SPECIAL COMMUNICATION

Cannabis and Its Derivatives: Review of Medical Use

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Background: **Use of cannabis is often an under-reported activity in our society. Despite legal restriction, cannabis is often used to relieve chronic and neuropathic pain, and it carries psychotropic and physical adverse effects with a propensity for addiction. This article aims to update the current knowledge and evidence of using cannabis and its derivatives with a view to the sociolegal context and perspectives for future research.**

Methods: **Cannabis use can be traced back to ancient cultures and still continues in our present society despite legal curtailment. The active ingredient, Δ9-tetrahydrocannabinol, accounts for both the physical and psychotropic effects of cannabis. Though clinical trials demonstrate benefits in alleviating chronic and neuropathic pain, there is also significant potential physical and psychotropic side-effects of cannabis. Recent laboratory data highlight synergistic interactions between cannabinoid and opioid receptors, with potential reduction of drug-seeking behavior and opiate sparing effects. Legal rulings also have changed in certain American states, which may lead to wider use of cannabis among eligible persons.**

Conclusions: **Family physicians need to be cognizant of such changing landscapes with a practical knowledge on the pros and cons of medical marijuana, the legal implications of its use, and possible developments in the future. (J Am Board Fam Med 2011;24:452–462.)**

Keywords: **Cannabis, Clinical Effects, Controversy, Drug Therapy, Marijuana, Substance Abuse**

Case 1

Scenario

You are a family physician in Ontario, Canada. A 54-year-old man suffering from multiple sclerosis came to your office asking for a prescription for medical marijuana to control his pain. He was taking continuous-release morphine, gabapentin, and lamotrigine, but this combination was still insufficient. He visited Florida a few times, where he smoked cannabis, which helped tremendously to reduce the neuropathic pain and detach his mind from it. He would like to continue using cannabis but is worried about the legal implications and the purity of sample he may obtain on the street.

Suggested Management

The evidence of various forms of cannabis (smoked, oral, and oromucosal spray) for treating neuropathic pain caused by multiple sclerosis should be discussed against the known harms and challenges of usage. Sativex (legally available form of cannabis in Canada; GW Pharmaceuticals, Salisbury, Wiltshire, UK) could be recommended as a first-line treatment. If the patient still decided to pursue a smoked or oral extract of cannabis, referral should be made to recognized specialists in Quebec for a full assessment of eligibility of patient's use and possession of medical marijuana. Close monitoring of the patient would be necessary.

Case 2

Scenario

You are a family physician in the state of California. A 65-year-old male veteran came to your office as a new patient. He had a history of chronic leg pain caused by a shrapnel injury he suffered during the Vietnam War in 1968. Since the 1970s, he has been treated at the local veterans hospital under a pain management program, but control has been unsatisfactory. When asked if he used any recreational

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drugs, including marijuana, he evaded your question and said he needed to stay on the pain program. You suspected he was using marijuana for his chronic pain.

Suggested Management

The patient should be informed of the new directive from the Veterans Health Administration regarding veterans' use of marijuana and be reassured that he would not be denied his pain management services at the veterans hospital on that basis. He also should be encouraged to discuss his marijuana use with you so that you can monitor his progress. Liaising with an addiction medicine specialist can be helpful to ensure the best follow-up of this patient.

Cannabis, also known as marijuana, refers to the preparation 53 from the plant belonging to the family *Cannabaceae*, the genus *Cannabis*, and the species *Cannabis sativa*, which possess psychoactive effects. The flowering tops, leaves, and stalks of the mature female plant are commonly used as the herbal form of cannabis, but sometimes the resinous extract of compressed herb is also used and is called "hash." Archaeologists have identified fibers from cannabis stems in specimens dating back to 4000 BC, and its incorporation into textiles and paper was found in the tombs of the Chinese Han dynasty (~100 BC).[1] The first record of cannabis as a medicine can be found in the oldest Chinese pharmacopeia, *Shen Nong Ben Cao Jing*, written in the Eastern Han Dynasty (AD 25 to AD 220), which was indicated for rheumatic pain, malaria, constipation, and disorders of the female reproductive system.[2] Though the cannabis leaf and stem is rarely used nowadays in Chinese herbal medicine, cannabis seeds, which contain very few psychoactive ingredients, are still commonly prescribed for their laxative effects.[2] Smoking cannabis is often an under-reported behavior in our society, with a reported prevalence from the World Health Organization of 3.9% among the global population aged 15 to 64 years.[3] There are more than 70 psychoactive compounds called "cannabinoids" that have been identified in cannabis,[4] among which Δ9-tetrahydrocannabinol (THC) accounts for most of the psychological and physical effects, and its content is often used as a measure of sample potency. We now know that THC acts on 2 types of cannabinoid receptors: CB_1 and CB_2. CB_1 receptors are mainly found in the brain, peripheral nerves, and autonomic nervous system,[5] whereas CB_2 receptors are found both in the neurons and immune cells.[6] THC exerts its effects primarily via CB_1 receptors.

