Medical Marijuana Program

165 Capitol Avenue, Room 145, Hartford, CT 06106-1630 • (860) 713-6066
E-mail: dcp.mmp@ct.gov • **Website:** www.ct.gov/dcp/mmp

Petition to Add a Medical Condition, Medical Treatment or Disease to the List of Debilitating Conditions

INSTRUCTIONS: Please complete each section of this Petition and attach all supportive documents. All attachments must include a title referencing the Section letter to which it responds. Any Petition that is not fully or properly completed will not be submitted to the Board of Physicians.

Please Note: Any individually identifiable health information contained in a Petition shall be confidential and shall not be subject to disclosure under the Freedom of Information Act, as defined in section 1-200, Connecticut General Statutes.

Section A: Petitioner's Information			
Name (First, Middle, Last): [redacted]			
Home Address (including Apartment or Suite #): [redacted]			
City: [redacted]		State: [redacted]	Zip Code: [redacted]
Telephone Number: [redacted]	E-mail Address: [redacted]		

Section B: Medical Condition, Medical Treatment or Disease
Please specify the medical condition, medical treatment or disease that you are seeking to add to the list of debilitating medical conditions under the Act. Be as precise as possible in identifying the condition, treatment or disease.
Complex Regional Pain Syndrome (CRPS), Type I and Type II

Section C: Background
Provide information evidencing the extent to which the condition, treatment or disease is generally accepted by the medical community and other experts as a valid, existing medical condition, medical treatment or disease. • Attach a comprehensive definition from a recognized medical source. • Attach additional pages as needed.
Complex Regional Pain Syndrome (CRPS), also commonly known as Reflex Sympathetic Dystrophy (RSD) is a pro

Section D: Negative Effects of Current Treatment
If you claim a treatment, that has been prescribed for your condition causes you to suffer (i.e. severe or chronic pain, spasticity, etc.), provide information regarding the extent to which such treatment is generally accepted by the medical community and other experts as a valid treatment for your debilitating condition. • Attach additional pages as necessary. • If not applicable, please indicate N/A.
There are no approved medications to treat CRPS. Individuals with CRPS were routinely excluded from clinical trial

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Section E: Negative Effects of Condition or Treatment

Provide information regarding the extent to which the condition or the treatments thereof cause severe or chronic pain, severe nausea, spasticity or otherwise substantially limits one or more major life activities.

- Attach additional pages as necessary.

In 2004, RSDSA conducted an on-line survey of people with CRPS in conjunction with the Johns Hopkins School of

Author: Connolly S, Prager J, RN Harden Review A Systematic Review of Ketamine for Complex Regional Pain S

Section F: Conventional Therapies

Provide information regarding the availability of conventional medical therapies, other than those that cause suffering, to alleviate suffering caused by the condition or the treatment thereof.

- Attach additional pages as necessary.

As mentioned in Section D, there are evidenced-based Guidelines to treat CRPS from the Netherlands, United King

Author: Ackerman, III, MD, William E., Zhang, MSc, MD, Jun-Ming Title: Efficacy of Stellate Ganglion Blockade for

Section G: General Evidence of Support for Medical Marijuana Treatment

Provide evidence, generally accepted among the medical community and other experts, that supports a finding that the use of marijuana alleviates suffering caused by the condition or the treatment thereof.

- Attach additional pages as necessary.

Section H: Scientific Evidence of Support for Medical Marijuana Treatment

Provide any information or studies regarding any beneficial or adverse effects from the use of marijuana in patients with the condition, treatment or disease that is the subject of the petition.

- Supporting evidence needs to be from professionally recognized sources such as peer reviewed articles or professional journals.
- Attach complete copies of any article or reference, not abstracts.

We are attaching four peer-reviewed articles which attest to the efficacy and low adverse effects associated with the

Section I: Professional Recommendations for Medical Marijuana Treatment

Attach letters in support of your petition from physicians or other licensed health care professionals knowledgeable about the condition, treatment or disease at issue.

See letter written by [redacted], a [redacted]

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Section J: Submission of Petition
In the event you are unable to answer or provide the required documentation to any of the Sections above (excluding Section D); provide a detailed explanation indicating what you believe is "good cause" for not doing so. • Attach additional pages as necessary.

I hereby certify that the above information is correct and complete.	
My signature below attests that the information provided in this petition is true and that the attached documents are authentic. I formally request that the commissioner present my petition and all supporting evidence to the Board of Physicians for consideration.	
Signature: [redacted]	Date Signed: 4/29/15

Medical Marijuana Program

Section A: Petitioner's Information

Section B: Medical Condition, Medical Treatment, or Disease

Complex Regional Pain Syndrome (CRPS), Type I and Type II

Section C: Background

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[1].

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.

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[1] Author: Bruehl S, Chung OY
Title: How common is complex regional pain syndrome Type I?
Source: *Pain.* 2007;129:1-2.

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.

Section D: Negative Effects of Current Treatment

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.[2]

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.

Section E: Negative Effects of Condition or Treatment

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.[3]

---

[2] Author: Connolly S, Prager J, RN Harden Review A Systematic Review of Ketamine for Complex Regional Pain Syndrome, published on-line Pain Medicine 2015

[3] 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.

Section F: Conventional Therapies

As mentioned in Section D, there are evidenced-based Guidelines to treat CRPS from the Netherlands, United Kingdom, and the United States. However, the major obstacle facing people suffering with CRPS is that medical care is not delivered in a coordinated, multidisciplinary manner. Relatively few physicians and allied medical personnel are familiar with the diagnosis and treatment for CRPS. Hence patients often see four or more medical professional s before receiving a CRPS diagnosis.
Individuals with CRPS may receive sympathetic nerve blocks (SNBs) to relieve the pain and facilitate rehab therapy. The blocks work well if initiated within the first three months after onset. [4] There have been few randomized controlled trials (RCTs) in CRPS.

Clinicians are encouraged to extrapolate from RCTs, metaanalyses, and systematic reviews concerning treatments for related neuropathic conditions, and ultimately utilize empirical drug trials in each patient based on consideration of what mechanisms seem most germane. CRPS differs from many other neuropathic pain syndromes by having additional tissues and systems involved, including the microcirculation, bone, and inflammatory pathways. Reliable data now show variable involvement of central sensitization, motor abnormalities, and sympathetic efferent features at different times and in different individuals. [5]
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Section G: General Evidence of Support for Medical Marijuana Treatment

Chronic pain is common and debilitating with too few effective therapeutic options. Cannabinoids represent a relatively new pharmacologic option as part of a multi-model treatment plan. Randomized controlled trials of cannabinoids in patients with neuropathic pain have consistently shown a significant analgesic effect of cannabinoids compared with placebo and several reported significant improvements in sleep. There were no serious adverse effects... overall there is evidence that cannabinoids are safe and modestly effective in neuropathic pain. [7]

Section H: Scientific Evidence of Medical Marijuana Treatment

We are attaching four peer-reviewed articles which attest to the efficacy and low adverse effects associated with the use of cannabinoids in the treatment of neuropathic pain and Complex Regional Pain Syndrome.

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[7] Author: Lynch, M, Campbell, F Title: Cannabinoids for treatment of chronic non-cancer; a systematic review of randomized trials Source: BJCP 72:5 735-744

Section H: Professional Recommendations for Medical Marijuana Treatment

See letter written by [redacted] Connecticut based pain specialist.

I hereby certify that the above information is correct and complete.

[redacted]

March 24, 2015

rsdsa
SUPPORTING THE CRPS COMMUNITY

Medical Marijuana Program

Section A: Petitioner's Information

[redacted]

Section B: Medical Condition, Medical Treatment, or Disease

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Source: Southern Medical Journal, Vol. 99, Number 10, October 2006

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[7] Author: Lynch, M, Campbell, F Title: Cannabinoids for treatment of chronic non-cancer; a systematic review of randomized trials Source: BJCP 72:5 735-744

Section H: Professional Recommendations for Medical Marijuana Treatment

See letter written by [redacted]

I hereby certify that the above information is correct and complete.

[redacted]

Section H: Professional Recommendations for Medical Marijuana Treatment

Plea for including Complex Regional Pain Syndrome (CRPS) on the list of approved conditions for Medical Marijuana in the state of CT

Mr. Jonathan A. Harris
Commissioner, Department of Consumer Protection, CT, and Board of Physicians, CT

Dear Mr. Harris and Board of Physicians,

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 clinicians 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, 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 times 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,

[redacted]

[redacted]

March 20, 2015

To the Advisory Board on Medical Marijuana:

I am a 72-year-old physician who has suffered from complex regional pain syndrome (CRPS) since 2009. This occurred after surgery on my left foot. The nerve on the top of my foot was pulled aside during surgery and lost its blood supply. When the CRPS developed the only pain I could compare with my pain was that of having cigarettes pressed onto the skin of my foot.

The McGill Pain Index is a scientific compilation comparing severity of pain among sample diseases. CRPS is listed at the ***top*** the index in severity of pain.

CRPS controls my life. The pain is excruciating. I have no other option but to use strong opioids (Dilaudid) to get even minimum control. My need for them is slowly increasing. I have had to have 14 sympathetic blocks (injection into my spinal area) in my six years with CRPS. These are invasive procedures and have risks. (I suffered a serious complication after my last sympathetic block). I also have to use a compounded cream which contains five neuroactive agents (amitriptyline, baclofen, ketoprofen, lidocaine and ketamine) applied to my foot when the opioids don't control the buming.

I also have extreme pain with anything touching the affected area of the foot (allodynia). I use Cymbalta (90 mg a day) for nerve pain and gabapentin and a TENS unit when everything else fails to work. The opioids cause me to itch severely and I have to take two medications just for that. With acetaminophen added to the opioids, my CRPS requires ***six*** oral medications and ***five*** cream ingredients just to make the pain tolerable. Even then I miss family events when my CRPS is not under good control. Many times I am unable to wear a shoe on that foot; my life is very restricted on a regular basis. This condition is progressive and lifelong. The pain has already spread to my other foot.

The severity of the pain of CRPS has made it one of the conditions with the highest suicide rate. Good medical studies have shown that CRPS sufferers have no more psychiatric diagnoses than normal before getting CRPS but many suffer from depression and hopelessness after getting it.

There are articles in the medical literature which support the benefit of cannabis for CRPS. I know that the Reflex Sympathetic Dystrophy Association is sending these along to your committee.

Please approve CRPS, the most painful condition in the McGill Index of Pain, as one of the conditions which benefits from cannabis therapy.

Sincerely,

(signed)

[redacted]

[redacted]

[redacted]

[redacted]

March 25, 2015

[redacted]

RSDSA

Dear [redacted]

I am writing in response to your note. You have asked to offer support of the RSDSA's petition asking the State of Connecticut to add the diagnosis/conditions of Complex Regional Pain Syndrome (types 1 and 2, CRPS/RSDS) to the list of disabling medical conditions already approved for the State's Medical Marijuana program.

I have been in practice for over 25 years, 22 in Connecticut. I treat many patients afflicted with this most disabling and crippling disorder of the nervous system. In my career I have seen several patients commit suicide as a direct result of this terribly painful condition.

Medical marijuana has been approved in our state for a number of conditions associated with pain. I do not believe a simple diagnosis of chronic pain is sufficient to merit access to marijuana. That being said, I do endorse the addition of CRPS/RSDS to the approved medical conditions. The reason is though I am skeptical marijuana will improve pain, I do believe it may be a reasonable means to allow for relaxation, sleep and muscle spasm reduction. Any pain relief would in my mind be a bonus.

Marijuana is a relatively safe anxiolytic. It may help with sleep. And it may ease some pain resulting directly or indirectly from CRPS/RED. If used appropriately, it may be safer than other prescribed medications.

Sincerely,

[redacted]

The Journal of Pain, Vol 9, No 6 (June), 2008: pp 506-521
Available online at www.sciencedirect.com

ELSEVIER

A Randomized, Placebo-Controlled, Crossover Trial of Cannabis Cigarettes in Neuropathic Pain

Barth Wilsey,* Thomas Marcotte,† Alexander Tsodikov,‡ Jeanna Millman,§ Heather Bentley,‖ Ben Gouaux,‖ and Scott Fishman§

*VA Northern California Health Care System, Department of Anesthesiology and Pain Medicine, University of California, Davis Medical Center, Davis, California.
†Department of Psychiatry, University of California, San Diego, California.
‡UC Davis/VANCHCS General Clinical Research Center and Department of Public Health Sciences, University of California, Davis Medical Center, Davis, California.
§Department of Anesthesiology and Pain Medicine, University of California, Davis Medical Center, Davis, California.
‖University of California Center for Medicinal Cannabis Research, University of California, San Diego, California.

Abstract: The Food and Drug Administration (FDA), Substance Abuse and Mental Health Services Administration (SAMHSA), and the National Institute for Drug Abuse (NIDA) report that no sound scientific studies support the medicinal use of cannabis. Despite this lack of scientific validation, many patients routinely use "medical marijuana," and in many cases this use is for pain related to nerve injury. We conducted a double-blinded, placebo-controlled, crossover study evaluating the analgesic efficacy of smoking cannabis for neuropathic pain. Thirty-eight patients with central and peripheral neuropathic pain underwent a standardized procedure for smoking either high-dose (7%), low-dose (3.5%), or placebo cannabis. In addition to the primary outcome of pain intensity, secondary outcome measures included evoked pain using heat-pain threshold, sensitivity to light touch, psychoactive side effects, and neuropsychological performance. A mixed linear model demonstrated an analgesic response to smoking cannabis. No effect on evoked pain was seen. Psychoactive effects were minimal and well-tolerated, with some acute cognitive effects, particularly with memory, at higher doses.

Perspective: *This study adds to a growing body of evidence that cannabis may be effective at ameliorating neuropathic pain, and may be an alternative for patients who do not respond to, or cannot tolerate, other drugs. However, the use of marijuana as medicine may be limited by its method of administration (smoking) and modest acute cognitive effects, particularly at higher doses.*

Key words: Neuropathic pain, analgesia, cannabis, clinical trial, neuropsychological testing.

