similar effects to THC, was approved for use in AIDS-related wasting in 1992. But neither of these drugs has been widely used because patients have found it difficult to obtain therapeutic doses that did not also produce unwanted adverse side effects [7,41]. This largely reflects the drawbacks of using the oral route to take THC. When taken orally, THC has a delayed onset of effect and patients either receive insufficient THC for therapeutic benefit or too much and experience adverse side effects [6,41].

Pharmaceutical companies have not developed better cannabinoids than dronabinol and nabilone for a number of reasons. First, it is costly to develop and test new cannabinoids [7] and difficult to recoup these costs when the indications for their medical uses are uncommon and more effective drugs have been developed for nausea and vomiting [7,42]. Second, regulations controlling the medical use of prohibited substances make it difficult to conduct basic and clinical research on drugs that are chemically similar to or derived from a prohibited drug. Third, these regulations also impose restrictions on medical use of any cannabinoids that may be approved for human use, thereby discouraging physicians from using them [4,7,43].

Cannabis extracts such as Sativex have been trialled in the United Kingdom [6,8], with considerable support from U.K. pharmaceutical regulatory authorities [44]. U.K. manufacturers of Sativex (Guy Pharmaceuticals) have patented the processes used to produce Sativex (rather than its natural constituents THC and CBD). After controlled clinical trials, Sativex has been approved for use in patients with MS in Canada, Czech Republic, Denmark, Germany, New Zealand, Spain, Sweden, and the United Kingdom [45]. Sativex has been approved for clinical use in the United Kingdom, but it has not been approved for publicly subsidized use under the National Health System. It has not yet been approved in the United States, and it remains to be seen if Sativex (and other cannabis extracts) are more acceptable to patients than dronabinol and nabilone have been.

Allowing the Medical Use of Cannabis Products

The lack of acceptable pharmaceutical cannabinoids and the restricted research access schemes prompted some U.S. advocates of medical cannabis use to campaign for state laws that would allow patients to smoke cannabis for medical reasons. According to surveys, "medical marijuana" enjoys majority support in the U.S. population, and this has been reflected in the passage of referenda in around half of the U.S. states that allow the use of marijuana for medical purposes [46]. The challenge for U.S. state governments in responding to these calls has been in finding ways to allow patients to access cannabis products for medical use while recreational cannabis use has remained illegal.

MEDICAL MARIJUANA INITIATIVES IN THE UNITED STATES

Compassionate Access Schemes and Medical Necessity Defenses

Between 1975 and 1992, the U.S. government allowed patients with a restricted list of medical conditions to have compassionate access to cannabis under the Investigational New Drug (IND) program [47]. Eight U.S. states legislated to allow the medical use of cannabis under similar conditions, but only a very small numbers of patients were able to access cannabis for medical purposes under these schemes, and the Reagan administration refused to allow new patients to enter the scheme after the 1970s [47].

Some states have allowed "medical necessity" as a defense against prosecution for using cannabis to treat symptoms of serious illnesses [47]. This approach has provided guidance to police in deciding whether to prosecute patients who have defined medical conditions but who were left to obtain cannabis from the illegal market in the absence of legal medical supply.

Medical Marijuana Referenda

Because of the restrictiveness of the federal IND program and lack of access to cannabis under states that allowed a medical necessity defense, medical marijuana advocates in the 1990s campaigned to pass citizen-initiated referenda that would allow patients to use cannabis for medical purposes. In 1996, Californian voters passed Proposition 215 (by 56 percent to 44 percent). This allowed patients to use marijuana for a broad set of medical indications that included those supported by evidence (namely, nausea, weight loss, pain, and muscle spasm). It also allowed medical use under an open-ended category, namely, any "serious medical condition." This term was not well defined but left to the discretion of a medical practitioner who decided whether a patient had an illness serious enough that could only be relieved by their using marijuana [48].