The Laws Regarding Cannabis

In the United States, cannabis is an illicit drug either to possess or trade. Since the inception of the Controlled Substance Act in 1970, the US Federal Law penalizes any act of possessing, dispensing, and prescribing marijuana. Enforcement of prohibition carries an annual price tag of up to $7.7 billion in the United States alone.[7] However, since 1996 the situation has been changing rapidly—14 states (California, Alaska, Oregon, Washington, Maine, Hawaii, Colorado, Nevada, Vermont, Montana, Rhode Island, New Mexico, Michigan, and New Jersey) already have amended their state laws to allow the use of marijuana by persons with debilitating medical conditions as certified by licensed physicians.[8,9] The impact has been significant: a recent study in Washington estimated that per annum, up to 2000 licensed physicians have prescribed medical cannabis[10]; in California, more than 350,000 patients already possess a physician's recommendation to use cannabis.[11] Nevertheless, among these 14 states, there is substantial variation in the regulation of the quality control, prescription limit, patient registry, and dispensing outlets. For example, in Oregon and Washington, it is legal to possess up to 24 ounces of marijuana, but in Nevada, Montana, and Alaska, the legal limit is only 1 ounce.[8] Cannabis is currently schedule I; additional research would be facilitated if the drug were reclassified to schedule II.[8] From a public health standpoint, there is some evidence that decriminalization of cannabis could free up law enforcement resources to curtail other trafficking activities without leading to increased cannabis abuses.[12] Overall, however, the US Federal law remains unchanged regarding the penal stance toward marijuana, creating various ambiguities and difficulties. For those veterans who are permitted to use medical marijuana by law of their state, these difficulties have been lessened. This has posed an administrative dilemma for those veterans who are allowed to use; the Department of Veterans Affairs issued a directive in July 2010 that permits veterans to continue their use of medical marijuana in states where it is legal without losing their medical benefits from Veterans Affairs.[13]

Recent news from *USA Today*[14] reports that the US federal government has issued warning letters to several states that have approved the use of medical marijuana with an implication that anyone involved in the growth, operation, or legal regulation of medical marijuana will be subjected to prosecution. These states include Washington, California, Montana, and Rode Island. This was coupled by recent large-scale raids at marijuana growing operations in Montana. Despite reassurance from Eric Holder, US Attorney General, that the penal policy is directed at those who violate both deferral and state laws, this unexpected siren from the federal government has been heard loud and clear, leading Governor Chris Gregoire, of the state of Washington, to abort a proposal to create licensed marijuana dispensaries and Governor Chris Christie, of the state of New Jersey, to postpone plans for marijuana operators.

In Canada, it is also illegal to trade or possess 104 marijuana according to provincial and government laws. However, access to marijuana for medical use is possible under Health Canada's Marijuana Medical Access Regulations, which came into force on July 30, 2001.[14] The regulations clearly outline 2 categories of persons who can apply to possess for an authorization to possess marijuana for medical purposes. Category 1 refers to people with end-of-life care; seizures from epilepsy; severe pain and/or persistent muscle spasms caused by multiple sclerosis, spinal cord diseases, or spinal cord injury; severe pain; cachexia; anorexia; weight loss and/or severe nausea from cancer or HIV/AIDS infection. A medical declaration from a licensed medical practitioner is required. Category 2 refers to people who have debilitating symptom(s) of medical condition(s), other than those described in category 1, which have failed conventional medical treatment. An assessment by a designated specialist is necessary along with a medical declaration from a licensed medical practitioner.

Under the regulations, the maximum amount of marijuana that can be possessed by any authorized user is a 30-day total of daily requirement. Health Canada sources its supply of dried marijuana and seeds from Prairie Plant Systems Incorporated (Saskatoon, Saskatchewan, Canada), a company that specializes in the growing, harvesting, and processing of plants for pharmaceutical products and research. Alternatively, authorized marijuana users can apply for a permit to produce and grow their own supply provided they meet specific and detailed criteria.

The Harms of Cannabis

Physical and Psychiatric Effects

Among naive users, cannabis smoking often leads to adverse effects. Physical symptoms include increased heart rate and fluctuations in blood pressure[15]; psychomotor sequelae include euphoria, anxiety, psychomotor retardation, and impairment of cognition and memory.[16] The estimated lethal dose for humans is between 15 g and 70 g.[3] When compared with cigarette smoke, cannabis contains a similar array of detrimental and carcinogenic compounds, some of which are present even at higher concentrations.[17] Among chronic users, population studies have associated cannabis use with decreased pulmonary function, chronic obstructive airway diseases, and pulmonary infections,[18] although data may be confounded by concomitant tobacco smoking and other social factors. In vitro and in vivo animal studies have demonstrated mutagenic effects of cannabis smoke, and precancerous pulmonary pathology as seen in tobacco smokers has been described in cannabis users.[19] Nevertheless, there is still inconsistency from the published literature regarding an increased risk for upper respiratory tract cancer caused by cannabis smoking.[3,18] Various reports have associated cannabis with cardiac arrhythmias,[20,21] coronary insufficiency[22–24] and myocardial infarction.[25,26] A retrospective cross-sectional study revealed a 4.8-times increased risk of developing myocardial infarction within the first hour after smoking cannabis. Earlier data from population studies[27,28] and meta-analysis[29] have associated cannabis smoking with low birth weight,[29] which is maybe confounded by cigarette smoking and socioeconomic status and is not supported by more recent studies.[30,31] Finally, the controversial link of cannabis use and psychosis has found more support in recent publications.[32–34]

Dependence and Abuse

Cannabis is recognized as a substance with a high potential for dependence, which occurs in 1 out of 10 people who have ever used cannabis. It leads to behaviors of preoccupation, compulsion, reinforcement, and withdrawal after chronic use.[35] An Australian survey found that symptoms of cannabis

withdrawal satisfied the diagnostic criteria of both International Classification of Diseases 10 and Diagnostic and Statistical Manual of Mental Disorders IV for substance dependence, which included sleep disturbance, anorexia, irritability, dysphoria, lethargy, and cravings.[36] In the United States, cannabis is now ranked among alcohol and tobacco as one of the most common substances of among adolescents.[37] There is also ample evidence indicating that regular use of cannabis predicts subsequent psychosocial problems and abuse behavior of other addictive substances. A review of cohort studies by McLaren et al[38] supported a causal link between cannabis use and psychosis. A recent 10-year follow-up study of adolescents in Australia who used cannabis occasionally were found to be at higher risks of drug abuse and educational problems.[39] However, several issues have been identified in the published literature about cannabis, which have limited our understanding on the adverse effects of cannabis: (1) lack of consensus on the definition and classification of different types of cannabis users (heavy, regular, occasional, and nonusers); (2) variable quality of studies regarding design, effect sizes, and control of confounding factors; and (3) the polarization of the approach to either studying nonusers versus light/infrequent users or, infrequent/light/nondependent users versus frequent/heavy/dependent users.[40]