The case for the clinical utility of cannabis as an analgesic derives from experimental studies as well as anecdotal reports. Activation of the endocannabinoid system suppresses behavioral responses to acute and persistent noxious stimulation through both central[71] and peripheral[45] mechanisms. Cannabinoid receptors are localized in neuroanatomic regions intimately involved with transmission and modulation of pain signals: The periaqueductal gray (PAG), the rostral ventromedial medulla (RVM),[49,66] and the dorsal horn of the spinal cord.[66] Animal experimentation has clearly demonstrated that synthetic and endogenous cannabinoids not only produce analgesia but also interact in some manner to potentiate opioids,[18,70] particularly in neuropathic pain.[41]

Surveys involving the use of medicinal marijuana reveal that pain, sleep, and mood improve with only modest side effects.[72,73] In one human pain experiment, subjects had a significant dose-dependent antinociception (increased finger withdrawal latency) effect that was not reversed by opioid antagonism.[31] In a somewhat contradictory manner, hyperalgesic activity and enhancement

Received June 25, 2007; Revised December 10, 2007; Accepted December 18, 2007.
Supported by grant C01-DA-114 from the University of California Center for Medicinal Cannabis Research.
Alexander Tsodikov is currently at the School of Public Health, University of Michigan, Ann Arbor, MI.
Address reprint requests to Dr. Barth L. Wilsey, Pain Academic Office, UC Davis Medical Center, 3020 Ellison Ambulatory Care Center, 4860 Y Street, Sacramento, CA 95817. E-mail: blwilsey@ucdavis.edu
1526-5900/$34.00

doi:10.1016/j.jpain.2007.12.010

of the perception of pain on acute exposure in chronic users of marijuana was reported.[20] Experience with cancer pain revealed that 120 mg codeine and 20 mg delta-9-tetrahydrocannabinol (9-THC) were similar to each other and significantly superior to placebo for the sum of the pain intensity differences and total pain relief.[55,56] However, there was a clear dose-response relationship for sedation, mental clouding, and other central nervous system (CNS) related side effects from the 9-THC.

When taken alone, 9-THC or dronabinol does not fully replicate the effect of the total cannabis preparation, indicating that there might be other active cannabinoids needed for a full range of effects.[77] As a result, combinations of cannabinoids are being sought for clinical implementation. Sativex is one of the first cannabis-based medicines to have been approved as a prescription medicine in Canada.[5] It has been found to be effective in reducing pain and sleep disturbances in patients with multiple sclerosis who have central neuropathic pain, and it appears to be well-tolerated.[62] The rationale for a combination is that the cannabidiol, normally present in insignificant concentrations in cannabis, purportedly antagonizes undesirable effects of 9-THC such as intoxication, sedation, and tachycardia while contributing analgesic, anti-emetic, and anti-carcinogenic properties.[64] However, in one direct comparison between this combination and 9-THC alone, additional effectiveness was not evident.[11] Therefore, evaluating herbal cannabis remains a worthwhile endeavor awaiting more definitive proof of a specific combination of cannabinoids that can enhance effectiveness.

Despite support from the basic and clinical sciences, the clinical utility of cannabis in the United States remains mired in controversy.[13,48,57] Akin to the medical and social controversy surrounding the use of opioids in chronic pain,[23] clinical trials will be a critical factor in the debate concerning medical marijuana. In defense of this position, the National Institutes of Health (NIH) Workshop on the Medical Utility of Marijuana[1] concluded, "Inhaled marijuana merits testing in controlled, double-blind, randomized trials . . .". Furthermore, the NIH panel concluded that neuropathic pain is a condition in which currently available analgesics are, at best, marginally effective, suggesting that cannabis might hold promise as a treatment. To address this issue, we examined whether smoking cannabis produces dose-dependent analgesia on both spontaneous and evoked pain in patients with neuropathic pain. In addition, we studied the adverse effects of cannabis to better understand its potential detrimental effects on patients.

Materials and Methods

Patients

This study was approved by the Human Subjects Institutional Review Boards at the UC Davis Medical Center (UCDMC) and the Veterans Affairs of Northern California Health Care System (VANCHCS). At the state level, endorsement by the Research Advisory Panel of California was obtained to proceed with the investigation of a Schedule I controlled substance. The approval process also included national review by the Food and Drug Administration, the National Institute on Drug Abuse, and the Department of Health and Human Services.

Participants were recruited from the UCDMC and VANCHCS pain clinics through initial contact by providers intimately involved in the patient's care as well as newspaper advertisements and postings in newsletters. All candidates were initially screened via a brief telephone interview. Qualified candidates with complex regional pain syndrome (CRPS type I), spinal cord injury, peripheral neuropathy, or nerve injury were interviewed and examined by the principal investigator who invited those meeting inclusion and exclusion criteria to enroll in the study. The diagnostic criteria for CRPS type I followed a decision rule compiled by a research consortium working with the International Association for the Study of Pain (IASP),[14,27,33] which required at least 2 signs and 4 symptoms to be positive. The specific historic and physical findings included burning pain, skin sensitivity to light touching or cold, skin color changes, swelling, limited movement of the affected body part, motor neglect or abnormalities in skin temperature, hair growth, nail growth, and/or sweating.

To reduce the risk of adverse psychoactive effects in naive individuals, previous cannabis exposure was required of all participants. All participants were required to refrain from smoking cannabis or taking oral synthetic delta-9-THC medications (ie, Marinol; Solvay Pharmaceuticals, Inc., Marietta, GA) for 30 days before study sessions to reduce residual effects; each participant underwent urine toxicology screening to confirm this provision. To further reduce unsystematic variation, subjects were instructed to take all other concurrent medications as per their normal routine during the 3- to 4-week study period.

To ensure that potential subjects did not have depression profound enough to compromise their ability to tolerate the psychoactive effects of cannabis, the Beck Depression Inventory-II (BDI-II) was administered as a screening tool. Candidates with a BDI-II score of 17 or higher were then evaluated with the Composite International Diagnostic Interview, a structured interview used to assess mental disorders and to provide diagnoses according to the definitions and criteria of the ICD-10 (World Health Organization 1992, 1993) and DSM-IV (American Psychiatry Association, 1994). If the criteria for severe major depressive disorder were met, the candidate was excluded from participation. Because the effects of cannabis can exacerbate mental illness[24,54] and have been linked to an increase in the risk of suicide,[22] candidates with a history or diagnosis of schizophrenia or bipolar depression were also excluded. Medical illnesses were also evaluated, and exclusion criteria included uncontrolled hypertension, cardiovascular disease, chronic pulmonary disease (eg, asthma, chronic obstructive pulmonary disease), and active substance abuse. Routine laboratory analysis included a hematology screen, blood chemistry panel, and urinalysis. Urine drug toxicologies for opioids, benzoylecgonine (cocaine metabolite), benzodiazepines, cannabinoids, and amphetamines were also performed through the use of urine quick tests.

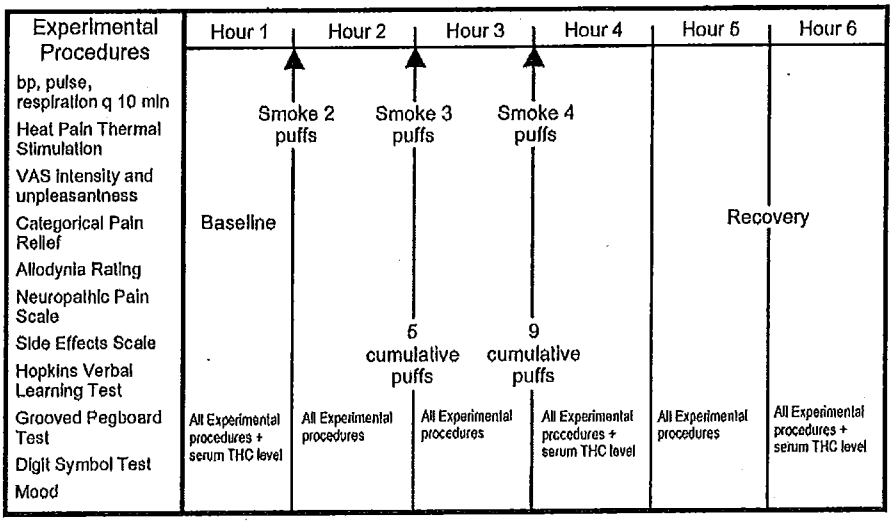

Figure 1. Experimental procedures. THC, tetrahydrocannabinol; VAS, visual analog scale.

Design

The study used a randomized, double-blinded, placebo-controlled, crossover design, using high-dose cannabis (7% delta-9-THC), low-dose cannabis (3.5% delta-9-THC), and placebo cigarettes. Two doses of medication and a cumulative dosing scheme[17,31] were used to determine dosing relationships for analgesia and psychoactive and cognitive effects.

The cannabis was harvested and machine-rolled into cigarettes at the University of Mississippi under the supervision of the National Institute on Drug Abuse (NIDA). NIDA routinely is able to provide cigarettes ($8 each) ranging in strength from 3% to 7% THC, subject to the availability of current crop potency. Placebo cigarettes are made from whole plant with extraction of cannabinoids. After overnight delivery, the cigarettes were stored in a freezer securely bolted to the floor of the Sacramento Veterans Administration Research Pharmacy. Further precautions against theft of the study drug included limited password access to the pharmacy, with a state-of-the-art entry detection system and a direct connection of the alarm system of the room housing the freezer to the Sacramento Veterans Administration Police Department. In addition to security precautions for storing the study drug, a background check of all members of the investigative team was performed by the Drug Enforcement Agency during the process of obtaining a Schedule I license.

Procedures

After informed consent was obtained, participants were scheduled for 3, 6-hour experimental sessions at the UC Davis/Sacramento VA Medical Center General Clinical Research Center (GCRC). The sessions were separated by at least 3 days to permit the metabolic breakdown of residual cannabis. The intervals between sessions ranged from 3 to 21 days, with a mean (SD) of 7.8 (3.4) days. Participants received either low-dose, high-dose, or placebo cannabis cigarettes at each visit in a crossover design using a Web-based random number–generating program, "Research Randomizer" (http://www.randomizer.org/). Each patient received each treatment once, in random order. The allocation schedule was kept in the pharmacy and concealed from other study personnel. Patients were assigned to treatment after they signed a consent form. Patients and assessors were blinded to group assignments.

The cigarettes were stored in a freezer at −20°C until the day before use. At least 12 hours before each session, 2 marijuana cigarettes were thawed and humidified by placing them above a saturated NaCl solution in a closed humidifier at room temperature. The cigarettes were smoked under a standard laboratory fume hood with constant ventilation in ambient room temperature at 22°C and a humidity of 40% to 60%. A cued-puff procedure[17] standardized the administration of the cannabis. Participants were verbally signaled to "light the cigarette" (30 seconds), "get ready" (5 seconds), "inhale" (5 seconds), "hold smoke in lungs" (10 seconds), "exhale," and to wait before repeating the puff cycle (40 seconds). A nurse continuously supervised the participant during the smoking session via a closed-circuit monitor in an adjoining room. Participants were observed constantly and could signal that they wanted to stop smoking for whatever reason by raising their hand. Participants completed a standardized cued-puff procedure[9,21] of 2 puffs after baseline measurements, 3 puffs an hour later, and 4 puffs an hour after that. The cumulative dose for each session was thus 9 puffs (Fig 1).

Hourly assessment periods were scheduled before and after each set of puffs and for 2 additional hours during the recovery period (Fig 1). Plasma levels for delta-9-THC, cannabidiol (CBD), cannabinol (CBN), 11-nor-9-carboxy-delta-9-tetrahydrocannabinol (11-nor-9-carboxy THC), and 11-hydroxy-tetrahydrocannabinol (11-hydroxy-THC) were measured at baseline, 5 minutes after the first puff

bout, and again at 3 hours after the last puff cycle. After each blood draw, plasma was separated by centrifugation and immediately frozen. Plasma samples were subsequently evaluated for enzyme-linked immunosorbent assay of delta-9-THC and metabolite content. Vital signs (aural temperature, blood pressure, respiratory rate, and heart rate) were recorded at baseline and at every hour.

Participants were allowed to engage in normal activities, such as reading or listening to music, between puff cycles and measurement periods. After each session, participants were accompanied home by a responsible adult. After completing all 3 study sessions, participants were debriefed and paid a modest stipend (prorated at $25 per hour) for their participation.

Outcome Measurements

Spontaneous pain relief, the primary outcome variable, was assessed by asking participants to indicate the intensity of their current pain on a 100-mm visual analog scale (VAS) between 0 (no pain) and 100 (worst possible pain). Pain unpleasantness, a measure of the emotional dimension of pain, was also measured by using a similar VAS. In addition, the degree of pain relief was monitored with a standard 7-point patient global impression of change scale.[26]

The Neuropathic Pain Scale,[28] an 11-point box ordinal scale with several pain descriptors, was a secondary outcome. When present, allodynia (the sensation of unpleasantness, discomfort, or pain when the skin in a painful area of the patient's body was stroked with a foam paint brush) was measured using a 100-mm VAS. Heat-pain threshold was determined by applying mild-to-moderately painful heat to the most painful area of the subjects' body[32] with the commercially available Medoc TSA 2001 Peltier thermode (Medoc Ltd. Advanced Medical Systems, Ramat Yishai, Israel). This device was used to apply a constant 1°C per second increasing thermal stimulus until the patient pressed the response button to show that a temperature change was considered painful; the heat pain threshold (mean of 3 attempts) was recorded in degrees Centigrade. Subjective intensities for "any drug effect," "good drug effect," and "bad drug effect" were measured using a 100-mm VAS anchored by "no side effect" at 0 and "strongest side effect" at 100. In addition, psychoactive effects, including "high," "drunk," "impaired," "stoned," "like the drug effect," "sedated," "confused," "nauseated," "desire more of the drug," "anxious," "down," and "hungry" were measured similarly. Mood was measured using 6, 100-mm VAS ratings for: Feeling sad versus happy; anxious versus relaxed; jittery versus calm; bad versus good; paranoid versus self-assured; and fearful versus unafraid. Subjects were prompted to provide their current rating for the foregoing items at each measurement of these subjective states.

Neurocognitive assessments focused on 3 domains: Attention and concentration, learning and memory, and fine motor speed. Subjects completed the Wechsler Adult Intelligence Scale (WAIS-III) Digit Symbol Test,[75] a test of concentration, psychomotor speed, and graphomotor abilities. This pen and paper test involves having subjects substitute a series of symbols with numbers as quickly and accurately as possible during a 120-second period. The results are expressed as the number of correct substitutions. The Hopkins Verbal Learning Test Revised (HVLT)[7] provided information on the ability to learn and immediately recall verbal information as well at the ability to retain, reproduce, and recognize this information after a delay. Alternate forms (A–F) were used to minimize practice effects.[6,8] A list of 12 words (4 words from each of 3 semantic categories) were presented, and the subject was asked to recall as many words as possible in any order. After a 20-minute delay, the subject was asked to recall the words once again (ie, delayed recall). The Grooved Pegboard Test,[47] a test of fine motor coordination and speed, was also administered. In this test, subjects were required to place 25 small metal pegs into holes on a 3 × 3-inch metal board as quickly as possible. All pegs are alike and have a ridge on one side, which corresponds to a randomly oriented notch in each hole on the metal board. First the dominant hand is tested and then repeated with the nondominant hand, and the total time for each test is recorded. A 5-minute limit is used for those unable to complete the task.

