MMP-038

New Jersey Department of Health
Medicinal Marijuana Program
PO 360
Trenton, NJ 08625-0360

MEDICINAL MARIJUANA PETITION
(N.J.A.C. 8:64-5.1 et seq.)

INSTRUCTIONS

This petition form is to be used only for requesting approval of an additional medical condition or treatment thereof as a "debilitating medical condition" pursuant to the New Jersey Compassionate Use Medical Marijuana Act, N.J.S.A. 24:6I-3. Only one condition or treatment may be identified per petition form. For additional conditions or treatments, a separate petition form must be submitted.

NOTE: This Petition form tracks the requirements of N.J.A.C. 8:64-5.3. Note that if a petition does not contain all information required by N.J.A.C. 8:64-5.3, the Department will deny the petition and return it to petitioner without further review. For that reason the Department strongly encourages use of the Petition form.

*This completed petition **must** be postmarked **August 1 through August 31, 2016** and sent by **certified mail** to:*

New Jersey Department of Health
Office of Commissioner - Medicinal Marijuana Program
Attention: Michele Stark
369 South Warren Street
Trenton, NJ 08608

Please complete each section of this petition. If there are any supportive documents attached to this petition, you should reference those documents in the text of the petition. If you need additional space for any item, please use a separate piece of paper, number the item accordingly, and attach it to the petition.

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1. Petitioner Information

Name: **James Broatch**

Street Address: **99 Cherry Street**

City, State, Zip Code: **Milford, CT 06460**

Telephone Number: **203 877-3790**

Email Address: **info@rsds.org**

2. Identify the medical condition or treatment thereof proposed. Please be specific. Do not submit broad categories (such as "mental illness").

Complex Regional Pain Syndrome Type 1 and TYpe 11

3. Do you wish to address the Medical Marijuana Review Panel regarding your petition?

☐ Yes, in Person

☒ Yes, by Telephone

☐ No

4. Do you request that your personally identifiable information or health information remain confidential?

☐ Yes

☒ No

If you answer "Yes" to Question 4, your name, address, phone number, and email, as well as any medical or health information specific to you, will be redacted from the petition before forwarding to the panel for review.

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OFFICE OF THE CHIEF OF STAFF

5. **Describe the extent to which the condition is generally accepted by the medical community and other experts as a valid, existing medical condition.**

Complex Regional Pain Syndrome (CRPS), also commonly known as Reflex Sympathetic Dystrophy (RSD) is a progressive neuroinflammatory disorder characterized by intense severe pain, swelling, and hypersensitivity to touch. The CRPS/RSD pain experienced 24 hours/seven days a week, is described as intense, stabbing, and burning, and is much fiercer than would be expected for the type of injury that occurred. CRPS, often worsens, rather than improves over time and may spread from the original injury site to the whole limb or to the arm or leg on the opposite side of the body.
While it can occur in children it is most common in adults especially women. We suspect that hundreds of thousands worldwide have the illness, but there are no epidemiological studies that provide an accurate determination. Although classified as a rare disorder by the FDA, it is estimated that 50,000 people with CRPS are diagnosed in the US annually .

CRPS is a severely painful disorder that commonly follows injury such as fracture, sprain, surgery, crush injury, or immobilization. CRPS Type II pain is ranked as a 42 on McGill Pain Index; higher than the pain associated with the amputation of a digit or cancer pain. It can become debilitating and profoundly disabling. In addition, the disease affects many other systems within the body: People in chronic pain do not sleep more than 2 or 3 hours during the night; resulting in exhaustion that makes it more difficult to cope with the pain. People with CRPS are often diagnosed late, misdiagnosed or disbelieved by people who would otherwise be well-meaning. Care delayed is care denied. This phenomenon is primarily due to a lack of knowledge, awareness, education and experience among healthcare professionals as well as among policy makers, insurance carriers, employers and even the sufferer's family and friends.

6. **If one or more treatments of the condition, rather than the condition itself, are alleged to be the cause of the patient's suffering, describe the extent to which the treatments causing suffering are generally accepted by the medical community and other experts as valid treatments for the condition.**

NA

7. **Describe the extent to which the condition itself and/or the treatments thereof cause severe suffering, such as severe and/or chronic pain, severe nausea and/or vomiting or otherwise severely impair the patient's ability to carry on activities of daily living.**

In 2004, RSDSA conducted an on-line survey of people with CRPS in conjunction with the Johns Hopkins School of Medicine. 888 individuals met inclusion criteria. The investigators reported that "the syndrome commonly progressed and spread to involve other body areas. Affected patients failed multiple pharmacological and non-pharmacological interventions. The syndrome frequently interfered with job (~62% disability rate), sleep (~96%), mobility (~86%), and self-care (~57%). Remissions and relapses were both common.

The average person with CRPS must see four or more practitioners to receive the proper diagnosis and to receive appropriate and necessary treatment. Today, the importance of self-advocacy is essential. Many people with CRPS experience anxiety, depression, alienation and loneliness. Almost 40% of people with chronic CRPS, who were previously well employed, never return to work after the onset of the disease. The suicide rate of people with CRPS is 2.5 times higher than sufferers of any other painful condition. Families dissolve or are forced into bankruptcy and people with CRPS often lose access to care and lose hope.

Author: Agarwal S, Broatch J, Raja SN
Title: Web-based Epidemiological Survey of Complex Regional Pain Syndrome
A demographically-based epidemiological clinical study on CRPS diagnosis and treatment.

8. **Describe the availability of conventional medical therapies other than those that cause suffering to alleviate suffering caused by the condition and/or the treatment thereof.**

There are no approved medications to treat CRPS. Individuals with CRPS were routinely excluded from clinical trials because of the lack of a "gold standard' to diagnostic CRPS. Although the recently validated Budapest Diagnostic Criteria is much more specific, most medications used to treat neuropathic pain are considered "off-label" for CRPS and often insurers deny reimbursement. According to surveys conducted by the RSDSA, more than 50 percent of individuals suffering with CRPS are on opioid therapy which is controversial for CRPS. Unfortunately, while opioids have many positive qualities for patients with normal acute-injury pain (e.g. relative efficacy, relative lack of toxicity), opioids are known for activating changes in glial cells in the central nervous system. Those glial cells release inflammatory cytokines, leading to central sensitization. Thus, in the case of CRPS, the opioids prescribed may actually make the problem worse. Constipation and the development of Tolerance are common undesirable side effects.

The Dutch, UK, and the RSDSA Treatment Guidelines recommend a multidisciplinary approach to treat CRPS yet there are limited multidisciplinary pain programs available in the United States. Most individuals with CRPS are treated by an interventional pain specialist without the recommended functional restoration component. Most physical and occupational therapists are not familiar with CRPS.
During the last decade, Ketamine, a NMDA receptor antagonist has been increasingly used to treat CRPS. Insurers however regularly deem it as an experimental treatment and do not pay for it.

Spinal Cord Stimulation (SCS) is utilized to treat CRPS with a response rate of 50% for > 50%pain relief in patients with >6 months duration. With time, the SCS effect does slowly diminish.

9. **Describe the extent to which evidence that is generally accepted among the medical community and other experts supports a finding that the use of marijuana alleviates suffering caused by the condition and/or the treatment thereof.** ***[Note:*** *You may attach articles published in peer-reviewed scientific journals reporting the results of research on the effects of marijuana on the medical condition or treatment of the condition and supporting why the medical condition should be added to the list of debilitating medical conditions.]*

See peer-reviewed articles included with this application

10. **Attach letters of support from physicians or other licensed health care professionals knowledgeable about the condition. List below the number of letters attached and identify the authors.**

We are attaching a number of peer-reviewed articles for your review on the efficacy and safety of medical marijuana for treating CRPS. Here is a letter from Dr. Pradeep Chopra, a CRPS pain specialist.

Plea for including Complex Regional Pain Syndrome (CRPS) on the list of approved conditions for Medical Marijuana in the state of NJ
I am writing this letter at the request of the Reflex Sympathetic Dystrophy Association (RSDSA) to include Complex Regional Pain Syndrome (also known as RSD or Reflex Sympathetic Dystrophy) as one of the medical conditions for the use of Medical Marijuana.
As a background, I am a pain medicine specialist in RI. I have a special interest in treating complex pain conditions. Medical Marijuana has been approved in RI for many years and over this time clinician have seen the benefits of Medical Marijuana for managing debilitating conditions.
Complex Regional Pain Syndrome is a chronic pain condition which presents as intractable neuropathic pain. It is severely painful condition with no known treatments. McGill pain scale describes Complex Regional Pain Syndrome pain as more intense than amputation of digit, cancer pain, phantom limb pain, post herpetic neuralgia and fractures. It affects 20,000 people in the USA every year.
Medications often used to treat Complex Regional Pain Syndrome include anti-epileptics (gabapentin etc.), anti-depressants (amitriptyline, duloxetine etc.). Opioids have not been known to help neuropathic pain. In fact, opioids increase Central Sensitization by increasing glial cell activation which in turn causes release of cytokines causing neuroinflammatory changes. Medications from the NSAID class play a minimal role in managing the intractable neuropathic pain. They may help with the nociceptive component of the pain. Most physicians that treat Complex Regional Pain Syndrome often use a multi-medication approach using a mix of anti-seizure, anti-depressants and opioids.
Physical therapy is an important component of managing Complex Regional Pain Syndrome. Unfortunately, without good pain

management, physical therapy becomes counterproductive.
Complex Regional Pain Syndrome is also commonly associated with intractable nausea. The nausea is maybe either or all of the following, related to medications used to control pain, gastroparesis (a features of Complex Regional Pain Syndrome), neuropathic pain of the gastrointestinal tract (common complication of Complex Regional Pain Syndrome).
Dystonic muscle spasms and spasticity is a feature of Complex Regional Pain Syndrome. The muscle symptoms are unresponsive to commonly used muscle relaxants and other therapies used for muscle spasms. The dystonias, tremors and spasticity are mediated through the central nervous system.
In summary, Complex Regional Pain Syndrome is an intractable pain condition that affects adults and children. It affects approximately 20,000 adults annually in USA. The pain suffered by these patients is worse than amputation of a digit, cancer pain, and fracture or labor pain. Usual treatments have not been able to alleviate this pain. Treatment with opioids is ineffective and the risk of opioid hyperalgesia in this group is high – opioids are not known to help neuropathic pain and often time's physicians are forced to increase opioids in these patients for lack of better treatments. Experience from states where Medical Marijuana has been approved for some years has shown that a large number of patients with Complex Regional Pain Syndrome respond to it. There have been anecdotal reports of patients responding to topical Medical Marijuana. Experience has shown that patients with Complex Regional Pain Syndrome report better function once their pain is controlled with Medical Marijuana. Based on the Department of Consumer Protection's approved list, patients with Complex Regional Pain Syndrome fulfill 2 of the criteria of intractable nausea and spasticity.
I will be happy to provide you with more details if you should need them. I sincerely hope that you will consider Complex Regional Pain Syndrome as one of the approved conditions for Medical Marijuana.
Thank you,
Regards,
Pradeep Chopra, MD

I certify, under penalty of perjury, that I am 18 years of age or older; that the information provided in this petition is true and accurate to the best of my knowledge; and that the attached documents are authentic.

Signature of Petitioner	Date
James W Brown	8/30/2016 8/10/2016

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Cannabinoids for treatment of chronic non-cancer pain; a systematic review of randomized trials

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Effective therapeutic options for patients living with chronic pain are limited. The pain relieving effect of cannabinoids remains unclear. A systematic review of randomized controlled trials (RCTs) examining cannabinoids in the treatment of chronic non-cancer pain was conducted according to the PRISMA statement update on the QUORUM guidelines for reporting systematic reviews that evaluate health care interventions. Cannabinoids studied included smoked cannabis, oromucosal extracts of cannabis based medicine, nabilone, dronabinol and a novel THC analogue. Chronic non-cancer pain conditions included neuropathic pain, fibromyalgia, rheumatoid arthritis, and mixed chronic pain. Overall the quality of trials was excellent. Fifteen of the eighteen trials that met the inclusion criteria demonstrated a significant analgesic effect of cannabinoid as compared with placebo and several reported significant improvements in sleep. There were no serious adverse effects. Adverse effects most commonly reported were generally well tolerated, mild to moderate in severity and led to withdrawal from the studies in only a few cases. Overall there is evidence that cannabinoids are safe and modestly effective in neuropathic pain with preliminary evidence of efficacy in fibromyalgia and rheumatoid arthritis. The context of the need for additional treatments for chronic pain is reviewed. Further large studies of longer duration examining specific cannabinoids in homogeneous populations are required.

Linked Article
This article is linked to a themed issue in the *British Journal of Pharmacology* on Respiratory Pharmacology. To view this issue visit http://dx.doi.org/10.1111/bph.2011.163.issue-1

Introduction

Chronic pain is common and debilitating with too few effective therapeutic options. Cannabinoids represent a relatively new pharmacological option as part of a multimodel treatment plan. With increasing knowledge of the endocannabinoid system [1–3] and compelling preclinical work supporting that cannabinoid agonists are analgesic [4, 5] there is increasing attention on their potential role in the management of pain [6–9]. A previous systematic review done a decade ago identified the need for further randomized controlled trials (RCTs) evaluating cannabinoids in the management of chronic pain indicating that there was insufficient evidence to introduce cannabinoids into widespread use for pain at that time [10]. A subsequent review identified a moderate analgesic effect but indicated this may be offset by potentially serious harm [11]. This conclusion of serious harm mentioned in the more recent review is not consistent with our clinical experience. In addition there have been a number of additional RCTs published since this review. We therefore conducted an updated systematic review examining RCTs of cannabinoids in the management of chronic pain.

Methods

We followed the PRISMA update on the QUORUM statement guidelines for reporting systematic reviews that evaluate health care interventions [12].

Systematic search

A literature search was undertaken to retrieve RCTs on the efficacy of cannabinoids in the treatment for chronic pain. The databases searched were: PubMed, Embase, CINAHL (EBSCO), PsycInfo (EBSCO), The Cochrane Library (Wiley), ISI Web of Science, ABI Inform (Proquest), Dissertation Abstracts (Proquest), Academic Search Premier (EBSCO), Clinical Trials.gov, TrialsCentral.org, individual pharmaceutical company trials sites for Eli Lilly and GlaxoSmithKline,

OAIster (OCLC) and Google Scholar. None of the searches was limited by language or date and were carried out between September 7 and October 7, 2010. The search retrieved all articles assigned the Medical Subject Headings (MeSH) *Cannabis, Cannabinoids, Cannabidiol, Marijuana Smoking* and *Tetrahydrocannibinol* as well as those assigned the Substance Name *tetrahydrocannabinol-cannabidiol combination*. To this set was added those articles containing any of the keywords *cannabis, cannabinoid, marijuana, marihuana, dronabinol* or *tetrahydrocannibinol*. Members of this set containing the MeSH heading Pain or the title keyword *'pain'* were passed through the 'Clinical Queries: therapy/narrow' filter to arrive at the final results set. For the pain aspect, the phrase *'Chronic pain'* along with title keyword *'pain'* was used to retrieve the relevant literature. We contacted authors of original reports to obtain additional information. Bibliographies of included articles were checked for additional references.

Inclusion and exclusion criteria

Included were RCTs comparing a cannabinoid with a placebo or active control group where the primary outcome was pain in subjects with chronic non-cancer pain. Relevant pain outcomes included any scale measuring pain, for example the numeric rating scale for pain (NRS), visual analogue scale for pain (VAS), the Neuropathy Pain Scale or the McGill Pain Scale. We excluded (i) trials with fewer than 10 participants, (ii) trials reporting on acute or experimental pain or pain caused by cancer, (iii) preclinical studies and (iv) abstracts, letters and posters where the full study was not published.

Data extraction and validity scoring

One author (ML) did the initial screen of abstracts, retrieved reports and excluded articles that clearly did not meet the inclusion criteria. Both authors independently read the included articles and completed an assessment of the methodological validity using the modified seven point, four item Oxford scale [13, 14] (Figure 1). After reading the complete articles it was clear that several additional papers did not meet inclusion criteria and these were excluded. Discrepancies on the quality assessment scale were resolved by discussion. Trials that did not include randomization were not included and a score of 1 on this item of the Oxford scale was required and the maximum score was 7.

Information about the specific diagnosis of pain, agent and doses used, pain outcomes, secondary outcomes (sleep, function, quality of life), summary measures, trial duration and adverse events was collected. Information on adverse events was collected regarding serious adverse events, drug related withdrawals and most frequently reported side effects. A serious adverse event according to Health Canada and ICH[1] guidance documents

Modified Oxford Scale
Validity score(0–7)

Randomization

0 None
1 Mentioned
2 Described and adequate

Concealment of allocation

0 None
1 Yes

Double-blinding

0 None
1 Mentioned
2 Described and adequate

Flow of patients

0 None
1 Described but incomplete
2 Described and adequate

Figure 1
Modified Oxford scale

is defined as any event that results in death, is life threatening, requires prolonged hospitalization, results in persistent of significant disability or incapacity or results in congenital anomaly or birth defects [15].

Results

Trial flow

Eighty abstracts were identified of which 58 did not meet inclusion criteria on the initial review of records (Figure 2). Twenty-two RCTs comparing a cannabinoid with either a placebo or active control group where pain was listed as an outcome were found and full text articles were reviewed, four further studies were excluded, two because pain was not the primary outcome (Zajicek [16, 17]), one because there were fewer than 10 participants in the study (Rintala [18]). A further study was excluded because there were two studies reporting on what appeared to be the same group of participants (Salim [19], Karst [20]), in this case we included the first study in which the pain outcomes were reported (Karst). References of the included trials were reviewed for additional trials meeting inclusion criteria. This revealed no further studies. Eighteen trials met the study criteria for inclusion. We did not retrieve any unpublished data. Given the different cannabinoids, regimens, clinical conditions, different follow-up periods, and

1. International Conference on Harmonization of Technical Requirements for the Registration of Pharmaceuticals for Human Use.

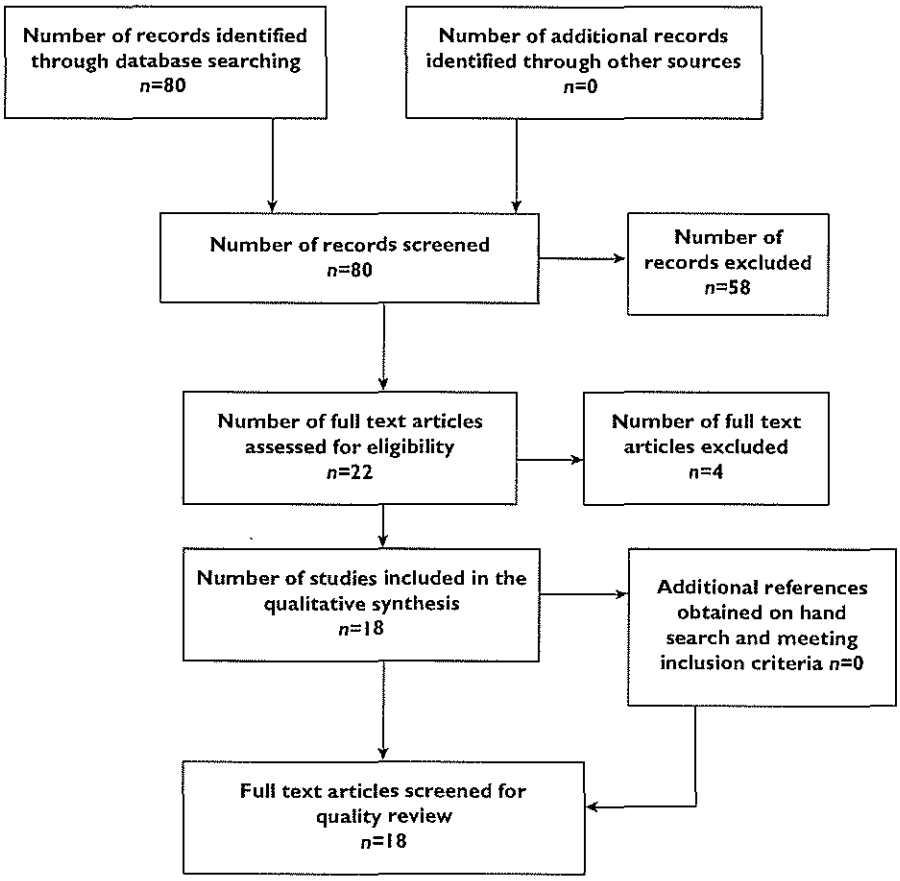

Figure 2
Flow diagram of systematic review

outcome measures used in these trials, pooling of data for meta-analysis was inappropriate. Results were therefore summarized qualitatively.