New Kids on the Block

Recently, synthetic analogues of marijuana, known generically as "spice" or "K2," have gained rapid popularity among youths in the Unites States and Europe. Marketed as an incense or herbal blend, the exact constituents of spice has been a myth, and its place of origin is often unclear. Despite sharing similar psychotropic effects as genuine cannabis, spice cannot be reliably tested by drug screens and poses a technical problem for the law enforcement; hence it is capable of evading legal scrutiny among most states in America. A report from the Drug Enforcement Administration of the US Department of Justice in June 2010 had divulged the possible constituents of spice (or K2), which included HU-210, JWH-018, JWH-073 and CP-47,497,[41] all of which were synthetic cannabinoids legally endorsed for scientific research. This was echoed by a recent research publication that identified a synthetic cannabinoid in commercially obtained spice, JWH-018, which activated CB_1.[42]

Analgesic Potential and Synergism With Opioids

Despite legal curtailment, cannabis is still used by 10% to 15% of patients with multiple sclerosis[43] and noncancer types of chronic pain[44] for both analgesia and psychological detachment. Various well-designed, randomized, placebo-controlled trials have shown that smoked cannabis can relieve peripheral,[45] posttraumatic,[46] and HIV-induced[47,48] neuropathic pain. Evidence has been accumulating from molecular and cell-signaling studies that suggest that the opioids and cannabinoid systems can interact synergistically to enhance analgesic effects.[49] Animal studies have shown that topical cannabinoid enhances the action of topical morphine,[50] an effect that is preserved in a morphine-tolerant state.[51] Moreover, cannabinoids are increasingly being recognized in animal models for their potential sparing effects with opioids[52] of neuropathic pain and arthritic pain.[53] Although similar effects have not been translated to human studies, Robert et al[54] found a synergistic affective analgesia between Δ9-THC and morphine in experimentally induced pain in human volunteers.

Evidence from Clinical Studies

To review the latest evidence of cannabis use and its derivatives, a literature search was conducted from the MEDLINE, EMBASE, PsycINFO, and Cochrane Database of Systematic Reviews from their inception dates to 30 November 2010, using the following keywords: "cannabis," "marijuana," "Δ9-tetrahydrocannabinol," "clinical trial," "benefits," and "side effects." Relevant articles were selected and their quality of evidence was rated according to the Strength of Recommendations Taxonomy (SORT),[56] with recommendations rated as A, B, or C. The results are summarized in Table 1. In brief, the efficacy of smoked cannabis has been studied for Gilles de la Tourette syndrome, glaucoma, and pain, with good evidence for clinical benefits in HIV-induced neuropathic pain. Oral extract of cannabis has better evidence of relieving self-reported symptoms of spasticity caused by multiple sclerosis. Finally, the oromucosal form of cannabis extract (Sativex, GW Pharmaceuticals) is efficacious for peripheral and central neuropathic pain, especially that caused by multiple sclerosis.

Table 1. Clinical Studies of Cannabis and Its Derivatives with SORT Level of Recommendation[56]

Agent	Condition Indicated	Form of delivery	Nature of Study	Patients (n)	Outcome Measures	Outcome	SORT Level of Recommendation	Reference
Cannabis	Gilles de la Tourette Syndrome	Smoking	Case report	3	Self-reported frequency of motor tics	50% to 70% remission	C	Sandyk et al[57]
Cannabis	Gilles de la Tourette Syndrome	Smoking	Case report	1	Self-reported symptoms	100% remission	C	Hemming et al[58]
Cannabis	Glaucoma	Smoking single dose	Double-blinded cross-over placebo-controlled RCT	18	Intraocular pressure	Significant reduction	B	Merritt et al[59]
Cannabis	Neuropathic pain in HIV patient	Smoking 5 days a week for 2 weeks	Prospective placebo-controlled RCT	28	Pain intensity using Descriptor Differential Scale	Improvement in pain ($P = .016$)	A	Ellis et al[49]
Cannabis	Sensory neuropathic pain in HIV patient	Smoking 3 times a day for 5 days	Double-blinded cross-over placebo-controlled RCT	50	Chronic pain ratings	Reduction of pain by 34% ($P = .03$)	A	Abrams et al[48]
Cannabis	Capsaicin-induced pain in volunteers	Smoking single dose at various concentrations	Double-blinded cross-over placebo-controlled RCT	15	Pain scores and McGill Pain Questionnaire	Pain reduction at medium dose within a certain time frame only	B	Wallace et al[60]
Cannabis	Acute inflammatory pain in volunteers	Single oral dose of encapsulate extract	Double-blinded cross-over placebo-controlled RCT	18	Threshold to heat and electricity in areas with UV-induced sunburnt	No effect on pain thresholds	B	Kraft et al[61]
Cannabis	Spasticity due to multiple sclerosis	Escalating dose of oral encapsulate extract	Double-blinded cross-over placebo-controlled RCT	50	Spasms frequency and mobility	Improvement in spasms frequency ($P = .013$) and mobility ($P = .01$)	A	Vaney et al[62]
Cannabis	Spasticity caused by multiple sclerosis	Titrating oral dose of cannabis extract	Double-blinded placebo-controlled RCT	327	Ashworth score and self-reported spasticity	Improvement of self-report ratings of pain and spasticity ($P = .003$)	A	Zajicek et al[63]
Δ^9-THC	Gilles de la Tourette Syndrome	Single oral dose	Cross-over placebo-controlled RCT	12	TSSL, STSS, YGTSS scores	Significant reduction in TSSL score ($P = .015$), nil for STSS and YGTSS	A	Müller-Vahl et al[64]
Δ^9-THC	Gilles de la Tourette Syndrome	Daily oral dose for 6 weeks	Placebo-controlled RCT	24	TSSL,TS-CGI, STSS; YGTSS	Significant reduction in TSSL score using ANOVA ($P = .037$), nil for TS-CGI, STSS, YGTSS	A	Müller-Vahl et al[65]
Δ^9-THC	Spasticity caused by multiple sclerosis	Escalating dose for 5 days	Double-blinded cross-over placebo-controlled RCT	13	Subjective rating and objective measure of spasticity	Significant in both scores	A	Ungerleider et al[66]
Δ^9-THC	Spasticity due to multiple sclerosis	Titrating oral dose of Δ^9-THC	Double-blinded placebo-controlled RCT	330	Ashworth score and self-reported spasticity	Improvement of self-report ratings of pain and spasticity ($P = .003$)	A	Zajicek et al[63]
Δ^9-THC	Postoperative pain	Single oral dose on postoperative day 2	Double-blinded placebo-controlled RCT	40	Summed pain intensity difference 6 hours after administration	No significant difference	B	Buggy et al[67]
Δ^9-THC	Refractory neuropathic pain	Titrating oral dose	Open label pilot	8	Neuropathic pain score and quality of life	No apparent effect	C	Attal et al[68]

