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Medical Cannabis and Pain

Few topics in pain management are as popular and controversial as the use of cannabis (marijuana) in the management of pain. Widely covered in the media, the medical use of cannabis has become a lightning rod for political, economic, and social commentary. Opinions are often sharply polarized, and within the medical profession—and more specifically in the pain management community—debates rage about the role (if any) of cannabis in modern medicine.

The pain-management community, struggling with the rational use of opioids in treating chronic pain, is becoming increasingly sensitized to such issues as abuse potential, diversion, long-term safety, patient screening, and monitoring for functional outcomes—many of which apply equally to concerns around the medical use of cannabis. Many doctors are considering the use of cannabis and cannabinoids as adjunctive therapies in the context of multimodal pain management strategies to more efficiently support patients suffering from unrelieved pain. Yet the medical use of cannabis is poorly taught in medical training programs because of the paucity of clinical assessments and randomized controlled trials (RCTs).

This issue of *Pain: Clinical Updates* reviews the history, basic science, epidemiology, and clinical data of the use of cannabis in pain management and suggests strategies for pain clinicians who may find themselves increasingly asked about a topic for which they often feel unprepared.

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Historical Perspective

Marijuana is the street name for the herb *Cannabis sativa*. Cannabis is the third most widely used drug globally, after alcohol and tobacco.[1] The cultivation, possession, and distribution of cannabis are governed by international narcotics-control regulations, though individual states and nations have chosen varying interpretations of these regulations. Some countries have decriminalized cannabis possession (the Netherlands and Portugal), and two U.S. states (Colorado and Washington) and Uruguay recently have moved to legalize and regulate cannabis for recreational purposes.

The medical potential for cannabis has been described in various forms throughout history, and crude extracts and tinctures of cannabis flowers, leaves, and roots were used for a range of therapeutic purposes around the turn of the 19th century.[2] However, the lack of standardization of these preparations, increased interest in synthetic analgesics, and global prohibition of cannabis in the middle of the 20th century led to a halt in the investigation and development of therapeutic applications of cannabis and its constituents.

Cannabinoids Enter the Scientific Arena

In the 1960s, two significant paradigm shifts took place. In 1964, Israeli scientists Mechoulam and Gaoni identified delta-9-tetrahydrocannabinol (THC) as the primary psychoactive ingredient of cannabis, extracted from hashish (a concentrated form of the active resins expressed on the surface of the cannabis flower).[3] This discovery led to the isolation of a series of compounds unique to cannabis called cannabinoids; it is currently thought that cannabis contains over 100 such compounds, some of which continue to undergo clinical evaluation.

While the active components of cannabis were being isolated, Western society witnessed a surge of interest in the recreational use of cannabis as part of a counterculture movement in politics, music, and freedom of expression. Cannabis use became a statement of civil disobedience and launched a massive social experiment. In this context,

it was only a matter of time before the medical use of cannabis resurfaced. In 1971, Harvard psychiatrist Lester Grinspoon published a book of case histories of patients with intractable conditions whose use of cannabis allegedly led to powerful and positive results.[4]

Cannabinoid Drug Development

While efforts to reconsider the prohibition against cannabis possession were underway (e.g., the Le Dain Commission in Canada in 1973), the possibility that the active ingredients of cannabis could have therapeutic value led to the development in the 1980s of drugs based on the THC molecule for the treatment of anxiety, nausea, anorexia, and pain. Two of these early compounds, dronabinol (synthetic THC) and nabilone (a synthetic THC analog), approved in the mid-1980s, remain in generic form on drug formularies worldwide.

It was only in the early 1990s that the target for these "cannabinoid" drugs was identified. The discovery of the ubiquitously expressed G-protein-coupled cannabinoid receptors type 1 and 2 (CB_1 and CB_2 respectively)[5,6] triggered a chase for endogenous cannabinoid ligands and mechanisms, and it is now clear that the endocannabinoid system (ECS) plays a physiological role in the modulation of a broad range of neurological and immunological functions. The ECS appears to be remarkably well preserved from an evolutionary standpoint,[7] and it may be found in a wide variety of species, including humans. In an age where few novel mechanisms for pain management have yielded therapeutic agents, the ECS offers a valuable mechanistic rationale for the therapeutic actions of cannabinoid medicines. Today, efforts continue to harness the ECS using pharmacological, genetic, and medicinal chemistry tools.