Primary outcome – efficacy

Eighteen trials published between 2003 and 2010 involving a total of 766 completed participants met inclusion criteria (Table 1). The quality of the trials was very good with a mean score of 6.1 on the 7 point modified Oxford scale. The majority (15 trials) demonstrated a significant analgesic effect for the cannabinoid agent being investigated. Several trials also noted significant improvements in sleep [21–24]. Treatment effects were generally modest, mean duration of treatment was 2.8 weeks (range 6 h–6 weeks) and adverse events were mild and well tolerated.

Cannabis Four trials examined smoked cannabis as compared with placebo. All examined populations with neuropathic pain and two involved neuropathic pain in HIV neuropathy [21, 25–27]. All four trials found a positive effect with no serious adverse effects. The median treatment duration was 8.5 days treatment (range 6 h–14 days).

Oromucosal extracts of cannabis based medicine (CBM) Seven placebo controlled trials examined CBM [22–24, 28–30]. Five examined participants with neuropathic pain, one rheumatoid arthritis and one a mixed group of people with chronic pain, many of whom had neuropathic pain. Six of the seven trials demonstrated a positive analgesic effect. Of note in the one trial examining pain in rheumatoid arthritis, the CBM was associated with a significant decrease in disease activity as measured by the 28 joint disease activity score (DAS28) [23].

Nabilone Four trials studied nabilone [31–34]. Three of these trials were placebo controlled and found a significant analgesic effect in spinal pain [34], fibromylagia [32] and spasticity related pain [33]. The fourth compared a daily dose of nabilone 2 mg with dihydrocodeine 240 mg in neuropathic pain. Mean baseline pain was 69.6 mm on

Table 1

Randomized controlled trials examining cannabinoids in treatment of chronic non-cancer pain

Author and date	Agent (control group)	Population (*n*) completed/randomized *design*	Core outcomes*	Summary measures used	Oxford scale score	Duration of RCT	Results (brief comments)	AEs†	Outcome summary
Ware *et al.* [21]	Cannabis smoked 0%, 2.5%, 6%, 9.4% (placebo)	Neuropathic pain 21/23 *crossover*	NRS Pain Leeds sleep POMS	Difference in means	7	14 day treatment periods	Significantly lower average daily pain intensity on 9.4% THC (5.4) than 0% (6.1) Improved sleep No change in mood	No serious AEs Headache Dry eyes Burning sensation Dizziness Numbness Cough	+
Ellis *et al.* [26]	Cannabis smoked 1–8% (Placebo)	HIV neuropathy 28/34 *crossover*	DDS pain McGill VAS pain POMS	Median difference pain intensity change	6	5 day treatment periods	Pain reduction significantly greater with cannabis than placebo median difference in pain reduction = 3.3 DDS points, effect size = 0.60 Also proportion achieving >30% reduction greater for active 0.46 *vs.* placebo 0.18 NNT 3.5 for 30% reduction	No serious AEs Two participants experienced treatment limiting side effects most common AEs Decreased concentration Reduced salivation Fatigue sleepiness Sedation	+
Frank *et al.* [31]	Nabilone 2 mg (dihydrocodeine) 240 mg	Chronic neuropathic pain 96 *crossover*	VAS pain Hamilton depression SF-36	Difference in means	7	6 weeks	Both agents resulted in approximately a 10 mm reduction in a 0–100 mm VAS pain Baseline 69.6 mm Nabilone 59.6 mm Dihydrocodeine 58.6 mm with dihydrocodeine providing marginally better pain relief	No serious AEs Tiredness Sleepiness Sickness	+/–
Narang *et al.* [36]	Dronabinol 10, 20 mg (placebo)	Chronic pain on opioids 29/30 *crossover*	NRS pain intensity and pain relief	Difference in average pain intensity and total pain relief	7	1 day each treatment RCT 4 week open extension	Dronabinol at both doses significantly less pain and greater relief than placebo SPID –6.4 placebo, 10 mg (–17.4, $P < 0.01$), 20 mg (–19.7, $P < 0.01$) TOTPAR placebo (31.1), 10 mg (39.7, $P < 0.5$) 20 mg (41.7, $P < 0.01$ in both the RCT and the extension	No serious AEs Drowsiness Sleepiness Dizziness Dry mouth	+
Wilsey *et al.* [27]	Cannabis smoked 7.7%, 3.5% (placebo)	Neuropathic pain 38/44 *crossover*	VAS pain intensity Pain relief PGIC	Difference in mean pain	7	6 h sessions	Cannabis both doses significantly less pain and pain unpleasantness (combined 3.5 and 7% cannabis *vs.* placebo differences per minute –0.0035, 95% $P = 0.016$)	No serious AEs or withdrawals Feeling high Stoned Impaired greater with high dose, side effects stated to be relatively inconsequential	+
Skrabek *et al.* [32]	Nabilone 0.5–1 mg twice daily (placebo)	Fibromyalgia 40 *parallel group*	VAS pain FIQ	Difference in means	6	4 weeks treatment	Significant decrease in 10 cm VAS pain (–2.04, $P < 0.02$), total FIQ (–12.07, $P < 0.02$) and 10 point FIQ anxiety (–1.67, $P < 0.02$) with nabilone *vs.* placebo	Three withdrew due to side effects Dizziness Disorientation Nausea Poor co-ordination Drowsiness Dry mouth Vertigo Ataxia Headache	+
Abrams *et al.* [25]	Cannabis smoked 3.56% (placebo)	HIV sensory neuropathy 50/55 *parallel group*	VAS pain	Difference in Median daily pain ratings	7	5 day inpatient 7 day outpatient	Significant reduction in pain with cannabis *vs.* placebo Median reduction in pain was 34% (17% placebo) >30% relief 52% (*vs.* 24%) NNT=3.6	All side effects were mild and included Anxiety Sedation Disorientation Paranoia Confusion Dizziness Nausea	+

Numikko *et al.* [30]	Cannabis based medicine THC/CBD (placebo)	Neuropathic pain with allodynia 125 *crossover*	NRS pain PGIC PDI HQ-12 Sleep NRS NPS	Mean change VAS pain	7	5 weeks plus open label extension option	Significantly less pain with Sativex *vs.* placebo Mean change of −1.48 Sativex *vs.* −0.52 P a 22% reduction On Sativex 26% had 30% reduction and 20% a 50% reduction *vs.* P 15% and 8% NNT 8.5 (50%) 8.6 (30%) Secondary outcomes also improved – sleep, NPS, PGIC Open label extension showed initial pain relief maintained without dose escalation or toxicity for 52 weeks	18% withdrew on Sativex *vs.* 3% on placebo No serious AEs by definition below Most described as mild Dizziness Nausea Fatigue Dry mouth But seven in Sativex group and five in placebo group graded them as 'severe' Paranoid thinking was reported in one patient while on Sativex	+
Wissel *et al.* [33]	Nabilone 1 mg day^{-1} (placebo)	Spasticity related pain in UMNS 11/13 *crossover*	11-point box test Ashworth scale for spasticity Motor ADLs	Difference in median pain	3	4 week treatment periods	Significant decrease in spasticty related pain with reduction of median 2 points with nabilone *vs.* placebo but no significant change in spasticity according to Ashworth scale or motor or ADL	Two patients withdrew one due to a relapse felt not to be related to the nabilone, the other due to leg weakness, rest described as mild Drowsiness (2) Slight weakness legs (1)	+
Pinsger *et al.* [34]	Nabilone 0.25–1 mg day^{-1} (placebo)	Chronic pain (spinal) 30 *crossover*	VAS pain intensity Cohen QOL	Difference in median pain	3	4 week treatment periods	Significant decrease in spinal pain intensity (0.6) (0.0) $P = 0.006$ on nabilone *vs.* placebo	# leg after fall possibly related to dizziness caused by interaction of nabilone with concurrent meds during crossover Fatigue Dry mouth Dizziness	+
Rog *et al.* [22]	Cannabis based medicine THC/CBD (9 6 sprays/day 2–25) (placebo)	Central pain in MS 64/66 *parallel group*	NRS pain and sleep HADS PGIC NPS	Differences in mean intensity pain	7	4 week	Significant reductions in pain (NRS, NPS) and sleep disturbance (NRS) with CBM 3.85 *vs.* placebo 4.96 NNT=3.7 NNH=5 13 No significant changes in blood pressure, weight, haematology, blood chemistry	No serious AEs Two AEs led to withdrawal from trial (agitation and paranoia) Dizziness Somnolence Dissociation Dry mouth Nausea Weakness	+
Blake *et al.* [23]	Cannabis based medicine mean dose 5.4 sprays/day (placebo)	Rheumatoid arthritis 58 *parallel group*	NRS pain, sleep SF-MPQ DAS28	Differences in means	4	5 weeks	Significant improvements in pain on movement (difference mean/median = 0.95, $P = 0.04$ at rest, 1.04, $P = 0.01$, quality of sleep 1.17, $P = 0.02$, DAS28, 0.76, $P = 0.002$, and SF-MPQ, 3.00, $P = 0.30$ with CBM *vs.* placebo)	No serious AEs No treatment related withdrawals All mild to moderate Dizziness Lightheaded Dry mouth Nausea Two noted severe constipation Fall (two patients)	+
Berman *et al.* (2004) [24]	Cannabis based medicine THC/CBD, THC 8 sprays day^{-1} (placebo)	Neuropathic pain brachial plexus avulsion 48 *crossover*	NRS pain BS-11 for sleep quality SF-MPQ PDI	Difference in means	7	2 week treatment periods extension	Statistically significant reductions in pain (NRS) and sleep disturbance (NRS) but not to the full 2 point reduction (i.e. reduction of 0.58, $P = 0.005$ and 0.64, $P = 0.002$)	No serious AEs One drug related withdrawal feeling faint The rest mild-moderate and resolved spontaneously Dizziness Somnolence Bad taste	±
Svendsen *et al.* [35]	Dronabinol 10 mg (placebo)	Central pain in MS (24) *crossover*	NRS pain Pain relief SF36	Difference in median	7	3 weeks	Significant reductions in pain (NRS) modest reductions 1 point on a 0–10 point scale NNT for 50% relief=3.45	Dizziness Headache Tiredness Myalgia Muscle weakness Dose reduction resolved the AEs in the four who experienced 'intolerable level' of the AE Four experienced aggravation of MS, one during drug treatment, two during placebo and one during washout	+

Table 1

Continued

Author and date	Agent (control group)	Population (*n*) completed/randomized *design*	Core outcomes*	Summary measures used	Oxford scale score	Duration of RCT	Results (brief comments)	AEs‡	Outcome summary
Wade *et al.* [28]	Cannabis based medicines HC/CBD (placebo)	MS 160 where 37 had pain as target symptom *parallel group*	VAS pain spasticity, spasms, bladder problems, tremor	Difference in means	6	6 weeks	No significant difference in pain scores (VAS) between CBM and placebo all decreased There was a significant reduction in spasticity (VAS) scores	Dizziness† Fatigue Headache Disturbance in attention Application site discomfort Mouth ulceration	–
Karst *et al.* [37]	CT-3 Synthetic analogue of THC-11-oic acid (placebo)	Neuropathic pain with hyperlagesia or allodynia 19/21 *crossover*	VAS pain Pain relief	Differences in means	7	1 week treatment periods	Significant improvement in pain intensity 3 h after study drug (-11.54 or 9.86, $P = 0.02$) §difference between CT-3 and P abated by 8 h No significant change pain relief	No serious AEs One withdrawal from excessive drowsiness Tiredness Dizziness Dry mouth Decreased concentration Sweating	+
Notcutt *et al.* [57]	Cannabis based medicine THC CBD THC/CBD (placebo)	Chronic pain 24 of 34 *'N of 1'* 2 week open/RCT 1 week Rx periods × 2 for each CBME *crossover*	VAS pain for Two worst pain symptoms BDI GHQ Sleep	Difference in medians	4	Two 1 week treatment periods or each agent	Significant reduction in pain (VAS) for THC and THC:CBD Cumulative VAS (median, interquartile range for worst pain Placebo 5.9 (2.8–7.3) CBD 5.45 (3.6–7.4) THC 4.63 (1.74–6.06) THC:CBD 4.4 (2.6–5.8 ($P < 0.001$) 9/24 had a reduction of >50%with THC or THC : CBD	No serious AEs One withdrawal due to medication AE Dry mouth Drowsiness Euphoria/dysphoria Vasovagal episode on initial dosing	+
Wade *et al.* [29]	Cannabis based medicine THC CBD THC/CBD (placebo)	Neurogenic symptoms in MS/spinal cord injury/brachial plexus injury/limb amputation 24 *'N of 1'* where 12 had target symptom of pain *crossover*	VAS pain Intoxication Alertness Appetite Happiness etc	Difference in means	7	2 week study periods	Difference in mean VAS pain between CBM and placebo = 10.3 for CBD, 10.1 for THC, $P = 0.05$ Significant reductions in pain CBD and THC but not the combination	Three withdrawals One vasovagal One intoxication One psychoactive effects marked Hypotension if given too quickly Diarrhoea Sleepiness Sore mouth	+

*Examples:
Pain: NRS, VAS other scale
- At least 50% pain reduction
- At least 30% pain reduction
- Patient global impression
- Other key measures, sleep,

†side effects were for the whole group.
‡Adverse events:
Note serious adverse events defined by:
- results in death
- is life threatening
- requires or prolongs inpatient hospitalization
- results in persistent or significant disability or incapacity
- results in congenital anomaly or birth defects

Clinical Research in Canada; Edition: January 1, 2006, Book 11, Section title, Guidance for Industry, Clinical Safety Data Management : Definitions and Standards for Expedited Reporting (ICH-E2A); definition is on page 3 of this section, under the heading of 'Serious Adverse Event or Adverse Drug Reaction'
§The larger difference in the group receiving CT-3 first.
DDS, descriptor differential scale, ratio scale 24 words describe pain 0–20; PGIC, patient global impression of change; POMS, profile of mood states; PDI, Pain Disability Index; HADS, Hospital anxiety and depression scale; SF-MPQ, McGill Pain Questionnaire, short form; DAS28, 28 joint disease activity score; UMNS, Upper Motor Neuron Syndrome; TOTPAR, total pain relief; SPID, sum pain intensity difference; BDI, Beck Depression Inventory; GHQ, General Health Questionnaire.
#means fractured.

the 100 mm VAS and dropped to 59.93 mm for participants taking nabilone and 58.58 mm for those taking dihydrocodeine [31].

Dronabinol Two trials involved dronabinol. The earlier trial found that dronabinol 10 mg day^{-1} led to significant reduction in central pain in multiple sclerosis [35], a subsequent trial found that dronabinol at both 10 and 20 mg day^{-1} led to significantly greater analgesia and better relief than placebo as adjuvant treatment for a group of participants with mixed diagnoses of chronic pain on opioid therapy [36].

THC-11-oic acid analogue (CT-3 or ajulemic acid) Two studies reported on various aspects of this trial examining ajulemic acid in a group of participants with neuropathic pain with hyperalgesia or allodynia [37, 38]. Nineteen of 21 completed the trial. It was found that ajulemic acid led to significant improvement in pain intensity at 3 h but no difference at 8 h as compared with placebo.

Secondary outcome – level of function

Several trials included secondary outcome measures relating to level of function. Two trials examining cannabis based medicines included the Pain Disability Index (PDI) [24, 30]. Numikko found that six of seven functional areas assessed by the PDI demonstrated significant improvement on CBM (–5.61) as compared with placebo (0.24) (estimated mean difference –5.85, $P = 0.003$) in 125 participants with neuropathic pain while Berman [24] noted no significant difference from placebo in 48 participants with central pain from brachial plexus avulsion. Two studies included the Barthel index for activities of daily living (ADL) [28, 33] and noted no significant improvement in ADLs with nabilone for spasticity related pain [33] or with CBMs for multiple sclerosis [28]. In one trial examining nabilone for the treatment of fibromyalgia the FIQ [39] demonstrated significant improvement as compared with placebo. This measure includes a number of questions regarding function in several areas including shopping, meal preparation, ability to do laundry, vacuum, climb stairs and ability to work. The FIQ also includes questions relating to pain, fatigue, stiffness and mood. The total scores presented in this study were not presented separately so the reader cannot be certain. However given that the majority of questions relate to function it is likely that there were some improvements in function.

Drug related adverse effects

There were no serious adverse events according to the Health Canada definition described above and in Table 1, The most common adverse events consisted of sedation, dizziness, dry mouth, nausea and disturbances in concentration. Other adverse events included poor co-ordination, ataxia, headache, paranoid thinking, agitation, dissociation, euphoria and dysphoria. Adverse effects were generally described as well tolerated, transient or mild to moderate and not leading to withdrawal from the study. This is a significant difference from the withdrawal rates seen in studies of other analgesics such as opioids where the rates of abandoning treatment are in the range of 33% [40]. Except where specifically noted in Table 1 there was no specific mention of whether adverse effects caused limitations in function. The most severe treatment related event in the entire sample was a fractured leg related to a fall that was thought to be related to dizziness [34]. Details regarding specific trials are presented in Table 1.

Discussion

Efficacy and harm

All of the trials included in this review were conducted since 2003. No trials prior to this date satisfied our inclusion criteria. This review has identified 18 trials that taken together have demonstrated a modest analgesic effect in chronic non-cancer pain, 15 of these were in neuropathic pain with five in other types of pain, one in fibromyalgia, one in rheumatoid arthritis, one as an adjunct to opioids in patients with mixed chronic pain and two in mixed chronic pain. Several trials reported significant improvements in sleep. There were no serious adverse events. Drug related adverse effects were generally described as well tolerated, transient or mild to moderate and most commonly consisted of sedation, dizziness, dry mouth, nausea and disturbances in concentration.

Limitations

The main limitations to our findings are short trial duration, small sample sizes and modest effect sizes. Thus there is a need for larger trials of longer duration so that efficacy and safety, including potential for abuse, can be examined over the long term in a greater number of patients. It is also important to recognize that cannabinoids may only reduce pain intensity to a modest degree. It remains for the patients to decide whether this is clinically meaningful.

The context of chronic pain

Pain is poorly managed throughout the world. Eighty percent of the world population has no or insufficient access to treatment for moderate to severe pain [41]. Chronic pain affects approximately one in five people in the developed world [42–46] and two in five in less well resourced countries [47]. Children are not spared [48, 49] and the prevalence increases with age [43, 50]. The magnitude of the problem is increasing. Many people with diseases such as cancer, HIV and cardiovascular disease are now surviving their acute illness with resultant increase in quantity of life, but in many cases, poor quality of life due to persistent pain caused either by the ongoing illness or nerve damage caused by the disease after resolution or cure of the disease. In many cases the pain is also caused by

the treatments such as surgery, chemotherapy or radiotherapy needed to treat the disease [51–53].

Chronic pain is associated with the worst quality of life as compared with other chronic diseases such as chronic heart, lung or kidney disease [50]. Chronic pain is associated with double the risk of suicide as compared with those living with no chronic pain [54].

In this context, patients living with chronic pain require improved access to care and additional therapeutic options. Given that this systematic review has identified 18 RCTs demonstrating a modest analgesic effect of cannabinoids in chronic pain that are safe, we conclude that it is reasonable to consider cannabinoids as a treatment option in the management of chronic neuropathic pain with evidence of efficacy in other types of chronic pain such as fibromyalgia and rheumatoid arthritis as well. Of special importance is the fact that two of the trials examining smoked cannabis [25, 26] demonstrated a significant analgesic effect in HIV neuropathy, a type of pain that has been notoriously resistant to other treatments normally used for neuropathic pain [52]. In the trial examining cannabis based medicines in rheumatoid arthritis a significant reduction in disease activity was also noted, which is consistent with pre-clinical work demonstrating that cannabinoids are anti-inflammatory [55, 56].

Conclusion

In conclusion this systematic review of 18 recent good quality randomized trials demonstrates that cannabinoids are a modestly effective and safe treatment option for chronic non-cancer (predominantly neuropathic) pain. Given the prevalence of chronic pain, its impact on function and the paucity of effective therapeutic interventions, additional treatment options are urgently needed. More large scale trials of longer duration reporting on pain and level of function are required.

Competing Interests

The authors have no competing interests.