Continued

Table 1. Continued

Agent	Condition Indicated	Form of delivery	Nature of Study	Patients (n)	Outcome Measures	Outcome	SORT Level of Recommendation	Reference
Δ^9-THC	Glioblastoma multiforme	Daily intracranial tumour injection up to 64 days	Phase I cohort pilot study	9	Safety of intracranial route of administration	Intracranial route seems to be safe and may slow down tumour growth	C	Guzman et al[69]
Dronabinol (synthetic Δ^9-THC)	Alzheimer's disease	Twice-daily oral dose for 6 weeks	Double-blinded cross-over placebo-controlled RCT	15	Body weight, triceps skin fold, disturbed behavior, affect	A trend of improvement reported but no significance quoted	B	Volicer et al[70]
Dronabinol (synthetic Δ^9-THC)	Alzheimer's disease	Daily oral dose for 2 weeks	Open label pilot	6	Nocturnal motor activity score and Neuropsychiatric Inventory	Significant improvement in both (P = .028 and P = 0027)	C	Walther et al[71]
Dronabinol (synthetic Δ^9-THC)	Anorexia and weight loss in AIDS	Twice-daily oral dose for 6 weeks	Placebo-controlled RCT	139	VAS for appetite, mood, and nausea	Significant change in appetite (38%; P = .015); mood (10%; P = .06); and nausea (20%; P = .05)	A	Beal et al[72]
Nabilone	Spasticity caused by spinal cord injury	Twice-daily oral dose for 4 weeks	Double-blinded cross-over placebo-controlled RCT	12	Ashworth Scale , Total Ashworth Score	Significant reduction, P = .003 and 0.001 respectively	A	Pooyania et al[73]
Nabilone	Pain caused by fibromyalgia	Oral dose for 4 weeks	Double-blinded placebo-controlled RCT	40	VAS and Fibromyalgia impact questionnaire	Significant reduction in both scores ($P < .02$)	A	Skrabek et al[74]
Sativex (extract of cannabis containing Δ^9-THC and cannabidiol)	Peripheral neuropathic pain	Self-titrating dose of oromucosal spray for 5 weeks	Double-blinded placebo-controlled RCT	125	Various pain intensity scores	Significant reduction, (P = .001 to P = .04)	A	Nurmikko et al[75]
Sativex (extract of cannabis containing Δ^9-THC and cannabidiol)	Intractable neurogenic symptoms	Self-titrating dose of oromucosal spray for 2 weeks	Double-blinded cross-over placebo-controlled RCT	20	Self-report symptoms and adverse effects	Significant relief in pain with certain domains reaching significance of $P < .05$	A	Wade et al[76]
Sativex (extract of cannabis containing Δ^9-THC and cannabidiol)	Central pain in multiple sclerosis	Self-titrating dose of oromucosal spray for 4 weeks	Double-blinded placebo-controlled RCT	66	11-point scale for pain and sleep disturbance	Significant reduction of pain (P = .005) and sleep disturbance (P = .003)	A	Rog et al[77]
Sativex (extract of cannabis containing Δ^9-THC and cannabidiol)	Bladder dysfunction in multiple sclerosis	Single daily dose for 8 weeks	Open label pilot study	15	Occurrence of urinary incontinence, frequency, nocturia	Significant reduction in all 3 domains ($P < .05$)	A	Brady et al[78]

RCT, randomized controlled trial; UV, ultraviolet; TSSL, ; STSS, ; YGTSS, ; TS-CGI, ANOVA, analysis of variance; VAS, Visual Analog Scale; THC, tetrahydrolcannabinol.