Performance on neuropsychological tests often improves as a result of practice effects.[39] This can be somewhat ameliorated by the use of alternate forms[8] and, since the largest practice effects typically occur between the first and second testing,[21] preexposure to the measures (ie, dual baselines) are recommended.[6,69] For this study, we used 6 separate versions of the Hopkins Verbal Learning Test, and incorporated a practice testing session at the time of the screening interview to lessen early practice effects. Despite our attempts to limit practice effects (using alternate forms, conducting a prebaseline practice session), these effects cannot be completely eliminated when subjects are tested repeatedly over a brief period. However, this is likely to result in increased variance, thus attenuating the treatment effect. In addition, practice effects were also mitigated by the use of a placebo arm.

To estimate the level of functioning at baseline and to provide a common metric for interpreting treatment effects on cognition, the raw scores on each test were converted to demographically corrected T scores (adjusting for age, gender, highest educational level achieved, and ethnicity).[37,38] In normal control groups, T scores have a mean of 50 with a standard deviation of 10. Based on previous research to determine the optimal cut-point that balances sensitivity and specificity in mild impairments,[36] a T score below 40 was classified as an impaired performance. Neuropsychological test performance was also summarized using the global deficit score (GDS), a validated approach for detecting neuropsychological impairments across multiple measures.[16] The GDS emphasizes both the number and the severity of deficits, giving less weight to average and above performances. T scores on the individual neuropsychological measures were converted using the following algorithm:

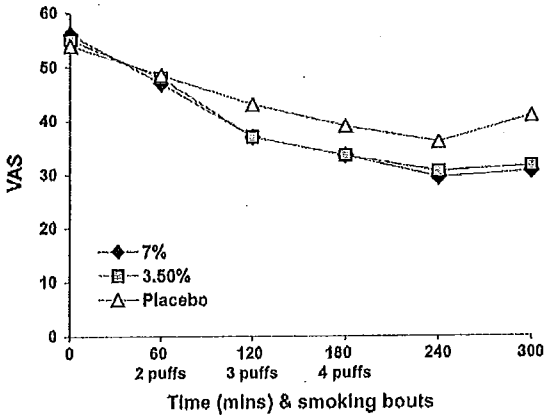

Figure 2. Visual analog scale (VAS) pain intensity.

T score ≥ 40 = 0; no impairment
T score = 35 to 39 = 1; mild impairment
T score = 30 to 34 = 2; mild-to-moderate impairment
T score = 25 to 29 = 3; moderate impairment
T score = 20 to 24 = 4; moderate-to-severe impairment
T score < 20 = 5; severe impairment.

An arithmetic mean of the deficit scores was used to create the GDS.

Statistical Methodology

A linear mixed model with a random intercept was used to model pain intensity (the primary response measure) and secondary outcomes (pain unpleasantness, global impression of change, neuropathic pain scale, allodynia, quantitative sensory testing score, mood, subjective, and psychoactive effects, and neuropsychological tests). The random intercept term is used to model the subject-specific component of the response that is shared by measurement performed on the same subject but differs between subjects. Time is modeled as a continuous variable. To reproduce the U-shaped character of the response (recovery phase) noted toward the end of observation period on the subjects (eg, Fig 2, which represents the primary outcome measure VAS pain intensity), a quadratic term in time was introduced. Treatment (high dose, low dose, and placebo) is modeled as a categorical variable with a simple contrast. The main effects of time (linear and quadratic terms) in this analysis model the response pattern over time from the baseline values.

The main effect of treatment as well as treatment by time interaction effects were considered in the model. The main effect of treatment models treatment differences in mean response at any time point, including the baseline measurement at hour 1 (Fig 1). If subjects do not show any difference at this time, before the treatment is administered, this term would not be significant with all of the possible treatment effect expressed as an interaction. This is the situation shown in Fig 2, which indicates that response curves start at the same point at the beginning of hour 1. Overall treatment difference modification over time as well as treatment differences at specific time points over the course of treatment are modeled and tested using treatment by time interaction terms. All available patient data, including information from patients who did not complete all experimental sessions, was included in this model. α was set at 0.05, and all tests were 2-tailed. No adjustment for multiple statistical comparisons was performed. Models were fitted using maximum likelihood methods to enable Wald and likelihood ratio tests of statistical hypotheses. *R* statistics software was used for all analyses.

Results

Recruitment and Withdrawals

Of 44 patients recruited between June 2004 and February 2006, 23 were men and 21 were women. The mean age (range) was 46 years (21–71 years). Six subjects were excluded and did not receive study medication, 3 because they withdrew consent before commencing the study and 3 because they were excluded after medical evaluation. Of the remaining 38 patients (Table 1), 32 completed all 3 study sessions, 1 completed 2 sessions, and 5 completed only 1 session; a total of 103 study ses-

Table 1. Demographics and Characteristics of Patients (N = 38)

Sex (No.)	
Male	20
Female	18
Age (y)	
Median	46
Range	21–71
Education level (y)	
Median	14
Range	12–21
Race	
Caucasian	33
African American	1
Hispanic	1
Asian American	1
American Indian	1
Other	1
Cause of pain (No.)	
CRPS type I	22
Spinal cord injury	6
Multiple sclerosis	4
Diabetic neuropathy	3
Ilioinguinal neuralgia	2
Lumbosacral plexopathy	1
Intensity of pain at baseline	5.6 ± 2.10
Duration of pain	
Mean (y)	6
Range (mo)	10–290
Concomitant medications (No.)	
Opioids	31
Antidepressants	19
NSAIDS	9
Anticonvulsants	22

Abbreviations: CRPS, complex regional pain syndrome; NSAIDS, nonsteroidal anti-inflammatory drugs.

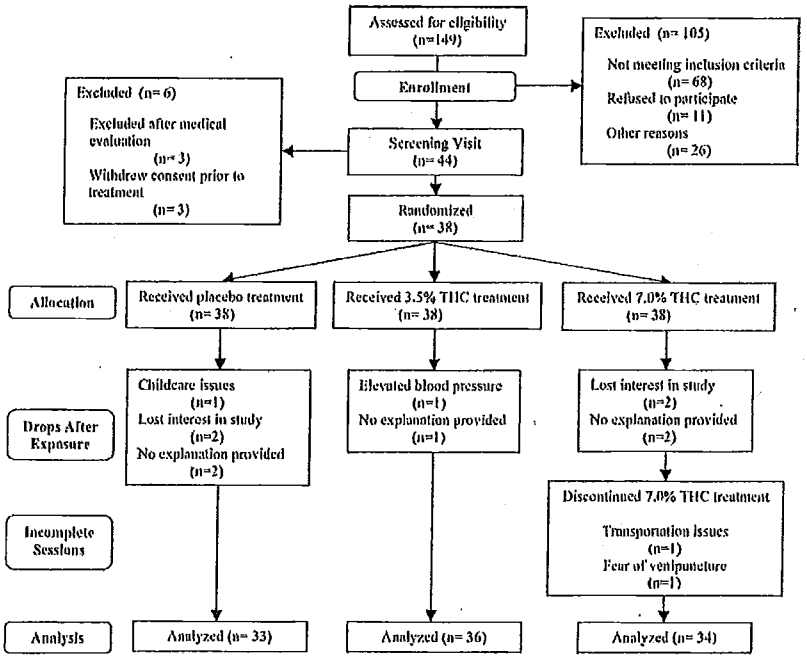

Figure 3. Consort flow chart. THC, tetrahydrocannabinol.

sions took place. One participant was removed from the study because of high blood pressure that manifested itself before their third session. Five participants did not complete 10 other sessions because of personal reasons not related to the study. Two subjects did not complete all 6 hours of their high-dose sessions; neither dropped because of medical issues. One had to leave early and the other left before the final hour of the study to avoid a repeat blood draw (Fig 3, consort flowchart). There were no adverse cardiovascular side effects, and no participant dropped out because of an adverse event related to an experimental intervention.

The average (SD) pain intensity at baseline was 55 (21) on a 0- to 100-mm VAS. The minimally acceptable VAS at baseline was 30/100. Subjects were studied if they did not meet the 30-mm minimal VAS score if they had completed at least the first session. None of the 34 patients were below this minimal score during the 7% visits, 4 of 36 patients were below this score at the time of the 3.5% visits, and 2 of 33 subjects were below 30/100 at the placebo visit.

Of the 38 patients who completed the study, 22 met the IASP diagnostic criteria for CRPS type I,[14,27,33] 10 had central neuropathic pain related to spinal cord injury or multiple sclerosis, and 6 had peripheral neuropathic pain related to diabetic neuropathy or focal nerve injury. Mean (range) time from the diagnosis of neuropathic pain to study enrollment was 6 years (10 months to 24 years). All patients had used cannabis before, as required by the protocol. The median (range) time from previous exposure, disclosed by historic account during the screening interview, was 1.7 years (31 days to 30 years), with a median (range) exposure duration of 2 years (1 day to 22 years). As required by the inclusion criteria, urine toxicology screening for cannabis was negative in all patients before study entry.

Primary Efficacy Measurement: Pain Intensity

The primary analysis compared patients' mean VAS pain intensity before and after smoking marijuana (Table 2). Predictably, no treatment differences were found at baseline before the treatment administration started (3.5% vs 7% at time 0: $P = .93$; placebo vs 7% at time 0: $P = .35$). A "ceiling effect" was noted with cumulative dosing as the 3.5% and 7% cigarettes produced equal antinociception at every time point with no difference between the 3.5% and 7% doses over time (treatment by time interaction: $P = .95$, Table 2). Significant analgesia expressed as a 0.0035 reduction in VAS pain intensity per minute was noted from both 3.5% and 7% cannabis compared with placebo (Fig 2; combined 3.5% and 7% treatment group vs placebo difference per minute: −0.0035, 95% CI: [−0.0063,−0.0007], $P = .016$). Analysis by specific time points was done using a categorical effect of time. Although a trend for separation of the active agents from placebo is visible by time 120 minutes (Fig 2), significant separation for a specific time point occurred only after a cumulative dose of 9 puffs at time 240 minutes (time = 60, 2 puffs, $P = .13$; time = 120, 3 puffs, $P = .11$; time = 180, 4 puffs, $P = .11$, time = 240, recovery hour 1, $P = .02$).

The linear main effect of time coefficient was negative (the downward sloping lines on the left in Fig 2), signifying a basic pattern of increasing analgesia; mean reduc-

Table 2. Visual Analog Scale (VAS) Pain Intensity Primary Efficacy Analysis

	Effect	Mean Difference	Standard Error	Confidence Interval		P Value
Differences at baseline	7% vs 3.5%	−0.02	0.23	−0.47	0.43	.93
	7% vs placebo	−0.21	0.23	−0.66	0.24	.35
	3.5% vs placebo	−0.19	0.23	−0.64	0.26	.40
Dose effect on top of basic pattern, treatment by time interaction	7% vs 3.5%	−0.0001	0.0017	−0.0034	0.0032	.95
	7% vs placebo	**−0.0035**	**0.0017**	**−0.0068**	**−0.0002**	**.04**
	3.5% vs placebo	**−0.0036**	**0.0017**	**−0.0069**	**0.0003**	**.03**
	7%+3.5% vs placebo	**−0.0035**	**0.0014**	**−0.0063**	**−0.0007**	**.02**
Basic analgesia pattern, placebo, combined 3.5%+7% fit	Pain intensity reduction per minute, time linear term	**−0.0050**	**0.0012**	**−0.0073**	**−0.0026**	**< .01**
	Pain intensity reduction over time, quadratic term	**0.00003**	**0.0001**	**0.00002**	**0.00005**	**< .01**
Absolute effects by time, Pain intensity reduction per minute	Placebo	**−0.0040**	**0.0010**	**−0.0060**	**−0.0021**	**< .01**
	3.5% dose	**−0.0085**	**0.0010**	**−0.010**	**−0.0066**	**< .01**
	7% dose	**−0.0085**	**0.0010**	**−0.010**	**−0.0065**	**< .01**

NOTE. Significant results ($P < .05$) are **bolded.** Point estimates of differences at baseline represent mean difference in pain intensity at time before treatment. Dose effect point estimate represents a difference in VAS pain intensity change per minute (slope) between 2 dose levels. A zero dose effect point estimate and zero difference at baseline would produce identical mean VAS curves over time in the 2 groups.

tion VAS pain intensity per minute in the placebo group [−0.0050, 95% CI: (−0.0073, −0.0026)]. The quadratic time coefficient for recovery was positive (ie, represented by the U-shaped pattern seen on the right-hand side of Fig 2), signifying a change in direction toward baseline; with the quadratic term being 3.3×10^{-5}, 95% CI: (0.00002, 0.00005). Both of these time effects were highly significant ($P < .0001$), suggesting that cannabis produced an analgesic response with cumulative dosing that began to reverse within 1 to 2 hours after the last dose.

Using the model, we considered whether there is any evidence that the results might differ by the type of pain condition. No significant differences were found; a test of no effect of pain type showed a P value of .39. Pairwise tests did not show any significant differences, either. It should be noted, however, that the sample size in the above analysis was small, and a type II error may have been present.

Order of treatment administration (placebo, 3.5% or 7%) in this crossover study was not a significant factor ($P = .37$) in analyzing the primary outcome variable. However, the study may not have enough power to detect order or carryover effects. Generous spacing of patient visits was designed to alleviate this concern.

Secondary Outcomes

A sample of the results of model fit to secondary pain end points is shown in Table 3.