The Medical Cannabis "Movement"

While the scientific field of enquiry was expanding in the 1990s, the therapeutic potential for herbal cannabis, coupled with prohibition of possession, became a source of patient-led legal challenges in several countries. These efforts ultimately gave rise to compassionate access programs in Holland, Canada, and Israel, which used various regulatory mechanisms to exempt bona fide patients from prosecution for cannabis possession and authorized cannabis cultivation programs to provide access to a quality-controlled and standardized herbal cannabis product. In the United States, at the time of writing, 22 states have passed voter initiatives and referenda to allow the medical use of cannabis, despite federal resistance and a refusal to reschedule cannabis from Schedule 1, where it is deemed to have no medical value and to be too dangerous for use even under medical supervision.

It is poignant to note that patient-led efforts have been at the core of cannabinoid drug development. Reports of the effects of cannabis on symptoms such as anxiety, insomnia, nausea, appetite loss, pain, and spasticity triggered the clinical development and evaluation of cannabinoid drugs, which have, to a limited extent, validated these original claims.

The Pain Management Perspective

Chronic pain is the most common reason for patients to report the medical use of cannabis. Within chronic pain clinics, estimates of the prevalence of use range from 12% to 15%,[8] while population-based studies of patients with fibromyalgia, arthritis, spinal cord injury, and multiple sclerosis (MS) have all described cannabis use for the relief of pain.[9] Data from medical cannabis programs in Europe and the United States suggest that self-reported pain conditions are responsible for up to 90% of cannabis authorizations.

At the fundamental level, the ECS has been identified as a valid and promising target for therapeutic analgesic drug development. The CB_1 receptor is strategically located in regions of the peripheral and central nervous system where pain signaling is intricately controlled, including the distal ends of primary afferent neurons, the dorsal horn of the spinal cord, the periaqueductal gray matter, the ventroposterolateral thalamus, and cortical regions associated with central pain processing, including the anterior cingulate cortex, amygdala, and prefrontal cortex.[10] Preclinical studies have reported analgesic properties of CB_1 agonists in a wide array of animal pain models, and imaging studies have demonstrated the dissociative effects of cannabis on the pain neuromatrix.[11] The therapeutic potential of CB_2 receptors also deserves attention because the modulation of these receptors, in addition to direct action on neurotransmitter release, decreases the liberation of pro-inflammatory mediators participating in antinociceptive effects, thus strengthening their role as endogenous compounds with immunomodulatory and neuroinflammatory properties.[12]

The hunt is now on for novel pharmaceutical agents to selectively target peripheral CB_1 and CB_2 receptors, to inhibit endogenous cannabinoid uptake and metabolism in identified tissues where increased levels of endocannabinoids is desirable, to harness opioid-cannabinoid synergies, and to deliver cannabinoids through novel delivery mechanisms, including skin patches and oromucosal sprays.

At the clinical level, the evidence base is accumulating. A growing

number of RCTs published in the past 10 years with a range of cannabinoid drugs show promising signals in a range of pain disorders.[13] The early cannabinoid antiemetic drugs dronabinol and nabilone have been rediscovered as having analgesic potential, and the herbal cannabis extract nabiximols has been approved in Canada as analgesic in neuropathic pain associated with multiple sclerosis and in advanced cancer pain. Inhaled cannabis (smoked and vaporized) has been shown to have analgesic properties, particularly in neuropathic pain conditions related to HIV/AIDS, trauma, and MS. Trials are generally small and of short duration, however, and the evidence for long-term efficacy is currently limited to two studies of oral cannabis extracts.[14, 15]

Safety Concerns

The safety profile of cannabinoids is often touted as either a barrier to their clinical use or a reason for their more widespread use. This paradox stems from differing interpretations of the data; population-based studies of recreational cannabis use suggest that the toxicity of cannabis is extremely low (owing in part to the lack of CB receptors in critical brainstem regions controlling respiratory drive), although associations are reported between recreational cannabis use and early-onset psychosis, myocardial infarction, stroke, impairments in driving, and increased risk of accidents; risks of chronic bronchitis are associated with smoking of herbal cannabis.[16] Although some of these adverse events have been established with a relatively high level of confidence,[17] few if any of these associations have been prospectively evaluated in clinical populations, in which potentially confounding factors include age of use, comorbid conditions, polypharmacy, and disease severity. In clinical trials, however, the adverse events associated with cannabinoids are similar in quality and quantity to those of many other conventional centrally acting analgesics, and serious adverse drug reactions to cannabinoids are extremely rare.[18]

The Future of Cannabis Research

Because primary afferent fibers are an important target for the development of new analgesic therapies, research is ongoing on peripherally restricted cannabinoid compounds. Nociceptors contain functionally important molecules that are not found in other cells, such as voltage-gated sodium channel $Na_v1.8$.[42] Only a subpopulation of nociceptors appears to contribute to the development of a given pathological condition; analgesics that act peripherally may therefore reduce input of pain signals into the central nervous system. Additionally, analgesics whose effects are restricted to the periphery would not have central effects.