Since 1996, a total of 23 U.S. states have legislated to allow the medical use of marijuana. This has been done either by passing a referendum proposal or at the initiative of the legislature [49]. Not all these state schemes

allow access to marijuana for medical purposes in the same liberal fashion as California. State medical cannabis laws and regulations vary in how many and what type of patients they allow to use marijuana and the conditions under which they are allowed to obtain the drug [50].

The approved indications for medical use vary from very narrow to the very broad [50]. Some states define medical use as the use of cannabis to treat only indications for which there is evidence of efficacy from controlled trials (i.e., nausea in cancer, appetite stimulation in AIDS, and analgesia). A few states have followed California's example in defining a broadly inclusive set of indications that allow medical use for any condition that a physician believes may benefit from the use of marijuana [51-53]. States also differ in whether they require physicians to examine a patient, advise them about the risks of using marijuana, and monitor the health of patients who use marijuana [52].

Prescriber Conundrums

Medical marijuana schemes create problems for prescribers. Laws allowing physicians to prescribe cannabis conflict with U.S. federal law, which does not allow the use of cannabis for any purpose. Under the U.S. Constitution, federal laws pre-empt state laws [4,48]. The Bush administration threatened to strip doctors of their licenses to practice if they recommended marijuana to their patients. Even when the U.S. courts removed this threat, physicians remained reluctant to recommend cannabis because of concerns that they would be legally liable for any harms experienced by their patients [47,51]. In the absence of data, physicians also found it difficult to decide to whom they should recommend cannabis, in what amounts, and for how long [54,55]. These challenges have been ignored by a small number of physicians, who advertised their preparedness to provide patients with a medical recommendation for a fee.

Obtaining Medical Cannabis

In 2001, the U.S. Supreme Court ruled that persons who supplied cannabis for medical use were not protected from federal criminal prosecution by state laws that allowed medical marijuana use [4]. Patients either had to secure their cannabis from the black market or, in some states, were allowed to grow cannabis for their own medical use or have a carer grow it on their behalf. The Bush administration enforced federal laws against cannabis cultivation and supply in medical marijuana states, but in 2009, the Obama administration indicated that it would refrain from doing so [51].

The Obama administration enforced federal laws against the large-scale commercial cultivation of cannabis, but it tolerated commercial cannabis "dispensaries," provided that they only sold marijuana to patients who had a doctor's letter of recommendation [56]. The number of dispensaries increased rapidly in California, Colorado, and Washington State after the 2009 decision. The dispensaries were not licensed to produce cannabis and so had to obtain it from the illicit market [51], creating a quasi-legal cannabis distribution system. The combination of a commercial cannabis supply system and very liberal criteria for what constituted medical cannabis use effectively allowed recreational users to obtain and use cannabis without fear of prosecution, provided that they had a doctor's letter recommending that they use it for medical reasons [52,53,57].

Studies of the characteristics of approved medical marijuana users in California indicate that substantial numbers of recreational users have accessed cannabis via medical cannabis dispensaries. A survey of 4,117 patients in the San Francisco Bay Area in 2001-2007 reported that 77 percent were male with an average age of 32 years. Most (89 percent) had started using cannabis before the age of 19, and 90 percent were daily smokers who used between an eighth and a quarter of an ounce per week [58]. There were no data on the medical indications for which they used cannabis. Similar results emerged in another survey of 1,746 medical marijuana patients in California in 2006: three quarters were male, only 13 percent were older than 55 years, and two-thirds were daily smokers and had been so since adolescence [59].

A survey of self-reported "medical marijuana use" in a representative sample of the Californian population confirms the findings on dispensary clients [60]. In total, 7 percent of Californian adults reported "medical cannabis use." The highest rate of self-reported medical use was among adults aged 18-24 years (10 percent). The lowest rate (1.5 percent) was among persons over the age of 65 years, the age group in which one would expect to find more persons with cancers, neurological disorders, and chronic pain. These findings indicate that there is a "porous boundary" between recreational and medical cannabis use in California [4,52,53,59].