The Challenges of Using Cannabis

Despite the evidence of benefits in certain conditions, the use of medical marijuana within a legal jurisdiction still faces a number of challenges:

- *Method of delivery and quality control*. Smoking raw cannabis remains the most common and easiest route of delivery, but the actual amount of cannabinoids deliverable to the alveolar space varies considerably depending on the individual's techniques of inhalation/exhalation, the percentage of aeroingestion, and the individual's functional lung capacity. Without prior training, it could be difficult for a family physician in daily practice to advise an eligible patient on the proper techniques of administration and quality control of prescription regarding medical marijuana. The content of THC in cannabis may vary remarkably according by geographic origin,[56] the parts of plant being used (buds versus stem and seeds), the methods of storage, and the techniques of cultivation.[79] There are 2 main strains used in medical marijuana: the Sativa and the Indica. The Sativa plant is usually taller with longer leaves that grow better outdoors, whereas the Indica plant is more bushy with shorter leaves that thrive better indoors. Although both strains exist in pure forms, various combinations of the 2 strains are packaged as medical marijuana, which may result in variable therapeutic and side effects. Health Canada's policy of adopting a centralized source of medical marijuana from an approved plantation is a good way to assure quality; however, it is still technically difficult to endorse it globally for all licensed users and growers. As a prescription, standardization and titration of dose efficacy remain a challenge for medical marijuana.
- *Adequate monitoring and prevention of addiction*. As with other substances of abuse, cannabis may lead to varying adverse effects and addiction potential among different individuals. Before facilitating an eligible person to receive medical marijuana, family physicians should possess the knowledge and skills to screen for addiction potential. During the course of treatment, close surveillance of the patient to prevent addiction and adverse effects, in collaboration with a specialist when necessary, remains a top priority. In Canada and in those American states where it is legal to use medical marijuana, more training and educational resources should be made available for the practicing family physician to enhance their competence in approaching cannabis.
- *Contaminants in cannabis*. Studies have reported an alarming level of biological contaminants in cannabis, which include *Aspergillus* fungus[80,81] and bacteria,[82] potentially leading to fulminant pneumonia, especially among the immunosuppressed.[83] Nonbiological contaminants also have been found, which include heavy metals from soil like aluminum[84] and cadmium, the latter of which seems to be absorbed by the cannabis plant in particularly high concentrations.[85] Organophosphate pesticides are other nonbiological contaminants that are found less in cannabis cultivated outdoors than indoors.[36] Finally, tiny glass beads or sand have been found in street samples of cannabis, which were added for weight to boost profits and can cause damage to the oral mucosa and lungs.[86]
- *Contamination by cannabis*. Secondary inhalation of cannabis fumes released by primary smokers is a theoretical but negligible threat, as shown by a study of airborne particulates in urban Spain[87] and another study of passive exposure to cannabis smoke in a Netherlands coffee shop.[88] More research in this area is warranted from the perspective of public health.

The Controversy Remains

In 1969, an article published in the *New England Journal of Medicine* quoted from the Wootton Report that cannabis is "a potent drug, having as wide a capacity as alcohol to alter mood, judgment, and functional ability, and admitted that it is a dangerous drug in that sense, but in terms of physical harmfulness much less dangerous than opiates, amphetamines, and barbiturates and also less dangerous than alcohol."[89] Since then, scientific and clinical data have helped us understand the mechanisms of actions of cannabis and its derived compounds for treating chronic and neuropathic pain, highlighting the potential analgesic synergism with opioids and the potential of an opiate sparing effect in clinical settings. In particular, animal studies have recently shown that cannabidiol (CBD), a nonpsychoactive constituent of marijuana, is capable of decreasing self-administration and drug-seeking behavior caused by heroin,[90] in addition to other anti-in-

flammatory antipsychotic and neuroprotective effects.[91,92] Another observational study of the ratio of CBD:THC from street cannabis samples suggests that a higher CBD content reduced reinforcing behavior and attention bias to marijuana. Further directions of research include a better understanding of the mechanisms of action of CBD and its interplay with THC, plus bioengineering a safer marijuana strain that contains the appropriate composition of CBD and THC for optimal therapeutic effects with the least adverse profile and addictive potential. Thus, important issues of dosage standardization, quality control, adverse effects profiling, and prevention of addiction could be resolved. Until then, family physicians in North America and Canada continue to face the underreported use of cannabis in our society and its risks of abuse.