Although purified analogs and extracts of cannabis are available as prescription medicines, the clinical study of inhaled cannabinoids (through smoking or vaporization) is limited by restricted access to supplies of clinical grade material, lack of intellectual property incentives, and concerns that studying the medical benefits of cannabis runs contrary to global antidrug and antismoking strategies. Until such issues are addressed, it is unlikely that we will ever see the sort of large-scale phase III trials needed to definitively establish the efficacy of herbal cannabis. Small proof-of-concept studies, as described earlier, remain the best available evidence. Efforts are underway in jurisdictions where medical cannabis use is legal to implement monitoring programs to inform the safety and effectiveness of long-term medical cannabis use in real-world settings. Thus, in drug development terms, we have

Table I
Randomized controlled trials of cannabinoids in pain-related disorders 2004-14

Nabilone	**Nabiximols (oromucosal spray; 2.5mg THC + 2.5mg CBD)**
Neuropathic pain (Frank et al.[19])	Brachial plexus avulsion (Berman et al.[30])
Fibromyalgia pain (Skrabek et al.[20]) and sleep (Ware et al.[21])	Rheumatoid arthritis (Blake et al.[31])
Spinal cord injury (Pooyania et al.[22])	MS neuropathic pain (Rog et al.[32])
Diabetic neuropathy (Toth et al.[23])	MS Spasticity (Novotna et al.[33])
Dronabinol (oral capsule)	Cancer pain (Portnoy et al.[34])
MS spasticity (Svensen et al.[24])	**Herbal cannabis (1.8-9.4%THC)**
Chronic pain + opioids (Narang et al.[25])	HIV neuropathy (Abrams et al.[35], Ellis et al.[36])
Spinal cord injury (Rinatala et al.[26])	Neuropathic pain (Wilsey et al.[37,38])
Chronic pain + opioids (Issa et al.[27])	Post traumatic neuropathy (Ware et al.[39])
Cannador (oral capsule; 2.5mg THC + 1.2mg CBD)	MS spasticity (Corey-Bloom et al.[40])
Spasticity in MS (Zajicek et al.[14,28,29])	Crohn's disease (Naftali et al.[41])

witnessed this complex botanical drug jump straight from phase II to phase IV.

What Does the Practicing Pain Clinician Need to Know?

With the enormous public and media interest in marijuana and the widely held perception that cannabis is effective for pain control, many clinicians are being asked about cannabis use and pain. Given the existing scientific knowledge base around cannabis and cannabinoids, some of which the patient may already know (patients may bring copies of scientific papers to their physicians to argue their case), the response to such patients that there is "not enough information" is disingenuous at best, and at worst, an abnegation of clinical responsibility. A refusal to discuss medical cannabis candidly with a patient does two things: (1) it undermines the doctor-patient relationship, and (2) it drives the patient to sources where information may be less robust and to "pot docs" where clinical evaluation and bona fide relationships may be minimal or nonexistent.

The first step for clinicians faced with such questions is to examine their own perspectives around cannabis. The drug has been around long enough for most clinicians to have some experience—personally, professionally, socially, or otherwise—on which to base their attitudes toward social or medical cannabis use. It is a worthwhile reflective exercise to explore how such positive, negative, or neutral attitudes could influence the clinical encounter and decision to authorize use of the drug.[43] It is assumed that practicing clinicians can and will put aside their own biases and prejudices (in any direction) and base their therapeutic decisions on clinical need, known risks and benefits, and the context in which the consultation occurs.