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The Pharmacologic and Clinical Effects of Medical Cannabis

Laura M. Borgelt, Kari L. Franson, Abraham M. Nussbaum, and George S. Wang

Cannabis, or marijuana, has been used for medicinal purposes for many years. Several types of cannabinoid medicines are available in the United States and Canada. Dronabinol (schedule III), nabilone (schedule II), and nabiximols (not U.S. Food and Drug Administration approved) are cannabis-derived pharmaceuticals. Medical cannabis or medical marijuana, a leafy plant cultivated for the production of its leaves and flowering tops, is a schedule I drug, but patients obtain it through cannabis dispensaries and statewide programs. The effect that cannabinoid compounds have on the cannabinoid receptors (CB_1 and CB_2) found in the brain can create varying pharmacologic responses based on formulation and patient characteristics. The cannabinoid Δ^9-tetrahydrocannabinol has been determined to have the primary psychoactive effects; the effects of several other key cannabinoid compounds have yet to be fully elucidated. Dronabinol and nabilone are indicated for the treatment of nausea and vomiting associated with cancer chemotherapy and of anorexia associated with weight loss in patients with acquired immune deficiency syndrome. However, pain and muscle spasms are the most common reasons that medical cannabis is being recommended. Studies of medical cannabis show significant improvement in various types of pain and muscle spasticity. Reported adverse effects are typically not serious, with the most common being dizziness. Safety concerns regarding cannabis include the increased risk of developing schizophrenia with adolescent use, impairments in memory and cognition, accidental pediatric ingestions, and lack of safety packaging for medical cannabis formulations. This article will describe the pharmacology of cannabis, effects of various dosage formulations, therapeutics benefits and risks of cannabis for pain and muscle spasm, and safety concerns of medical cannabis use.

Key Words: medical marijuana, cannabis, cannabinoids, marijuana therapeutics, medical cannabis, pain, pharmacology.
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Cannabis, or marijuana, was first used for medicinal purposes in 2737 B.C.[1, 2] The United States Pharmacopeia initially classified marijuana as a legitimate medical compound in 1851.[3] Although criminalized in the United States in 1937 against the advice of the American Medical Association, cannabis was not removed from the United States Pharmacopoeia until 1942.[2] Given the schedule I status of this drug, patients have continued to obtain cannabis for medical purposes through statewide programs and cannabis dispensaries, which are facilities or locations where medical cannabis is made available to qualified patients.

Two categories of cannabinoid medicines are currently used in North America. First, cannabis-derived pharmaceuticals include dronabinol (schedule III), nabilone (schedule II), and nabiximols (not approved by the U.S. Food and Drug Administration [FDA]). Dronabinol and nabilone were approved in 1985 for the treatment of nausea and vomiting associated with cancer chemotherapy in patients who have failed to respond adequately to conventional antiemetic therapy.[4–6] In 1992, dronabinol was also approved for the treatment of anorexia associated with weight loss in patients with acquired immune deficiency syndrome.[5, 6] Nabiximols is a cannabis-derived liquid extract formulated from two strains of *Cannabis sativa* into an oromucosal spray. It is approved in Canada, New Zealand, and eight European countries for three indications: (1) symptomatic relief of spasticity in adults with multiple sclerosis who have not responded adequately to other therapy and who demonstrate meaningful improvement during an initial trial of therapy, (2) symptomatic relief of neuropathic pain in patients with multiple sclerosis, and (3) intractable cancer pain.[7] It is being evaluated in several trials in the United States, and it is anticipated that it may receive FDA approval by the end of 2013.[8–11]

Second, phytocannabinoid-dense botanicals (i.e., medical cannabis or marijuana) include the schedule I medicinal plants *Cannabis sativa* or *Cannabis indica*. *Cannabis ruderalis*, a third cannabis variety, has little psychogenic properties. The patients that are enrolled in U.S. medical cannabis studies are provided with a cannabis strain or blend grown and created under contract at a federal research farm at the University of Mississippi.[2] However, most patients in the United States grow their own medical cannabis or purchase it from dispensaries.

Currently, 18 U.S. states and the District of Columbia have laws that allow the use and possession of cannabis for medicinal reasons (Table 1).[12] Colorado and Washington have also passed legislation for recreational use of marijuana. With a growing number of states allowing medical cannabis and with patient use increasing, it has becomes progressively important for pharmacists and other health care providers to understand the potential benefits and risks of medical cannabis. The purpose of this article is to describe the pharmacology, therapeutic benefits and risks, and various dosage formulations that have been studied with medical cannabis. Specifically, medical cannabis for pain and muscle spasms, the most common uses of medical cannabis, will be evaluated using an in-depth evidence-based approach.

Clinical Pharmacology of Medical Cannabis

Marijuana is classified as a schedule I substance by the FDA, so it is difficult for contemporary researchers to study marijuana even though its therapeutic properties have been known for more than 5000 years.[13] Cannabis contains many compounds, of which at least 60 are known to be cannabinoids (active components of cannabis).[13] In the 1960s, when marijuana was increasingly used as a recreational drug, the cannabinoid Δ^9-tetrahydrocannabinol (THC) was isolated and determined to be the principal cause of marijuana's psychoactive effects.[14] Other cannabinoids have been isolated and found to be present in cannabis, but they are not nearly as psychoactive.

Pharmacodynamics

In the 1990s, the mechanism of action for many of the cannabinoids was determined with the discovery of the cannabinoid CB_1 and CB_2 receptors. The CB_1 receptors are found in high densities in the neuron terminals of the basal ganglia (affecting motor activity), cerebellum (motor coordination), hippocampus (short-term memory), neocortex (thinking), and hypothalamus and limbic cortex (appetite and sedation).[13] To a lesser extent, the CB_1 receptors are found in periaqueductal gray dorsal horn (pain) and immune cells. CB_2 receptors are primarily found on immune cells and tissues and, when activated, can affect inflammatory and immunosuppressive activity.[15] For example, CB_2 receptors on leukocytes may modulate cell migration, although these effects are difficult to elicit from standard dosing. CB_2 receptors are also found in the brain

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Table 1. States with Enacted Laws to Allow Marijuana Use for Medical Purposes[12]

State	Year Passed	Possession Limit
Alaska	1998	1 oz usable; 6 plants (3 mature, 3 immature)
Arizona	2010	2.5 oz usable; 0–12 plants[a]
California	1996	8 oz usable; 6 mature or 12 immature plants
Colorado	2000	2 oz usable; 6 plants (3 mature, 3 immature)
Connecticut	2012	1-mo supply (exact amount to be determined)
District of Columbia	2010	2 oz dried; limits on other forms to be determined
Delaware	2011	6 oz usable
Hawaii	2000	3 oz usable; 7 plants (3 mature, 4 immature)
Maine	1999	2.5 oz usable; 6 plants
Massachusetts	2012	60 day supply for personal medical use
Michigan	2008	2.5 oz usable; 12 plants
Montana	2004	1 oz usable; 4 plants (mature), 12 seedlings
Nevada	2000	1 oz usable; 7 plants (3 mature, 4 immature)
New Jersey	2010	2 oz usable
New Mexico	2007	6 oz usable; 16 plants (4 mature, 12 immature)
Oregon	1998	24 oz usable; 24 plants (6 mature, 18 immature)
Rhode Island	2006	2.5 oz usable; 12 plants
Vermont	2004	2 oz usable; 9 plants (2 mature, 7 immature)
Washington	1998	24 oz usable; 15 plants

[a]If the patient lives > 25 miles from the nearest dispensary, the patient or caregiver may cultivate up to 12 marijuana plants in an enclosed, locked facility.

on microglia; thus, cannabinoids have begun to be studied for the treatment of Alzheimer's disease, but their role has not been established. Numerous cannabinoid compounds present in medical cannabis interact with these receptors to create varying responses (Figure 1). It is unknown how the major nonpsychotropic compound in cannabis, cannabidiol (CBD), exerts its activity, but it may be an inverse agonist, because several studies have shown that it decreases the psychotropic activity of THC.[15] It has no direct affinity for CB_1 and CB_2 receptors, yet it appears to enhance the activity of the endogenous cannabinoid, anandamide.[16] Because of the uncontrolled production of medical cannabis in various preparations (dried to be smoked or in oils to be applied, eaten, or drunk), there can be vastly different concentrations of the cannabinoid compounds in each product. As such, it is difficult to predict what pharmacologic response any cannabis product is likely to elicit. However, because of the relative efficacy (the ability of a drug to induce a biologic response at its molecular target when bound) of THC compared to other cannabinoids, it is routinely found to be the compound associated with the most pharmacologic effects of cannabis. Current researchers are trying to further differentiate the poorly binding cannabinoids by looking into the noncannabinoid targets linked to pain.[13] In these studies, other G-protein receptors (e.g., GPR55), G-protein–coupled receptors (coupling with μ- and δ-opioid receptors), and transient receptor potential channels (TRPVs), which are responsive to capsaicin, are being identified as targets.[13] In the TRPV example, it is interesting that non-CB_1 and non-CB_2 active phytocannabinoids (and not THC) have been shown to have the most effects.[15]

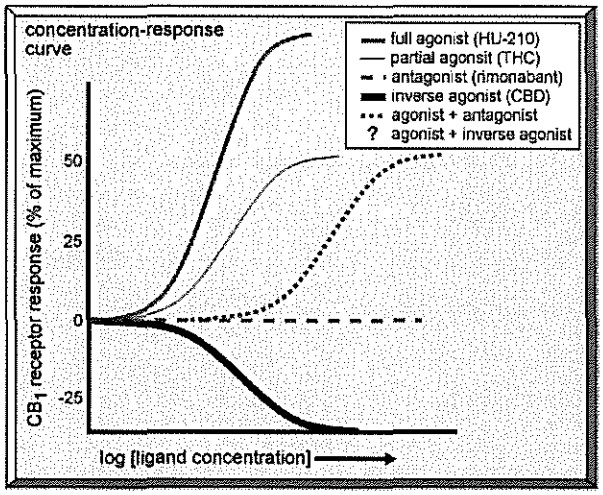

Figure 1. Concentration-response curves of cannabinoid compounds on the CB_1 receptor. The full agonist is the compound HU-210, which is a synthetic cannabinoid; the partial agonists are Δ^9-tetrahydrocannabinol (THC), which is a cannabinoid found in cannabis, and anandamide, which is an endocannabinoid found in humans; the antagonist is rimonabant, a synthetic cannabinoid studied for weight control; the inverse agonist is cannabidiol (CBD), which has no direct CB_1 activity but is postulated to be an example of an inverse agonist. It is unknown what the exact combination of agonists, antagonists, and inverse agonists are in cannabis and the result of this combination.

Pharmacokinetics

The pharmacokinetic characteristics of cannabinoids have been primarily evaluated in small clinical pharmacology studies. The half-life of the distribution phase is 0.5 hour, whereas the half-life for the terminal phase is highly variable with a mean of 30 hours.[17] Both are consistent with THC being highly lipophilic. Cannabidiol has a similar lipophilic profile to THC but has a terminal half-life of 9 hours.[16]

Smoking cannabis turns approximately 50% of the THC content into smoke, with the remainder lost by heat or from smoke that is not inhaled. Up to 50% of inhaled smoke is exhaled again, and some of the remaining smoke undergoes localized metabolism in the lung. The end result is that the estimated bioavailability of a smoked dose of THC is between 0.10 and 0.25.[18, 19] The absorption of smoked THC occurs within minutes, and the half-life of the distribution phase and that of terminal phase of smoked cannabis mimics those of intravenously administered THC.[18]

Although smoking remains the most common mode of ingestion for medical cannabis, vaporization of cannabis is becoming increasingly popular among medical cannabis users due to its perceived reduction of harm given the release of a significantly lower percentage of noxious chemicals.[20, 21] Given the volatility of cannabinoids, they will vaporize at a temperature much lower than the actual combustion of plant matter. When heated air is drawn through the cannabis, the active components will aerosolize and can be inhaled without the generation of smoke.[2]

Orally administered THC has a bioavailability ranging from 5–20% in the controlled environments of clinical studies but is often lower in users because of variations in gastric degradation (with the presence of acids) and extensive first-pass effects.[18, 22] The bioavailability of oral cannabidiol is also variable (reported to be 13–19%), but one primate model found that intoxication required 20–50 times an oral versus an intravenous dose.[16, 23] The peak concentrations of the THC component of orally administered medical marijuana are delayed compared to intravenous or inhaled administration and are reached in 1–3 hours.[22] Orally administered medical cannabis presents concerns because absorption may be incomplete and delayed, resulting in intrapatient variability and difficulty with self-titration for appropriate dosing.

Drug–Dose, Drug–Disease and Drug–Drug Relationships

There is wide variation in the reported dose of THC needed to produce central nervous system effects. A review of 165 clinical pharmacology studies attempted to normalize the various doses and routes of administration of THC and defined a low dose as less than 7 mg, a medium dose as 7–18 mg, and a high dose as greater than 18 mg.[24] However, there is known tolerance to THC through downregulation of CB_1 receptors and G-protein activation. There is a high probability of tolerance with as few as 4 days of daily use, and low probability with intermittent use. In this review, it was determined that an elevation in heart rate (average > 19 beats/min), an increase in subjectively feeling "high," a decrease in subjective alertness, and a decrease in motor stability were the consistent pharmacodynamic effects of THC regardless of route of administration. When the pharmacokinetics and pharmacodynamics of these physiologic effects were modeled after pulmonary administration of THC, a delay was found between the serum concentrations and peak cardiac (8 min) and central nervous system (> 30 min) effects. There was also evidence that THC accumulates in the brain, and serum concentrations do not correlate with effects because the effects in the brain lasted longer than the elevated serum concentrations and peripheral cardiac effects. In addition, it was determined that the maximal effects at some compartments (heart) plateau, whereas effects on alertness are linear presumably to the point of loss of consciousness. These results indicate that it is difficult to correlate a single serum concentration to any physiologic effect or impairment, as is often done reliably with alcohol.[24]

Different patient populations may have varying responses to medical cannabis. Levels of hormones such as luteinizing hormone, follicle-stimulating hormone, prolactin, and growth hormone are known to decline with long-term exposure to medical cannabis. Hormones alter the pharmacodynamic profile of THC, as female patients with higher estrogen levels are more sensitive to the effects of medical cannabis on pain, behavior, and reward.[25] Using marijuana concomitantly with tobacco leads to greater increases in heart rate and carbon monoxide levels, despite lower THC concentrations.[26] Conversely, medical cannabis may complicate the clinical picture of a patient who has various disorders and is receiving other

medications. Cannabis may increase the risks in patients with psychiatric and cardiovascular conditions. Patients with cardiovascular conditions who use cannabis are subjected to increases in heart rate and decreases in heart rate variability (a known cardiovascular parameter associated with reduced autonomic response and increased morbidity and mortality).[24] These effects may be worsened if the patient is receiving other medications that increase heart rate (e.g., anticholinergics, α-agonists, theophylline, tricyclic antidepressants, naltrexone, and amphetamines).[27] The decrease in alertness experienced with marijuana can be potentiated by benzodiazepines, opiates, and tricyclic antidepressants.[27] Because medical cannabis is not controlled or regularly used in mainstream medicine, the actual drug–disease and drug–drug interaction profiles remain to be elucidated.

Clinical Effects of Medical Cannabis

In 1999, the Institute of Medicine released a report indicating cannabinoids may have a role in the treatment of pain, movement, and memory but observed that risks are associated with use.[28] Their report made six major recommendations to the medical community to better establish the safety and efficacy of marijuana. These recommendations included the evaluation of the physiologic and psychological effects, individual health risks, and various delivery systems of medical cannabis, as well as short-term (< 6 mo) clinical trials to determine effectiveness of medical cannabis for targeted medical conditions. Despite this call to action, there have been relatively few controlled clinical trials to evaluate the effects of various delivery systems for medical cannabis. Some states that permit the use of medical cannabis have incorporated patient registries for possession of a predetermined amount of cannabis for conditions such as cachexia, cancer, glaucoma, human immunodeficiency virus infection/acquired immune deficiency syndrome, muscle spasms, seizures, severe nausea, severe pain, and sleep disorders. At this time, Colorado and Arizona have the most robust state medical marijuana registries, which provide demographic data about who is permitted to use medical cannabis and for which indication. In both states, where a person may use medical cannabis for more than one condition, 89% (Arizona) and 94% (Colorado) of patients are registered for severe or chronic pain and 14% (Arizona) and 17% (Colorado) are registered for muscle spasms.[29, 30] Given that pain and muscle spasms are the most common reasons that medical cannabis is used, this article focuses on the therapeutic effects of medical cannabis for these two conditions.

Pain

The analgesic effects of cannabis may be due to several different mechanisms including, but not limited to, modulation of rostral ventromedial medulla neuronal activity, antinociceptive effects in descending pain pathways, and antiinflammatory properties by acting through prostaglandin synthesis inhibition.[2] Various forms of medicinal cannabis have provided mostly positive responses for patients with different types of pain: neuropathic, chronic, postoperative, and that related to fibromyalgia, rheumatoid arthritis, multiple sclerosis, and cancer.[28, 31–37]

In studies evaluating smoked cannabis compared to placebo, significant improvements in pain were observed (Table 2).[38–43] These studies included a small number of patients (15–56) and used cigarettes with varying THC contents. THC content varies based on the strain of cannabis plant that is used. In general, a higher THC content (up to 9.4%) appears to be more effective for pain relief. One group of investigators considered the neuropathic pain reduction from smoked cannabis to be modest compared to that from other drugs used for neuropathic pain, such as gabapentin and pregabalin (0.7 reduction on a 10-cm scale compared to 1.2 and 1.3, respectively).[42] Although relatively few serious adverse effects were reported in these studies, some mild-to-moderate adverse effects were commonly noted: somnolence, headache, dry mouth, sedation, dizziness, conjunctival irritation/dry eyes, hypotension, and difficulty with concentration and/or memory. The range of doses used in these trials is shown in Table 2. Although it appears that some dose-response relationship occurs (i.e., higher THC content provides better therapeutic response), many other variables factor into an effective dose, such as individual tolerance, dosage form used, frequency of dosing, and adverse effects experienced. Therefore, the most effective dose for pain will vary among individuals.

Nabiximols, the oromucosal spray with an equal mixture of THC and CBD not yet approved by the FDA, is being evaluated in several trials of patients with neuropathic and chronic pain.[44–47] Each of these studies

Table 2. Clinical Trials of Smoked Cannabis for Pain

Study Drug (% of THC)	Condition Studied	No. of Patients	Outcome	Adverse Effects
Smoked cannabis only (11%), oral cannabis only (46%), combined oral + smoked cannabis (43%) vs nonuser of cannabis[41]	Fibromyalgia	56 (28 users and 28 nonusers)	Improvement in pain and stiffness ($p<0.001$), enhancement of relaxation ($p<0.05$), and increased somnolence ($p<0.05$) and feeling of well-being ($p<0.001$) on visual analog scale	Most frequent adverse effects were somnolence (18/28), dry mouth (17/28), sedation (12/28), dizziness (10/28), high (9/28), tachycardia (8/28), conjunctival irritation (7/28), and hypotension (6/28); no serious events occurred
Smoked cannabis (0%, 2.5%, 6%, 9.4%) 3 times/day × 5 days (crossover every 14 days)[42]	Posttraumatic or postsurgical neuropathic pain	21	Daily pain intensity was lower with cannabis with 9.4% THC content than with 0% ($p=0.023$) on numeric rating scale	Total of 248 mild and 6 moderate adverse events reported; no serious or unexpected adverse events; most frequent events in group receiving cannabis with 9.4% THC content were headache, dry eyes, burning sensation, dizziness, numbness, and cough
Smoked cannabis (1–8%) or placebo 5 days/wk × 2 wks[43]	Neuropathic pain in patients infected with human immunodeficiency virus	28	Improvement in pain on descriptor differential scale with cannabis ($p<0.016$)	Most events were mild and self-limiting; 3 were treatment-limiting toxicities (cannabis-induced psychosis, cough, intractable diarrhea); other effects that were more frequent with cannabis use were concentration difficulties, fatigue, sleepiness, and sedation
Smoked cannabis (3.5% or 7%) or placebo[40]	Central and peripheral neuropathic pain	38	Cannabis improved pain on visual analog scale ($p=0.016$); cannabis improved the following types of pain: sharp ($p<0.001$), burning ($p<0.001$), aching ($p<0.001$), sensitive ($p=0.03$), superficial ($p<0.01$), and deep ($p<0.001$); cannabis provided greater relief as shown on the global impression scale ($p<0.01$)	Psychoactive effects were minimal and well-tolerated; some acute cognitive effects were noted at high doses, especially with memory
Smoked cannabis (3.56%) or placebo TID × 5 days[39]	Human immunodeficiency virus–associated sensory neuropathy	50 (25 users and 25 nonusers)	> 30% pain reduction reported by 52% of the cannabis group and by 24% of the placebo group ($p<0.04$)	No serious events reported
Smoked cannabis single doses (2%, 4%, and 8%) given in random order or placebo[38]	Capsaicin-induced pain and hyperalgesia	15	Pain reduction with medium dose only on pain scores and McGill Pain Questionnaire at 45 min after cannabis administration	Generally well tolerated; dyspnea, dry mouth, feeling cold, and somnolence were reported

demonstrated a statistically significant reduction of pain intensity compared to placebo. In most of these trials, the patients continued their existing analgesic medication in addition to starting the study medication; therefore, symptom relief obtained from the study drug was beyond the effects achieved with the patients' existing analgesia. Adverse events reported included dizziness, sedation, feeling intoxicated, and nausea. As a limitation, most of these studies had varying definitions for types of pain and included patients already using standard analgesic agents; therefore, nabiximols may be best reserved for patients with refractory pain.