Some may argue that the high rates of use in California reflect the use of cannabis to self-medicate anxiety and depression. The self-medication of depression is indeed a common reason for young people begin using alcohol and cannabis [61]. Initially, use of cannabis improves mood but continued use is associated with a continuation of symptoms of anxiety and depression [61] and with an increased risk of developing cannabis dependence [30]. The latter is indicated by the large proportion of medical cannabis patients using Californian dispensaries who have been daily cannabis users since adolescence.

It is instructive to compare the characteristics of Californian medical cannabis users with those in the Netherlands, where recreational cannabis use by adults has been decriminalized since the 1970s [63], and hence, recreational users have no need to access medical cannabis. The Netherlands legislated to allow the medical use of cannabis in 2003, and cannabis is provided in a form suitable for oral use at pharmacies on the prescription of a physician [62]. The estimated annual use of medical cannabis in the Netherlands has varied between 8 and 10

per 100,000 between 2005 and 2010 [64] compared with estimated rates of 7,000 per 100,000 in California. Dutch medical cannabis users were much older than their Californian counterparts (55.6 years versus 40.7 years), and used lower daily doses (0.68 g versus 2.4-3.8 g). The other drugs that these patients were prescribed suggest that they more often used cannabis to treat chronic pain rather than symptoms of AIDS and cancer.

SHOULD WE LEGALIZE CANNABIS?

Grinspoon and Bakalar [2] have argued that the simplest way to enable patients to use cannabis for medical purposes would be to legalize all adult use of cannabis. This would enable patients who wanted to use cannabis for medical purposes to do so at their own risk and without needing a medical prescription. It would also be legal to grow, supply, and purchase cannabis. Legalization would sever the Gordian knot of regulatory issues that surround cannabis prescription programs and medical marijuana initiatives.

Until very recently, the major political and legal obstacle to legalization has been the United Nations Single Convention, which prohibits the nonmedical use of cannabis [63]. This policy has consistently enjoyed majority public support in most developed countries [63] but this recently changed in the United States with the passage of citizen-initiated referenda that legalized recreational cannabis use in Colorado and Washington in 2012 and Alaska and Oregon in 2014 [65]. Colorado and Washington implemented legal cannabis markets for recreational use in 2013 and 2014, respectively [66,67].

The fact that cannabis use has been legalized in these U.S. states creates an interesting issue for the regulation of medical cannabis use. Colorado's regulations allow medical cannabis users to pay a lower rate of tax on their cannabis than recreational users. This has created an incentive for tax evasion. Recreational users appear to have recognized this, judging by a large increase in the numbers of persons registering to use cannabis for medical reasons in Colorado after the passage of cannabis legalization [68]. This policy choice will prevent Colorado from receiving the large tax income windfall that was predicted by advocates of legalization when campaigning for voters to support cannabis legalization [69,70].

One could argue that medical cannabis use should only be given a tax advantage for medical indications in which there is evidence of efficacy. But this would require a system of medical approval and registration that could be expensive to run, creating another regulatory expense that cannabis legalization was supposed to remove. It would be arguably simpler and better policy if medical users paid the same price for their cannabis as everyone else. This price will be considerably cheaper under a legal regime than it has been in dispensaries operating under a nominal policy of prohibition [71].

SUMMING UP: MEDICAL MARIJUANA CONUNDRUMS

Controlled clinical trials indicate that cannabinoids have some efficacy in controlling emesis in cancer patients, in stimulating appetite in AIDS patients, and in relieving pain and spasticity. There are, however, now much more effective drugs available for most of these indications. If cannabinoids have a medical role in these conditions, it is as second- or third-line treatments or as adjunctive treatments.

Pharmaceutical synthetic cannabinoids have been approved for medical use (e.g., dronabinol), but they have not been widely used because patients find it difficult to achieve therapeutic doses. These drugs have not been very profitable for the companies that produced them. The small market for cannabinoids, the lack of profitability, and the regulatory costs and burdens of their clinical use are major disincentives to the development of more effective cannabinoids [7].

A pharmaceutical cannabis extract, Sativex, has been approved for medical use in multiple sclerosis and neuropathic pain in a number of countries but not yet the United States. It has shown modest efficacy in clinical trials in controlling these symptoms, but regulators in some countries have found the evidence unconvincing. It remains to be seen if Sativex proves more acceptable to patients than dronabinol and nabilone.