The second step is to appreciate important risk factors in cannabis use. The most important contraindications are a personal or family history of psychosis or schizophrenia and unstable ischemic heart disease. These concerns are based on epidemiological studies that have shown associations between adolescent recreational cannabis use and schizophrenia onset[44] and increased risk of myocardial infarction following recreational cannabis smoking.[45]

Other concerns include cautions in pregnant or breastfeeding women and in patients with severe liver or kidney disease. Use of cannabis in the elderly warrants cautious dosing and considerations of drug interactions, and in persons younger than 25, particular caution is advised. Clinicians should be certain that other appropriate medical specialists and family members are actively involved and aware that such use is being considered. As with opioids, a careful screening for substance-abuse risk factors is prudent and may guide decision making and follow-up strategies.

The third step for clinicians is to explore all reasonable standard therapeutic approaches, pharmacological and nonpharmacological, before suggesting cannabis use. The medical use of cannabis is not an end in itself; the patient demanding cannabis and refusing to consider options may have motivations other than amelioration of pain and improvement in quality of life.

Any decision to incorporate cannabis in therapy will depend on the severity of the underlying pain condition and the success or extent of other approaches that have been tried or considered. Clinicians considering cannabinoid therapy should be aware of prescription cannabinoid alternatives and such harm-reduction strategies as vaporizers to avoid smoking and the possible use of other non-smoked ("edible") preparations. These alternatives depend on local availabilities, cost, and