Oral THC (dronabinol 5–20 mg) has not demonstrated significant improvements in visual analog pain assessments for healthy volunteers (under experimental pain conditions) or patients with chronic gastrointestinal pain or posthysterectomy pain.[48–50] Among patients with cancer pain given a single dose of placebo or THC 5, 10, 15, or 20 mg, analgesia was achieved only with THC at the higher 15- and 20-mg doses.[51, 52] The authors stated that 10 and 20 mg of oral THC were equivalent to 60 and 120 mg of codeine, respectively, for pain relief, but that the adverse effects of oral THC (somnolence, dizziness, ataxia, and blurred vision) may not make it an ideal medication for chronic cancer pain. The analgesic effect of dronabinol 10 mg/day for 3 weeks in 24 patients with multiple sclerosis revealed a relative reduction in pain scores (−20.5%, 95% confidence interval [CI] −37.5% to −4.5%) compared to placebo.[53] No serious adverse events were reported, but patients receiving dronabinol reported more dizziness and light-headedness.

Nabilone has also been evaluated for the treatment of pain. In a randomized double-blind study of 40 patients with fibromyalgia, pain and quality-of-life measurements were assessed using a visual analog scale and the Fibromyalgia Impact Questionnaire. The visual analog scale was a continuous scale from 0–10 on a 10-cm (or 100-mm) line that was anchored by descriptors (e.g., 0 is "no pain" and 10 is "worst imaginable pain"). The Fibromyalgia Impact Questionnaire is an instrument designed to quantify the overall impact of fibromyalgia over many dimensions (e.g., function, pain level, fatigue, sleep disturbance, and psychological distress) and is scored from 0–100, with the latter number being the worst case. Significant decreases in scores from the visual analog scale (−2.04, $p<0.02$), Fibromyalgia Impact Questionnaire (−12.07, $p<0.02$), and 10-point anxiety scale (−1.67, $p<0.02$) were observed after 4 weeks of nabilone treatment when the drug was titrated from 0.5 mg/day to 1 mg twice/day; these results indicate that pain, disease impact, and anxiety were significantly reduced.[54] Although no serious events were reported, the patients receiving nabilone experienced more adverse effects (1.54, $p<0.05$), with the most common being drowsiness, dry mouth, vertigo, and ataxia. The authors stated that the pain relief seen in the treatment group was similar to that for other treatments used for fibromyalgia, including fluoxetine, tramadol, and pramipexole. In a different study, high-dose nabilone (2 mg given at 8-hour intervals for 24 hours) showed an increase or worsening in pain scores for patients also receiving morphine after surgery compared to ketoprofen and placebo.[55] The authors concluded that this unexpected finding may have been due to paradoxical or sedative effects of cannabinoids at high doses.

Two meta-analyses have evaluated various forms of cannabis treatment for pain. The first was a systematic review and meta-analysis of 18 double-blind randomized controlled trials that compared any cannabis preparation to placebo among patients with chronic pain.[36] The cannabis preparation contained THC and could be administered by any route of administration. Most trials included nabiximols, dronabinol, or nabilone. Cannabis treatment demonstrated a statistically significant standardized mean difference of −0.61 (95% CI −0.84, −0.37) in pain intensity from baseline scores. This review and meta-analysis also evaluated harms and found significant changes with cannabis use for mood disturbances such as euphoria (odds ratio [OR] 4.11, 95% CI 1.33–12.72, number needed to harm [NNH] 8). Other harms found to be significantly associated with cannabis use included alterations in perception (OR 4.51, 95% CI 3.05–6.66, NNH 7), events affecting motor function (OR 3.93, 95% CI 2.83–5.47, NNH 5), and events that altered cognitive function (OR 4.46, 95% CI 2.37–8.37, NNH 8) for patients taking cannabis compared to those taking placebo or another analgesic drug. The authors concluded that cannabis may offer moderate efficacy for treatment of chronic pain, but benefits may be partially or completely offset by potential harms.

Painful human immunodeficiency virus–associated sensory neuropathy has been evaluated through a systematic review and meta-analysis involving 14 randomized controlled trials.[37]

Interventions that showed greater efficacy for pain on a visual analog scale included smoked cannabis (relative risk 2.38, 95% CI 1.38–4.10, NNT 3.38), topical capsaicin 8% patch (p=0.0026, NNT 6.46), and recombinant human nerve growth factor, which is not available clinically. No superiority over placebo was reported for amitriptyline, gabapentin, pregabalin, prosaptide, peptide-T, acetyl-L-carnitine, mexilitine, lamotrigine, and topical capsaicin 0.075%. The authors concluded that although smoked cannabis may have superior effectiveness, other routes of cannabis should be investigated to avoid the potential negative impact of smoking.

Overall, these studies show statistically significant improvement in various types of pain when medical cannabis is used. Trials indicate that smoked cannabis or cannabis extract (THC:CBD) are effective for several different types of pain, primarily neuropathic pain. Oral THC (dronabinol) does not appear to be as effective for pain but has not been widely studied in various pain conditions. Nabilone may be effective for pain related to fibromyalgia but also has not been widely studied. There is a paucity of well-designed studies evaluating medical cannabis for pain. Limitations of these studies include widely varying doses and dosage forms of medical cannabis, lack of validated criteria or assessment for some types of pain (e.g., neuropathic), lack of comparative trials for various formulations and routes of administration, self-selection bias (i.e., some patients have already had a previous positive response to the drug), difficulty blinding participants to potentially psychoactive substances, and small study populations. Given its legal status, the need for more efficacy data, and its unknown safety and tolerability profile, medical cannabis should be considered only when treatment failure with standard therapy has occurred or when adjunctive therapy is appropriate.

Muscle Spasms

Nabiximols (THC:CBD extract) has been the primary cannabis agent studied for the treatment of spasticity in patients with multiple sclerosis. Spasticity is commonly associated with painful spasms and sleep disturbance and contributes to increased morbidity.[56] Endogenous and exogenous cannabinoids have been shown to be effective for multiple sclerosis spasticity in animal models, primarily through effects at the CB_1 receptor.[57] Nabiximols has been shown to be effective as monotherapy and as add-on therapy for patients not fully relieved with other antispasticity therapy.[31]

One large multicenter parallel-group, double-blind, randomized placebo-controlled study included 160 patients with multiple sclerosis who were experiencing primary symptoms of spasticity, spasms, bladder problems, tremor, or pain.[58] Treatment evaluated was oromucosal sprays of matched placebo or whole plant cannabis–based medicinal extract (CBME) containing equal amounts of THC and CBD at a dosage of 2.5–120 mg/day, in divided doses. A visual analog scale score for each patient's most troublesome symptom was used. This primary symptom score improved in both groups with no statistically significant difference; the scores of patients using CBME reduced from a mean ± standard error of 74.36 ± 11.1 to 48.89 ± 22.0, and those using placebo from 74.31 ± 12.5 to 54.79 ± 26.3. Spasticity scores were significantly reduced with CBME in comparison to placebo (p=0.001). No significant adverse effects on cognition or mood were reported, and intoxication was generally mild.

In another double-blind study evaluating nabiximols, 189 patients with diagnosed multiple sclerosis and spasticity were randomized to receive daily doses of active preparation (124 patients) or placebo (65 patients) over 6 weeks.[59] The primary efficacy analysis on the intent-to-treat population (184 patients) showed the active preparation to be significantly superior (p=0.048) as measured with a numeric rating scale of spasticity. For the responders, 40% of patients receiving active preparation achieved greater than 30% benefit (p=0.014). Eight withdrawals were attributed to adverse events: six received active preparation and two received placebo.

A meta-analysis of three studies (two of which were described here earlier) evaluated 666 patients with multiple sclerosis and spasticity.[32] These were randomized, placebo-controlled, double-blind parallel-group studies of nabiximols. On a 0–11 numeric rating scale, the adjusted mean decrease from baseline was 1.30 with nabiximols compared to 0.97 with placebo. Using a linear model, the treatment difference was −0.32 (95% CI −0.61 to −0.04, p=0.026). A greater proportion of the treated patients were responders (OR 1.62; 95% CI 1.15–2.28, p=0.0073) and they also reported greater improvement (OR 1.67; 95% CI 1.05–2.65, p=0.030). Many patients experienced at least one adverse event (288 of 363 patients for nabiximols, 169 of 303 patients for placebo),

although most events were mild to moderate in severity and all serious adverse events resolved. Forty (11%) and 11 (3.6%) patients withdrew from the study due to adverse events in the nabiximols and placebo groups, respectively.

A consecutive series of randomized, double-blind placebo-controlled single-patient crossover trials evaluated muscle spasms as one outcome for 24 patients (18 with multiple sclerosis) with plant extracts of THC and CBD and a 1:1 mixture of THC:CBD in a sublingual spray.[60] The THC and THC:CBD groups both reported significant improvement in the spasticity severity rating versus placebo ($p<0.05$). Three patients experienced transient hypotension and intoxication with rapid initial dosing of CBME. The authors acknowledged that this was a preliminary study and that larger well-controlled studies were needed.

Oral cannabis has been evaluated in several trials for spasticity due to multiple sclerosis. In a double-blind crossover placebo-controlled randomized trial of 50 patients, the intent-to-treat analysis showed no significant difference in Ashworth spasticity scores compared to placebo.[61] However, in the 37 patients who received more than 90% of the treatment (per protocol analysis), there was a significant improvement in the number of spasms and spasticity scores ($p=0.013$) and mobility ($p=0.01$). In a large multicenter double-blind randomized controlled trial of 630 patients with multiple sclerosis, 576 responded to questions about their spasticity. There was a significant improvement in patient-reported pain and spasticity ($p=0.003$) with a reduction in spasticity of 61% for the 197 patients receiving cannabis extract (95% CI 54.6–68.2) and of 60% for the 181 patients receiving oral THC (95% CI 52.5–66.8).[62, 63] Of note, of the 198 patients receiving placebo, 46% reported improvement in spasticity (95% CI 39.0–52.9). A double-blind placebo-controlled crossover study in 13 patients showed significant improvement in patient-reported subjective spasticity scores after receiving THC at doses ranging from 7.5 to 15 mg/day for 5 days.[64] No objective outcomes were measured.

In one double-blind crossover placebo-controlled randomized trial of 12 patients, nabilone twice/day was given for 4 weeks to determine if it improved spasticity caused by spinal cord injury.[65] There was a significant reduction in the Ashworth scale and total Ashworth score ($p=0.003$ and $p=0.001$, respectively).

Overall, cannabis-derived pharmaceuticals appear effective for muscle spasticity related to multiple sclerosis. Nabiximols is approved for this purpose in 10 different countries. Limited data exist on the use of other forms and doses of medical cannabis for muscle spasms. Furthermore, most states list "muscle spasm" as an indication for medical cannabis use but do not require that the diagnosis of multiple sclerosis be present. The evidence of effectiveness of medical cannabis in muscle spasm not related to multiple sclerosis is scarce. Limitations of published studies include differences in spasticity assessment between patients (subjective) and providers (objective with Ashworth scale scoring), presence of other multiple sclerosis symptoms, lack of comparative trials for various formulations and routes of administration, self-selection bias, blinding participants to potentially psychoactive substances, and having many studies (especially those evaluating nabiximols) sponsored by the manufacturer or the medical marijuana industry. Most of these studies evaluated patients with inadequate spasticity relief using existing treatments, suggesting that the included patient populations would likely respond well to medical cannabis. Nabiximols or medical cannabis may be best reserved for the patient population who have not shown efficacy or are intolerant to other standard therapies for muscle spasm.

Safety Concerns

Adverse Effects, Drug Interactions, and Contraindications

Although most trials indicate that medical cannabis produces mild to moderate adverse effects, one of the ongoing concerns about using medical cannabis is the unfavorable and somewhat variable adverse effect profile when used in different formulations as a medicinal product. In a systematic review of 31 studies (23 randomized controlled trials and 8 observational studies), 4779 adverse events were reported in patients receiving a medicinal cannabinoid for 8–12 months.[66] Most (4615 [96.6%] events) were not serious, with the most common nonserious event being dizziness (714 [15.5%] events). Of the 164 serious events, the most common were relapse of multiple sclerosis (21 [12.8%] events), vomiting (16 [9.8%] events), and urinary tract infection (15 [9.1%] events). More nonserious adverse events were

reported in the treatment groups compared to the control groups (rate ratio 1.86, 95% CI 1.57–2.21); however, there was no significant difference in the rate of serious events (rate ratio 1.04, 95% CI 0.78–1.39). Limitations of this review include lack of inclusion of smoked cannabis and short-term evaluation of cannabis use (up to 12 mo).

There is minimal information available about drug interactions and contraindications with cannabis-derived pharmaceuticals and medical cannabis. A contraindication to dronabinol use is hypersensitivity to the drug; one noted drug interaction is with ritonavir, when increased dronabinol serum concentrations may occur leading to potential toxicity.[67] The Canadian product insert for nabiximols states the following contraindications: known or suspected allergy to cannabinoids, propylene glycol, ethanol or peppermint oil (ingredients/excipients in the product); serious cardiovascular disease (such as ischemic heart disease), arrhythmias, poorly controlled hypertension or severe heart failure; history of schizophrenia or any other psychotic disorder; children under 18 years of age; women of child-bearing potential not on a reliable contraceptive or men intending to start a family; and pregnant or nursing women.[7] A serious drug interaction warning is provided for patients receiving sedatives, drugs with sedating or psychotropic effects, and hypnotics, as there may be an additive effect with nabiximols. In addition, alcohol may interact with nabiximols, particularly in affecting coordination, concentration, and ability to respond quickly. No clinically apparent drug interactions were noted in clinical trials where nabiximols was taken with other cytochrome P450 (CYP) agents; however, there may be a potential risk of drug–drug interactions due to CYP inhibition by nabiximols.[7] The product monograph recommends caution be exercised in patients taking drugs known to be substrates for CYP3A4 or CYP2C19.[7] Given the lack of information about medical cannabis, it would be reasonable to apply these contraindications and drug interaction concerns especially with the variability in formulation, dose, and frequency of administration with these products.

Psychiatric Implications

Marijuana's chief psychoactive ingredient, THC, is a partial agonist at the CB_1 receptors, the predominant endocannabinoid receptors in the brain that help modulate appetite, mood, and motivation.[68, 69] While the response to marijuana depends on dose, strain, and frequency of use, most cannabis users experience mild euphoria, sedation, relaxation, hunger, and enhanced sensory input but also impaired attention, balance, cognition, judgment, memory, and sense of time. Some users experience anxiety, disorientation, paranoia, and psychosis; there is some reason to believe that strains with greater relative cannabidiol concentrations are associated with fewer psychotic symptoms.[70, 71]

Frequent use of cannabis, especially in adolescence, is associated with the development of schizophrenia, a chronic neurodevelopmental disorder. During adolescence, when schizophrenia typically presents, profound changes occur in the brain, often through synaptic pruning, a process that endocannabinoids help regulate.[72] Using cannabis interferes with adolescent neurodevelopment, and imaging studies associate marijuana use with adverse development of the hippocampus and the cerebellum.[73–75] Epidemiologic data associate heavy adolescent use of marijuana with both an earlier onset of schizophrenia and a 2-fold increased risk of developing schizophrenia.[76] To be clear, the use of cannabis in adolescence does not cause schizophrenia but increases the risk of its onset, suggesting interplay between marijuana use and genetic predisposition for schizophrenia.[77] For people who develop schizophrenia, ongoing use of marijuana is associated with more severe psychosis and impaired performance on tests of attention and impulsivity.[78, 79] Marijuana is a psychoactive substance whose psychiatric complications are known to increase with early onset and regular use.

Cannabis use is associated with impairments in memory and cognition. Heavy cannabis users have deficits in the encoding, storage, and retrieval of memory.[80] A recent animal model found that cannabis impairs working memory by activating astroglial cannaboid receptors in the hippocampus.[81] These findings correlate well with the association between heavy marijuana use and bilateral volume reduction of structures involved in memory like the amygdala and hippocampus.[82] Marijuana users often perform poorly on tests of executive function, information processing, and visuospatial perception.[83]

The use of cannabis is more modestly associated with depression and suicide in epidemiologic data. Frequent cannabis use is significantly associated with depressive disorders in both

animal models and epidemiologic studies.[84] Hyperactivity of the endocannabinoid system is associated with impulsivity and suicidality, which is borne out in epidemiologic studies where a significant association is observed between marijuana use and suicidal ideation and attempt.[85]

Finally, cannabis is the most commonly used and abused illicit substance in the world. In the United States each year, approximately 6500 individuals begin to use marijuana daily, of whom 10–20% will develop cannabis dependence.[86, 87] Among people admitted to substance treatment facilities in the United States, marijuana is the most frequently identified illicit substance.[88]

Pediatric Implications

The National Poison Data Center reported 5371 calls pertaining to marijuana exposures in 2011; 358 (7%) were for children aged 12 years or younger.[89] Compared to previous years, total calls and calls pertaining to children aged 12 years or younger increased (Figures 2 and 3). Acute cannabinoid toxicity usually presents with various neurologic symptoms: decreased coordination, decreased muscle strength, lethargy, sedation, difficulties concentrating, altered psychomotor activity, slurred speech, and slow reaction time. Other common symptoms include tachycardia and dry mouth. These effects can be more pronounced in children, especially at lower doses. Common symptoms include ataxia, somnolence, lethargy, altered mental status, and obtundation. Rarely, pediatric patients present with more severe symptoms such as apnea, cyanosis, bradycardia, hypotonia, and opisthotonus (severe hyperextension and spasticity).[90]

With the increased availability of cannabinoids in states with legalized medical cannabis, there is also an increased risk for accidental exposure. Several reports of adverse events relating to cannabis exposure in children and adolescents have been made.[91–93] In Colorado, we reported a case series of five patients over 4 months who presented to the emergency department with altered mental status and lethargy.[94] After most patients received an extensive work up, including lab work, lumbar puncture, and imaging, urine drug screens showed they had been exposed to cannabis. Only on further questioning did care providers admit to the cannabis exposure. Four of the five sources of cannabis were confirmed to be marijuana card

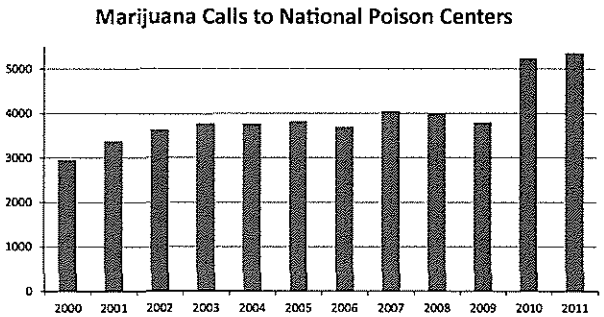

Figure 2. Telephone calls to national poison control centers pertaining to marijuana exposures.[89]

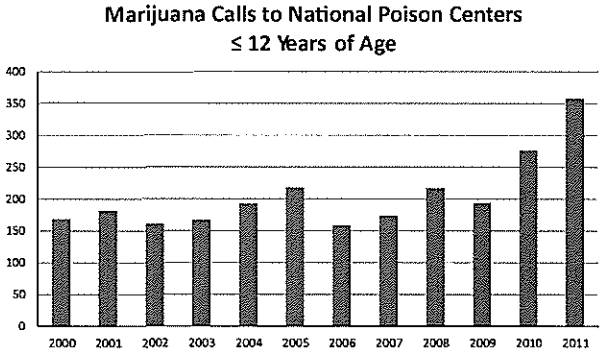

Figure 3. Telephone calls to national poison control centers pertaining to marijuana exposures in children aged 12 years or younger.[89]

holders (registered patients using medical marijuana), and the products ingested included food products in many of the cases (e.g., cookies, candies). Since the time of the report, there have been several additional cases of pediatric exposure at our institution, mostly from medical marijuana in the form of food. Although no deaths related to marijuana have been reported to national poison centers, there can be significant morbidity. When patients present with an unclear history, they often receive invasive procedures (e.g., urine catheterization, intravenous lines, and lumbar punctures) and imaging (e.g., head computed tomography scans).