Medical marijuana advocates in the United States have used referenda to circumvent the pharmaceutical regulatory system and enable patients to smoke cannabis. These initiatives have created problems for physicians who have been reluctant to prescribe cannabis because of uncertainty about clinical indications and fears of being legally liable for any harm that patients experience.

Securing a legal supply of cannabis has been a problem for medical cannabis users. Some governments have allowed cannabis dispensaries to provide approved patients with access to cannabis. Even under these systems, physicians have been reluctant to prescribe cannabis for medico-legal reasons.

In some U.S. states, medical cannabis schemes have been used as a "Trojan horse" for the legalization of recreational cannabis use. This outcome has been facilitated by state laws that 1) define the criteria for medical cannabis use very broadly; 2) allow the decisions as to whether a patient meets these criteria to be made by doctors and patients, without any independent scrutiny; and 3) allow for-profit businesses to supply cannabis to approved patients. This policy has arguably facilitated the legalization of cannabis in Colorado and Washington State, which have enacted these types of medical cannabis laws. If governments want to legalize cannabis, it would be better, on the grounds of honesty and transparency, to do this after an informed public debate about the pros and cons of legalization, rather than by stealth in the guise of providing medical access to cannabis. This would involve a consideration of both the potential benefits (e.g., reduced law en-

forcement costs, elimination of criminalizing cannabis users, taxation of cannabis products) and potential costs of legalization (e.g., increased cannabis users and cannabis-related harm) [63,71].

A better-informed policy toward the medical use of cannabinoids requires more evidence. First, we need clinical trials of the safety and efficacy of CBD and other cannabinoids in treating intractable epilepsy and chronic pain. In the interim, governments can allow medical necessity as a defense against criminal prosecution for patients with these conditions who use cannabis. The uncertainties about the potential adverse effects of sustained use of cannabis for medical use need to be clearly communicated to patients considering their use. Second, we need long-term follow-up studies of patients who use cannabis preparations and medical cannabinoids over periods of years to assess the risks of developing cannabis dependence, exacerbating cardiovascular disease, precipitating psychotic disorders, and developing cancer [5,37].