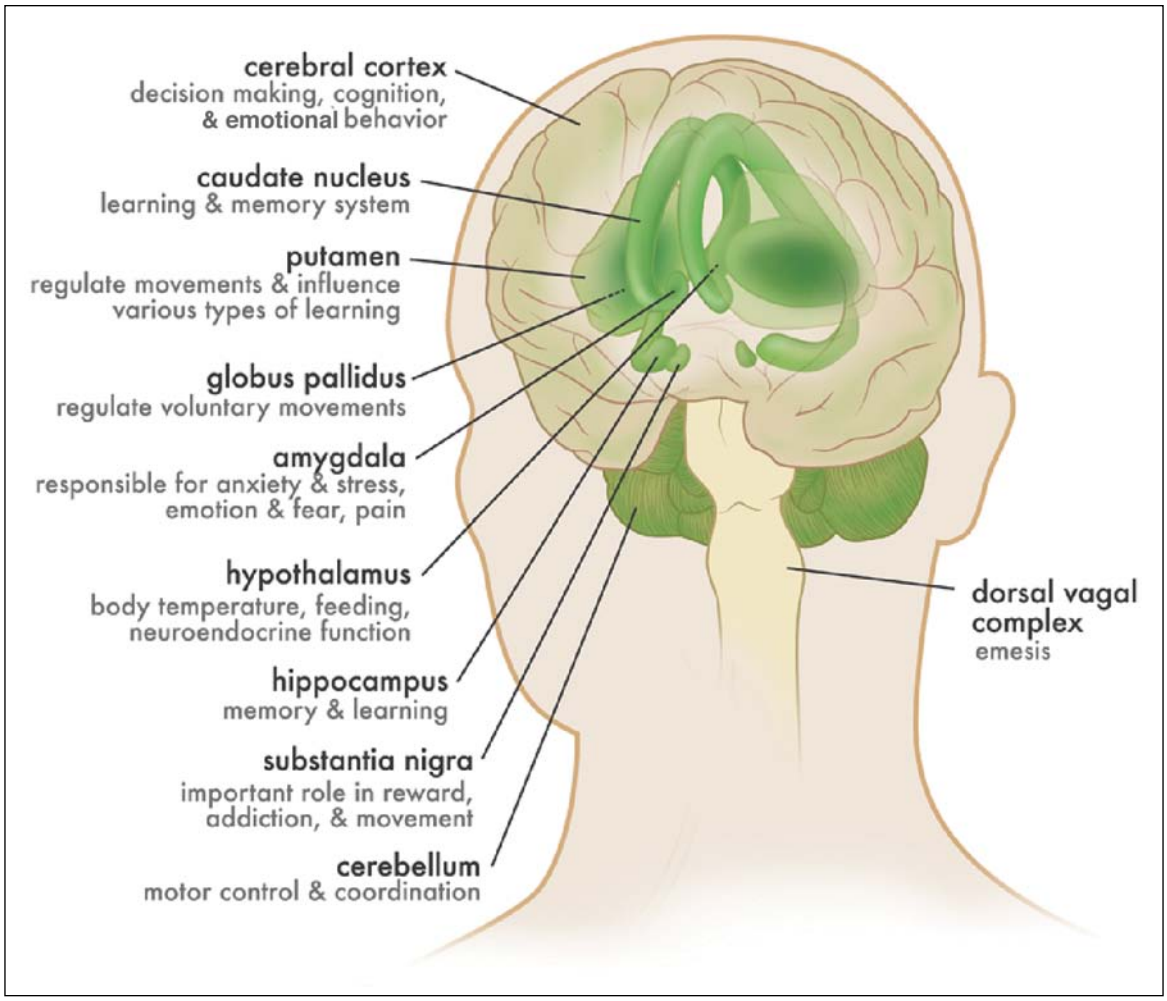

Fig. 1. Distribution of CB_1 receptors. Image courtesy of the Canadian Consortium for the Investigation of Cannabinoids (www.ccic.net).

existing patient-support mechanisms. Cannabinoids have been listed as third- or fourth-line agents for chronic neuropathic pain,[46] rising to second-line therapy in the case of central neuropathic pain caused by MS.[47]

Clinicians who initiate cannabinoid therapy should explain the drug's class (what cannabinoids are and how they work), the relevant indication (the patient's pain condition may not be covered under the standard indication for the drug), and dosing. Dosing for prescription cannabinoids is easier to discuss than for herbal cannabis because prescription cannabinoids are well characterized with standardized dose forms; it always is prudent to begin therapy with low doses and gradually increase the dose as tolerated to maximum benefit with minimum adverse events. With herbal cannabis, prudence suggests a "start low, go slow" strategy using non-smoked delivery mechanisms, quality-controlled products, and the lowest level of THC required to achieve therapeutic aims and minimize adverse effects. The role of the non-psychoactive cannabidiol (CBD), while potentially anxiolytic and anti-inflammatory, has not been adequately evaluated in pain management.

A carefully constructed treatment plan and follow-up strategy is essential in any pain-management program, and the medical use of cannabis is no exception. In addition to pain relief, mutually agreed-upon treatment goals (such as reduction in other medications), realistic expectations, and functional outcomes are essential yardsticks in measuring therapeutic progress, and failure to demonstrate positive outcomes in a reasonable time frame should prompt reconsideration and possible cessation of therapy.

Monitoring the amount of cannabis intake also is important. Hard data on average doses of herbal cannabis are difficult to come by, but estimates of average daily doses of one to three grams per day are not unreasonable.[48] Certainly, doses of five grams per day or more warrant careful review

Table II
Different forms of cannabinoids for the treatment of pain conditions

Cannabinoid	Forms	Indications	Posology	Pharmacokinetics	Comments
Cannabis	Smoked or inhaled through vaporization	No formal approval; widely used for pain conditions	Individual. Average dose: 1–3g/day	Onset of action : 5 min. Duration: 2–4 h	Authorized by physicians where medical marijuana is legal
Dronabinol (Marinol®)	Oral capsule containing 2.5, 5, or 10 mg	Severe nausea and vomiting associated with cancer chemotherapy; AIDS-related anorexia associated with weight loss	2.5 to 5 mg q 12 h. Max. 20 mg/day	Onset of action : 30–60 min. Duration: 4–6 h	Also used for the treatment of chronic pain conditions
Nabilone (Cesamet®)	Oral capsule containing 0.25, 0.5, and 1 mg	Severe nausea and vomiting associated with cancer chemotherapy	0.25 to 2 mg q 12 h. Max. 6 mg/day	Onset of action : 60–90 min. Duration: 8–12 h.	Also used for the treatment of chronic pain conditions
Nabiximols: Tetrahydrocannabinol (THC)/ Cannabidiol (CBD) and other cannabinoids, terpenoids, and flavonoids (Sativex®)	Oromucosal spray with 2.7 mg THC + 2.5 mg CBD per 100 µL	Adjunctive treatment for the symptomatic relief of spasticity in adult patients with multiple sclerosis who have not responded adequately to other therapy	1 spray every 4 h. Average dose : 5 sprays/day. Max. 16 sprays/day.	Onset of action : 15–40 min. Duration: 2–4 h	Also marketed (with conditions) as an adjunctive treatment for the symptomatic relief of neuropathic pain in adults with MS and as adjunctive analgesic in adult patients with advanced cancer

and caution; risks of diversion almost certainly rise with increasing dosage. There are reports of patients using and tolerating much higher amounts, and the safety profile of cannabis neither suggests that significant toxic effects occur at high doses nor shows strong evidence of tolerance developing to cannabinoid medicines. Clinicians who suggest high doses are entering uncharted waters, however, and caution is advised. The same is true for the use of oral cannabinoids because a recent RCT showed that oral dronabinol produces psychoactive effects, mimicking those produced by smoked cannabis in patients with chronic noncancer pain.[27]