The availability of medical cannabis in consumer-friendly forms (soda drinks, desserts, candies, and tinctures) continues to increase and most, if not all, products lack regulatory or safety packaging. These products are concerning because they have labels and packaging that can be easily mistaken for conventional food products by young children. Consumption of these products may be tempting to young children, and it seems likely that exposures will increase. Like any other medication, patients should be instructed of the risks of the products and to

store them safely and securely. Manufacturers may also consider warnings and child-proof packaging. Finally, health care providers should consider marijuana exposure in pediatric patients who present with altered mental status, somnolence, or lethargy.

Future Directions

Medical cannabis appears to have some benefit in patients with certain conditions. However, the use of medical cannabis within the current legal system faces a number of challenges.[34] First, the method of delivery (e.g., smoked, vaporized, oral) and patient individuality (e.g., severity of condition, inhalation and exhalation habits, functional lung capacity, gastrointestinal absorption) cause great variability in the effect of medical cannabis. The lack of quality control (e.g., contaminated products, nonstandardized doses) makes it difficult for clinicians to recommend particular formulations. Other concerns about medical cannabis include the need for adequate monitoring and prevention of addiction. Close surveillance of patients will ensure appropriate use of these medications, and training and education should be made available to providers whose patients use cannabis. Unfortunately, surveillance, training, and education are not available in most health systems, which often delimit the patient–physician relationship to a recommendation to use cananbis.[95] Similar to any other medication, improved safety measures and regulations for packaging should be examined. Additional research is needed to understand the role of the endocannabinoid system in various pathways such as antinociception (pain) and antispasticity. Improved study methodologies, including the use of standard formulations and/or dosages and larger study populations, are needed for future investigative efforts to determine appropriate uses of medical cannabis. Further research evaluating the addition of CBD to THC needs to occur to determine if the nonpsychotropic effects of this compound can improve the tolerance and safety of THC. Therefore, education and research are needed to address these concerns and to review the original intent of the Institute of Medicine's report to determine the safe and effective use of marijuana.

Conclusion

Cannabinoids produce a variety of actions by activating CB_1 and CB_2 receptors and through other possible effects in the central nervous system. The pharmacologic and pharmacodynamics effects of cannabis can vary widely based on patient and drug characteristics, which can make it difficult to use effectively and safely. Various cannabis-derived pharmaceuticals are available. Dronabinol and nabilone are oral agents available in the United States as schedule III and II medications, respectively. Nabiximols is an oromucosal spray containing a 1:1 mixture of THC: CBD, which is available in 10 countries and will be evaluated this year by the FDA for approval in the United States. Medical cannabis containing hundreds of various cannabinoids is available in 18 U.S. states and the District of Columbia and will most likely be made more widely available in the next legislative year.

Medical cannabis has been evaluated for many different purposes, and medical cannabis registrants are using it particularly for pain and muscle spasms. Data indicate medical cannabis may be effective for these conditions, especially when standard therapy has failed. However, common adverse effects involving the central nervous system and gastrointestinal system may not make this an appropriate option in many patients. Extreme caution should be used in patients with a history of cardiovascular disease or mental disorders and in adolescents. Just as is recommended with other medications, patients using medical cannabis should minimize the risk of accidental pediatric ingestion by securing the drug in a safe place with child-proof locks. Although dronabinol and nabilone are regulated in the United States and have demonstrated sufficient efficacy and safety, evidence for medical cannabis is still lacking; thus, the drug should be used with caution in patients.

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Cannabis provides some reduction in neuropathic pain

Daily POEMs

Published: 2010-12-23

Clinical question
Is smoked cannabis an effective treatment for chronic neuropathic pain?

Bottom line
Smoked cannabis reduces the intensity of neuopathic pain and improves sleep, though the benefits are modest. (LOE = 1b)

Reference
Ware MA, Wang T, Shapiro S, et al. Smoked cannabis for chronic neuropathic pain: a randomized controlled trial. CMAJ 2010;182(14):E694-E701.

Study design: Cross-over trial (randomized)

Funding source: Government

Setting: Outpatient (specialty)

Synopsis
In this Canadian trial, the researchers identified 21 adults with neuropathic pain for at least 3 months following trauma or surgery. Patients with pain that was not neuropathic, not caused by surgery, who were already using cannabis, who were older than 70 years, had logistical or transportatjon problems, or had significant comorbidities were excluded. A large number (25 of the 116 originally approached) were excluded for "other reasons." There were four 5-day treatment periods, separated by 9-day washout periods. Two patients left the study during the initial treatment period: one because THC was detected in his bloodstream while he was in the placebo group and one because of worsening pain. During each treatment period, patients were randomly assigned to receive placebo or 25 mg of 1 of 3 cannabis doses (2.5%, 6.0%, and 9.4% tetrahydrocannabinol [THC]) 3 times daily. Treatment was administered via a titanium 1-hit pipe (RayDiaTor, Mori Designs, Auburn, WA), and outcomes included pain and sleep scores, as well as assessments of how happy, stressed, high, and relaxed they felt. Analysis was by intention to treat, patients and outcome assessors were masked, and no patients were lost to follow-up (who would leave this study?). The authors found that only the highest dose of cannabis had statistically significant benefits. These benefits were modest, though, and were of borderline significance, but included reduced pain (5.4 vs 6.1 on an 11-point scale) and improved sleep. They detected no safety problems or mood changes during this short study -- though, of course, smoking anything daily for the rest of your life may carry pulmonary and cardiovascular risks. Eighteen of the participants had used marijuana in the past.

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Efficacy and adverse effects of medical marijuana for chronic noncancer pain

Systematic review of randomized controlled trials

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Abstract

Objective To determine if medical marijuana provides pain relief for patients with chronic noncancer pain (CNCP) and to determine the therapeutic dose, adverse effects, and specific indications.

Data sources In April 2014, MEDLINE and EMBASE searches were conducted using the terms *chronic noncancer pain*, *smoked marijuana* or *cannabinoids*, *placebo* and *pain relief*, or *side effects* or *adverse events*.

Study selection An article was selected for inclusion if it evaluated the effect of smoked or vaporized cannabinoids (nonsynthetic) for CNCP; it was designed as a controlled study involving a comparison group, either concurrently or historically; and it was published in English in a peer-review journal. Outcome data on pain, function, dose, and adverse effects were collected, if available. All articles that were only available in abstract form were excluded.

Synthesis A total of 6 randomized controlled trials (N=226 patients) were included in this review; 5 of them assessed the use of medical marijuana in neuropathic pain as an adjunct to other concomitant analgesics including opioids and anticonvulsants. The 5 trials were considered to be of high quality; however, all of them had challenges with masking. Data could not be pooled owing to heterogeneity in delta-9-tetrahydrocannabinol potency by dried weight, differing frequency and duration of treatment, and variability in assessing outcomes. All experimental sessions in the studies were of short duration (maximum of 5 days) and reported statistically significant pain relief with nonserious side effects.

Conclusion There is evidence for the use of low-dose medical marijuana in refractory neuropathic pain in conjunction with traditional analgesics. However, trials were limited by short duration, variability in dosing and strength of delta-9-tetrahydrocannabinol, and lack of functional outcomes. Although well tolerated in the short term, the long-term effects of psychoactive and neurocognitive effects of medical marijuana remain unknown. Generalizing the use of medical marijuana to all CNCP conditions does not appear to be supported by existing evidence. Clinicians should exercise caution when prescribing medical marijuana for patients, especially in those with nonneuropathic CNCP.

EDITOR'S KEY POINTS

- Medical marijuana has been proposed as a potential treatment for use in pain management. However, there is still uncertainty about the specific indications, ideal doses, and adverse effects that are related to this substance when used for medical purposes.
- While statistical reduction in pain was reported in all studies in this review, a more fundamental outcome is clinically meaningful pain reduction (a decrease of 2 points on a 0-to-10 numerical pain rating or a 30% improvement in pain intensity); only 3 of the 6 studies reported positive findings in this respect. Most of the studies employed medical marijuana as an adjunct to participants' existing opioids and adjuvant medications, suggesting it might only have a role in refractory pain in conjunction with other analgesics.
- Neurocognitive adverse effects such as learning, memory, and psychomotor deficits are common even with low-dose, short-term use of medical marijuana but they appear well tolerated. However, the long-term consequences of medical marijuana remain unknown.

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Few therapeutic options for chronic noncancer pain (CNCP) provide consistently successful outcomes; many fail to provide *clinically meaningful reduction in pain*, defined as a decrease in pain scores by at least 30%.[1] Even with the widespread use of opioids, improvements in outcomes such as function and mood remain limited.[2]

Cannabis has had a long history of use for spiritual and religious purposes, as well as for various medical conditions.[3] In 1999, an Institute of Medicine report[4] supported the use of marijuana in medicine; however, the debate about the usefulness and safety of marijuana remains unresolved.

In Canada, the federal government brought forward the Marihuana for Medical Purposes Regulation in March 2014, replacing the previous Marihuana Medical Access Regulations (MMAR).[5] In response to physicians' concerns, most of the regulatory medical colleges in Canada have published recommendations for prescribing medical marijuana. Most colleges acknowledge the fact that proper studies have not yet been conducted, and one college in the province of Quebec restricts the use of medical marijuana to the context of a research framework.[6]

The primary objective of this systematic review was to determine whether smoked or vaporized cannabis provides pain relief in the CNCP population. Secondary objectives included determining its effect on function, identifying therapeutic doses, and documenting commonly associated adverse effects.

DATA SOURCES

Literature search

In April 2014, we identified eligible studies through an electronic search of MEDLINE, EMBASE, and the International Pharmaceutical Abstracts. The search strategy encompassed a theme that included the following terms: *chronic noncancer pain*, *smoked marijuana* or *cannabinoids*, *placebo* and *pain relief*, or *side effects* or *adverse events*.

Study selection

We selected an article for inclusion if it evaluated the effect of smoked or vaporized cannabinoids (nonsynthetic) for CNCP; it was designed as a controlled study involving a comparison group, either concurrently or historically; and it was published in English in a peer-reviewed journal. We excluded all articles that were only available in abstract form.

SYNTHESIS

Data extraction

Two independent reviewers (S.F.L., N.Z.) screened potentially eligible articles, assessed the methodologic quality of each study, and extracted data from included trials. Disagreements were resolved by consensus. For outcomes, pain scores were extracted using the visual analogue scale (VAS) or an alternative numerical pain rating tool. If pain scores were not reported, surrogate measures of effectiveness were included (sleep, function, and quality of life). Frequency of serious and most commonly reported adverse effects was collected. A serious adverse event was based on the definition supplied by Health Canada and the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use guidance documents.[7]

Quality assessment

To assess quality, we used the Jadad scale, a 5-item tool scored between 0 and 5.[8] We categorized the trials as high or low quality with scores greater than 2 or 2 or lower, respectively.

Literature search results

We found 2269 potentially eligible articles from the search strategy and 10 other potential articles through review of references. Sixteen relevant studies were subjected to full-text review (**Figure 1**) with one study[9] identified later in the references of the College of Family Physicians of Canada guidance document on medical marijuana.[10] Altogether, this review identified 6 randomized controlled trials,[9,11-15] with 5 of them having crossover designs[9,11-14]; 1 study was performed primarily for spasticity in multiple sclerosis (MS) with pain evaluated as a secondary outcome.[11] We did not identify any historically controlled comparative studies.

Study characteristics

Five studies were rated as high quality, scoring 3 out of 5.[9,12-15] Allocation concealment was reported in 4 studies.[9,13-15] Summaries of the final 6 articles in our review are presented in **Tables 1** and **2**.[8,9,11-15]

In total, 226 adults (mean age of 45 to 50 years across trials) with chronic neuropathic pain were randomized, with 189 adults specifically identified as having chronic neuropathic pain.[9,12-15] Two studies focused on HIV-associated neuropathy,[13,15] 1 on posttraumatic neuropathy,[12] and 2 on mixed neuropathic conditions.[9,14] The study involving patients with MS did not discriminate between spasticity pain and neuropathic pain.[11] Three studies limited enrolment to patients with previous cannabis exposure,[9,14,15] while 2 had no limitations.[11,12] All trials excluded individuals with a history of psychotic disorders and previous history of cannabis abuse or dependence. All trials, except 1,[15] reported the use of urine toxicology or other screening tools before starting the trial. Pain duration (6 to 9 years) was specifically mentioned in 3 trials,[9,14,15] with 4 trials identifying baseline pain in the moderate range.[9,12,14,15] Four[9,12-14] of the 5 trials[9,12-15] that allowed participants to

Figure 1. Articles retrieved through searches

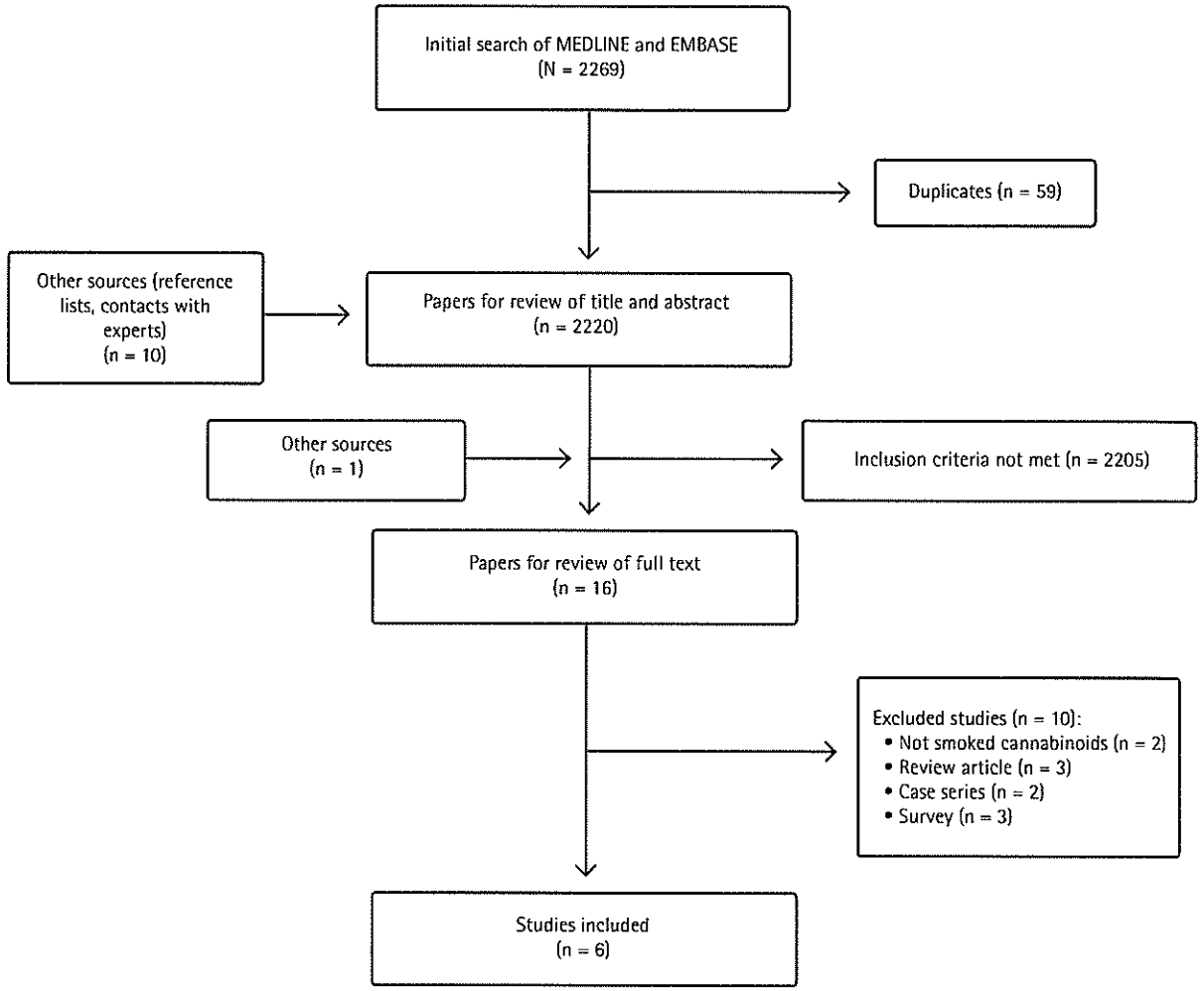

Table 1. Characteristics of the 6 studies in this review that examined the use of medical marijuana for CNCP

STUDY	COUNTRY	FUNDING SOURCE	STUDY DESIGN	QUALITY ASSESSMENT*
Abrams et al,[15] 2007	US	Center for Medicinal Cannabis Research	Randomized, double-blind trial	3 (High)
Corey-Bloom et al,[11] 2012	US	Center for Medicinal Cannabis Research	Randomized, double-blind, placebo-controlled, crossover trial	2 (Low)
Ellis et al,[13] 2009	US	Center for Medicinal Cannabis Research	Randomized, double-blind, placebo-controlled, crossover trial	3 (High)
Ware et al,[12] 2010	Canada	Canadian Institutes of Health Research	Randomized, double-blind, placebo-controlled, crossover trial	3 (High)
Wilsey et al,[9] 2013	US	National Institutes of Health	Randomized, double-blind, placebo-controlled, crossover trial	3 (High)
Wilsey et al,[14] 2008	US	Center for Medicinal Cannabis Research	Randomized, double-blind, placebo-controlled, crossover trial	3 (High)

CNCP—chronic noncancer pain, US—United States.
*Based on the Jadad scale.[8]

Table 2. Summaries of the 6 studies in this review that examined the use of medical marijuana for CNCP

STUDY	CLINICAL CONDITION	STUDY DURATION AND PROTOCOL	PRIMARY OUTCOME MEASURE	STUDY SAMPLE	CONTROL	INTERVENTION	OUTCOME	COMMENTS
Abrams et al,[15] 2007	HIV peripheral neuropathy	Study duration was 3 wk Adults with documented HIV and associated sensory neuropathy in 21-d trial with randomization to control group or intervention group for 5 d	Daily diary of pain ratings on a VAS (0-100 mm)	There were 55 participants enrolled: 28 randomized to control group, with 25 completing the study; 27 randomized to intervention group, with 25 completing the study	Cigarettes containing 0% delta-9-THC that appeared identical to the cannabis cigarettes	Cigarettes containing 3.56% delta-9-THC and weighing an average of 0.9 g; smoked 3 times per d	A total of 13 of 25 participants in intervention group had >30% reduction in pain from baseline to end of treatment compared with 6 of 25 participants in control group; median reduction of NP was 34% in the intervention group compared with 17% in the control group	Smoking the first cigarette reduced chronic pain ratings (AUC) by 72% (intervention) versus 15% (control) compared with chronic pain ratings after smoking the last cigarette of 51% (intervention) versus 5% (control)
Corey-Bloom et al,[11] 2012	MS	Study duration was 17 d Adults with MS and spasticity smoked 1 cigarette per d for 3 d	Pain intensity measured by VAS (secondary outcome)	There were 37 participants randomized, with 30 completing the study	Cigarettes containing 0% delta-9-THC that appeared identical to the cannabis cigarettes	Cigarettes containing 4% delta-9-THC and weighing an average of 0.8 g; smoked once daily	Smoking cannabis reduced pain scores on the VAS by 5.28 points (95% CI 2.48 to 10.01) more than the control group	There were 17 participants who correctly guessed treatment phase for all 6 visits, with 83% having previous exposure to cannabis. Participants had very low levels of pain to start
Ellis et al,[13] 2009	HIV peripheral neuropathy	Study duration was 7 wk HIV-infected adults with NP refractory to 2 other analgesics in 5-phase study: 1-wk wash-in phase; randomization to 5-d smoking phase; 2-wk washout phase; 5-d crossover phase; and final 2-wk washout phase	Pain intensity measured by DDS and VAS, a 10-cm line (secondary outcome)	There were 34 participants randomized, with 28 completing the study	Cigarettes that had all cannabinoids removed and that were identical in appearance to active cigarettes	Cigarettes with 1%-8% delta-9-THC potency titrated to tolerance on d 1, followed by 4 d of smoking target dose, with each d composed of 4 sessions separated by 90-120 min	Median difference in pain reduction was 3.3 DDS points (effect size=0.6; P=.016); proportion with ≥30% pain reduction was greater in the active cannabis wk than the placebo cannabis wk (0.46 [95% CI 0.28 to 0.65] vs 0.18 [95% CI 0.03 to 0.32]. The median (range) change in VAS pain scores were -17 (-58 to 52) for cannabis compared with -4 (-56 to 28) for placebo	Patients correctly guessed when they consumed delta-9-THC; however, subanalysis revealed no difference in final outcome. No breakdown of AEs experienced. There were 2 patients who exited the trial owing to psychosis and intractable cough from cannabis. The UKU and DAIDS side effect frequency was greater in the intervention group and there was a trend toward moderate to severe AEs. Greater increase in heart rate among cannabis group (13 of 28 patients) than placebo group (1 of 28 patients)