References

1. Zuardi AW. History of cannabis as a medicine: a review. Rev Bras Psiquiatr 2006;28(2):153–7.
2. Touw M. The religious and medicinal uses of Cannabis in China, India and Tibet. J Psychoactive Drugs 1981;13(1):23–34.
3. Hall W, Degenhardt L. Adverse health effects of non-medical cannabis use. Lancet 2009;374(9698): 1383–91.
4. Ashton CH. Pharmacology and effects of cannabis: a brief review. Br J Psychiatry 2001;178:101–6.
5. Tsou K, Brown S, Sanudo-Pena MC, Mackie K, Walker JM. Immunohistochemical distribution of cannabinoid CB1 receptors in the rat central nervous system. Neuroscience 1998;83(2):393–411.
6. Galiegue S, Mary S, Marchand J, et al. Expression of central and peripheral cannabinoid receptors in human immune tissues and leukocyte subpopulations. Eur J Biochem 1995;232(1):54–61.
7. Egan D, Miron JA. The budgetary implications of marihuana prohibition. In: Earleywine M, ed. Pot Politics: Marijuana and the Costs of Prohibition. New York: Oxford University Press; 2007:17–39.
8. Hoffmann DE, Weber E. Medical marijuana and the law. N Engl J Med 2010;362(16):1453–7.
9. MacDonald J. Medical marijuana: informational resources for family physicians. Am Fam Physician 2009;80(8):779.
10. Aggarwal SK, Kyashna-Tocha M, Carter GT. Dosing medical marijuana: rational guidelines on trial in Washington State. Med Gen Med 2007;9(3):52.
11. 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.
12. Single E, Christie P, Ali R. The impact of cannabis decriminalisation in Australia and the United States. J Public Health Policy 2000;21(2):157–86.
13. US Department of Veterans Affairs. Medical marijuana. VHA Directive 2010–035. Washington DC: Veterans Health Administration; July 2010. Available at: http://www.va.gov/vhapublications/ViewPublication.asp?pub_ID=2276. Accessed .
14. Lifland JB. States reassess medical marijuana laws after warnings. 3 May 2011. Available at: http://yourlife.usatoday.com/health/medical/story/2011/05/States-reassess-medical-marijuana-laws-after-warnings/46756064/1#uslPageReturn. Accessed 31 May 2011.
15. Health Canada. Fact sheet–medical access to marihuana. 2008. Available at: http://www.hc-sc.gc.ca/dhp-mps/marihuana/law-loi/fact_sheet-infofiche-eng.php. Accessed 31 May 2011.
16. Hall W, Solowij N. Adverse effects of cannabis. Lancet 1998;352(9140):1611–6.
17. Grotenhermen F. The toxicology of cannabis and cannabis prohibition. Chem Biodivers 2007;4(8):1744–69.
18. Moir D, Rickert WS, Levasseur G, et al. A comparison of mainstream and sidestream marijuana and tobacco cigarette smoke produced under two machine smoking conditions. Chem Res Toxicol 2008; 21(2):494–502.
19. Reid PT, Macleod J, Robertson JR. Cannabis and the lung. J R Coll Physicians Edinb 2010;40(4):328–34.
20. Tashkin DP. Smoked marijuana as a cause of lung injury. Monaldi Arch Chest Dis 2005;63(2):93–100.
21. Lehavi A, Shay M, Gilony C, Even L. [Marijuana smoking and paroxysmal atrial fibrillation]. Harefuah 2005;144(1):2–3, 72.
22. Baranchuk A, Johri AM, Simpson CS, Methot M, Redfearn DP. Ventricular fibrillation triggered by marijuana use in a patient with ischemic cardiomyopathy: a case report. Cases J 2008;1(1):373.
23. Basnet S, Mander G, Nicolas R. Coronary vasospasm in an adolescent resulting from marijuana use. Pediatr Cardiol 2009;30(4):543–5.
24. Bailly C, Merceron O, Hammoudi N, Dorent R, Michel PL. Cannabis induced acute coronary syndrome in a young female. Int J Cardiol 2010;143(1):e4–6.
25. Dwivedi S, Kumar V, Aggarwal A. Cannabis smoking and acute coronary syndrome: two illustrative cases. Int J Cardiol 2008;128(2):e54–7.
26. Kocabay G, Yildiz M, Duran NE, Ozkan M. Acute inferior myocardial infarction due to cannabis smoking in a young man. J Cardiovasc Med (Hagerstown) 2009;10(9):669–70.
27. Cappelli F, Lazzeri C, Gensini GF, Valente S. Cannabis: a trigger for acute myocardial infarction? A case report. J Cardiovasc Med (Hagerstown) 2008; 9(7):725–8.
28. Fergusson DM, Horwood LJ, Northstone K. Maternal use of cannabis and pregnancy outcome. BJOG 2002;109(1):21–7.