Finally, as with any use of controlled substances, clinicians must be aware of the limits of their own knowledge and practice and should be prepared to decline access based on the foregoing considerations. Cannabis dependency is increasingly well recognized,[49] and patients whose cannabis use does not meet therapeutic standards and whose use of cannabis is not controlled may warrant referral to substance-abuse specialists for evaluation and possible treatment.

Cannabis is not a panacea, and there are clearly patients whose use of cannabis may in fact be impairing their ability to improve their overall quality of life. This is a question of astute clinical judgment, but answers should be based on an adequate knowledge base and patient evaluation. Careful consideration of cannabis use in pain medicine provides an opportunity to deepen and refine our pain-management toolbox, understand our patients' needs and wishes, strengthen our relationships, and improve the quality of our care, while we wait for more long-term RCTs to provide more definitive evidence. There are many possibilities, as the study of the cannabinoid system is rapidly increasing, and clinical studies are just beginning to characterize and exploit this system. The next few years will better define the role and importance of cannabinoids and evaluate their therapeutic potential in various pathologies that are currently not well managed. Our patients deserve no less.

References

1. Degenhardt L, Hall W. Extent of illicit drug use and dependence, and their contribution to the global burden of disease. Lancet 2012;379:55–70.

2. Mechoulam R. The pharmacohistory of Cannabis sativa. In: Mechoulam R, editor. Cannabinoids as therapeutic agents. Boca Raton: CRC Press; 1986. p. 1–19.

3. Gaoni Y, Mechoulam R. Isolation, structure and partial synthesis of an active constituent of hashish. J Am Chem Soc 1964;86:1646–7.

4. Grinspoon L. Marijuana reconsidered, 1st ed. Cambridge, MA: Harvard University Press; 1971.

5. Munro S, Thomas KL, Abu-Shaar M. Molecular characterization of a peripheral receptor for cannabinoids. Nature 1993;365:61–5.

6. Matsuda LA, Lolait SJ, Brownstein MJ, Young AC, Bonner TI. Structure of a cannabinoid receptor and functional expression of the cloned cDNA. Nature 1990;346:561–4.

7. Elphick MR. The evolution and comparative neurobiology of endocannabinoid signalling. Philos Trans R Soc Lond B Biol Sci 2012;367:3201–15.

8. Ware MA, Doyle CR, Woods R, Lynch ME, Clark AJ. Cannabis use for chronic non-cancer pain: results of a prospective survey. Pain 2003;102:211–6.

9. Ware MA, Adams H, Guy GW. The medicinal use of cannabis in the UK: results of a nationwide survey. Int J Clin Pract 2005;59:291–5.

10. Herkenham M, Lynn AB, Little MD, Johnson MR, Melvin LS, de Costa BR, Rice KC. Cannabinoid receptor localization in brain. Proc Natl Acad Sci USA 1990;87:1932–6.

11. Lee MC, Ploner M, Wiech K, Bingel U, Wanigasekera V, Brooks J, Menon DK, Tracey I. Amygdala activity contributes to the dissociative effect of cannabis on pain perception. Pain 2013;154:124–34.

12. Rom S, Persidsky Y. Cannabinoid receptor 2: potential role in immunomodulation and neuroinflammation. J Neuroimmune Pharmacol 2013;8:608–20.

13. Lynch ME, Campbell F. Cannabinoids for treatment of chronic non-cancer pain; a systematic review of randomized trials. Br J Clin Pharmacol 2011;72:735–44.

14. Zajicek JP, Sanders HP, Wright DE, Vickery PJ, Ingram WM, Reilly SM, Nunn AJ, Teare LJ, Fox PJ, Thompson AJ. Cannabinoids in multiple sclerosis (CAMS) study: safety and efficacy data for 12 months follow up. J Neurol Neurosurg Psychiatry 2005;76:1664–9.

15. Wade DT, Makela PM, House H, Bateman C, Robson P. Long-term use of a cannabis-based medicine in the treatment of spasticity and other symptoms in multiple sclerosis. Mult Scler 2006;12:639–45.