Table 3. Secondary Pain Measures Analysis

Pain Measure	Effect		Mean Difference	Standard Error	Confidence Interval		P Value
Unpleasantness	Basic analgesia pattern, placebo	Time, linear term	**23.67**	**8.42**	**7.16**	**40.18**	**< .01**
		Time, quadratic	**0.14**	**0.050**	**0.044**	**0.23**	**< .01**
	Treatment effect, interaction by time	3.5% vs placebo	**−0.21**	**0.06**	**−0.33**	**−0.09**	**< .01**
		7% vs Placebo	**−0.21**	**0.06**	**−0.33**	**−0.09**	**< .01**
Global impression of change	Basic analgesia pattern, placebo	Time, linear term	**−22.62**	**4.04**	**−30.53**	**−14.70**	**< .01**
		Time, quadratic	**−0.13**	**0.023**	**−0.18**	**−0.08435**	**< .01**
	Treatment effect, interaction by time	3.5% vs placebo	**0.12**	**0.029**	**0.064**	**0.18**	**< .01**
		7% vs Placebo	**0.12**	**0.029**	**0.065**	**0.18**	**< .01**
Allodynia	Basic pattern	Time, linear term	3.66	3.66	−3.50203	10.83	.32
		Time, quadratic	0.022	0.021	−0.01938	0.063	.30
	Treatment effect, interaction by time	3.5% vs placebo	0.00007	0.034	−0.066	0.066	.99
		7% vs placebo	−0.009	0.034	−0.076	0.058	.79
Heat stimuli	Basic pattern	Time, linear term	−2.64	6.52	−15.42	10.14	.69
		Time, quadratic	−0.015	0.038	−0.089	0.059	.69
	Treatment effect, interaction by time	3.5% vs placebo	0.11	0.06	−0.0046	0.23	.06
		7% vs placebo	0.085	0.060	−0.034	0.20392	.16

NOTE. Significant results ($P < .05$) are **bolded.**

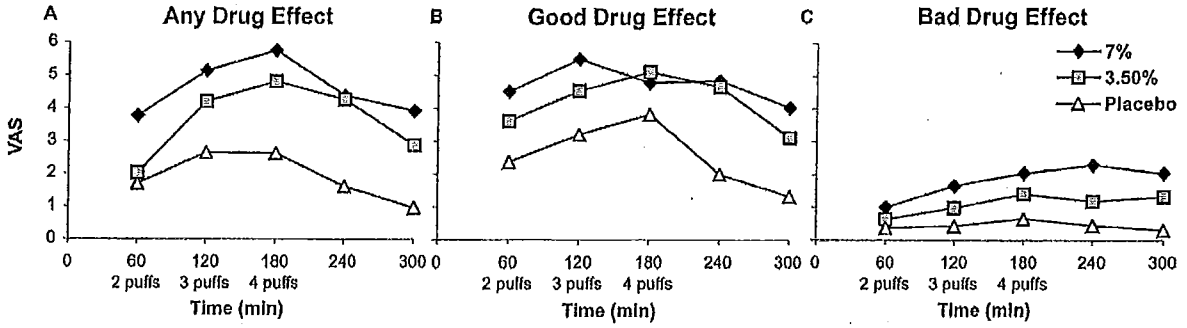

Figure 4. Subjective side effects.

Pain Unpleasantness

Pain unpleasantness, a measure of the emotional response to pain, was also measured by using a similar 100-mm VAS bordered by "not at all" at 0 and "extremely unpleasant" at 100. A trend for the treatment difference increase over time is found to be the same in 3.5% and 7% dose groups (mean difference change per minute = −0.21, 95% CI: (−0.33, −0.09), $P < .01$), indicating that pain was more tolerable at higher cumulative doses of cannabis that it was with placebo.

Global Impression of Change

In addition to VAS ratings for pain intensity and unpleasantness, the degree of relief was monitored by a 7-point scale of patient global impression of change. As with the VAS ratings, cannabis provided a greater degree of relief than placebo (3.5% or 7% placebo = 0.12, 95% CI: (0.064, 0.18), $P < .01$). Once again, the low- and high-dose groups showed virtually identical results and did not differ significantly ($P = .76$).

Neuropathic Pain Scale

Measurements from the Neuropathic Pain Scale (NPS) indicate that smoking cannabis positively affected several of the multidimensional pain descriptors associated with neuropathic pain. Modeling of sharp ($P < .001$), burning ($P < .001$), aching ($P < .001$), sensitive ($P = .03$), superficial ($P < .01$) and deep pain ($P < .001$) showed that cannabis improved pain scores more than placebo. The higher dose provided no additional benefit on these dimensions, except that the high dose lowered superficial pain more than the low dose ($P = .04$). Cannabis improved neither cold nor itching over placebo ($P > .05$ for both dimensions).

Allodynia

The mean values of allodynia were relatively low throughout all sessions, with the average VAS for the 6 hourly measurements ranging between 20 and 35 on a 100 millimeter scale. These low scores are related to the fact that 15 of the 38 participants (39%) did not have allodynia. No effect of treatment with different concentrations of cannabis ($P = .40$) or cumulative dose ($P = .29$) was observed.

Quantitative Sensory Testing

Mild to moderately painful heat stimuli delivered to the most painful area of the participant's body produced no significant change in response to treatment over time ($P > .2$) as well as no indication of any trend in treatment differences ($P > .1$).

Subjective and Psychoactive Effects

The linear mixed effects modeling explored side effects data using several variables. A continuous linear effect of time, a categorical main effect of treatment (low dose vs high dose vs placebo), and an interaction of time with treatment was used.

Subjective Effects

The "any drug effect" approached a VAS of 60/100 in the high-dose group after the maximum cumulative dose, but the effect receded rapidly thereafter (Fig 4A). The analysis of this end point showed significant main effect of treatment (Fig 4A), with the low-dose and placebo values being lower than the corresponding responses for the high-dose values ($P = .002$, $P < .001$, respectively). Time did not modify this treatment effect ($P > .17$).

The low-dose and high-dose groups had more of a "good drug effect" (Fig 4B) than placebo ($P < .001$). The maximum "good drug effect" was between 30/100 and 50/100 for the 2 doses (Fig 4B) and was greater in magnitude than the 25/100 recorded for a "bad drug effect" (Fig 4C). A "bad drug effect" (Fig 4C) was not evident for the low-dose group when compared with placebo ($P > .2$), and initially the high dose-group did not differ significantly from placebo either. Eventually, however, this effect built up with time for the high dose (effect change per unit time = 0.275, $P = .03$).

Psychoactive Effects

"Feeling high" (Fig 5A) scored greatest for the high-dose group ($P < .001$), and both dose groups differed from placebo ($P < .05$). Recovery was gradual after smoking cessation; no interaction with time occurred ($P > .2$), implying that the differences between active and placebo cigarettes remained similar at all time points despite cumulative dosing. "Feeling stoned" (Fig 5B) was

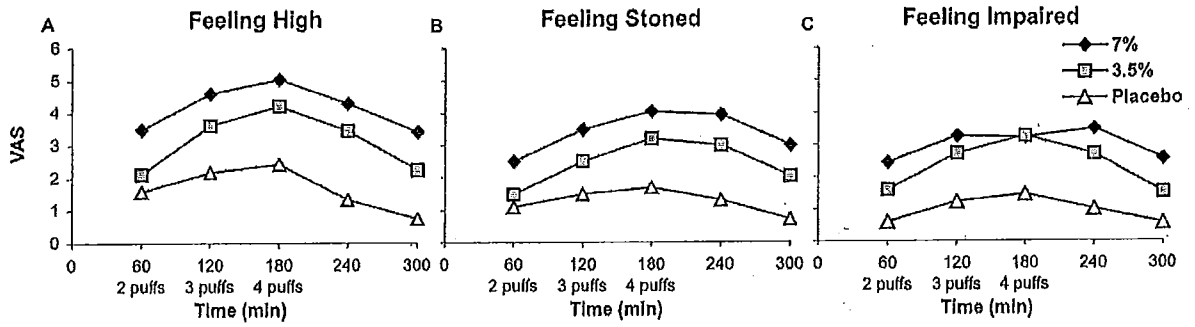

Figure 5. Psychoactive side effects.

also scored greater for the high-dose group ($P = .001$); again, both dose groups differed from placebo ($P < .05$). The treatment groups differed from placebo on "Feeling drunk" ($P = .054$), but this was of questionable clinical significance as the VAS was only 10/100 for both groups over time.

Somewhat more clinically relevant was the sensation of being "impaired" (Fig 5C), which rose just above 30 on a 100 millimeter VAS for both dose groups and differed from placebo ($P = .003$), and then declined with time. There was no change in "desire more of the drug" with time in either of the 2 treatment groups ($P = .72$). In the placebo group, however, the "desire more of the drug" decreased (probably because smoking cigarettes was unpleasant), and this decrease resulted in a significant difference between the treatment groups and placebo over time ($P = .03$). There was no difference between the 2 dose groups ($P = .99$) as to "desire more of the drug."

Sedation occurred in both dose groups compared with placebo ($P < .01$), but there was no interaction with time ($P = .82$). Cannabis produced significantly more confusion than placebo ($P = .03$). Hunger increased over time in both treatment groups compared with placebo ($P < .001$), and the difference between the dose groups was not significant ($P = .61$). Anxiety was not a prominent effect of marijuana in this study. The only significant difference was between the high-dose and placebo groups ($P < .02$), but the maximum VAS value was less than 20/100. Similarly, feeling down was not a major factor; all the VAS values were just above 10/100 and did not differ significantly between groups ($P > .05$).

Mood

Mood was measured using VAS for feeling happy versus feeling sad, feeling relaxed versus feeling anxious, feeling calm versus feeling jittery, feeling good versus feeling bad, feeling self-assured versus feeling paranoid, feeling unafraid versus feeling fearful. There was no clear indication that mood changes accompanied marijuana use. Calmness was more noticeable over time with the 3.5% and placebo cigarettes ($P < .03$) but not with 7% cigarettes ($P = .6$). However, the effect size was approximately 1 and thus probably

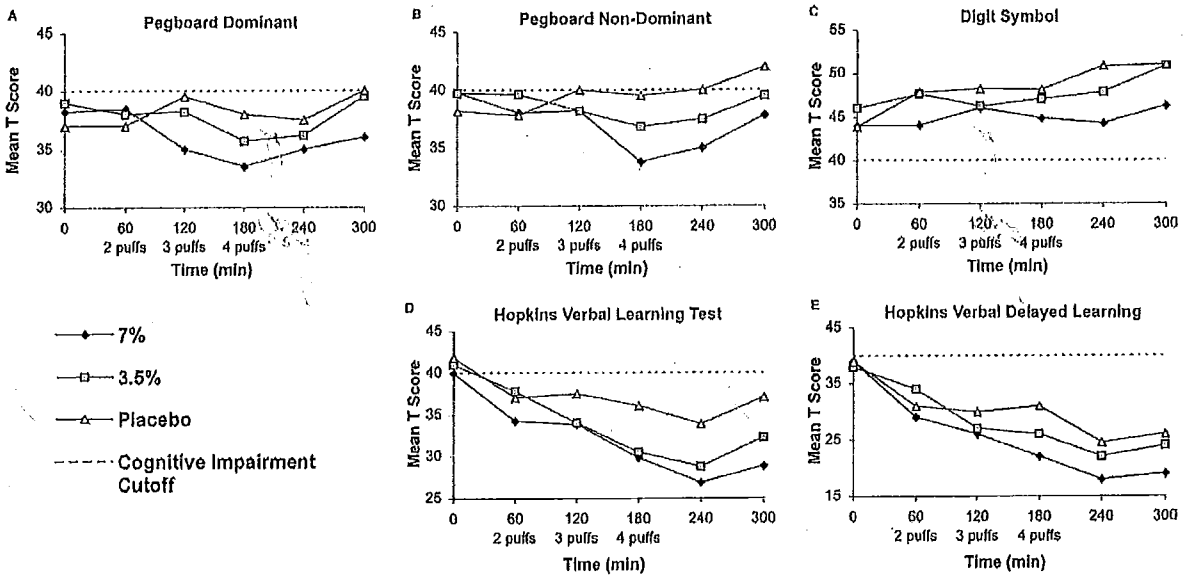

Figure 6. Neuropsychological test scores.

Table 4. Neuropsychological T Scores

Score	Effect		Mean Difference	Standard Error	Confidence Interval		P Value
Pegboard dominant hand	Initial impairment	7% vs 3.5%	0.07	1.6	−3.07	3.21	.97
		7% vs placebo	−1.77	1.63	−4.96	1.42	.28
	Change per minute in mean difference	7% vs 3.5%	0.46	0.41	−0.34	1.26	.27
		7% vs placebo	**1.14**	**0.42**	**0.32**	**1.96**	**.007**
		3.5% vs placebo	0.68	0.41	−0.12	1.48	.1
	Recovery effect	Last point vs linear trend	**3.22**	**1.03**	**1.20**	**5.24**	**.002**
Pegboard nondominant hand	Initial impairment	7% vs 3.5%	0.29	1.51	−2.67	3.25	.85
		7% vs placebo	−2.52	1.53	−5.52	0.48	.1
	Change per minute in mean difference	7% vs 3.5%	0.33	0.39	−0.43	1.09	.39
		7% vs placebo	**1.34**	**0.39**	**0.58**	**2.10**	**< .001**
		3.5% vs placebo	**1.01**	**0.39**	**0.25**	**1.77**	**< .01**
	Recovery effect	Last point vs linear trend	**3.19**	**0.96**	**1.31**	**5.07**	**< .01**
Digit symbol test	Initial impairment	7% vs 3.5%	2.09	1.82	−1.48	5.66	.25
		7% vs placebo	0.18	1.85	−3.45	3.81	.92
	Change per minute in mean difference	7% vs 3.5%	0.43	0.47	−0.49	1.35	.36
		7% vs placebo	0.93	0.48	−0.01	1.87	.051
		3.5% vs placebo	0.50	0.47	−0.42	1.42	.28
	Recovery effect	Last point vs linear trend	**1.30**	**1.16**	**−0.97**	**3.57**	**.001**
HVLT–Learning	Initial impairment	7% vs 3.5%	1.59	2.22	−2.76	5.94	.47
		7% vs placebo	0.15	2.26	−4.28	4.58	.95
	Change per minute in mean difference	7% vs 3.5%	0.28	0.57	−0.84	1.40	.62
		7% vs placebo	**1.31**	**0.58**	**0.17**	**2.45**	**.02**
		3.5% vs placebo	1.03	0.57	−0.09	2.15	.07
	Recovery effect	Last point vs linear trend	**6.19**	**1.42**	**3.41**	**8.97**	**< .001**
HVLT–Recall	Initial impairment	7% vs 3.5%	1.5	2.25	−2.91	5.91	.5
		7% vs placebo	−0.45	2.30	−4.96	4.06	.84
	Change per minute in mean difference	7% vs 3.5%	0.48	0.58	−0.66	1.62	.41
		7% vs placebo	**1.30**	**0.59**	**0.14**	**2.46**	**.03**
		3.5% vs placebo	0.82	0.58	−0.32	1.96	.16
	Recovery effort	Last point vs linear trend	**6.16**	**1.44**	**3.34**	**8.98**	**< .000**

Significant results ($P < .05$) are **bolded**. HVLT, Hopkins Verbal Learning Test Revised.

not an important consideration. The other measurements were similarly of little clinical significance.