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Table 2 *continued from page e376*

STUDY	CLINICAL CONDITION	STUDY DURATION AND PROTOCOL	PRIMARY OUTCOME MEASURE	STUDY SAMPLE	CONTROL	INTERVENTION	OUTCOME	COMMENTS
Ware et al,[12] 2010	Posttraumatic neuropathy	Study duration was 8 wk Adults ≥ 18 y with posttraumatic or postsurgical pain for at least 3 mo randomized to a sequence of 4 treatment periods, each 14-d period beginning with 5 d on the study drug followed by a 9-d washout period	11-Point numeric rating scale (secondary measures included sleep, mood, and quality of life)	There were 23 participants randomized, with 21 completing the study	Cannabis containing 0% delta-9-THC prepared by ethanolic extraction	Over 3, 14-d periods, 25-mg doses of various delta-9-THC potencies (2.5%, 6.0%, 9.4%) were delivered through a pipe 3 times per d for the first 5 d of each cycle, followed by a 9-d washout period	Mean (SD) daily pain intensity was lower among intervention group (5.4 [1.6]) than control group (6.1 [1.7]); difference of 0.7 (95% CI 0.02 to 1.4)	Overall, use of cannabis associated with improvements in pain, sleep, and anxiety. Frequency of AEs increased with potency and was greatest for psychiatric disorders (12 events vs 1). Fixed dose and limited quantity (25 mg) might have limited potential AEs
Wilsey et al,[9] 2013	NP	Study duration was 3, 6-h experimental sessions; there were 3- to 14-d intervals between sessions Adults with type 1 CRPS, spinal cord injury, peripheral neuropathy, or nerve injury	Measured with VAS (0-100 mm) and the NP scale	There were 39 participants randomized and who completed at least 1 session (no dropouts from AEs or experimental intervention)	Placebo cannabis made from whole plant with cannabinoid extraction	Participants were randomized to 1 of 3, 6-h sessions. Cued puff (vaporized) procedure of 0%, 1.29% (low dose), or 3.53% (medium dose) delta-9-THC, with cumulative 8-12 puffs per session	A 30% reduction in pain intensity: 10 of 38 (26%) placebo patients; 21 of 37 (57%) low-dose patients; 22 of 36 (61%) medium-dose patients. For placebo vs low dose, NNT was 3.2 (P=.0069); for placebo vs medium dose, NNT was 2.9 (P=.0023)	Both 1.29% and 3.53% delta-9-THC potencies produced equal antinociception with minimal effect on cognitive testing. Greatest dose effects were noted in learning and memory, with effect sizes in small or medium range
Wilsey et al,[14] 2008	NP	Study duration was 3, 6-h experimental sessions; there were 3- to 14-d intervals between sessions Adults with type 1 CRPS, spinal cord injury, peripheral neuropathy, or nerve injury	Measured with VAS (0-100 mm) and the NP scale	There were 38 participants randomized, with 32 completing all sessions	Cigarettes made from whole cannabis with cannabinoid extraction	Participants were randomized to 1 of 3, 6-h sessions. Cued puff procedure of 0%, 3.5%, or 7% delta-9-THC	A 0.0035 reduction in VAS pain intensity per min was noted from both 3.5% and 7% cannabis, with cumulative 9 puffs per session	Ceiling effect noted with cumulative dosing, as 3.5% and 7% potencies produced equal antinociception; secondary outcomes improved, including pain unpleasantness (mean difference= -0.21 [95% CI -0.33 to -0.09]; P<.01) and global impression of change (mean difference= 0.12 [95% CI 0.064 to 0.18]; P<.01)

AE—adverse event, AUC—area under curve, CRPS—complex regional pain syndrome, DAIDS—Division of AIDS, DDS—descriptor differential scale, delta-9-THC—delta-9-tetrahydrocannabinol, MS—multiple sclerosis, NNT—number needed to treat, NP—neuropathic pain, UKU—Udvalg for Kliniske Undersøgelser, VAS—visual analogue scale.

continue to use opioids, anticonvulsants, and antidepressants reported that more than 50% of participants used concomitant opioids. Studies did not report the baseline dose of concurrent analgesics.

Trial duration varied from 17 days[11] to 8 weeks,[12] with the actual intervention (smoking cannabinoids) varying from a minimum of 3 experimental session days each lasting 6 hours[9,14] to a maximum of 5 days.[12,13,15] One study had an intervention period of 3 days.[11]

Only 1 trial administered delta-9-tetrahydrocannabinol (delta-9-THC) through the use of a vaporizer.[9] The strength of delta-9-THC employed in the trials for smoked

cannabinoids ranged from a low of about 1%[9,12] to a high of 9.4%[12] as measured by the percentage of dry weight. The total daily delta-9-THC consumption was reported only in 1 trial.[14] In 3 studies the total daily delta-9-THC consumption was calculated based on the reported percentage of dry weight delta-9-THC and the cigarette weight.[11,12,15] The total daily delta-9-THC exposure could not be determined in 1 study because of missing information[13] and in another study owing to flexible dosing.[9] The total daily delta-9-THC consumed during the trials ranged between a low of 1.875 mg per day[12] and a high of 34 mg per day[14] (**Table 3**).[9,11-15]

The 2 trials open to cannabis-naïve participants reported dropouts or withdrawals owing to potential adverse effects of smoked cannabis[11,12] such as psychosis (n=1), persistent cough (n=1), feeling "high" (n=2), dizziness (n=2), and fatigue (n=1). Causes for the remaining dropouts in the 5 studies were unrelated to delta-9-THC consumption (eg, personal reasons, withdrawal of consent, medical causes unrelated to cannabis).

Efficacy

A meta-analysis of the efficacy of using delta-9-THC could not be completed owing to the heterogeneity of interventions and outcome variables.

All studies reported a statistically significant benefit in terms of pain relief. Ware et al reported a difference of 0.7 in average daily VAS between the placebo group (score of 6.1) and the 9.4% delta-9-THC intervention group (score of 5.4).[12] The cigarettes with the lower delta-9-THC potency (2.5% and 6.0%) were associated with more modest reductions in average daily pain scores of 5.9 and 6.0, respectively.[12] Wilsey et al reported statistically significant improvement in the cannabis group for pain reduction over time (0.0035 reduction in VAS per minute),[14] noting a ceiling effect with equal antinociception between the high (7%) and low (3.5%) delta-9-THC concentrations. A 2013 study also by Wilsey et al reported similar findings, in which vaporized cannabis provided substantial analgesia compared with placebo, while noting that the 1.29% and 3.53% delta-9-THC doses were equianalgesic to one another.[9] While there was a statistically significant mean difference in VAS reduction between the delta-9-THC group and the placebo group in the study involving MS patients, the baseline pain level of participants was low, 14.51 (95% CI 9.16 to 21.75) and 16.61 (95% CI 10.79 to 24.93) in the placebo and intervention groups, respectively.[11] Clinically meaningful pain reduction was reported in 3 studies,[9,13,15] with 46%, 52%, and 61% of cannabis users reporting benefit versus 18%, 24%, and 26% of the placebo group (Ellis et al,[13] Abrams et al,[15] and Wilsey et al,[9] respectively). The effect of medical marijuana on the dose of other analgesic drugs, including opioids, was reported in 1 study, which noted that opioid doses did not differ statistically significantly from baseline.[13]

Functional outcomes were absent in all studies; however, 2 studies assessed quality of life and both reported no statistically significant improvement.[12,13]

Adverse events

While there were no serious adverse events reported in any of the trials, smoking cannabis was associated with a greater incidence of adverse events compared with placebo in each of the studies (**Table 3**).[9,11-15]

While all trials captured neurocognitive side effects, only 1 trial reported detailed incidence of adverse effects across multiple organ systems (eg, visual symptoms, gastrointestinal, musculoskeletal).[12] Adverse neurologic or psychiatric events (eg, headaches, sedation, dysphoria, and poor concentration) increased with cannabis use versus placebo and with higher delta-9-THC concentrations.[12] Another study noted statistically significantly ($P<.001$) increased incidence of sedation, disorientation, confusion, and dizziness in the cannabis group.[15] Wilsey et al reported that feeling "high," "stoned," and "impaired" scored statistically greater in the cannabis group compared with the placebo group and appeared to be dose dependent.[14] On specific neuropsychological tests, the 7% delta-9-THC concentration was associated with impaired attention, learning, memory, and psychomotor speed, while the 3% delta-9-THC concentration resulted in learning and memory decline.[14] For patients using lower doses (1.29% and 3.53%) and a vaporizer, similar effects were noted in a dose-dependent manner for feeling "high," "stoned," "drunk," and "sedated"; however, the effect sizes for all psychoactive outcomes were small.[9] In the same study, outcomes of neuropsychological testing noted a general cognitive decline (small effect size) with the greatest effect on learning and memory (small to medium effect size). In the study involving patients with MS, 6% of the delta-9-THC group reported feeling "too high" posttreatment as compared with 0% of the placebo group.[11] For noncognitive effects, fatigue, throat irritation, and anxiety were noted in a number of studies.[11,13]

DISCUSSION

This systematic review found that the use of medical marijuana in the management of CNCP of primarily neuropathic origin was associated with a reduction in pain and a number of short-term neurocognitive adverse effects. While most of the trials were of high quality, the psychoactive effect of delta-9-THC versus inactive placebo resulted in unmasking in many trials. Only 2 studies reported maintaining a positive but smaller effect size when correcting for this factor,[9,13] consistent with the finding that inappropriate blinding has been shown to cause larger treatment effects.[16]

Table 3. Incidence of AEs reported in the 6 studies in this review

	DELTA-9-THC POTENCY, %			DELTA-9-THC POTENCY DOSE, mg/D		AEs	
STUDY	MINIMUM	MAXIMUM	DOSING FREQUENCY	MINIMUM	MAXIMUM	NEUROCOGNITIVE	NONCOGNITIVE
Abrams et al,[15] 2007	3.56	3.56	3 times daily	32	32	Mean side effect scores (95% CI) were as follows for cannabis group and placebo group, respectively: • 0.25 (0.14 to 0.44) and 0.10 (0.05 to 0.22) for anxiety • 0.54 (0.36 to 0.81) and 0.08 (0.04 to 0.17) for sedation • 0.16 (0.07 to 0.34) and 0.01 (0.00 to 0.04) for disorientation • 0.17 (0.07 to 0.39) and 0.01 (0.00 to 0.06) for confusion • 0.15 (0.07 to 0.31) and 0.02 (0.01 to 0.05) for dizziness	NR
Corey-Bloom et al,[11] 2012*	4	4	1 time daily	32	32	Dizziness, feeling "too high," and headaches were all greater in treatment group	Fatigue and nausea were higher in treatment group
Ellis et al,[13] 2009	1	8	4 times daily	NR	NR	Combined UKU and DAIDS side effect (concentration difficulties, fatigue, sleepiness or sedation, increased duration of sleep) frequency was greater in cannabis group than in placebo group. There was a trend for moderate or severe AEs to be more frequent during active cannabis than placebo administration	Increases in heart rate by ≥30 points were more frequent in cannabis group than placebo group
Ware et al,[12] 2010†	2.5	9.4	3 times daily	1.875	7	Of the total number of neurocognitive events, 15 of 91, 23 of 91, 23 of 91, and 30 of 91 reported AEs for 0%, 2.5%, 6.0%, and 9.4% delta-9-THC, respectively	Of the total number of noncognitive events, 12 of 52, 13 of 52, 14 of 52, 13 of 52 reported AEs at site of administration for 0%, 2.5%, 6.0%, and 9.4% delta-9-THC, respectively; 5 of 28, 5 of 28, 7 of 28, and 7 of 28 for respiratory AEs, respectively; and 9 of 39, 9 of 39, 12 of 39, 9 of 39 for systemic and nonspecific AEs, respectively
Wilsey et al,[9] 2013†	1.29	3.53	8-12 puffs per session	Unknown	19.25[5]	Feeling "high" or feeling "stoned" was greater in treatment groups and was dose dependent, but effect was relatively small. Feeling "anxiety" or feeling "down" was not prominent. Neuropsychological tests found psychomotor slowing in dominant hand and impaired learning or memory that was dose dependent, while delayed memory was not affected by delta-9-THC use. Effect sizes were generally small across groups	NR

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Table 3 *continued from page e379*

STUDY	DELTA-9-THC POTENCY, %		DOSING FREQUENCY	DELTA-9-THC POTENCY DOSE, mg/D		AEs	
	MINIMUM	MAXIMUM		MINIMUM	MAXIMUM	NEUROCOGNITIVE	NONCOGNITIVE
Wilsey et al,[14] 2008	3.5	7	9 puffs per session	19.25[||]	34[||]	Feeling "high" scored greatest for the high-dose group ($P<.001$) and both dose groups differed from placebo group ($P<.05$). Sedation occurred more in both dose groups compared with placebo group ($P<.01$). Cannabis produced significantly more confusion than placebo ($P=.03$). The 7% cannabis demonstrated evidence of neurocognitive impairment in attention, learning and memory, and psychomotor speed, whereas the 3.5% cannabis resulted in a decline in learning and memory only. When looking across at all measures, participants using 7% cannabis had greater impairment than those using 3.5% cannabis, who in turn had greater impairment than placebo participants	NR

AE—adverse events, DAIDS—Division of AIDS, delta-9-THC—delta-9-tetrahydrocannabinol, NR—not reported, UKU—Udvalg for Kliniske Undersøgelser.
[*]There were 5 participants who withdrew from treatment owing to AEs including uncomfortable "high" (n = 2), dizziness (n = 2), and fatigue (n = 1).
[†]Overall, 248 mild and 6 moderate AEs. Total number of AEs and number of participants reporting at least 1 AE increased with delta-9-THC potency.
[‡]While there were neurocognitive symptoms, there were generally small-medium effect sizes and the authors believed that they were not likely to affect daily functioning.
[§]Study authors were unable to comment on dose owing to flexible dosing (*maximum* assumes participant inhaled all medication in vaporizer).
[||]Based on average cigarette weight.

While statistical reduction in pain was reported in all studies, a more fundamental outcome is clinically meaningful pain reduction (a decrease of 2 points on a 0-to-10 numerical pain rating or a 30% improvement in pain intensity), which has been associated with an improvement in a patient's global impression of change.[17,18] Only 3 of the 6 trials evaluated and reported positive findings in this respect. Functional assessment has also been designated as a core outcome domain in CNCP trials,[17] but its measurement was absent in all included studies. With quality of life unchanged in 2 trials, the question of whether patients experience functional improvement with medical marijuana remains unanswered. Finally, there was a notable absence of effectiveness trials comparing outcomes with other known treatments in CNCP. Most studies, in fact, employed medical marijuana as an adjunct to participants' existing opioids and adjuvant medications suggesting it might only have a role in refractory pain in conjunction with other analgesics.

The trials in our review reported short-term psychoactive and neuropsychological effects without evidence of serious adverse effects, measured over hours or days. Of note, one study specifically commented that the small to medium effect sizes of cognitive effects were unlikely to affect daily functioning.[9] These cognitive adverse effects in the short term are similar to those experienced with opioids[19] and suggest that the same precautions employed with opioids would be in order with the use of medical marijuana. In particular, its use in elderly patients or those with pre-existing cognitive impairments might not be ideal. These short-term findings contrast with a recent review of observational data collected over years reporting several high-confidence-level adverse effects (eg, addiction, diminished life achievement, and motor vehicle accidents).[20] Analogous to trials of opioids, medical marijuana trials, including those in our review, have been of short duration and not designed to detect longer-term sequelae.[21]

Finally, the amount of exposure to delta-9-THC in all studies was extremely low in contrast to that available in the marketplace. According to Health Canada's website, the average amount of dried marijuana dispensed under the old MMAR was 1.0 to 3.0 g per day containing delta-9-THC concentrations of 12.5%.[22] With an average dry weight of only 2.0 g per day, the available delta-9-THC exposure under the old MMAR program was 250 mg, or nearly 8-fold the maximum amount used in clinical trials. Now, under the newer regulations (Marihuana for Medical Purposes Regulation), industry producers can provide even higher delta-9-THC concentrations (up to 20% delta-9-THC by dried weight as shown on industry websites), suggesting a potential gap between evidence and product offerings.

Comparison with previous systematic reviews

Previous systematic reviews have assessed the available evidence for the use of cannabinoids in chronic pain[23,24]; however, none commented systematically on the level of delta-9-THC consumption. The review by Martín-Sánchez and colleagues assessed the use of cannabinoids in chronic pain of any cause, with a third of the trials focused on cancer pain and interventions restricted to synthetic cannabinoids only.[23] The authors commented on a positive, moderate, short-term trend toward pain reduction but noted serious adverse effects.

The Lynch and Campbell review on cannabinoids in CNCP included oral or smoked synthetic and natural cannabinoids.[24] The authors included 4 trials contained in our review.[12-15] While they opined that larger trials were necessary with additional reporting requirements, they concluded that there was support for the use of cannabinoids in CNCP to provide modestly effective and safe treatment.[24]

Conclusion

The current evidence suggests that very low-dose medical marijuana (<34 mg/d) is associated with an improvement in refractory neuropathic pain of moderate severity in adults using concurrent analgesics. There were no studies evaluating other CNCP causes including rheumatologic conditions.[25] The generalizability of the results in CNCP is limited by factors such as the quality of studies, small sample sizes, very short duration, and dose and scheduling variability. Neurocognitive adverse effects such as learning, memory, and psychomotor deficits are common even with low-dose, short-term use but they appear well tolerated. However, the longer-term consequences of medical marijuana still remain unknown. These findings are consistent with existing guidance documents.[10] Future trials should consider incorporation of standard outcome measures beyond pain, such as function and quality of life, similar to other interventions in CNCP.[26] It might also be advantageous to enable prospective observational studies through creation of registries, protocols, and mandatory reporting of adverse events. Without additional evidence and a clear understanding as to the indications for and dosing of cannabis, there remains a risk that clinicians might unwittingly propagate similar issues that we now face with opioids in the management of CNCP.

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Contributors

All authors contributed to the concept and design of the study and data gathering. **Ms Lakha, Dr Zoheiry,** and **Dr Deshpande** contributed to the analysis of the study. **Dr Deshpande** and **Dr Mailis-Gagnon** contributed to the interpretation of the study and preparing the manuscript for submission.

Competing interests

None declared

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Clinical Crossroads

Medical Marijuana for Treatment of Chronic Pain and Other Medical and Psychiatric Problems
A Clinical Review

Kevin P. Hill, MD, MHS

IMPORTANCE As of March 2015, 23 states and the District of Columbia had medical marijuana laws in place. Physicians should know both the scientific rationale and the practical implications for medical marijuana laws.

OBJECTIVE To review the pharmacology, indications, and laws related to medical marijuana use.

EVIDENCE REVIEW The medical literature on medical marijuana was reviewed from 1948 to March 2015 via MEDLINE with an emphasis on 28 randomized clinical trials of cannabinoids as pharmacotherapy for indications other than those for which there are 2 US Food and Drug Administration–approved cannabinoids (dronabinol and nabilone), which include nausea and vomiting associated with chemotherapy and appetite stimulation in wasting illnesses.

FINDINGS Use of marijuana for chronic pain, neuropathic pain, and spasticity due to multiple sclerosis is supported by high-quality evidence. Six trials that included 325 patients examined chronic pain, 6 trials that included 396 patients investigated neuropathic pain, and 12 trials that included 1600 patients focused on multiple sclerosis. Several of these trials had positive results, suggesting that marijuana or cannabinoids may be efficacious for these indications.

CONCLUSIONS AND RELEVANCE Medical marijuana is used to treat a host of indications, a few of which have evidence to support treatment with marijuana and many that do not. Physicians should educate patients about medical marijuana to ensure that it is used appropriately and that patients will benefit from its use.

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Dr Burns Mr Z is a 60-year-old man who fell at work 19 years ago and has had chronic low back pain and left leg radicular symptoms since that time. None of the numerous interventions performed in an effort to treat this pain were effective. These include an L2-3 laminectomy in 1996, multiple lumbar epidural steroid injections, selective nerve root blocks, lidocaine infusions, and a trial of a spinal cord stimulator. He has been to a pain psychologist and received physical therapy. Several medications have helped, such as gabapentin, sertraline, and nortriptyline.

His most recent magnetic resonance imaging scan showed posterior disk bulges at L2-3, L3-4, L4-5, and L5-S1, with the largest bulge at L2-3. Mild effacement of the thecal sac and narrowing of the left-sided neural foramina were seen. Mr Z was diagnosed as having failed back syndrome (chronic back pain following a laminectomy) and treated with long-term narcotics. He signed a narcotics contract with his primary care physician and has never violated the contract. Since signing his narcotics contract, Mr Z has decreased his narcotic requirements and is now taking oxycodone, 10 mg, along with ibuprofen, 600 mg, every 6 hours.