16. Hall W, Degenhardt L. Adverse health effects of non-medical cannabis use. Lancet 2009;374:1383–91.

17. Volkow ND, Baler RD, Compton WM, Weiss SR. Adverse health effects of marijuana use. N Engl J Med 2014;370:2219–27.

18. Wang T, Collet JP, Shapiro S, Ware MA. Adverse effects of medical cannabinoids: a systematic review. CMAJ 2008;178:1669–78.

19. Frank B, Serpell MG, Hughes J, Matthews JN, Kapur D. Comparison of analgesic effects and patient tolerability of nabilone and dihydrocodeine for chronic neuropathic pain: randomised, crossover, double blind study. BMJ 2008;336:199–201.

20. Skrabek RQ, Galimova L, Ethans K, Perry D. Nabilone for the treatment of pain in fibromyalgia. J Pain 2008;9:164–73.

21. Ware MA, Fitzcharles MA, Joseph L, Shir Y. The effects of nabilone on sleep in fibromyalgia: results of a randomized controlled trial. Anesth Analg 2010;110:604–10.

22. 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;91:703–7.

23. Toth C, Mawani S, Brady S, Chan C, Liu C, Mehina E, Garven A, Bestard J, Korngut L. An enriched-enrolment, randomized withdrawal, flexible-dose, double-blind, placebo-controlled, parallel assignment efficacy study of nabilone as adjuvant in the treatment of diabetic peripheral neuropathic pain. Pain 2012;153:2073–82.

24. Svendsen KB, Jensen TS, Bach FW. Does the cannabinoid dronabinol reduce central pain in multiple sclerosis? Randomised double blind placebo controlled crossover trial. BMJ 2004;329:257–8.

25. Narang S, Gibson D, Wasan AD, Ross EL, Michna E, Nedeljkovic SS, Jamison RN. Efficacy of dronabinol as an adjuvant treatment for chronic pain patients on opioid therapy. J Pain 2008;9:254–64.

26. Rintala DH, Fiess RN, Tan G, Holmes SA, Bruel BM. Effect of dronabinol on central neuropathic pain after spinal cord injury: a pilot study. Am J Phys Med Rehabil 2010;89:840–8.

27. Issa MA, Narang S, Jamison RN, Michna E, Edwards RR, Penetar DM, Wasan AD. The subjective psychoactive effects of oral dronabinol studied in a randomized, controlled crossover clinical trial for pain. Clin J Pain 2014;30:472–8.

28. Zajicek JP, Hobart JC, Slade A, Barnes D, Mattison PG. Multiple sclerosis and extract of cannabis: results of the MUSEC trial. J Neurol Neurosurg Psychiatry 2012;83:1125–32.

29. Zajicek J, Fox P, Sanders H, Wright D, Vickery J, Nunn A, Thompson A. Cannabinoids for treatment of spasticity and other symptoms related to multiple sclerosis (CAMS study): multicentre randomised placebo-controlled trial. Lancet 2003;362:1517–26.

30. Berman JS, Symonds C, Birch R. Efficacy of two cannabis based medicinal extracts for relief of central neuropathic pain from brachial plexus avulsion: results of a randomised controlled trial. Pain 2004;112:299–306.

31. Blake DR, Robson P, Ho M, Jubb RW, McCabe CS. Preliminary assessment of the efficacy, tolerability and safety of a cannabis-based medicine (Sativex) in the treatment of pain caused by rheumatoid arthritis. Rheumatology (Oxford) 2006;45:50–2.

32. Rog DJ, Nurmikko TJ, Young CA. Oromucosal delta9-tetrahydrocannabinol/cannabidiol for neuropathic pain associated with multiple sclerosis: an uncontrolled, open-label, 2-year extension trial. Clin Ther 2007;29:2068–79.

33. Novotna A, Mares J, Ratcliffe S, Novakova I, Vachova M, Zapletalova O, Gasperini C, Pozzilli C, Cefaro L, Comi G, Rossi P, Ambler Z, Stelmasiak Z, Erdmann A, Montalban X, Klimek A, Davies P. A randomized, double-blind, placebo-controlled, parallel-group, enriched-design study of nabiximols (Sativex®), as add-on therapy, in subjects with refractory spasticity caused by multiple sclerosis. Eur J Neurol 2011;18:1122–31.