Neuropsychological Testing

The linear mixed effects modeling for this data includes the main effect of time (continuous), a categorical main effect of treatment (7% vs 3.5% vs placebo cannabis), an interaction of time with treatment, and a categorical effect associated with the last time point (recovery effect). The recovery effect involving measurement of the last time point was performed as this point estimate showed departure from the linear pattern (Fig 6, A–E) of earlier measurements in other models. For this reason, we used this special model term to address reversal of the neuropsychological decline. Detailed results for the normalized data are presented in Table 4.

The main effect of time models the cognitive impairment associated with the cumulative dose of cannabis. The pretreatment scores (intercept terms) were equal because participants did not have residual effects from previous treatments and had been instructed not to use marijuana for 30 days before study entry or during the intervals between study sessions. Cannabis produced a general cognitive decline, as indicated by the difference in the slopes of scores over time between treatment groups. The high-dose and placebo groups differed significantly on all dimensions, except the Digit Symbol Test, where the difference bordered on significant, at $P = .051$. The low- and high-dose groups did not differ significantly; however, point estimates (Table 4) indicate that the high-dose group had greater cognitive impairment. More notably, many of the neurocognitive results in the low-dose group did not differ significantly from those in the placebo group. The deviation of the last point from the general time pattern is modeled by the categorical recovery effect constructed using an indicator dummy variable representing the last time point. Recovery at the last observed time point after discontinuation of cannabis was significant for all scores, with the average score showing a P value of $< .01$.

The analysis comparing the effect of smoking cannabis in the low- and high-dose and placebo sessions using mean values could minimize group differences on neuropsychological testing since above average performers may offset poor performance by others. To obviate this potential bias, deficit scores were used to reduce the influence of the high-functioning individuals.[16] Using this approach, both low- and high-dose cannabis induced moderate to severe impairment for verbal learn-

Table 5. Global Deficit Scores (GDS)

	Treatment	0 Min	60 Min 2 Puffs	120 Min 3 Puffs	180 Min 4 Puffs	240 Min	300 Min
Pegs Dom	7%	1.3	1.5	2.0	2.0	2.0	1.7
	3.5%	1.3	1.5	1.4	1.8	1.7	1.3
	Placebo	1.8	1.4	1.2	1.4	1.6	1.3
Pegs	7%	1.2	1.4	1.5	2.0	1.9	1.7
Nondom	3.5%	1.1	1.3	1.4	1.5	1.5	1.3
	Placebo	1.4	1.4	1.2	1.4	1.3	1.1
Digit Symbol	7%	0.9	0.9	0.9	1.1	1.3	0.8
	3.5%	0.6	0.8	0.9	0.7	0.7	0.5
	Placebo	0.8	0.6	0.5	0.5	0.5	0.5
HVLT–Learn	7%	**1.2**	**2.2**	**2.4**	**2.8**	**3.3**	**2.9**
	3.5%	**1.1**	**1.9**	**2.2**	**2.7**	**2.9**	**2.7**
	Placebo	**1.2**	**1.6**	**1.3**	**1.6**	**2.1**	**1.7**
HVLT–Delay	7%	**1.5**	**2.8**	**3.3**	**3.7**	**4.2**	**3.8**
	3.5%	**1.6**	**2.3**	**3.1**	**3.4**	**3.9**	**3.5**
	Placebo	**1.5**	**2.5**	**2.6**	**2.5**	**3.5**	**3.3**
Average	7%	1.2	1.8	2.0	2.3	2.5	2.2
GDS	3.5%	1.1	1.5	1.8	2.0	2.2	1.8
	Placebo	1.3	1.5	1.4	1.5	1.8	1.6

Abbreviation: HVLT, Hopkins Verbal Learning Test Revised.

NOTE. Significant results ($P < .05$) are **bolded.**

Categorization of each raw deficit score was performed using clinically relevant cutoff points.

$T \geq 40$ (deficit score (DS = 0; no impairment), $35 \leq T \leq 39$ (DS = 1; mild impairment), $30 \leq T \leq 34$ (DS = 2; mild-to-moderate impairment), $25 \leq T \leq 29$ (DS = 3; moderate impairment), $20 \leq T \leq 24$ (DS = 4; moderate-to-severe impairment), $T < 20$ (DS = 5; severe impairment).

ing and recall (Table 5). Of note, subjects on placebo also declined in learning and recall, most likely due to proactive interference resulting from exposure to multiple learning lists in a short time frame. Nonetheless, despite this pattern, performance on these measures still differed by cannabis levels, and one would expect that any potential confounding might likely lessen any discernible treatment effects. Since cannabis may affect individuals differently and the impact on cognitive performance may be obscured if one just analyzes individual tests, the global deficit score was used to determine whether treatment with low-and high-dose cannabis affected overall cognitive performance. As can be seen in Table 5, there were significant group differences on global cognitive functioning at each treatment level. Participants using low-dose cannabis had poorer cognitive function than placebo and performed least well when on the high dose.

In summary, 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 all measures, subjects on 7% cannabis had greater impairment than those on 3.5%, who in turn had greater impairment than subjects on placebo. Of note, a significant proportion of subjects had cognitive impairment at baseline: Grooved Pegboard Dominant (71%) and non-Dominant (68%), Digit Symbol (61%), and HVLT Learning (76%) and Recall (76%). Twenty-nine of the 38 subjects (76%) had a global deficit score in the impaired range (>.50) at baseline before smoking cannabis.

Cannabinoid Levels

The mean (range) consumption of cigarettes was 550 mg (200–830 mg) during the low-dose sessions and 490 mg (270–870 mg) for the high-dose sessions. These amounts represent smoking slightly more than about one-half of a cigarette. The amount of delta-9-THC consumed was estimated to be 19 mg during the low-dose sessions and 34 mg during the high-dose sessions. Serum levels of the primary active cannabinoid D9-THC, secondary active cannabinoids, cannabidiol (CBD), cannabinol (CBN), the primary active metabolite, 11-hydroxy THC, and the primary inactive metabolite 1-NOR THC were evaluated using linear mixed modeling, with results presented in Table 6. There was no correlation of these serum levels with analgesia. As expected, several psychomimetic effects correlated with levels of delta-9-THC, CBD, and the active metabolite 1-NOR THC. However, neuropsychological testing did not show a relationship with serum values with the exception of delta-9-THC levels and performance on the Digit Symbol test ($P = .034$).

Discussion

In the present study, standardized doses of smoked *Cannabis sativa* were administered using a uniform puff and breath-hold procedure.[46] The analgesic, subjective, and neuropsychological effects of cannabis were then measured. A linear analgesic dose response for both 3.5% delta-9-THC and 7% delta-9-THC cannabis substantiated previous empirical reports of pain relief. Identical levels of analgesia were produced at each cumulative dose level by both concentrations of active agent (Fig 2).

Table 6. Linear Mixed Model Fit of Psychometric Responses Regressed on a Panel of Blood Levels of 5 Cannabinoids

Blood Level	Psychomimetic Response	Regression Coefficient	Standard Error	Confidence Interval		P Value
Cannabidiol	High	**0.73**	**0.30**	**0.13**	**1.00**	**.019**
	Impaired	**0.59**	**0.27**	**0.07**	**1.00**	**.029**
	Stoned	**0.79**	**0.24**	**0.31**	**1.00**	**.002**
	VAS Intensity	−0.24	0.23	−0.69	0.22	.315
Delta-9-THC	High	**0.01**	**0.004**	**0.00**	**0.02**	**.007**
	Impaired	0.007	0.004	0.00	0.01	.061
	Stoned	**0.007**	**0.003**	**0.00**	**0.01**	**.031**
	VAS Intensity	−0.001	0.003	−0.01	0.00	.662
Cannabinol	High	−0.003	0.10	−0.20	0.20	.971
	Impaired	−0.01	0.09	−0.19	0.17	.894
	Stoned	−0.11	0.08	−0.27	0.05	.194
	VAS Intensity	−0.08	0.08	−0.23	0.08	.334
11-Hydroxy THC	High	−0.05	0.13	−0.29	0.20	.706
	Impaired	−0.03	0.11	−0.25	0.19	.783
	Stoned	0.05	0.10	−0.14	0.25	.593
	VAS Intensity	−0.02	0.003	−0.02	−0.01	.662
1-NOR THC	High	**−0.01**	**0.006**	**−0.03**	**0.00**	**.036**
	Impaired	−0.003	0.006	−0.01	0.01	.574
	Stoned	−0.005	0.006	−0.02	0.01	.424
	VAS Intensity	0.004	0.005	−0.01	0.01	.734

Abbreviations: THC, tetrahydrocannabinol; VAS, visual analog scale.

NOTE. Regression coefficients represent mean change of response as a result of unit change in the respective blood level. Significant results ($P < .05$) are **bolded.**

The plateau or "ceiling effect" indicates that within the range of the doses used, the top of the dose-response curve was reached. In addition to pain intensity, participants completed a rating scale to measure pain unpleasantness. This instrument has been validated in pain states amplified by emotional turmoil[59] and provides insight into a drug's relative effectiveness on alleviating the affective component of the pain experience as opposed to the more familiar sensory experience.[60,61] In the present experiment, cannabis reduced pain intensity and unpleasantness equally. Thus, as with opioids,[61] cannabis does not rely on a relaxing or tranquilizing effect (eg, anxiolysis) but rather reduces both the core component of nociception and the emotional aspect of the pain experience to an equal degree.

Separate appraisals using the patient global score and the multidimensional NPS revealed that both active agents alleviated pain compared with placebo. Interestingly, evoked pain brought about by lightly touching skin using a foam paintbrush or through testing heat pain threshold with the commercially available Medoc TSA 2001 Peltier thermode (Medoc, Ramat Yishai, Israel) did not confirm an analgesic effect of cannabis. These results are similar to those in a recent study demonstrating the efficacy of smoked cannabis in patients with human immunodeficiency virus (HIV)-associated sensory neuropathy.[2] As in the present investigation, there was little effect on the painfulness of noxious heat stimulation. However, relief to experimentally induced hyperalgesia to both brush and von Frey hair stimuli was evident in the HIV-associated sensory neuropathy study.[2] The lack of response to allodynia in the present study may reflect the challenge of alleviating this condition as it is notable for resistance to treatment.[63] The lack of an increase in heat pain threshold in both the HIV study and the present analysis, however, has no apparent explanation. A simultaneous effect on heat pain induced experimentally and clinical pain has been documented with opioids[60] and theoretically should have been evident in the present study provided the effect size was large enough to be discernable.

Undesirable consequences of smoking cannabis were clearly identifiable. However, consistent with the notion that these side effects are acceptable to patients with chronic pain,[65,72] no participant withdrew because of tolerability issues. Subjects receiving active agent endorsed a "good drug effect" (Fig 4B) more than a "bad drug effect" (Fig 4C), and the latter was at issue only for the higher dose of cannabis. Similarly, feeling "high," "stoned," or "impaired" were less problematic for the lower strength cigarettes (Fig 5A–C). In general, side effects and changes in mood were relatively inconsequential. These findings are consistent with the observation that many patients find treatment with cannabis to be a satisfactory experience.[65,72] A reasonable explanation would be that a patient self-titrates cannabis, balancing analgesia against side effects. However, beyond the benign psychoactive effects, administration of cannabis may be deleterious in that it impairs cognition. Previous investigations have reviewed processing speed, attention, memory, reaction time, and psychomotor abilities after smoking cannabis.[25,53,58] Results have varied and depend on several variables including cigarette potency, smoking technique, individual variation in bioavailabil-

ity, and previous exposure to the drug. As in the present study, although analgesia appears to be consistent across the low and high dosages, cognitive changes were more problematic with a high dose of delta-9-THC.[4,35] This suggests that a therapeutic window may exist that might be exploited for clinical purposes. However, there is an additional problem with using cannabis in the chronic pain population. Severe pain coupled with psychological distress is associated with below average scores on cognitive performance tests.[43,44,76] As in these previous reports, the patients in our study were either below or nearly below the cutoff for impairment before receiving study medication. Our study indicates that modest declines in cognitive performance occur with cannabis, particularly in learning and recall, and especially at higher doses. In combination with the deficits in baseline neurocognitive performance, however, cannabis compounds this problem. This finding necessitates caution in the prescribing of medical marijuana for neuropathic pain, especially in instances in which learning and memory are integral to a patient's work and lifestyle.

Further vigilance is warranted in young patients because cannabis use in adolescence increases the risk of later schizophrenia-like psychoses, especially in genetically susceptible individuals.[24] There is an increased risk of a psychosis in those who have ever used cannabis (pooled adjusted odds ratio = 1.41; 95% CI, 1.20–1.65) and a dose-response effect, with greater risk in subgroups consuming cannabis very frequently (pooled adjusted odds ratio = 2.09; 95% CI, 1.54–2.84).[54] These effects of cannabis may be consequent on its impact on the dopamine system.[54] There is less evidence of cannabis playing a role in other mental disorders (ie, depression and anxiety). Further research is needed to understand the biological mechanisms underlying the effects of cannabis on psychiatric conditions, but the health risks of cannabis in patients with any propensity for psychosis mandate caution in this population. Consistent with this risk, a history of schizophrenia and bipolar depression were exclusionary criteria in the present study.