29. Zuckerman B, Frank DA, Hingson R, et al. Effects of maternal marijuana and cocaine use on fetal growth. N Engl J Med 1989;320(12):762–8.
30. English DR, Hulse GK, Milne E, Holman CD, Bower CI. Maternal cannabis use and birth weight: a meta-analysis. Addiction 1997;92(11):1553–60.
31. van Gelder MM, Reefhuis J, Caton AR, Werler MM, Druschel CM, Roeleveld N. Characteristics of pregnant illicit drug users and associations between cannabis use and perinatal outcome in a population-based study. Drug Alcohol Depend 2010;109(1–3):243–7.
32. Schempf AH, Strobino DM. Illicit drug use and adverse birth outcomes: is it drugs or context? J Urban Health 2008;85(6):858–73.
33. Le Bec PY, Fatseas M, Denis C, Lavie E, Auriacombe M. [Cannabis and psychosis: search of a causal link through a critical and systematic review]. Encephale 2009;35(4):377–85.
34. Shapiro GK, Buckley-Hunter L. What every adolescent needs to know: cannabis can cause psychosis. J Psychosom Res 2010;69(6):533–9.
35. Dragt S, Nieman DH, Becker HE, et al. Age of onset of cannabis use is associated with age of onset of high-risk symptoms for psychosis. Can J Psychiatry 2010;55(3):165–71.
36. Miller NS, Gold MS. The diagnosis of marijuana (cannabis) dependence. J Subst Abuse Treat 1989; 6(3):183–92.
37. Swift W, Gates P, Dillon P. Survey of Australians using cannabis for medical purposes. Harm Reduct J 2005;2:18.
38. Latimer W, Zur J. Epidemiologic trends of adolescent use of alcohol, tobacco, and other drugs. Child Adolesc Psychiatr Clin N Am 2010;19(3):451–64.
39. McLaren JA, Silins E, Hutchinson D, Mattick RP, Hall W. Assessing evidence for a causal link between cannabis and psychosis: a review of cohort studies. Int J Drug Policy 2010;21(1):10–9.
40. Degenhardt L, Coffey C, Carlin JB, Swift W, Moore E, Patton GC. Outcomes of occasional cannabis use in adolescence: 10-year follow-up study in Victoria, Australia. Br J Psychiatry 2010;196:290–5.
41. Temple EC, Brown RF, Hine DW. The 'grass ceiling': limitations in the literature hinder our understanding of cannabis use and its consequences. Addiction 2011;106(2):238–44.
42. Drug Enforcement Adminstration, US Department of Justice. Herbal high-legal synthetic cannabinoids produce illicit marijuana effects: spice, k2 and other "legal" products sold as marijuana alternatives. June 2010. Available at: www.wyptac.org/upload/DEA%20K2%20Fact%20Sheet.pdf. Accessed 31 May 2011.
43. Atwood BK, Huffman J, Straiker A, Mackie K. JWH018, a common constituent of 'Spice' herbal blends, is a potent and efficacious cannabinoid CB receptor agonist. Br J Pharmacol 2010;160(3):585–93.
44. Clark AJ, Ware MA, Yazer E, Murray TJ, Lynch ME. Patterns of cannabis use among patients with multiple sclerosis. Neurology 2004;62(11):2098–100.
45. Ware MA, Doyle CR, Woods R, Lynch ME, Clark AJ. Cannabis use for chronic non-cancer pain: results of a prospective survey. Pain 2003;102(1–2):211–6.
46. Wilsey B, Marcotte T, Tsodikov A, et al. A randomized, placebo-controlled, crossover trial of cannabis cigarettes in neuropathic pain. J Pain 2008;9(6):506–21.
47. Ware MA, Wang T, Shapiro S, et al. Smoked cannabis for chronic neuropathic pain: a randomized controlled trial. CMAJ 2010;182(14):E694–701.
48. Abrams DI, Jay CA, Shade SB, et al. Cannabis in painful HIV-associated sensory neuropathy: a randomized placebo-controlled trial. Neurology 2007; 68(7):515–21.
49. Ellis RJ, Toperoff W, Vaida F, et al. Smoked medicinal cannabis for neuropathic pain in HIV: a randomized, crossover clinical trial. Neuropsychopharmacology 2009;34(3):672–80.
50. Bushlin I, Rozenfeld R, Devi LA. Cannabinoid-opioid interactions during neuropathic pain and analgesia. Curr Opin Pharmacol 2010;10(1):80–6.
51. Yesilyurt O, Dogrul A, Gul H, et al. Topical cannabinoid enhances topical morphine antinociception. Pain 2003;105(1–2):303–8.
52. Yesilyurt O, Dogrul A. Lack of cross-tolerance to the antinociceptive effects of systemic and topical cannabinoids in morphine-tolerant mice. Neurosci Lett 2004;71(2–3):122–7.
53. Elikkottil J, Gupta P, Gupta K. The analgesic potential of cannabinoids. J Opioid Manag 2009;5(6): 341–57.
54. Cox ML, Haller VL, Welch SP. Synergy between delta9-tetrahydrocannabinol and morphine in the arthritic rat. Eur J Pharmacol 2007;567(1–2):125–30.
55. Roberts JD, Gennings C, Shih M. Synergistic affective analgesic interaction between delta-9-tetrahydrocannabinol and morphine. Eur J Pharmacol 2006;530(1–2):54–8.
56. Ebell MH, Siwek J, Weiss BD, et al. Strength of recommendation taxonomy (SORT): a patient-centered approach to grading evidence in the medical literature. J Am Board Fam Pract 2004;17(1):59–67.
57. Sandyk R, Awerbuch G. Marijuana and Tourette's syndrome. J Clin Psychopharmacol 1998;8(6):444–5.
58. Hemming M, Yellowlees PM. Effective treatment of Tourette's syndrome with marijuana. J Psychopharmacol 1993;7(4):389–91.
59. Merritt JC, Crawford WJ, Alexander PC, Anduze AL, Gelbart SS. Effect of marihuana on intraocular and blood pressure in glaucoma. Ophthalmology 1980;87(3):222–8.
60. Wallace M, Schulteis G, Atkinson JH, et al. Dose-dependent effects of smoked cannabis on capsaicin-induced pain and hyperalgesia in healthy volunteers. Anesthesiology 2007;107(5):785–96.