Because his overall goal remains pain relief, he has recently begun using marijuana. He received a recommendation from a cannabis clinic, a clinic whose primary function is to certify patients for the use of medical marijuana, but is now wondering if this is something his primary care physician could also agree with and therefore be responsible for the recommendation of in the future. He uses marijuana at home in the evening after returning from work. He has found marijuana to have a sedative effect, enabling him to get a good night's sleep and to have less pain the next day.

Mr Z's medical history is notable for hyperlipidemia, prediabetes, basal cell carcinoma, and anxiety. His other medications include bupropion, 150-mg sustained-release tablet twice daily; clonazepam, 0.5 mg twice daily as needed; and simvastatin, 20 mg once daily. Previously he was received disability benefits but currently works as an arborist. He drinks alcohol socially and continues to smoke cigarettes, although he has been able to cut down from 1½

packs to a half pack daily since starting bupropion. He lives at home with his adult son.

Mr Z: His View

My first experience with what would later blossom into chronic pain was about 3 weeks postsurgically after I had the L2-3 and L4-5 levels of my back worked on. Since then, I went through everything from cortisone shots to lidocaine infusions. I actually had a test for the spinal cord stimulator and there was even talk about an intrathecal morphine pump. I totally exhausted every option that was there, and my final procedure was going to be a lysis of spinal adhesions.

When I first went through my medical requirements and was screened by the doctor, I told her that it really was not a matter of needing a lot of it, as I was going to use it at home after work. So there was no question of still being under its influence at any point in time where I would be going to work or driving. I felt that my medical history alone warranted at least my looking at it as an alternative medication. The [Massachusetts 2012 medical marijuana] ballot initiative made me more comfortable with my decision.

Search Methods and Results

Dr Hill Mr Z is a 60-year-old man with a long history of chronic low back pain refractory to multiple procedures and medications. In an effort to obtain better control of his chronic pain, he began using medical marijuana after receiving a certification from a local specialty medical marijuana clinic. He thought that medical marijuana improved his pain control and approached his primary care physician about continued use of medical marijuana.

The medical literature on medical marijuana was searched from 1948 to March 2015 using MEDLINE. The search terms used included *cannabis*, *cannabinoids*, and *tetrahydrocannabinol*. The limits used were "administration and dosage" "adverse effects" "therapeutic use," or "clinical trial." The MEDLINE search resulted in 562 articles. Articles that discussed cannabinoids as pharmacotherapy in a clinical trial were selected for an initial brief review. After additional citations were obtained from references, a total of 74 articles were reviewed. There are no meta-analyses on the topic of medical marijuana; there are 3 systematic reviews.[1-3] Similarly, there is only 1 set of guidelines that addresses the use of medical marijuana as a treatment.[4] As a result, the main emphasis was on randomized clinical trials.

Medical Marijuana: Scientific Rationale and Practical Implications

As of March 2015, 23 states and the District of Columbia have enacted medical marijuana laws to facilitate access to marijuana as a treatment for a variety of medical conditions (Table 1). This is concerning to some because marijuana is the most commonly used illicit drug in the United States: approximately 12% of people aged 12 years or older reported use in the past year, and use among teens has drifted upward in recent years while their perception of its risk has declined.[6,7] With decriminalization of medical marijuana and Washington, Colorado, Alaska, Oregon, and the District of Columbia legalizing the recreational use of marijuana, there has been an increase in marijuana use. As a result, physicians are increasingly faced with questions from patients about marijuana and its medical applications.[8]

Pharmacology of Marijuana

Marijuana comprises more than 60 pharmacologically active cannabinoids.[9] Both exogenous ligands, such as the cannabinoids from marijuana, and endogenous ligands or endocannabinoids, such as anandamide and 2-arachidonylglycerol, act on cannabinoid receptors located throughout the body but mostly in the brain and spinal cord.[10] Activation of 2 types of G protein–coupled receptors, CB1 and CB2, exerts multiple actions by directly inhibiting the release of multiple neurotransmitters including acetylcholine, dopamine, and glutamate while indirectly affecting γ-aminobutyric acid, *N*-methyl-D-aspartate, opioid, and serotonin receptors.[11] CB1 receptors are concentrated primarily in the basal ganglia, cerebellum, hippocampus, association cortices, spinal cord, and peripheral nerves and CB2 receptors are found mainly on cells in the immune system, which may in part explain cannabinoids' effects on pain and inflammation. The physiological responses that result from cannabinoid receptor activation are euphoria, psychosis, impaired memory and cognition, reduced locomotor function, increased appetite, and antiemetic, pain-relieving, antispasticity, and sleep-promoting effects.[3]

The primary cannabinoids contained in marijuana are Δ^9-tetrahydrocannabinol (THC) and cannabidiol. THC produces the euphoria that comes from using marijuana, but it also can produce psychosis. Cannabidiol is not psychoactive and is thought to have antianxiety and possibly antipsychotic effects as well.[12,13] Marijuana's therapeutic effects depend on the concentration of THC in a given formulation as well as the ratio of THC to cannabidiol because of cannabidiol's ability to mitigate the psychoactive effects of THC. As a result, the THC-cannabidiol ratio for many strains of marijuana has been engineered to achieve desired effects.

Medical Indications for Cannabinoids

There are currently 2 US Food and Drug Administration (FDA)–approved cannabinoids available in the United States: dronabinol and nabilone.[14,15] Both are available in pill form and are FDA approved for nausea and vomiting associated with cancer chemotherapy as well as for appetite stimulation in wasting illnesses such as human immunodeficiency virus infection or cancer. Medical marijuana, which may be identical in form to recreational marijuana, is dried material from the *Cannabis* plant consisting of THC, cannabidiol, and other cannabinoids. Medical marijuana is purchased from dispensaries in a variety of preparations (Table 2) or grown by patients for the treatment of myriad illnesses. It is not available from pharmacies because of its status as federally illegal.

Table 1. Medical Marijuana Laws by State[a]

State	Approved Conditions	Legal Limit
Alaska, 1998	Cachexia, cancer, chronic pain, epilepsy and other disorders characterized by seizures, glaucoma, HIV/AIDS, MS and other disorders characterized by muscle spasticity, and nausea; other conditions are subject to approval by the Alaska Department of Health and Social Services	1 oz usable; 6 plants (3 mature, 3 immature)
Arizona, 2010	Cancer, glaucoma, HIV/AIDS, hepatitis C, ALS, Crohn disease, Alzheimer disease, cachexia, severe and chronic pain, severe nausea, seizures (including epilepsy), severe or persistent muscle spasms	2.5 oz usable; 0-12 plants
California, 1996	AIDS, anorexia, arthritis, cachexia, cancer, chronic pain, glaucoma, migraine, persistent muscle spasms (including spasms associated with MS), seizures (including seizures associated with epilepsy), severe nausea, other chronic or persistent medical symptoms	8 oz usable; 6 mature or 12 immature plants
Colorado, 2000	Cancer, glaucoma, HIV/AIDS, cachexia, severe pain, severe nausea, seizures (including those characteristic of epilepsy), persistent muscle spasms (including those characteristic of MS); other conditions are subject to approval by the Colorado Board of Health	2 oz usable; 6 plants (3 mature, 3 immature)
Connecticut, 2012	Cancer, glaucoma, HIV/AIDS, Parkinson disease, MS, damage to the nervous tissue of the spinal cord with objective neurological indication of intractable spasticity, epilepsy, cachexia, Crohn disease, PTSD, or any medical condition, medical treatment, or disease approved by the Department of Consumer Protection	1-mo supply (exact amount to be determined)
Washington, DC, 2010	HIV/AIDS, cancer, glaucoma, conditions characterized by severe and persistent muscle spasms such as MS, patients undergoing chemotherapy or radiotherapy or using azidothymidine or protease inhibitors	2 oz dried; limits on other forms to be determined
Delaware, 2011	Cancer, HIV/AIDS, decompensated cirrhosis (hepatitis C), ALS, Alzheimer disease A chronic or debilitating disease or medical condition or its treatment that produces ≥1 of the following: cachexia; severe, debilitating pain that has not responded to previously prescribed medication or surgical measures for more than 3 mo or for which other treatment options produced serious adverse effects; intractable nausea; seizures; severe and persistent muscle spasms including but not limited to those characteristic of MS	6 oz usable
Hawaii, 2000	Cancer, glaucoma, HIV/AIDS, a chronic or debilitating disease or medical condition or its treatment that produces cachexia, severe pain, severe nausea, seizures including those characteristic of epilepsy, or severe and persistent muscle spasms including those characteristic of MS or Crohn disease; other conditions are subject to approval by the Hawaii Department of Health	3 oz usable; 7 plants (3 mature, 4 immature)
Illinois, 2013	Cancer, glaucoma, HIV/AIDS, hepatitis C, ALS, Crohn disease, agitation related to Alzheimer disease, cachexia/wasting syndrome, muscular dystrophy, severe fibromyalgia, spinal cord disease (including but not limited to arachnoiditis), Tarlov cysts, hydromyelia syringomyelia, rheumatoid arthritis, fibrous dysplasia, spinal cord injury, traumatic brain injury and postconcussion syndrome, MS, Arnold-Chiari malformation and syringomelia, spinocerebellar ataxia, Parkinson disease, Tourette syndrome, myoclonus, dystonia, reflex sympathetic dystrophy (complex regional pain syndromes type 1), causalgia, complex regional pain syndrome type 2, neurofibromatosis, chronic inflammatory demyelinating polyneuropathy, Sjogren syndrome, lupus, interstitial cystitis, myasthenia gravis, hydrocephalus, nail patella syndrome or residual limb pain, or treatment of these conditions	2.5 ounces usable cannabis during 14-d period
Maine, 1999	Epilepsy and other disorders characterized by seizures, glaucoma, MS and other disorders characterized by muscle spasticity, and nausea or vomiting as a result of AIDS or cancer chemotherapy	2.5 oz usable; 6 plants
Maryland, 2014	Cachexia, anorexia, or wasting syndrome, severe or chronic pain, severe nausea, seizures, severe or persistent muscle spasms, or other conditions approved by the commission	30-d supply, amount to be determined
Massachusetts, 2012	Cancer, glaucoma, HIV/AIDS, hepatitis C, ALS, Crohn disease, Parkinson disease, MS, and other conditions as determined in writing by a qualifying patient's physician	60-d supply (10 oz) for personal medical use
Michigan, 2008	Cancer, glaucoma, HIV/AIDS, hepatitis C, ALS, Crohn disease, agitation of Alzheimer disease, nail patella syndrome, cachexia or wasting syndrome, severe and chronic pain, severe nausea, seizures, epilepsy, muscle spasms, MS, PTSD	2.5 oz usable; 12 plants
Minnesota, 2014	Cancer (if the underlying condition or treatment produces severe or chronic pain, nausea, severe vomiting, or cachexia or severe wasting), glaucoma, HIV/AIDS, Tourette syndrome, ALS, seizures/epilepsy, severe and persistent muscle spasms/MS, Crohn disease, terminal illness with a life expectancy of <1 y	30-d supply of nonsmokable marijuana
Montana, 2004	Cancer, glaucoma, HIV/AIDS, or the treatment of these conditions; cachexia or wasting syndrome, severe or chronic pain, severe nausea, seizures including those caused by epilepsy, severe or persistent muscle spasms including those caused by MS or Crohn disease, or any other medical condition or treatment for a medical condition adopted by the department by rule	1 oz usable; 4 plants (mature); 12 seedlings
Nevada, 2000	AIDS, cancer, glaucoma, and any medical condition or treatment for a medical condition that produces cachexia, persistent muscle spasms or seizures, severe nausea or pain, PTSD; other conditions are subject to approval by the health division of the state department of human resources	1 oz usable; 7 plants (3 mature, 4 immature)
New Hampshire, 2013	Cancer, glaucoma, HIV/AIDS, hepatitis C, ALS, muscular dystrophy, Crohn disease, agitation of Alzheimer disease, MS, chronic pancreatitis, spinal cord injury or disease, traumatic brain injury, or ≥1 injuries that significantly interferes with daily activities as documented by the patient's clinician; a severely debilitating or terminal medical condition or its treatment that has produced ≥1 of the following: elevated intraocular pressure, cachexia, chemotherapy induced anorexia, wasting syndrome, severe pain not responding to previously prescribed medication or surgical measures or for which other treatment options produced serious adverse effects, constant or severe nausea, moderate to severe vomiting, seizures, or severe, persistent muscle spasms	Two oz of usable cannabis during a 10-d period
New Jersey, 2010	Seizure disorder including epilepsy, intractable skeletal muscular spasticity, glaucoma, severe or chronic pain, severe nausea or vomiting, cachexia or wasting syndrome resulting from HIV/AIDS or cancer, ALS, MS, terminal cancer, muscular dystrophy, IBD including Crohn disease, terminal illness (physician-determined prognosis of <12 mo of life), or any other medical condition or its treatment approved by the Department of Health and Senior Services	2 oz usable
New Mexico, 2007	Severe chronic pain, painful peripheral neuropathy, intractable nausea/vomiting, severe anorexia/cachexia, hepatitis C, Crohn disease, PTSD, ALS, cancer, glaucoma, MS, damage to the nervous tissue of the spinal cord with intractable spasticity, epilepsy, HIV/AIDS, hospice care, cervical dystonia, inflammatory autoimmune-mediated arthritis, Parkinson disease, Huntington disease	6 oz usable; 16 plants (4 mature, 12 immature)

(continued)

Table 1. Medical Marijuana Laws by State[a] (continued)

State	Approved Conditions	Legal Limit
New York, 2014	Cancer, HIV/AIDS, ALS, Parkinson disease, MS, spinal cord damage causing spasticity, epilepsy, IBD, neuropathies, Huntington disease The Department of Health commissioner has the discretion to add or delete conditions and must decide whether to add Alzheimer disease, muscular dystrophy, dystonia, PTSD, and rheumatoid arthritis within 18 mo of the law becoming effective	30-d supply nonsmokable marijuana
Oregon, 1998	Cancer, glaucoma, HIV/AIDS, or treatment of these conditions; a medical condition or treatment for a medical condition that produces cachexia, severe pain, severe nausea, seizures including those caused by epilepsy, or persistent muscle spasms including those caused by MS; other conditions are subject to approval by the Health Division of the Oregon Department of Human Resources	24 oz usable; 24 plants (6 mature, 18 immature)
Rhode Island, 2006	Cancer, glaucoma, HIV/AIDS, hepatitis C, or treatment of these conditions; a chronic or debilitating disease or medical condition or its treatment that produces cachexia or wasting syndrome, severe debilitating chronic pain, severe nausea, seizures including but not limited to those characteristic of epilepsy, or severe and persistent muscle spasms including but not limited to those characteristic of MS or Crohn disease, agitation of Alzheimer disease, or any other medical condition or its treatment approved by the state department of health	2.5 oz usable; 12 plants
Vermont, 2004	Cancer, HIV/AIDS, MS, or the treatment of these conditions if the disease or the treatment results in severe, persistent, and intractable symptoms; a disease, medical condition, or its treatment that is chronic, debilitating, and produces ≥1 severe, persistent, intractable symptoms of cachexia or wasting syndrome, severe pain or nausea, or seizures	2 oz usable; 9 plants (2 mature, 7 immature)
Washington, 1998	Cachexia, cancer, HIV/AIDS, epilepsy, glaucoma, intractable pain (defined as pain unrelieved by standard treatment or medications), chronic renal failure, MS Crohn disease, hepatitis C with debilitating nausea or intractable pain, or diseases including anorexia that result in nausea, vomiting, wasting, appetite loss, cramping, seizures, muscle spasms, or spasticity when those conditions are unrelieved by standard treatments or medications	24 oz usable; 15 plants

Abbreviations: ALS, amyotrophic lateral sclerosis; HIV, human immunodeficiency virus; IBD, inflammatory bowel disease; MS, multiple sclerosis; PTSD, posttraumatic stress disorder.

[a] For up to date medical marijuana regulations, see http://medicalmarijuana.procon.org/view.resource.php?resourceID=000881.[5]

Aside from the 2 FDA-approved indications for cannabinoids, the scientific evidence supporting the medical use of marijuana and cannabinoids varies widely by disease entity from high-quality evidence to poor-quality evidence. High-quality evidence is defined herein as multiple randomized clinical trials with positive results (Table 3). Despite the variability in evidence supporting various uses for medical marijuana, state policies suggest the use of medical marijuana for many medical problems beyond nausea, vomiting, and anorexia. For some of the medical conditions approved for use in some states (eg, glaucoma), there are only preliminary data supporting the use of medical marijuana as pharmacotherapy.

Data from more than 40 clinical trials of marijuana and cannabinoids have been published; beyond the 2 indications for which dronabinol and nabilone are already approved by the FDA, the strongest evidence exists for the use of marijuana and cannabinoids as pharmacotherapies for chronic pain, neuropathic pain, and spasticity associated with multiple sclerosis. As of March 2015, there were 6 trials (n=325 patients) examining chronic pain, 6 trials (n=396 patients) that investigated neuropathic pain, and 12 trials (n=1600 patients) that focused on multiple sclerosis. Several of these trials had positive results, suggesting that marijuana or cannabinoids may be efficacious for these indications. The American Academy of Neurology (AAN) recently published evidence-based guidelines that recommended an oral cannabis extract containing both THC and cannabidiol (not available in the United States as an FDA-approved medication) as having the highest level of empirical support as a treatment for spasticity and pain associated with multiple sclerosis.[4] The AAN also published a systematic review of medical marijuana as a treatment for neurological disorders, suggesting nabiximols, a spray containing both THC and cannabidiol, as probably effective in treating spasticity, central pain, and urinary dysfunction associated with multiple sclerosis, and dronabinol as probably effective as a treatment for spasticity and central pain associated with multiple sclerosis.[6] Thus, while medical marijuana is not a first-line treatment for Mr Z's chronic pain, it is reasonable to consider medical marijuana as a treatment after other treatments have failed. In general, the evidence supporting the use of marijuana and cannabinoids for other conditions aside from the FDA indications and chronic pain, neuropathic pain, and spasticity resulting from multiple sclerosis is either equivocal or weak.

Marijuana contains numerous cannabinoids. It is not known how individual cannabinoids affect the various diseases currently treated by marijuana. Two of the cannabinoids, dronabinol and nabilone, are available in the United States and can be prescribed. When treating patients for conditions that would otherwise be treated by marijuana itself, it is reasonable to initiate therapy with dronabinol or nabilone. If these are not successful, treatment can be escalated to marijuana itself because it contains numerous pharmacologically active cannabinoids.

Some conditions might respond to cannabinoids not yet available in the United States such as cannabidiol. Under these circumstances, it is reasonable to treat with marijuana itself. A variety of cannabinoids are in development, so new cannabinoids, likely with new FDA indications, should reach the market in the future.