It is tempting to speculate that a lower strength of cannabis might avoid or at least reduce the adverse neurocognitive profile noted above. As the 7% and 3.5% cannabis were equianalgesic, it would be certainly be appropriate to test a lower concentration to see if the analgesic profile is maintained while cognitive decline is reduced or even obviated. Even if the pain-relieving properties are less than robust, a case could be made for using the lowest possible strength despite attenuation in analgesic potency. Moreover, as polypharmacy is common in the management of chronic pain,[12] the addition of the lowest effective dose of cannabis to another analgesic drug (ie, anticonvulsant, opioid, etc) might lead to an effective treatment of a neuropathic pain condition otherwise treatment resistant.[18,19] Additionally, the diversion potential could be reduced as cannabis with a very low THC content is less desirable for recreational use.[34] In addition to evaluating the efficacy of a lower concentration, the potential of use a cognitive enhancer with cannabis to reverse or at least mitigate cognitive impairment might be considered in the future. Such an agent (eg, modafinil) has been used with psychotropic medications to reduce sedation and cognitive impairment.[9,10,49,67,68,74] New cognitive enhancers are on the horizon as researchers test cholinergic agents, biogenic amines, and neuropeptides to treat learning and memory deficits associated with neurodegenerative states. Psychostimulants, excitatory amino acids, and a heterogeneous group of compounds of diverse chemical composition that allegedly facilitate learning and memory or overcome natural or induced cognitive impairments[50] might someday be useful in combination with cannabis or cannabinoids currently thought to be undesirable because of the depressant effects on the central nervous system that limit their use.[15]

In addition to the issues discussed above, the noxious pyrolytic byproducts released through combustion remain a public health deterrent to the use of smoked cannabis.[42,51] However, a method has been devised to provide a safer and more efficient delivery system. Cannabis vaporization is a technique that avoids the production of irritating respiratory toxins by heating the herbal medicine to a temperature at which active cannabinoid vapors form but below the point of combustion where toxins are released.[29,52] Gas chromatograph/mass spectrometer analysis reveals that the gas phase of the vapor consists overwhelmingly of cannabinoids. In contrast, more than 111 compounds are identifiable in samples of smoked cannabis, including several potentially harmful polynuclear aromatic hydrocarbons.[30] In a pilot study involving healthy volunteers,[3] vaporization delivered therapeutic doses of cannabinoids with a drastic reduction in pyrolytic smoke compounds. It is reasonable to assume that future clinical trials will utilize this alternative delivery method.

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Cannabinergic Pain Medicine

A Concise Clinical Primer and Survey of Randomized-controlled Trial Results

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Objectives: This article attempts to cover pragmatic clinical considerations involved in the use of cannabinergic medicines in pain practice, including geographical and historical considerations, pharmacokinetics, pharmacodynamics, adverse effects, drug interactions, indications, and contraindications. Topics include molecular considerations such as the 10-fold greater abundance of cannabinoid type 1 receptors compared to μ-opioid receptors in the central nervous system and anatomic distributions of cannabinoid receptors in pain circuits.

Methods: The article uses a narrative review methodology drawing from authoritative textbooks and journals of cannabinoid medicine, Food and Drug Administration-approved cannabinoid drug labels, and current and historical pain medicine literature to address core clinical considerations. To survey the current evidence base for pain management with cannabinergic medicines, a targeted PubMed search was performed to survey the percentage of positive and negative published randomized-controlled trial (RCT) results with this class of pain medicines, using appropriate search limit parameters and the keyword search string "cannabinoid OR cannabis-based AND pain."

Results: Of the 56 hits generated, 38 published RCTs met the survey criteria. Of these, 71% (27) concluded that cannabinoids had empirically demonstrable and statistically significant pain-relieving effects, whereas 29% (11) did not.

Discussion: Cannabis and other cannabinergic medicines' efficacies for relieving pain have been studied in RCTs, most of which have demonstrated a beneficial effect for this indication, although most trials are short-term. Adverse effects are generally nonserious and well tolerated. Incorporating cannabinergic medicine topics into pain medicine education seems warranted and continuing clinical research and empiric treatment trials are appropriate.

Key Words: cannabis, cannabinoid, endocannabinoid, medical marijuana, descending pain pathways

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The utility of cannabinergic or cannabinoid-based medicines in clinical pain practice is gaining increasing recognition as physicians, other health care practitioners, and drug regulators familiarize themselves with the endocannabinoid signaling system and the safety and efficacy of drugs that target it. *Cannabinioids* are a class of drugs that take their name from the cannabinoid botanical *Cannabis sativa* from which they were first isolated and include herbal preparations of cannabis as well as synthetic, semisynthetic, and extracted cannabinoid preparations. In addition to their millennia-long role in spiritual practice and inebriation, cannabis-based preparations have had an extensive history in pain management,[1] as documented in the *materia medica* of ancient civilizations, including those of India, Egypt, China, the Middle East, and elsewhere.[2] Cannabis-based preparations were produced and sold by numerous major pharmaceutical houses such as Eli Lilly from the mid-1850s to the early 1940s and were significantly utilized during that time in Western medical practice for their analgesic and antispasmodic properties with reported success.[3,4] This is evidenced, for example, by Sir William Osler, MD's recommendation of "*Cannabis indica*" as "probably the most satisfactory remedy" in the treatment of migraine in the first modern textbook of internal medicine in 1892 (the most recent edition of this textbook was published in 2001)[5] and by a nuanced 1887 description of the unique analgesic effects of cannabinoid-based extractions on pain perception published by Penn Clinical Professor Dr Hobart Amory Hare who conducted clinical, animal, and self-experiments: "During the time that this remarkable drug is relieving pain a very curious psychical condition sometimes manifests itself; namely, that the diminution of the pain seems to be due to its fading away in the distance, so that the pain becomes less and less, just as the pain in a delicate ear would grow less and less as a beaten drum was carried farther and farther out of the range of hearing."[6]

For complex political reasons, lack of understanding, and concern over its believed risk of inducing "homicidal mania,"[7–10] cannabis was removed from the United States Pharmacopoeia in 1942[11] and later placed in Schedule I by Congress in 1970,[12] only to be reintroduced into medical practice in the mid-1990s by popular vote and legislative acts, starting in California and gradually over 16 years in 16 states (Alaska, Arizona, California, Colorado, Delaware, Hawaii, Maine, Michigan, Montana, Nevada, New Jersey, New Mexico, Oregon, Rhode Island, Vermont, and Washington) and the District of Columbia, paralleling practices in several other countries. Although contrary to federal law, these state programs have been bolstered by official federal statements of cooperative noninterference by the Veteran's Health Administration (VA)[13] and the US Department of Justice,[14] and all, with the exception of New Jersey, where pain malingering was an overriding political concern, explicitly cite pain relief as an accepted application for which health providers may authorize their patients'

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medicinal use of in-state–produced or in-district–produced cannabinoid botanicals. Although the thousands of practitioners who professionally participate in-state medical cannabis programs[15] are legally protected[16] and maintain DEA registrations in good standing,[17] it must be noted that cannabis and many natural cannabinoids continue to be listed under (the slang term) *marijuana* in the federal Schedule I classification, which substantially restricts research, impedes development of a pharmacy-stocking system needed for in-patient and out-patient empiric treatment trials, and places cannabinoid botanical-using patients at risk for criminal sanction. Professional medical associations and expert study groups such as the Institute of Medicine (IOM), the American Medical Association, and the American College of Physicians, among others,[12] have called for a review of this classification.

Four patients receive cannabinoid botanicals by prescription on an ongoing basis supplied by the federal government as part of a now-closed empiric treatment program involving a federally contracted Mississippi farm and local pharmacies, with 75% of participating patients using the drug for chronic pain.[18] In addition, 2 Food and Drug Administration (FDA)-approved cannabinoids available since 1985, dronabinol (Marinol, Unimed Pharmaceuticals, Marietta, GA)[19] in Schedule III, the naturally occurring (-)trans isomer of delta-9-tetrahydrocannabinol (THC) dissolved in a sesame seed oil soft-gel cap, and nabilone (Cesamet, Valeant Pharmaceuticals North America, Aliso Viejo, CA)[20] in Schedule II, a THC analog, are used off-label by prescription for analgesia in routine clinical practice and research in many countries. Finally, nabiximols (Sativex, GW Pharmaceuticals, Salisbury, England, UK),[21] an oromucoal cannabis-based medicinal extract produced by mixing liquid carbon dioxide extractions of 2 types of herbal cannabis,[22] is currently undergoing FDA-approved phase III clinical trials in the United States for cancer pain refractory to maximal opioid management and has been approved for select pain indications internationally. Some drugs currently in early development seek to prolong or enhance endocannabinoid activity for pain relief.[23]

MATERIALS AND METHODS

By using a narrative review methodology that draws from authoritative textbooks and journals of cannabinoid medicine, FDA-approved cannabinoid drug labels, and current and historical pain medicine literature, the objectives of this article are to cover pragmatic clinical considerations involved in the use of cannabinergic medicines in pain practice, including geographical and historical considerations, pharmacokinetics, pharmacodynamics, adverse effects, drug interactions, indications, and contraindications. Close attention is paid to the oldest and most widespread "signature" cannabinoid botanical medicine, cannabis, and the interaction of its constituents with the endocannabinoid system. In addition, the adverse effects section is covered in greater depth to address clinical safety concerns.

In the latter section of the article, a targeted PubMed search is performed to survey the totality of published randomized-controlled trial (RCT) results for this class of pain medicines. To investigate the current RCT evidence database for cannabinoids in the management of pain, a PubMed search with the keywords "cannabinoid OR cannabis-based AND pain" and the Limits, Type of Article: Randomized Controlled Trial and Species: Human, was performed on December 13, 2010. Trials that investigated other variables, which may have stood as proxies for pain but did not specifically investigate pain, were excluded. Articles were reviewed for significant pain-relieving outcomes with investigated cannabinergic pain medicines.

RESULTS

Pharmacokinetics

Essentially a herbal cannabinoid drug, the resin-secreting flowers of select varietals of the female cannabis plant contain approximately 6 dozen of different *phytocannabinoids* or plant-derived cannabinoids; these compounds are generally classified structurally as terpenophenolics with a 21-carbon molecular scaffold.[24] Other compounds, such as terpenoids, flavonoids, and phytosterols, which are common to many other botanicals, are also produced by cannabis and have some demonstrated pharmacologic properties.[25,26] The best known naturally produced analgesic cannabinoids generally found in highest concentrations are THC and cannabidiol. They occur in their acid forms in herbal cannabis and must be decarboxylated to become activated. Five minutes of heating at 200 to 210°C has been determined as the optimal conditions for maximal decarboxylation; with a flame, where temperatures of 600°C are achieved, only a few seconds are needed.[27]

Cannabis is mainly administered by 3 routes: through the lungs by inhalation of vaporized or smoked organic plant material; through the gut with ingestion of lipophilic, alcoholic, or supercritical fluidic extracts of plant material, or through the skin by topical application of plant extracts.[28] Each of these routes has a distinct absorption and activity time course. Lung administration is akin to an IV (intravenous) bolus, with passive diffusion into alveolar capillaries and rapid onset in seconds to minutes, achieving maximal effect after 30 minutes, and lasting 2 to 3 hours in total. With oral administration of cannabinoid medicines, including cannabis-based medicinal extracts and single cannabinoid pills, the absorption is somewhat more variable, depending on gastric contents, with a slower onset of action of 30 minutes to 2 hours, and a longer, more constant, duration of action, over 5 to 8 hours in total. Little data are available on the pharmacokinetics of topically administered cannabinoids.[29]

THC and its metabolites are lipophilic compounds and their tissue distribution is governed by their physiochemical properties. In the plasma, about 95% to 99% of THC is bound to plasma proteins, primarily lipoproteins. Metabolism of THC occurs quickly, mainly in the liver by hydroxylation, oxidation, and conjugation through the cytochrome P-450 complex, specifically CYP2C9 and CYP3A.[30] The majority is rapidly cleared from the plasma, with 70% taken up by tissues, especially highly vascularized ones, and 30% converted by metabolism. First-pass liver metabolism occurs in oral administration, and a greater proportion of 11-OH-THC, a key active metabolite, is produced compared with that which occurs in pulmonary administration. As far as complete elimination is concerned, it occurs over several days given the slow rediffusion of THC from body fat and other tissues, with body fat being the major long-term storage site of THC and its biometabolites. In the perinatal setting, cannabinoids distribute into the breastmilk of lactating mothers (where endocannabinoids are also found in appreciable quantities[31]) and diffuse across the placenta (Pregnancy Category C). Excretion of THC occurs within days and weeks, mainly as metabolites, with approximately 20% to

35% found in urine and 65% to 80% found in feces, and < 5% as unchanged drug, when administered per os.[29]

Pharmacodynamics

The majority of the effects of THC are mediated through its partial agonism of cannabinoid receptors. Of relevance for pain management, in addition to analgesia, the following dose-dependent pharmacologic actions of THC have been observed in studies: muscle relaxation, anti-inflammatory effects, neuroprotection in ischemia and hypoxia, enhanced well-being, and anxiolysis.[32] To understand how this range of effects is possible, an understanding of cannabinoid molecular biology is needed.

Cannabinoids produce analgesia through supraspinal, spinal, and peripheral modes of action, acting on both ascending and descending pain pathways. Their mechanism of action was only recently understood with the discovery of the endogenous cannabinoid (or endocannabinoid) system, a 600 million-year-old signaling system in evolution,[33,34] which regulates neuronal excitability and inflammation[35] in well-described pain circuits and cascades.[36–39] The endocannabinoid system helps regulate the function of other systems in the body, making it an integral part of the central homeostatic modulatory system. It has been shown to play a regulatory role in movement, appetite, aversive memory extinction, hypothalamic-pituitary-adrenal axis modulation, immunomodulation, mood, blood pressure, bone density, tumor surveillance, neuroprotection, reproduction, inflammation, among other actions.[23,40] Studies in animals and humans that have assessed preexposure and postexposure endocannabinoid levels have suggested that the "runner's high,"[41] the effects of osteopathic manipulative treatment,[42,43] and the effects of electroacupuncture[44] are mediated by the endocannabinoid system.

The endocannabinoid system consists of receptors, their endogenous ligands, and ancillary proteins.[45] Cannabinoid receptors, CB_1 and CB_2, and likely others, are transmembrane G-protein–coupled receptors whose activation is negatively coupled to adenylyl cyclase and positively coupled to mitogen-activated protein kinase. In neural tissue, their activation suppresses neuronal Ca^{2+} conductance, activates inward rectifying K^+ conductance, and thus modulates neuronal excitability.[46] An adjective for anything that drives or stimulates this system is "cannabinergic."

The CB_1 receptor is the most highly expressed G-protein–coupled receptor in the brain and is 10 times more prevalent in the central nervous system as compared to the other well-studied receptor involved in pain: the μ-opioid receptor.[47] Among many other tissues, cannabinoid receptors have been found in abundance on cells in areas relevant to pain: the periaqueductal gray, basal ganglia, cerebellum, cortex, amygdala, hippocampus, dorsal primary afferent spinal cord regions, including peripheral nociceptors, spinal interneurons, and finally inflammatory cytokine-releasing immune cells.[46,47] In the brainstem, cannabinoid receptor expression is low, accounting for the lack of respiratory depression and absence of fatal overdose with cannabinoid drugs.[48]

Endocannabinoids such as arachidonylethanolamide (anandamide) and 2-arachidonylglycerol, and others, serve as tonically active retrograde synaptic neurotransmitters, meaning that they travel "backwards" across the synaptic cleft from postsynaptic to presynaptic neurons, thereby providing feedback that, in turn, directly upregulates or downregulates the release of other presynaptic neurotransmitters, such as gamma-aminobutyric acid, dopamine, norepinephrine, glutamate, and others.[32] This feedback has physiological implications for a host who may have succumb to insult or injury leading to pain.[49] Experiments have also shown that the endocannabinoid system is upregulated in animal models of nerve damage [50] and intestinal inflammation.[51] Ultimately, while there is much that is still poorly understood, the known pharmacodynamics of cannabinergic analgesic effects have been established through carefully designed experiments observing the physiological or radiologic effects of natural and synthetic exogenously administered cannabinoids in clinical and laboratory animal models and the blockade of those effects by genetic or pharmacological means.