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REFERENCES

1. Mechoulam R. The pharmacohistory of cannabis sativa. In: Mechoulam R, editor. Cannabinoids as therapeutic agents. Boca Raton, FL: CRC Press; 1986.
2. Grinspoon L, Bakalar J. Marihuana, the forbidden medicine. New Haven: Yale University Press; 1993.
3. Kalant H. Medicinal use of cannabis: history and current status. Pain Res Manag. 2001;6(2):80-91.
4. Bostwick JM. Blurred boundaries: the therapeutics and politics of medical marijuana. Mayo Clin Proc. 2012;87(2):172-86.
5. Hall WD, Degenhardt L. Adverse health effects of non-medical cannabis use. Lancet. 2009;374(9698):1383-91.
6. Iversen L. The science of marijuana. 2nd ed. Oxford: Oxford University Press; 2007.
7. Institute of Medicine. Marijuana and medicine: assessing the science base. Washington, DC: National Academy Press; 1999.
8. Russo E, Guy GW. A tale of two cannabinoids: the therapeutic rationale for combining tetrahydrocannabinol and cannabidiol. Med Hypotheses. 2006;66(2):234-46.
9. Ben Amar M. Cannabinoids in medicine: a review of their therapeutic potential. J Ethnopharmacol. 2006;105(1-2):1-25.
10. Di Marzo V, Petrocellis LD. Plant, synthetic, and endogenous cannabinoids in medicine. Annu Rev Med. 2006;57:553-74.
11. Tramer MR, Carroll D, Campbell FA, Reynolds DJM, Moore RA, McQuay HJ. Cannabinoids for control of chemotherapy induced nausea and vomiting: quantitative systematic review. Br Med J. 2001;323(7303):16-21.
12. Machado Rocha FC, Stéfano SC, De Cássia Haiek R, Rosa Oliveira LMQ, Da Silveira DX. Therapeutic use of Cannabis sativa on chemotherapy-induced nausea and vomiting among cancer patients: systematic review and meta-analysis. Eur J Cancer Care (Engl). 2008;17(5):431-43.
13. Navari RM. Pharmacological management of chemotherapy-induced nausea and vomiting: focus on recent developments. Drugs. 2009;69(5):515-33.
14. Lutge EE, Gray A, Siegfried N. The medical use of cannabis for reducing morbidity and mortality in patients with HIV/AIDS. Cochrane Database Syst Rev. 2013;4:CD005175.
15. Guindon J, Hohmann AG. Cannabinoid CB2 receptors: a therapeutic target for the treatment of inflammatory and neuropathic pain. Br J Pharmacol. 2008;153(2):319-34.
16. Christie MJ. Opioid and cannabinoid receptors: friends with benefits or just close friends? Br J Pharmacol. 2006;148(4):385-6.
17. Martin-Sanchez E, Furukawa TA, Taylor J, Martin JL. Systematic review and meta-analysis of cannabis treatment for chronic pain. Pain Med. 2009;10(8):1353-68.
18. Podda G, Constantinescu CS. Nabiximols in the treatment of spasticity, pain and urinary symptoms due to multiple sclerosis. Expert Opin Biol Ther. 2012;12(11):1517-31.
19. Zajicek J, Fox P, Sanders H, Wright D, Vickery J, Nunn A, et al. Cannabinoids for treatment of spasticity and other symptoms related to multiple sclerosis (CAMS study): multicentre randomised placebo-controlled trial. Lancet. 2003;362(9395):1517-26.
20. Zajicek JP, Sanders HP, Wright DE, Vickery PJ, Ingram WM, Reilly SM, et al. Cannabinoids in multiple sclerosis (CAMS) study: safety and efficacy data for 12 months follow up. J Neurol Neurosurg Psychiatry. 2005;76(12):1664-9.
21. Iskedjian M, Bereza B, Gordon A, Piwko C, Einarson TR. Meta-analysis of cannabis based treatments for neuropathic and multiple sclerosis-related pain. Curr Med Res Opin. 2007;23(1):17-24.
22. Devinsky O, Cilio MR, Cross H, Fernandez-Ruiz J, French J, Hill C, et al. Cannabidiol: pharmacology and potential therapeutic role in epilepsy and other neuropsychiatric disorders. Epilepsia. 2014;55(6):791-802.
23. Cunha JM, Carlini EA, Pereira AE, Ramos OL, Pimentel C, Gagliardi R, et al. Chronic administration of cannabidiol to healthy volunteers and epileptic patients. Pharmacology. 1980;21(3):175-85.
24. Gloss D, Vickrey B. Cannabinoids for epilepsy. Cochrane Database Syst Rev. 2012;6:CD009270.
25. Hill AJ, Williams CM, Whalley BJ, Stephens GJ. Phytocannabinoids as novel therapeutic agents in CNS disorders. Pharmacol Ther. 2012;133(1):79-97.
26. Dos Santos RG, Hallak JE, Leite JP, Zuardi AW, Crippa JA. Phytocannabinoids and epilepsy. J Clin Pharm Ther. 2014;40(2):135-43.
27. Wang T, Collet JP, Shapiro S, Ware MA. Adverse effects of medical cannabinoids: a systematic review. CMAJ. 2008;178(13):1669-78.
28. Fernandez O. Advances in the management of multiple sclerosis spasticity: recent clinical trials. Eur Neurol. 2014;72(Suppl 1):9-11.
29. Vachová M, Novotná A, Mares J, Taláb R, Fiedler J, Lauder H, et al. A multicentre, double-blind, randomised, parallel-group, placebo-controlled study of effect of long-term Sativex® treatment on cognition and mood of patients with spasticity due to multiple sclerosis. Journal of Multiple Sclerosis. 2014;1(122):2.
30. Hall WD. What has research over the past two decades revealed about the adverse health effects of recreational cannabis use? Addiction. 2015;110(1):19-35.
31. Hall WD, Swift W. The policy implications of cannabis dependence. In: Roffman RA, Stephens RS, editors. Cannabis dependence: its nature, consequences and treatment. Cambridge: Cambridge University Press; 2006. p. 315-39.
32. Anthony JC. The epidemiology of cannabis dependence. In: Roffman RA, Stephens RS, editors. Cannabis dependence: its nature, consequences and treatment. Cambridge: Cambridge University Press; 2006. p. 58-105.
33. AusPAR: Nabiximols. Australian Public Assessment Report. Australian Government Department of Health, Therapeutic Goods Administration [Internet]. [cited 2013]. Available from: https://www.tga.gov.au/auspar/auspar-nabiximols.
34. Degenhardt L, Hall WD. Is cannabis a contributory cause of psychosis? Can J Psychiatry. 2006;51(9):556-65.
35. Moore T, Zammit S, Lingford-Hughes A, Barnes T, Jones P, Burke M, et al. Cannabis use and risk of psychotic or affec-