61. Kraft B, Frickey NA, Kaufmann RM, et al. Lack of analgesia by oral standardized cannabis extract on acute inflammatory pain and hyperalgesia in volunteers. Anesthesiology 2008;109(1):101–10.
62. Vaney C, Heinzel-Gutenbrunner M, Jobin P, et al. Efficacy, safety and tolerability of an orally administered cannabis extract in the treatment of spasticity in patients with multiple sclerosis: a randomized, double-blind, placebo-controlled, crossover study. Mult Scler 2004;10(4):417–24.
63. Zajicek JP, Sanders HP, Wright DE, 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.
64. Muller-Vahl KR, Schneider U, Koblenz A, et al. Treatment of Tourette's syndrome with ^{9}-tetrahydrocannabinol (THC): a randomized crossover trial. Pharmacopsychiatry 2002;35(2):57–61.
65. Muller-Vahl KR, Schneider U, Prevedel H, et al. ^{9}-tetrahydrocannabinol (THC) is effective in the treatment of tics in Tourette syndrome: a 6-week randomized trial. J Clin Psychiatry 2003;64(4):459–65.
66. Ungerleider JT, Andyrsiak T, Fairbanks L, Ellison GW, Myers LW. Delta-9-THC in the treatment of spasticity associated with multiple sclerosis. Adv Alcohol Subst Abuse 1987;7(1):39–50.
67. Buggy DJ, Toogood L, Maric S, Sharpe P, Lambert DG, Rowbotham DJ. Lack of analgesic efficacy of oral -9-tetrahydrocannabinol in postoperative pain. Pain 2003;106(1–2):169–72.
68. Attal N, Brasseur L, Guirimand D, Clermond-Gnamien S, Atlami S, Bouhassira D. Are oral cannabinoids safe and effective in refractory neuropathic pain? Eur J Pain 2004;8(2):173–7.
69. Guzman M, Duarte MJ, Blazquez C, et al. A pilot clinical study of ^{9}-tetrahydrocannabinol in patients with recurrent glioblastoma multiforme. Br J Cancer 2006;95(2):197–203.
70. Volicer L, Stelly M, Morris J, McLaughlin J, Volicer BJ. Effects of dronabinol on anorexia and disturbed behavior in patients with Alzheimer's disease. Int J Geriatr Psychiatry 1997;12(9):913–9.
71. Walther S, Mahlberg R, Eichmann U, Kunz D. Delta-9-tetrahydrocannabinol for nighttime agitation in severe dementia. Psychopharmacology (Berl) 2006;185(4):524–8.
72. Beal JE, Olson R, Laubenstein L, et al. Dronabinol as a treatment for anorexia associated with weight loss in patients with AIDS. J Pain Symptom Manage 1995;10(2):89–97.
73. Pooyania S, Ethans K, Szturm T, Casey A, Perry D. A randomized, double-blinded, crossover pilot study assessing the effect of nabilone on spasticity in persons with spinal cord injury. Arch Phys Med Rehabil 2010;91(5):703–7.
74. Skrabek RQ, Galimova L, Ethans K, Perry D. Nabilone for the treatment of pain in fibromyalgia. J Pain 2008;9(2):164–73.
75. Nurmikko TJ, Serpell MG, Hoggart B, Toomey PJ, Morlion BJ, Haines D. Sativex successfully treats neuropathic pain characterised by allodynia: a randomised, double-blind, placebo-controlled clinical trial. Pain 2007;133(1–3):210–20.
76. Wade DT, Robson P, House H, Makela P, Aram J. A preliminary controlled study to determine whether whole-plant cannabis extracts can improve intractable neurogenic symptoms. Clin Rehabil 2003;17(1):21–9.
77. Rog DJ, Nurmikko TJ, Friede T, Young CA. Randomized, controlled trial of cannabis-based medicine in central pain in multiple sclerosis. Neurology 2005; 65(6):812–9.
78. Brady CM, DasGupta R, Dalton C, Wiseman OJ, Berkley KJ, Fowler CJ. An open-label pilot study of cannabis-based extracts for bladder dysfunction in advanced multiple sclerosis. Multiple Sclerosis 2004; 10(4):425–33.
79. Bocker KB, Gerritsen J, Hunault CC, Kruidenier M, Mensinga TT, Kenemans JL. Cannabis with high Delta(9)-THC contents affects perception and visual selective attention acutely: an event-related potential study. Pharmacol Biochem Behav 2010;96(1):67–74.
80. McLaren J, Swift W, Dillon P, Allsop S. Cannabis potency and contamination: a review of the literature. Addiction 2008;103(7):1100–9.
81. Kagen SL, Kurup VP, Sohnle PG, Fink JN. Marijuana smoking and fungal sensitization. J Allergy Clin Immunol 1983;71(4):389–93.
82. Kurup VP, Resnick A, Kagen SL, Cohen SH, Fink JN. Allergenic fungi and actinomycetes in smoking materials and their health implications. Mycopathologia 1983;82(1):61–4.
83. Ungerleider JT, Andrysiak T, Tashkin DP, Gale RP. Contamination of marihuana cigarettes with pathogenic bacteria–possible source of infection in cancer patients. Cancer Treat Rep 1982;66(3):589–91.
84. Chusid MJ, Gelfand JA, Nutter C, Fauci AS. Pulmonary aspergillosis, inhalation of contaminated marijuana smoke, chronic granulomatous disease. Ann Intern Med 1975;82(5):682–3.
85. Exley C, Begum A, Woolley MP, Bloor RN. Aluminum in tobacco and cannabis and smoking-related disease. Am J Med 2006;119(3):276.e9–211.
86. Shi G, Cai Q. Cadmium tolerance and accumulation in eight potential energy crops. Biotechnol Adv 2009;27(5):555–61.
87. Delourme J, Delattre C, Godard P, Steenhouwer F, Just N. [Respiratory consequences of inhalation of adulterated cannabis]. Rev Mal Respir 2009;26(5):552–6.
88. Viana M, Querol X, Alastuey A, et al. Drugs of abuse in airborne particulates in urban environments. Environ Int 2010;36(6):527–34.
89. Rohrich J, Schimmel I, Zorntlein S, et al. Concentrations of delta9-tetrahydrocannabinol and 11-nor-9-carboxytetrahydrocannabinol in blood and urine after passive exposure to Cannabis smoke in a coffee shop. J Anal Toxicol 2010;34(4):196–203.

90. Lister J. Cannabis controversy and other sundry troubles. N Engl J Med 1969;280(13):712–4.
91. Ren Y, Whittard J, Higuera-Matas A, Morris CV, Hurd YL. Cannabidiol, a nonpsychotropic component of cannabis, inhibits cue-induced heroin seeking and normalizes discrete mesolimbic neuronal disturbances. J Neurosci 2009;29(47):14764–9.
92. Zuardi AW. Cannabidiol: from an inactive cannabinoid to a drug with wide spectrum of action. Rev Bras Psiquiatr 2008;30(3):271–80.
93. Zuardi AW, Crippa JA, Hallak JE, Moreira FA, Guimaraes FS. Cannabidiol, a Cannabis sativa constituent, as an antipsychotic drug. Braz J Med Biol Res 2006;39(4):421–9.