Adverse Effects

The main adverse effects of cannabinoids to focus on presently are those that may arise with use of these drugs in a medical context rather than in a nonmedical setting; however, since there are far less data on the use of the drugs in the former setting, the latter, though less ideal, must be relied upon as well. Given cannabinergic drugs' psychoactive properties, adverse effects to consider would include overdose, abuse, dependence, psychomotor effects, cognitive effects, and adverse medical and psychiatric effects, both short and long term. Generally, as analgesics, cannabinoids have minimal toxicity and present no risk of lethal overdose.[48] End-organ failure secondary to medication effect has not been described and no routine laboratory monitoring is required in patients taking these medications. With regard to cannabinoid botanicals, the IOM concluded after a comprehensive government-commissioned review published in 1999 that "except for the harms associated with smoking, the adverse effects of marijuana [cannabinoid botanicals] use are within the range of effects tolerated for other medications."[52]

The FDA-approved product insert for dronabinol, the THC pill, reports the following adverse effects from overdose:

Signs and symptoms following MILD MARINOL Capsules intoxication include drowsiness, euphoria, heightened sensory awareness, altered time perception, reddened conjunctiva, dry mouth and tachycardia; following MODERATE intoxication include memory impairment, depersonalization, mood alteration, urinary retention, and reduced bowel motility; and following SEVERE intoxication include decreased motor coordination, lethargy, slurred speech, and postural hypotension. Apprehensive patients may experience panic reactions and seizures may occur in patients with existing seizure disorders.[19]

Regarding the dependence potential of THC and cannabinoid drugs, the IOM concluded that "Although few marijuana [cannabinoid botanicals] users develop dependence, some do. Risk factors…are similar to those for other forms of substance abuse. In particular, antisocial personality and conduct disorders…" With regard to withdrawal, although still a matter of dispute, the IOM concluded: "A distinctive marijuana [cannabinoid botanicals] withdrawal syndrome has been identified, but it is mild and short-lived. The syndrome includes restlessness, irritability, mild agitation, insomnia, sleep EEG disturbance, nausea, and cramping."[52]

The IOM report also discussed the adverse effects of cognitive and psychomotor impairment associated with acutely administered cannabinoid botanicals, although it did not take into consideration the possibility of tolerance

or preparation variability in modifying these effects. "The types of psychomotor functions that have been shown to be disrupted by the acute administration of marijuana [cannabinoid botanicals] include body sway, hand steadiness, rotary pursuit, driving and flying simulation, divided attention, sustained attention, and the digit-symbol substitution test." Given the concern for occurrence these adverse effects and that of cognitive impairment, which has been characterized as transient short-term memory interruption (see above MARINOL product insert), the panel recommended that "no one under the influence of marijuana [cannabinoid botanicals] or THC should drive a vehicle or operate potentially dangerous equipment."[52]

Another important source of adverse effects data is cannabinoid clinical trials; 2 reviews are summarized below. A 2008 review of reported adverse effects of medical cannabinoids[53] examined 31 clinical trials (23 RCTs and 8 observational studies) of cannabinoid single-molecule agents and cannabis-based medicinal extracts but not cannabinoid botanicals (due to the fact that such studies did not report adverse events in the standardized format investigators sought) in various patient populations and showed that the vast majority of adverse events with cannabinoid medications in clinical trials were nonserious (96.6%). In the 23 RCTs, the median duration of cannabinoid exposure was 2 weeks (range, 8 h to 12 mo). With respect to the "164 serious adverse events" that occurred, the most common were relapse of multiple sclerosis (21 events [12.8%]), vomiting (16 events [9.8%]), and urinary tract infection (15 events [9.1%]). However, investigators reported that "there was no evidence of a higher incidence of serious adverse events" in the groups assigned to cannabinoids "compared with control [drugs] (rate ratio [RR] 1.04, 95% confidence interval [CI], 0.78-1.39)."[53] In addition, serious adverse events were not evenly reported in the literature, with 99% coming from only 2 trials. The most commonly reported nonserious adverse events were dizziness (714 events [15.5%]), followed by somnolence (377 events [8.2%]), muscle spasm (289 events [6.3%]), other gastrointestinal tract disorder (285 events [6.2%]), pain (278 events [6.0%]), dry mouth (239 events [5.2%]), and bladder disorder (222 events [4.8%]). Unlike the serious adverse events, the rate of nonserious adverse events was nearly 2 times higher among participants assigned to cannabinoids than among controls (rate ratio [RR] 1.86, 95% CI, 1.57–2.21).

A more recent 2011 systematic review of RCTs of cannabinergic medicines specifically for the treatment of pain which pooled 18 trials of inhaled cannabinoid botanicals, oromucosal cannabis-based medicinal extracts, and cannabinoid single-molecule agents involving 766 patients in total found no occurrence of serious adverse events, with the most serious treatment-related event in the entire sample being a subject's fractured leg related to a fall that was thought to be related to dizziness in a treatment trial with nabilone. Nonserious adverse events most frequently reported included "sedation, dizziness, dry mouth, nausea and disturbances in concentration" and less commonly reported adverse events included "poor coordination, ataxia, headache, paranoid thinking, agitation, dissociation, euphoria and dysphoria." Investigators noted: "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%."[54]

With regard to severe psychiatric sequalae such as psychosis, if a very large dose of cannabinoid botanicals is consumed, which typically occurs through oral ingestion of a concentrated preparation, agitation and confusion, progressing to sedation, generally results.[55] This is self-limited and generally disappears entirely once the psychoactive components are fully metabolized and excreted. Some have called this an "acute cannabis psychosis," and this generates concern that cannabinoid use, in the long term, might lead to schizotypy such as chronic, debilitating psychosis. There is some documentation of a syndrome of acute schizophreniform reactions to cannabinoid botanicals that may occur in young adults who are under stress and have other vulnerabilities to schizophreniform illness. Furthermore, there is an association between cannabinoid botanicals use history and schizophrenia, but the causal direction of this link has not been established[56,57] and schizophrenia prevalence rates have not changed over the last 50 years despite increasing use rates of cannabis in the general population.[58]

Recent preliminary work has examined gene-environment interactions to identify the genetic background of populations at-risk for this cannabinoid-associated psychosis with retrospective, population-based studies, and empiric cannabinoid drug exposure studies, with candidate genes including a commonly studied functional polymorphism in the catechol-O-methyltransferase gene (COMT Val(158)Met)[59] and a brain-derived neurotrophic factor gene polymorphism (BDNF Val(66)Met),[60] among others. Given these risks, cannabinoid medical use should be closely monitored or potentially avoided in early teens or preteens who have preexisting symptoms of mental illness or patients with significant family or personal history of mental illness.

For physiological and pharmacological reasons,[61] smoking cannabinoid herbals does not seem to have a similar health hazard profile as tobacco smoking, aside from the potential for bronchial irritation and bronchitis. Smoking cannabis was not associated with an increased risk of developing chronic obstructive pulmonary disease (COPD) in a random sample of 878 people aged 40 years or older living in Vancouver, Canada who were surveyed about their respiratory history and lifetime cannabis and tobacco use exposure and subjected to spirometric testing before and after administration of 200 μg of salbutamol, a short-acting β2-receptor agonist. Investigators concluded that smoking both tobacco and cannabis synergistically increased the risk of respiratory symptoms and COPD but that smoking only cannabis was not associated with an increased risk of respiratory symptoms or COPD.[62] This finding was also confirmed in a recently published longitudinal study involving spriometric testing over a period of 20 years. Researchers followed more than 5000 people in several major American cities over 2 decades and found that the exposure equivalent of moderate inhalation of cannabinoid botanical smoke daily for 7 years did not impair spirometric-testing performance.[63]

With regard to the question of lung cancer risk, a variety of opinions and conflicting results are found in the literature, likely related to study sizes, designs, and confounding factors in existing research. However, the results of 2 well-designed, large studies conducted by senior investigators in this field are worth noting. A recent large, population-based retrospective case-control study involving

1212 incident cases of lung and upper aerodigestive tract cancer and 1040 cancer-free age-matched and gender-matched controls in the Los Angeles area demonstrated significant, positive associations with tobacco-smoking history and the incidence such cancers but failed to demonstrate any significant positive associations or dose dependence with cannabis-smoking history and the incidence of such cancers. In fact, a significant, albeit small, protective effect was demonstrated in 1 group of smoked cannabis consumers.[64] A second population-based case-control study involving smoked cannabis use and head and neck squamous cell carcinoma with 434 cases and 547 age-matched, gender-matched, and geographically matched controls in the greater Boston area similarly concluded that moderate cannabis use is associated with reduced risk of head and neck squamous cell carcinoma.[65] These 2 studies, while large and sensitive to confounders, need replication. Certainly, although hundreds of citations can now be found in the National Library of Medicine of studies demonstrating antitumor properties of cannabinoids in numerous tissue types in mostly lab settings, some of which are also reviewed on an online clinical knowledge database maintained by the National Cancer Institute,[66] the inhalation of fumes, combustion byproduct particulate matter, and polycyclic aromatic hydrocarbons attendant with inhaled cannabinoid botanical smoke can nevertheless be noxious for some patients and the use of vaporizers for lung administration should be encouraged. Heated air can be drawn through cannabinoid herbal matter and, due to the volatility of cannabinoids, which allows them to vaporize at a temperature much lower than actual combustion of plant matter, active compounds will vaporize into a fine mist which can then be dosed and inhaled without the generation of smoke.[67]

As to questions of overall adverse effects of long-term cannabinoid treatment in medical settings, there are essentially no long-term controlled longitudinal studies in such populations, with the exception of one 3-decade old, prospective, federally funded inhaled cannabinoid botanical clinical study mentioned previously in the Introduction section. Administered by the National Institute on Drug Abuse and FDA and now involving only 4 chronically ill patients, this study, now closed to new enrollment, has never systematically collected or disseminated clinical response data. One independent comprehensive health assessment in 2001 of 4 of the then 7 enrolled patients showed "mild changes in pulmonary function" in 2 patients and no other demonstrable adverse outcomes or "functionally significant attributable sequelae" based on a battery of tests, which included: magnrtic resonance imaging scans of the brain, pulmonary function tests, chest x-ray, neuropsychological tests, hormone and immunological assays, electroencephalography, P300 testing, history, and neurological clinical examination.[68]

Drug Interactions

Research suggests that when THC is coadministered with cannabidiol, as can occur with the usage of some strains of herbal cannabinoid medicines and certain cannabis-based extractions, the anxiogenic, dysphoric, and possibly short-term memory interrupting effects of THC are mitigated.[69,70] In addition, noncannabinoid components in cannabinoid botanicals such as terpenoids can also help to mitigate THC side effects.[71] There is increasing evidence suggesting that cannabinoid drugs can enhance the analgesic activity of opioids,[72,73] and thereby their concomitant use may reduce the dosages of opioids that chronic pain patients take.[74,75]

With the large number of individuals who have used cannabinoid botanicals concomitantly with numerous prescription medicines, no unwanted side effects of clinical relevance have been described in the literature to date. Nevertheless, cannabinoid medicines should be used with caution in patients taking other sedating psychotropic substances such as alcohol and benzodiazepines. Again, from the FDA-approved dronabinol product insert:

In studies...MARINOL Capsules has [sic] been co-administered with a variety of medications (e.g., cytotoxic agents, anti-infective agents, sedatives, or opioid analgesics) without resulting in any clinically significant drug/drug interactions...cannabinoids may interact with other medications through both metabolic and pharmacodynamic mechanisms. Dronabinol is highly protein bound to plasma proteins, and therefore, might displace other protein bound drugs. Although this displacement has not been confirmed in vivo...[19]

Indications

Indications mentioned below are bolded. A 2010 review counted at least 110 controlled clinical studies of cannabis or cannabinoids conducted around the world, mostly outside the United States, involving over 6100 patients investigating a wide range of conditions.[76] With regard to pain indications, cannabinoids are best researched clinically for their role in the management of **neuropathic pain**, but **malignant pain, other chronic pain syndromes**, especially those involving **hyperalgesia** and **allodynia**, as well as **acute pain** applications have also been described.[77]

Two recent systematic reviews of cannabinergic medicines for pain are worth mentioning. A 2011 systematic review of cannabinoids for treatment of chronic noncancer pain[54] analyzed studies of neuropathic pain, fibromyalgia, rheumatoid arthritis, and mixed chronic pain syndromes. In all, 18 cannabinoid RCTs, 4 of which tested inhaled cannabinoid botanicals, conducted from 2003 to 2010, involving 766 participants in total, with a mean duration of treatment of 2.8 weeks (range, 6 h to 6 wk), were reviewed. Investigators noted that "overall the quality of trials was excellent," with mean score of 6.1 on the 7-point modified Oxford scale [scores randomization (0-2), concealment of allocation (0-1), double blinding (0-2), and flow of patients (0-2)] and that "15 of the 18 trials that met inclusion criteria demonstrated a significant analgesic effect of cannabinoid as compared with placebo" with 4 also reporting "significant improvements in sleep." They concluded: "overall there is evidence that cannabinoids are safe and modestly effective in **neuropathic pain** with preliminary evidence of efficacy in **fibromyalgia** and **rheumatoid arthritis** [emphasis added]". Investigators also observed that in the trials involving cannabinergic medicines in rheumatoid arthritis, "a significant reduction in disease activity was also noted, [and] this is consistent with preclinical work demonstrating that cannabinoids are anti-inflammatory." In addition, authors made special mention of the fact that 2 of the trial examining smoked cannabinoid botanicals 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."