Risks and Benefits of Cannabinoids

Medical marijuana and cannabinoids have health risks and benefits. Mr Z and the physician recommending medical marijuana for him should discuss these risks and benefits thoroughly prior to starting treatment with medical marijuana because many adverse effects may result from either short-term (single-use or sporadic) or long-term use.[45] The acute effects of marijuana include impaired short-

Table 2. Common Cannabis Preparations

Preparations	Description
Marijuana[a]	Dried plant product consisting of leaves, stems, and flowers; typically smoked or vaporized
Hashish	Concentrated resin cake that can be ingested or smoked
Tincture[a]	Cannabinoid liquid extracted from plant; consumed sublingually
Hashish oil	Oil obtained from cannabis plant by solvent extraction; usually smoked or inhaled; butane hash oil (sometimes referred to as "dabs"), for example
Infusion[a]	Plant material mixed with nonvolatile solvents such as butter or cooking oil and ingested

[a] These preparations are available from state-approved medical marijuana dispensaries.

term memory, motor coordination, and judgment. This is especially relevant for driving; short-term use of marijuana doubles the risk of involvement in a motor vehicle crash.[46] Paranoid ideation and psychotic symptoms, albeit rare, may occur in response to high doses of THC. Long-term regular (daily or nearly every day) marijuana use is especially problematic for young people, whose brains continue to develop into their mid-20s.[47] A recent study showed structural brain changes in the nucleus accumbens and the amygdala in occasional marijuana users compared with controls, underscoring the need for additional research into the effects of nonregular marijuana use on the developing brain.[48] Impaired brain development as measured by functional connectivity may contribute to the association between early, regular marijuana use and decline in IQ.[45,49]

Marijuana is potentially addictive, causing significant problems for work, school, and relationships in about 9% of adult and 17% of adolescent users.[50,51] Regular marijuana use is associated with an increased risk of anxiety, depression, and psychotic illness, and marijuana use can worsen the courses of these disorders as well.[52-57] Mr Z has an anxiety disorder for which he takes multiple medications; this anxiety must be monitored closely if medical marijuana pharmacotherapy is used. Functional outcomes are also affected, with regular marijuana use leading to poor school performance, lower income, increased likelihood of requiring socioeconomic assistance, unemployment, criminal behavior, and decreased satisfaction with life.[58-60] The cessation of regular marijuana use is associated with a withdrawal syndrome marked by anxiety, irritability, craving, dysphoria, and insomnia.[61]

Regular marijuana use results in physical problems as well. It is associated with increased incidence of symptoms of chronic bronchitis and increased rates of respiratory tract infections and pneumonia. Preliminary research points to an association between marijuana use and myocardial infarction, stroke, and peripheral vascular disease.[62]

Evaluation of a Patient for Medical Marijuana Certification

Patient requests for medical marijuana are now common in clinical practice. Determining which patients may be appropriate for a medical marijuana certificate (eAppendix in the Supplement) is complicated (Box). Patients administered marijuana should have a condition known to be responsive to marijuana or cannabinoids based on high-quality evidence such as randomized clinical trials. Before receiving marijuana, patients should have undergone adequate trials of other evidence-based treatments. Medical conditions such as major depressive disorder, anxiety disorders, and viral upper respiratory tract infections that may be exacerbated by marijuana should not be present. Patients present to their primary care physicians seeking medical marijuana certification or they may be already using marijuana. Mr Z's case was the latter—he raised the issue with his primary care physician after initiating medical marijuana pharmacotherapy outside of his usual medical care with the assistance of a medical marijuana clinic.

Medical marijuana evaluations should be comprehensive assessments that include risk-benefit discussions. Certifications should only be written by physicians who have thoroughly assessed a patient, know him or her well, and have a full understanding of the patient's debilitating condition requiring treatment. If the certification does not come from the patient's primary care physician or the specialist treating the debilitating condition, it is essential for the certifying physician to communicate with the patient's other health care clinicians in the same manner as any other specialists would be expected to.

The clinical evaluation should start with the patient expressing how they think medical marijuana will be helpful to treat their medical condition. The physician should take a careful history with special focus on previous treatments for the debilitating condition and possible contraindications for medical marijuana such as anxiety disorders, mood disorders, psychotic disorders, and substance use disorders. A thorough risk-benefit discussion should follow, covering both the adverse health effects of marijuana along with the scientific evidence from studies investigating marijuana or cannabinoids as pharmacotherapy for the debilitating condition being treated. It may be useful to provide a context for medical consensus by informing the patient that there currently is little support from major medical organizations for the use of medical marijuana.[63]

If the physician decides to write the certification for medical marijuana, a discussion of marijuana's federal legal status and that state's regulations must follow. According to the US government, marijuana is an illegal drug that is classified as Schedule I under the Controlled Substances Act, meaning that it has no currently accepted medical use and a high potential for abuse.[64] Marijuana's status as a Schedule I substance that is illegal according to the federal government is the reason that physicians cannot prescribe medical marijuana and can only certify its use. Although the US Department of Justice has stated that it plans to leave the issue of medical marijuana to the states and not enforce the federal statute, the federal stance on marijuana still is a cause for concern for some physicians who are considering recommending medical marijuana as a treatment or aligning with medical marijuana dispensaries or treatment centers.

The medical marijuana certification must state the medical condition that the physician believes would be treated effectively with medical marijuana and, in some states, the recommended amount of marijuana needed to treat the condition. For example, a physician in Massachusetts must state the medical condition for

Table 3. Randomized Clinical Trials Beyond Current FDA Indications for Cannabinoids[a]

Source	Drug (Maximum Dose), Route	Control	Sample Size, Experimental Condition/Control	Primary Outcome	Results
Chronic pain					
Skrabek et al,[16] 2008	Nabilone (2 mg) orally	Placebo	n=20 Nabilone; n=20 placebo (fibromyalgia)	VAS	Significant decrease in VAS (−2.04; $P < .02$)
Narang et al,[17] 2008	Dronabinol (20 mg) orally	Placebo	n = 29 Placebo; n = 30 dronabinol, 10 mg; n = 29 dronabinol, 20 mg	Total pain relief at 8 h	Significant increase in Total pain relief, dronabinol conditions (20 mg vs placebo at $P < .01$; 10 mg vs placebo at $P < .05$)
Frank et al,[18] 2008	Dihydrocodeine (240 mg), nabilone (2 mg) orally	Crossover	n=48 Dihydrocodeine followed by nabilone; n=48 nabilone followed by dihydrocodeine (chronic neuropathic pain)	VAS	Dihydrocodeine provided better pain relief than nabilone (6.0; 95% CI, 1.4-10.5; $P=.01$)
Pinsger et al,[19] 2006	Nabilone (1 mg) add-on orally	Placebo	n=30 Crossover	VAS	Significant decrease in VAS ($P < .006$)
Wissel et al,[20] 2006	Nabilone (1 mg) orally	Placebo	n=13 Crossover	11-Point box test (pain rating)	Significant decrease in pain rating ($P < .05$)
Blake et al,[21] 2006	Nabiximols: THC (15 mg)/ cannabidiol (13.5 mg) oromucosal spray	Placebo	n=31 Nabiximols; n=27 placebo	Pain on movement	Significant decrease in pain (−0.95; 95% CI, −1.85 to −0.02, $P=.04$)
Neuropathic pain					
Ellis et al,[22] 2009	Cannabis (1%-8% THC) smoked	Placebo	n=34 Crossover	Change in pain intensity	Significant decrease in pain ($P=.02$)
Abrams et al,[23] 2007	Cannabis (3.56% THC) smoked	Placebo	n=27 Cannabis; n=28 placebo	VAS, percent achieving >30% pain reduction	Significant decrease in pain ($P=.03$); 52% cannabis group vs 24% placebo reported >30% pain reduction ($P=.04$)
Wilsey et al,[24] 2008	Cannabis (7%, THC) smoked	Placebo	n=38 Crossover	VAS	Significant decrease in pain (−0.0035; 95% CI, −0.0063 to −0.0007 ($P=.02$)
Nurmikko et al,[25] 2007	Nabiximols: THC (30 mg)/ cannabidiol (27.5 mg) oromucosal spray	Placebo	n=63 Nabiximols; n=62 placebo	Change in pain intensity (NRS)	Significant decrease in pain ($P=.004$; 95% CI, −1.59 to −0.32)
Berman et al,[26] 2004	Nabiximols: THC (129.6 mg)/ cannabidiol (120 mg) oromucosal spray	Placebo	n=48 Crossover	Mean pain severity	Significant decrease in pain (THC/cannabidiol, −0.58, 95% CI, −0.98 to −0.18, $P=.005$; THC, −0.64, 95% CI, −1.05 to −0.24, $P=.002$)
Multiple sclerosis					
Zajicek et al,[27] 2003, and Freeman et al,[28] 2006	OCE: THC (25 mg), cannabidiol (12.5 mg); THC (25 mg) orally	Placebo	n=211 OCE; n=206 THC; n=213 placebo	Change in spasticity (Ashworth scale)[27]; incontinence episodes[28]	No effect ($P=.40$) on spasticity; decrease in episodes for both OCE and THC ($P=.005$ OCE; $P=.04$ THC)
Zajicek et al,[29] 2012	OCE (THC, 25 mg) orally	Placebo	n=144 OCE; n=135 placebo	Change in muscle stiffness	Significant decrease in muscle stiffness (odds ratio, 2.26; 95% CI, 1.24-4.13; $P=.004$)
Aragona et al,[30] 2009	Nabiximols: THC (27 mg)/ cannabidiol (25 mg) oromucosal spray	Placebo	n=17 Crossover	Psychopathology, cognition (Paced Auditory Serial Addition Test, Symptom Checklist 90-Revised)	No effect (Symptom Checklist 90-Revised, $P=.36$-$.91$; Paced Auditory Serial Addition Test, $P=.39$)
Collin et al,[31] 2007	Nabiximols: THC (129 mg)/ cannabidiol (120 mg) oromucosal spray	Placebo	n=124 nabiximols; n=65 placebo	Change in spasticity (NRS)	Significant decrease in spasticity (−0.52, 95% CI, −1.029 to −0.004, $P=.048$)
Kavia et al,[32] 2010	Nabiximols: THC (129 mg)/ cannabidiol (120 mg) oromucosal spray	Placebo	n=67 Nabiximols; n=68 placebo (overactive bladder)	Incontinence episodes	No difference ($P=.57$)
Vaney et al,[33] 2004	OCE: THC (30 mg) orally	Placebo	n=57 Crossover	Change in spasticity (self-report, frequency of symptoms)	No difference (frequency, $P=.01$; 95% CI, 1.76-4.63)
Ungerleider et al,[34] 1987	THC (7.5 mg) orally	Placebo	n=13 Crossover	Change in spasticity (self-report)	Significant decrease in spasticity ($P < .03$)
Svendsen et al,[35] 2004	Dronabinol (10 mg) orally	Placebo	n=24 Crossover (central pain)	Median spontaneous pain intensity (NRS) in last week of treatment	Significant decrease in median spontaneous pain intensity ($P=.02$)
Rog et al,[36] 2005	Nabiximols: THC (129.6 mg)/ cannabidiol (120 mg) oromucosal spray	Placebo	n=34 Nabiximols; n=32 placebo (central pain)	Pain, sleep disturbance (NRS)	Significant decrease in pain ($P=.005$), significant decrease in sleep disturbance ($P=.003$)
Fox et al,[37] 2004	OCE: THC (10 mg) orally	Placebo	n=14 Crossover (upper limb tremors)	Change in tremor index	No significant improvements ($P=.55$)

(continued)

Table 3. Randomized Clinical Trials Beyond Current FDA Indications for Cannabinoids[a] (continued)

Source	Drug (Maximum Dose), Route	Control	Sample Size, Experimental Condition/Control	Primary Outcome	Results
Wade et al,[38] 2004	Nabiximols: THC (129.6 mg)/cannabidiol (120 mg) oromucosal spray	Placebo	n=80 Nabiximols; n=80 placebo	VAS, most troublesome symptom	No significant improvements (*P*=.12); significant decrease in spasticity (−22.79; 95% CI, −35.52 to −10.07; *P*=.001)
Kiltestein et al,[39] 2002	Dronabinol (5 mg); OCE: THC (5 mg) orally	Placebo	n=16 Crossover (spasticity)	Change in spasticity (Ashworth scale)	No significant improvements
Parkinson disease					
Carroll et al,[40] 2004	OCE: THC (10 mg) orally	Placebo	n=19 Crossover (levodopa-induced dyskinesia)	Change in Unified Parkinson Disease Rating Scale dyskinesia score	No significant improvements (*P*=.09)
Crohn disease					
Naftali et al,[41] 2013	Cannabis: THC (115 mg) smoked	Placebo	n=11 Cannabis; n=10 placebo	Induction of remission (Crohn's Disease Activity Index score <150 after 8 wk)	No significant difference (*P*=.43)
Amyotrophic lateral sclerosis					
Weber et al,[42] 2010	Sesame oil: THC (10 mg) orally	Placebo	n=27 Crossover (cramps)	VAS, cramp intensity	No significant difference (0.24; 95% CI, −0.32 to 0.81; *P*=.38)
Neurogenic symptoms					
Wade et al,[43] 2003	Nabiximols: THC (120 mg)/cannabidiol (120 mg); THC (120 mg); cannabidiol (120 mg) oromucosal spray	Placebo	n=24 Crossover (n=18 multiple sclerosis, n=4 spinal cord injury, n=1 brachial plexus damage, n=1 limb amputation due to neurofibromatosis)	VAS	Significant decrease in pain with cannabidiol, THC; significant decrease in spasm with THC, cannabidiol, THC; significant decrease in spasticity with THC (*P* < .05)

Abbreviations: NRS, numerical rating scale; OCE, oral cannabis extract; THC, δ-9-tetrahydrocannabinol; VAS, visual analog scale.

[a] Randomized clinical trials are graded as level 2 evidence (level 1 includes systematic reviews of randomized clinical trials) according to the Oxford Centre for Evidence-Based Medicine 2011 levels of evidence.[44]

Box. Practical Considerations for Medical Marijuana

An appropriate medical marijuana candidate should have

1. A debilitating medical condition that data from randomized clinical trials suggest would respond to medical marijuana pharmacotherapy, such as nausea and vomiting associated with cancer chemotherapy, anorexia from wasting illnesses like AIDS, chronic pain, neuropathic pain, or spasticity associated with multiple sclerosis
2. Multiple failed trials of first- and second-line pharmacotherapies for these conditions
3. A failed trial of an US Food and Drug Administration–approved cannabinoid (dronabinol or nabilone)
4. No active substance use disorder or psychotic disorder or no unstable mood disorder or anxiety disorder
5. Residence in a state with medical marijuana laws and meets requirements of these laws

which medical marijuana is the treatment and a recommended amount per 60-day period. The amount should be estimated from the route of administration and the anticipated number of treatments per day. Patients receive advice on which marijuana species or strain to purchase and dosing and administration from the dispensary, which differs from the manner in which prescriptions of FDA-approved medications are specified. Once the patient begins medical marijuana pharmacotherapy, close follow-up with the physician is imperative, as it would be with any medications having significant adverse effects and abuse potential. The patient should be seen in follow-up within a month's time with additional telephone contact as necessary. Patients may be followed up monthly for 3 months, with further follow-up determined by the patient's clinical situation.

Patients requesting medical marijuana may already be taking opioids for chronic pain. In these instances, narcotics contracts may be in effect as an additional safeguard to mitigate the potential for abuse. Physicians recommending medical marijuana to these patients can use the narcotics contract to their advantage because in addition to the patient specifying where her or she will fill narcotics prescriptions, the patient can be asked to specify where he or she will obtain marijuana. The contract may also stipulate that random urine drug screening results positive for substances other than the prescribed opioids and recommended medical marijuana may be grounds for discharge.

Recommendations for Mr Z

Mr Z has had extensive treatment for his chronic pain over an extended period. He was referred to a variety of health care practitioners from multiple disciplines for his chronic pain. His clinicians used multiple modalities including multiple medications resulting in limited pain control before Mr Z considered medical marijuana as a treatment for his chronic pain. Overall, it appears that his treatment course was reasonable and likely a result of thoughtful collaboration between Mr Z and his primary care physician.

Mr Z appears to meet all but 1 of the criteria listed in the Box: he has a debilitating condition that data suggest may respond to marijuana, he has had multiple failed treatment trials of first- and second-line medications, his anxiety disorder appears to be clinically stable, and he resides in Massachusetts, a state with an active medical marijuana law. Only a previous trial of an FDA-approved synthetic cannabinoid was not done.

The course of treatment may have been altered if Mr Z had a discussion with his primary care physician prior to obtaining a medical marijuana certification. Mr Z and his primary care physician may have opted for a trial of one of the FDA-approved cannabinoids dronabinol or nabilone, despite Mr Z's medical history of anxiety. This anxiety, which appears to be clinically stable now, should have been monitored closely and medications adjusted accordingly. A trial of dronabinol still makes sense at this time because it would allow for the use of an FDA-approved (and thus likely safer in terms of composition and quality control) medication under the close supervision of Mr Z's primary care physician. He went to a specialty medical marijuana clinic, however, and 4 to 6 weeks elapsed without follow-up prior to Mr Z notifying his primary care physician that he was taking a medication with potentially significant adverse effects. This lack of follow-up is one of the major concerns about specialty medical marijuana clinics that often certify large numbers of new patients for medical marijuana each day. Regardless of where patients receives certification, they must be followed up closely by the certifying physician because of the potential for significant adverse effects, and the certifying physician should communicate with all other health care professionals delivering care that may be affected by a patient's use of medical marijuana.

Initiation of medical marijuana pharmacotherapy by patients before consulting their physician is becoming more common as additional states enact medical marijuana laws. These patients, along with others contemplating medical marijuana pharmacotherapy for their own medical problems, will likely continue to comprise a growing proportion of physicians' patients. Although the medical marijuana landscape will change as novel cannabinoids are approved for additional medical indications, the question of the role of medical marijuana as a pharmacotherapy in medicine persists. Physicians must educate patients about proper use of medical marijuana to ensure that only appropriate patients use it and limit the numbers of patients inappropriately using this treatment.

Questions and Discussion

QUESTION One of my patients said that he found one strain that worked better than others for chronic pain. Do different strains of marijuana that are available at the dispensaries have different effects?

DR HILL Different strains may have different effects because of their THC and cannabidiol content and differing ratios of THC to cannabidiol in the strain.[65] Just as different people may respond differently to the same drug, some may report better results from a particular strain than other people might. Medical marijuana dispensaries may make claims about certain strains being useful for particular illnesses, but those claims are theoretical or anecdotal in nature and may be made with marketing in mind.

QUESTION As it stands right now in Massachusetts, can any physician write a medical marijuana certification? What if a physician wants to write a certification for a patient to use medical marijuana for a medical condition that is not specified by the laws?

DR HILL Yes, in Massachusetts and in every other state with medical marijuana laws, any physician can write a medical marijuana certification for any medical indication they choose, provided the physician has completed the requisite training.[66] This training usually consists of a few hours of continuing medical education activities related to the risks and benefits of marijuana.

QUESTION In Massachusetts, the state allows the certifying physician to stipulate how much medical marijuana a patient may possess in a 60-day period, and the recommended 60-day supply of marijuana is 10 oz. Is that an unnecessarily high amount? How does one determine the correct dose of marijuana to use?

DR HILL The 60-day supply of 10 oz is a recommended amount, but this may be exceeded if a physician provides a rationale for it in writing. According to the World Health Organization, a standard marijuana cigarette contains as little as 0.5 g of marijuana, so a 60-day supply of 10 oz is up to 560 marijuana cigarettes or almost 10 per day.[67] Thus, based on the estimate of 0.5 g per marijuana cigarette, a patient requiring the marijuana equivalent of 1 to 2 marijuana cigarettes per day would need 0.5 to 1 oz of marijuana per month. Although no one wants to keep a medication away from someone who might benefit from it, this 60-day supply estimate appears to be another example in which marijuana policy is ahead of the science. Circumstances in which people need 10 oz per 60 days to make tinctures or other forms of marijuana-based medicines should be rare. There are little data available for optimal dosing of marijuana for particular medical conditions.[68] Dosing differs based on the route of administration, which determines the pharmacology of the various cannabinoids in marijuana as well as the processes of absorption and metabolism.[69] Dosing is determined for an individual patient using a titration process. The marijuana dose is increased until the desired clinical effect—pain relief in Mr Z's case—is achieved. The necessary dose is highly dependent on the THC concentration of the marijuana being used. If using a vaporizer to heat the plant material into a vapor for inhalation, a patient should start with a single inhalation of marijuana vapor and monitor for effect. If 20 minutes pass with no effect, the patient may take 2 inhalations consecutively, then monitor for another 20 minutes. Inhalations are spaced out because numerous consecutive inhalations may result in missing the window of optimal treatment effect. This titration process must be repeated if a different strain of marijuana is used.

QUESTION What is the state of insurance coverage on some of these FDA-approved cannabinoid medications and medical marijuana?

DR HILL No insurance companies cover medical marijuana, and there has not been any movement toward increased coverage by insurance companies. The cannabinoids dronabinol and nabilone are expensive medications that are covered by insurance companies for their FDA indications as well as for other indications on a case-by-case basis.

Conclusions

Medical marijuana use is now common in clinical practice, and it is critical for physicians to understand both the scientific rationale and the practical implications of medical marijuana laws. Medical marijuana and cannabinoids have significant health risks as well as many potential medical benefits. While medical marijuana has been at times a controversial and contentious issue, physicians have a responsibility to provide evidence-based guidance on this important issue.

- With more states enacting medical marijuana laws, it is imperative for physicians to understand both the scientific rationale and the practical implications of medical marijuana laws.
- Aside from nausea and appetite stimulation, indications for which there are 2 FDA-approved cannabinoids (dronabinol and nabilone), chronic pain, neuropathic pain, and spasticity associated with multiple sclerosis are the indications for medical marijuana supported by high-quality evidence.
- Medical marijuana and cannabinoids have significant potential health risks, such as addiction and worsening of psychiatric illnesses such as some anxiety disorders, mood disorders, psychotic disorders, and substance use disorders, as well as many potential medical benefits.
- Evaluations to determine the appropriateness of medical marijuana for a patient should be comprehensive assessments that revolve around risk-benefit discussions.

ARTICLE INFORMATION

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