tive mental health outcomes: A systematic review. Lancet. 2007;370(9584):319-28.
36. Hall WD, Degenhardt L. What are the policy implications of the evidence on cannabis and psychosis? Can J Psychiatry. 2006;51(9):566-74.
37. Hall WD, Degenhardt L. Regulating opioid prescribing to provide access to effective treatment while minimizing diversion: an overdue topic for research. Addiction. 2007;102(11):1685-8.
38. Jouanjus E, Lapeyre-Mestre M, Micallef J. Cannabis use: signal of increasing risk of serious cardiovascular disorders. J Am Heart Assoc. 2014;3(2):e000638.
39. Thomas G, Kloner RA, Rezkalla S. Adverse cardiovascular, cerebrovascular, and peripheral vascular effects of marijuana inhalation: what cardiologists need to know. Am J Cardiol. 2014;113(1):187-90.
40. Huang YH, Zhang ZF, Tashkin DP, Feng B, Straif K, Hashibe M. An epidemiologic review of marijuana and cancer: an update. Cancer Epidemiol Biomarkers Prev. 2015;24(1):15-31.
41. Grotenhermen F. Cannabinoids for therapeutic use: designing systems to increase efficacy and reliability. Am J Drug Deliv. 2004;2(4):229-40.
42. Hall WD, Degenhardt L, Lynskey MT. The health and psychological effects of cannabis use. Canberra: Commonwealth Department of Health and Aged Care; 2001.
43. Cohen SP. Cannabinoids for chronic pain. BMJ. 2008;336(7637):167-8.
44. Taylor S. Remedicalising cannabis: science, medicine and policy, 1973 to the early twenty-first century. Unpublished doctoral thesis. London: School of Hygiene and Tropical Medicine; 2010.
45. Sativex. GW Pharmaceuticals [Internet]. Available from: http://www.gwpharm.com/Sativex.aspx.
46. Galston W, Dionne EJ. The new politics of marijuana legalization: why opinion is changing. Governance Studies at Brookings [Internet]. [cited 2013]. Available from: http://www.brookings.edu/research/papers/2013/05/29-politics-marijuana-legalization-galston-dionne.
47. Pacula RL, Chriqui JF, Reichman DA, Terry-McElrath Y. State medical marijuana laws: understanding the laws and their limitations. J Public Health Policy. 2002;23(4):411-37.
48. Conboy JR. Smoke screen: America's drug policy and medical marijuana. Food Drug Law J. 2000;55(4):601-17.
49. Medical marijuana pros and cons. 23 legal medical marijuana states and DC: law, fees and possession limits. ProCon.org [Internet]. [cited 2015]. Available from: http://medicalmarijuana.procon.org/view.resource.php?resourceID=00881.
50. Pacula RL, Powell D, Heaton P, Sevigny EL. Assessing the effects of medical marijuana laws on marijuana use: the devil is in the details. J Policy Anal Manage. 2015;34(1):7-31.
51. Hoffmann DE, Weber E. Medical marijuana and the law. N Engl J Med. 2010;362(16):1453-7.
52. Cohen PJ. Medical marijuana 2010: it's time to fix the regulatory vacuum. J Law Med Ethics. 2010;38(3):654-66.
53. Regan T. Joint ventures: inside America's almost legal marijuana industry. New York: Wiley; 2011.
54. Barnes RE. Reefer madness: legal and moral issues surrounding the medical prescription of marijuana. Bioethics. 2000;14(1):16-41.