A 2009 systematic review and meta-analysis counted 229 studies that had used cannabinoids on people with pain from 1975 to February 2008, with 18 of these having a

double-blind, randomized-controlled design. A meta-analysis with 7 of these trials, which included 6 with cross-over and 1 with parallel design and included a total of 142 pooled patients with **malignant pain, multiple sclerosis**, and **chronic upper motor neuron syndromes**, concluded that a statistically significant standardized mean difference favoring cannabinoids over placebo existed, −0.61 (−0.84 to −0.37), measured in terms of the change from the baseline (0) intensity of pain, with all studies yielding results in the same direction and with no statistical heterogeneity.[78]

Chart reviews can also suggest potential indications for cannabinergic pain medicines. An uncontrolled retrospective chart review conducted by this author and colleagues of 139 patients at a pain sub-specialty clinic who were authorized to use cannabinoid botanicals medicinally for a total of 236.4 patient-years found a variety of chronic pain syndromes, in accord with existing cannabinoid literature, being managed in this population (Table 1). Eighty-eight percent of the patients in the study had more than 1 type of chronic pain syndrome.[74]

To investigate the current published, randomized-controlled clinical trial (RCT) evidence database indexed in the National Library of Medicine for cannabinoids in the management of pain, a PubMed search was performed as described in the Materials and Methods section. Fifty-six hits were generated, and of these, 38 were actual RCTs of various cannabinoid medicines such as dronabinol, nabilone, cannabinoid herbals, cannabinoid-based medicinal extracts, and other synthetic cannabinoids versus placebos or other drugs in which pain efficacy was specifically assessed, either in patients with pain or healthy subjects with experimentally induced pain. Eighteen studies were excluded because they did not explicitly examine pain outcomes and instead examined spasticity, cramps, or a nonspecific global measure of benefit. Perusing abstracts and in case of ambiguity, full articles, of the 38 RCTs that met inclusion criteria, 27 (71%) concluded that cannabinoids had empirically demonstrable pain-relieving effects,[73,79–104] whereas 11 (29%) did not.[105–115] Of the 11 negative studies, 3 investigated postoperative pain, 3 experimentally induced pain in healthy volunteers, 1 neuropathic pain in spinal cord injury, 2 pain in multiple sclerosis, 1 central neuropathic pain in brachial plexus avulsion, and 1 painful diabetic peripheral neuropathy. The 27 positive RCTs, the largest of which enrolled 630 subjects,[103] investigated a variety of pain syndromes (Table 2), all of which could be considered as potential pain indications for this class of drugs.

TABLE 1. Diagnosed Chronic Pain Syndromes Documented In Cannabinoid Botanical Use-authorized Patient Series (n=139)[74]

Chronic Pain Syndrome	Frequency of Occurrence* (%)
Myofascial pain	82
Neuropathic pain	64
Discogenic back pain	51.7
Osteoarthritic pain	26.6
Central pain syndrome	23
Fibromyalgia	14
Visceral pain	10
Spinal cord injury	6
Rheumatoid arthritis	4
Diabetic neuropathy	4
Malignant pain	4
Phantom pain	1
HIV neuropathic pain	1

*Eighty-eight percent of the patients in the study had more than one type of chronic pain syndrome.
HIV indicates human immunodeficiency syndrome.

Contraindications

Cannabinoids are absolutely contraindicated in patients who have a rare hypersensitivity to THC or allergies to any of the inert materials with which cannabinoid medicines may be formulated. There is some concern in the basic science literature that cannabinoid's immunomodulatory properties through CB_2 activity can cause a shift from T_h1 to T_h2 type activity and that this might have severe consequences for a patient who is fighting an infection (such as *Legionella*) that requires T_h1 immunity activity for inhibition.[116,117] In these settings, cannabinoids should be used with caution. Early concern in the 1990s regarding the use of cannabinoids in HIV patients given possible immunomodulatory effects in already-immunosuppressed patients was addressed by Abrams et al's[118] randomized-controlled inpatient clinical trial with inhaled cannabinoid botanicals which showed no reduction in viral load or CD4 cell count in HIV patients. This conclusion was also recently bolstered in a primate study showing that SIV (simian immunodeficiency virus) viral loads in a cohort of rhesus macaques were not adversely affected by daily THC administration over a 6-month period, and in fact were associated with decreased early mortality, reductions in SIV viral load, and improvements in the ratio of CD4 to CD8 cells.[119] Finally, as mentioned previously, cannabinoids should be used cautiously in patients with a personal or family history of psychosis, with particular attention paid to adolescent patient populations under psychosocial stress who may be at increased risk for developing psychosis.

DISCUSSION

Cannabinergic pain medicine is an emerging field of pain practice that incorporates new and old cannabinoid pharmacotherapies with a clinically relevant physiological understanding of endocannabinoid signaling. By drawing from current and authoritative sources, this review concisely addressed relevant clinical considerations, including historical and geographical context, pharmacokinetics, pharmacodynamics, adverse effects, drug interactions, indications, and contraindications for utilization of this class of pain medicines. A focused PubMed literature survey, which was meant to be easily reproducible and to serve as a guide to evidence-based clinical practice queries, showed that there are over 30

TABLE 2. Descriptors of Pain Syndromes Investigated In Positive Outcome Randomized-controlled Trials of Cannabinoids[73,79–104]

Experimentally induced pain in healthy volunteers	Chronic pain in rheumatoid arthritis
Unspecified chronic noncancer pain	Chronic pain in multiple sclerosis
Chronic pain secondary to chronic upper motor neuron syndrome	Chronic neuropathic pain with hyperalgesia and allodynia
Cancer-related pain	Chronic neuropathic pain related to HIV, trauma, surgery, and CRPS
Chronic pain in fibromyalgia	

CRPS indicates complex regional pain syndrome; HIV, human immunodeficiency syndrome.

published RCTs indexed in the National Library of Medicine that have evaluated specific cannabinoid medications for strict pain indications, and nearly 3-quarters of these studies are positive and statistically significant.

An overall review of adverse effects from reviews of cannabinoid clinical trials and other sources does show that short-term use of existing cannabinoid medicines seems to increase the risk of nonserious adverse events, but in general these events are modest and well tolerated. Little data are available on the risks associated with long-term medical use in published clinical trials. Overall, based on the existing clinical trials database, cannabinergic pain medicines have been shown to be modestly effective and safe treatments in patients with a variety of chronic pain conditions, with more data for analgesia in noncancer pain than cancer-related pain available. Neuropathic pain is an indication for which cannabinoid botanicals seem to have a stronger evidence base. However, most studies are of short trial duration and enrolled small sample sizes. High-quality trials of cannabinergic pain medicines with large sample sizes, long-term exposure, including head-to-head trials with other analgesics, focused on pain relief and functional outcomes, are needed to further characterize safety issues and efficacy with this class of medications.

Nevertheless, for notoriously difficult to treat conditions such as HIV neuropathy, which significantly affects approximately 40% of HIV-infected individuals treated with antiretroviral therapies,[120] cannabinergic pain medicines, particularly inhaled cannabinoid botanicals, are one of the only treatments that have been shown to be safe and effective with the highest level of evidence. This was shown in a 2011 systematic review and meta-analysis of prospective, double-blinded RCTs investigating the pharmacological treatment of painful HIV sensory neuropathy. When analyzing he 14 trials which fulfilled the inclusion criteria, investigators found that the only interventions demonstrating greater efficacy than placebo were smoked cannabis, number needed to treat (NNT) 3.38, 95% CI (1.38-4.10); topical capsaicin 8% with a presumed NNT of 6.46, 95% CI (3.86-19.69); and recombinant human nerve growth factor, with no NNT calculable. No superiority over placebo was reported in RCTs that examined amitriptyline (100 mg/d), gabapentin (2.4 g/d), pregabalin (1200 mg/d), prosaptide (16 mg/d), peptide-T (6 mg/d), acetyl-L-carnitine (1 g/d), mexilitine (600 mg/d), lamotrigine (600 mg/d), and topical capsaicin (0.075% q.s.).[121]

CONCLUSIONS

The positive clinical evidence base for cannabinergic pain medicine is explained by extrapolating from an understanding of the properties and mechanism of action of these drugs derived from extensive basic science research. Cannabinoids have been shown to inhibit pain in "virtually every experimental pain paradigm" in supraspinal, spinal, and peripheral regions.[37] That cannabinergic therapeutics are of great interest in the field of pain medicine currently is evidenced in large part by the numerous review articles that have been published recently on this topic in pain and therapeutics journals and the recent convening of a "Cannabinoids and Pain" Satellite Symposium of the 13th World Congress on Pain held in Montreal, Canada in July 2010.

The limitations of this review article are that it did not exhaustively cover the cannabinoids and pain literature or all clinical details such as those regarding cannabinoid dosing, nor did it address the ongoing controversies regarding the implementation of medical marijuana programs in the United States or the necessary policy debates involved in the rescheduling of cannabis for general prescription use as an FDA-unapproved drug. In addition, the focused PubMed search was only targeted at determining the percentage of RCTs indexed in the National Library of Medicine showing efficacy for cannabinergic medications for pain and did not fully evaluate the pros and cons of each study. Nevertheless, by focusing on practical clinical considerations and drawing on established literature, including published systematic reviews and meta-analyses, attempts were made to compensate for these limitations. The implications of this study are that, with proper clinical education, the use of cannabinergic medicines could become one more needed tool in the pain physician's toolbox, with further research, clinical experience, and empiric treatment trials needed to better develop, improve, and expand these therapies.

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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.

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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

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

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

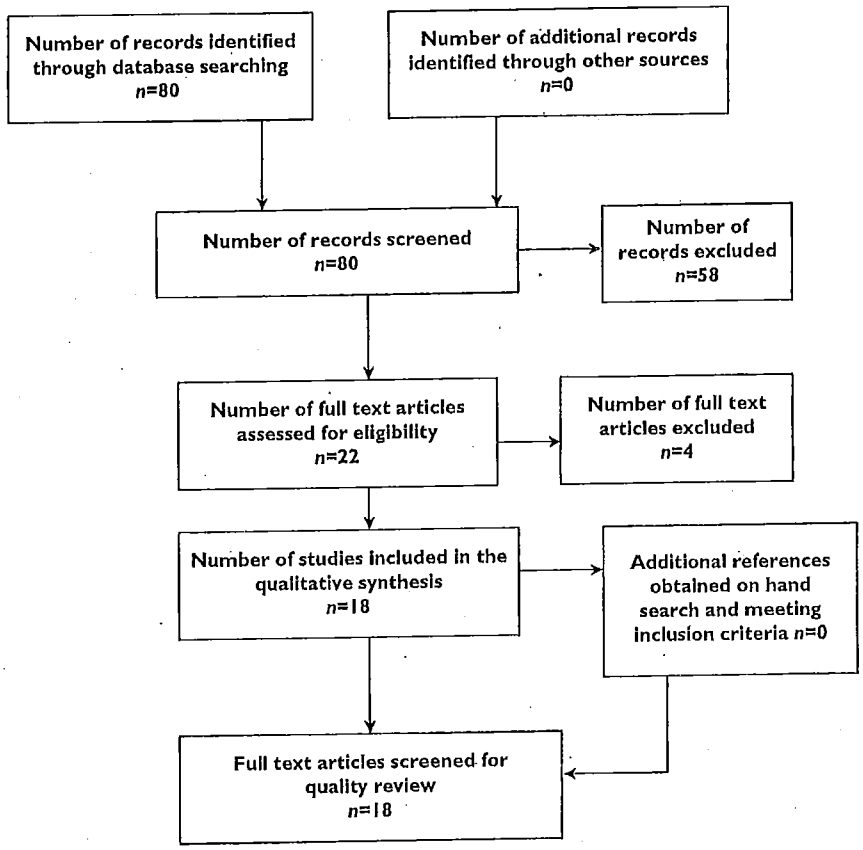

Figure 2
Flow diagram of systematic review

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 –5.4 placebo, 10 mg (–17.4, $P < 01$), 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 spasiticty 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 4.53 (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]

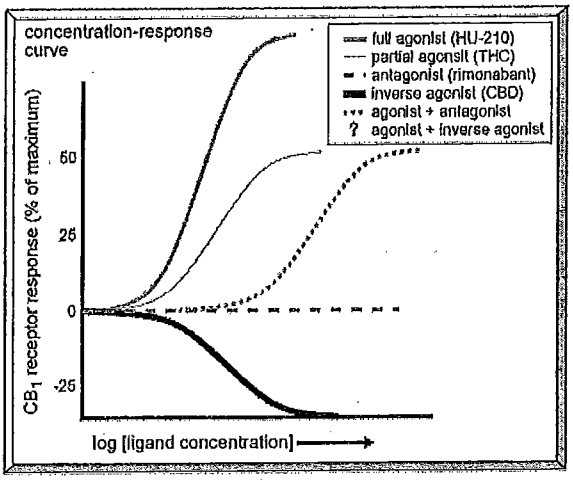

Figure 1. Concentration-response curves of cannabinoid compounds on the CB_1 receptor. The full agonist is the compound HU-210, which is a synthetic cannabinoid; the partial agonists are Δ^9-tetrahydrocannabinol (THC), which is a cannabinoid found in cannabis, and anandamide, which is an endocannabinoid 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

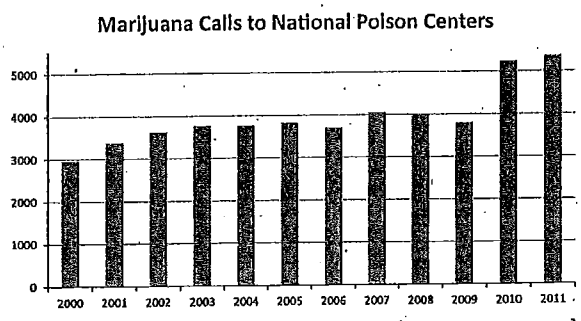

Figure 2. Telephone calls to national poison control centers pertaining to marijuana exposures.[89]

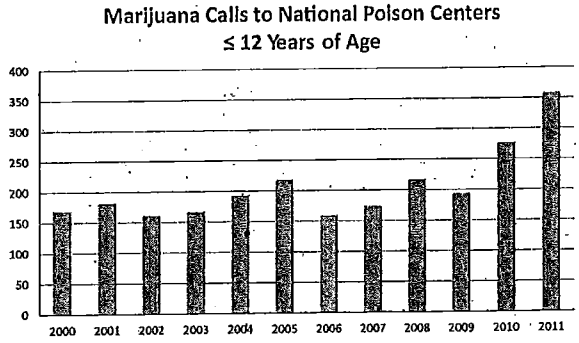

Figure 3. Telephone calls to national poison control centers pertaining to marijuana exposures in children aged 12 years or younger.[89]

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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