34. Portenoy RK, Ganae-Motan ED, Allende S, Yanagihara R, Shaiova L, Weinstein S, McQuade R, Wright S, Fallon MT. Nabiximols for opioid-treated cancer patients with poorly-controlled chronic pain: a randomized, placebo-controlled, graded-dose trial. J Pain 2012;13:438–49.

35. Abrams DI, Jay CA, Shade SB, Vizoso H, Reda H, Press S, Kelly ME, Rowbotham MC, Petersen KL. Cannabis in painful HIV-associated sensory neuropathy: a randomized placebo-controlled trial. Neurology 2007;68:515–21.

36. Ellis RJ, Toperoff W, Vaida F, van den Brande G, Gonzales J, Gouaux B, Bentley H, Atkinson JH. Smoked medicinal cannabis for neuropathic pain in HIV: a randomized, crossover clinical trial. Neuropsychopharmacology 2009;34:672–80.

37. Wilsey B, Marcotte T, Deutsch R, Gouaux B, Sakai S, Donaghe H. Low-dose vaporized cannabis significantly improves neuropathic pain. J Pain 2013;14:136–48.

38. Wilsey B, Marcotte T, Tsodikov A, Millman J, Bentley H, Gouaux B, Fishman S. A randomized, placebo-controlled, crossover trial of cannabis cigarettes in neuropathic pain. J Pain 2008;9:506–21.

39. Ware M, Wang T, Shapiro S, Robinson A, Ducruet T, Huynh T, Gamsa A, Bennett G, Collet J. Smoked cannabis for chronic neuropathic pain: a randomized controlled trial. CMAJ 2010;14:694–701.

40. Corey-Bloom J, Wolfson T, Gamst A, Jin S, Marcotte TD, Bentley H, Gouaux B. Smoked cannabis for spasticity in multiple sclerosis: a randomized, placebo-controlled trial. CMAJ 2012;184:1143–50.

41. Naftali T, Bar Lev L, Dotan I, Lansky EP, Sklerovsky BF, Konikoff FM. Cannabis induces a clinical response in patients with Crohn's disease: a prospective placebo-controlled study. Clin Gastroenterol Hepatol 2013;11:1276–80.

42. Agarwal N, Pacher P, Tegeder I, Amaya F, Constantin CE, Brenner GJ, Rubino T, Michalski CW, Marsicano G, Monory K, Mackie K, Marian C, Batkai S, Parolaro D, Fischer MJ, Reeh P, Kunos G, Kress M, Lutz B, Woolf CJ, Kuner R. Cannabinoids mediate analgesia largely via peripheral type 1 cannabinoid receptors in nociceptors. Nat Neurosci 2007;10:870–9.

43. Kondrad E, Reid A. Colorado family physicians' attitudes toward medical marijuana. J Am Board Fam Med 2013;26:52–60.

44. Moore TH, Zammit S, Lingford-Hughes A, Barnes TR, Jones PB, Burke M, Lewis G. Cannabis use and risk of psychotic or affective mental health outcomes: a systematic review. Lancet 2007;370:319–28.

45. Mittleman MA, Lewis RA, Maclure M, Sherwood JB, Muller JE. Triggering myocardial infarction by marijuana. Circulation 2001;103:2805–9.

46. Moulin DE, Clark AJ, Gilron I, Ware MA, Watson CP, Sessle BJ, Coderre T, Morley-Forster PK, Stinson J, Boulanger A, Peng P, Finley GA, Taenzer P, Squire P, Dion D, Cholkan A, Gilani A, Gordon A, Henry J, Jovey R, Lynch M, Mailis-Gagnon A, Panju A, Rollman GB, Velly A. Pharmacological management of chronic neuropathic pain: consensus statement and guidelines from the Canadian Pain Society. Pain Res Manag 2007;12:13–21.

47. Attal N, Cruccu G, Haanpaa M, Hansson P, Jensen TS, Nurmikko T, Sampaio C, Sindrup S, Wiffen P. EFNS guidelines on pharmacological treatment of neuropathic pain. Eur J Neurol 2006;13:1153–69.

48. Hazekamp A, Heerdink ER. The prevalence and incidence of medicinal cannabis on prescription in The Netherlands. Eur J Clin Pharmacol 2013;69:1575–80.

49. van der Pol P, Liebregts N, de Graaf R, Ten Have M, Korf DJ, van den Brink W, van Laar M. Mental health differences between frequent cannabis users with and without dependence and the general population. Addiction 2013;108:1459–69.

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