55. Cohen PJ. Medical marijuana, compassionate use, and public policy: expert opinion or vox populi? Hastings Cent Rep. 2006;36(3):19-22.
56. Eddy M. Medical marijuana: review and analysis of federal and state policies. Washington, DC: Congressional Research Service; 2009.
57. Samuels D. Dr Kush: how medical marijuana is transforming the pot industry. New Yorker [Internet]. [cited 2008]. Available from: http://www.newyorkerest.com/2008/dr-kush-how-medical-marijuana-is-transforming-the-pot-industry/.
58. O'Connell TJ, Bou-Matar CB. Long term marijuana users seeking medical cannabis in California (2001-2007): demographics, social characteristics, patterns of cannabis and other drug use of 4117 applicants. Harm Reduct J. 2007;4:16.
59. Reinarman C, Nunberg H, Lanthier F, Heddleston T. Who are medical marijuana patients? Population characteristics from nine California assessment clinics. J Psychoactive Drugs. 2011;43(2):128-35.
60. Ryan-Ibarra S, Induni M, Ewing D. Prevalence of medical marijuana use in California, 2012. Drug Alcohol Rev. 2015;34(2):141-6.
61. Teesson M, Degenhardt L, Lynskey M, Hall WD. The relationships between substance use and mental health problems: evidence from longitudinal studies. In: Stockwell T, Gruenwald PJ, Toumbourou JW, Loxley W, editors. Preventing harmful substance use: the evidence base for policy and practice. Chichester, UK: John Wiley; 2005. p. 43-51.
62. Bogdanoski T. Accommodating the medical use of marijuana: surveying the differing legal approaches in Australia, the United States and Canada. J Law Med. 2010;17(4):508-31.
63. Room R, Fischer B, Hall WD, Lenton S, Reuter P. Cannabis policy: moving beyond stalemate. Oxford: Oxford University Press; 2010.
64. Hazekamp A, Heerdink ER. The prevalence and incidence of medicinal cannabis on prescription in The Netherlands. Eur J Clin Pharmacol. 2013;69(8):1575-80.
65. Garvey T, Yeh BT. State legalization of recreational marijuana: selected legal issues. Washington, DC: Congressional Research Office; 2014.
66. Retail marijuana 2013. Colorado Department of Public Health and Environment [Internet]. [cited 2015]. Available from: https://www.colorado.gov/pacific/cdphe/retail-marijuana.
67. I-502 Implementation 2014. Washington State Liquor Control Board [Internet]. [cited 2015]. Available from: http://www.liq.wa.gov/marijuana/I-502.
68. Associated Press. Colorado medical marijuana rules are vulnerable to change. Herald-Tribune [Internet]. [cited 2015]. Available from: http://marijuana.heraldtribune.com/2015/01/04/colorado-medical-marijuana-rules-vulnerable-change/.
69. Hickenlooper GJW. Experimenting with pot: the state of Colorado's legalization of marijuana. Milbank Q. 2014;92(2):243-9.
70. Basu R. Colorado's marijuana law has brought tourists and tax revenues. Des Moines Register [Internet]. [cited 2014]. Available from: http://www.desmoinesregister.com/story/opinion/columnists/rekha-basu/2014/08/17/colorados-marijuana-law-brought-tourists-tax-revenues/14178219/.
71. Caulkins J, Hawken A, Kilmer B, Kleiman M. Marijuana legalization: what everyone needs to know. New York: Oxford University Press; 2012.