The Pharmacologic and Clinical Effects of Medical Cannabis

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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]

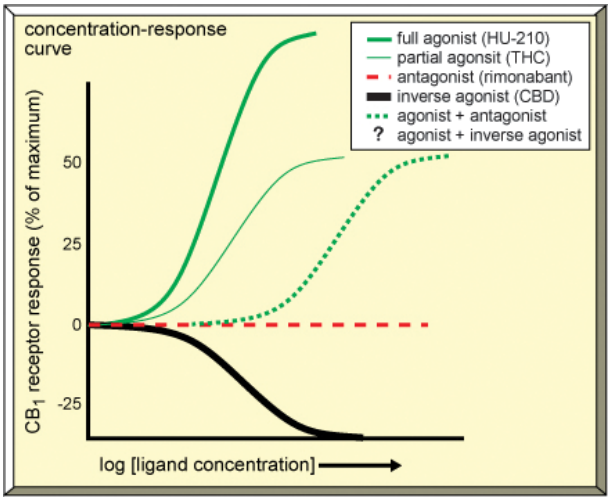

Figure 1. Concentration-response curves of cannabinoid compounds on the CB_1 receptor. The full agonist is the compound HU-210, which is a synthetic cannabinoid; the partial agonists are Δ^9-tetrahydrocannabinol (THC), which is a cannabinoid found in cannabis, and anandamide, which is an endocannabinoid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

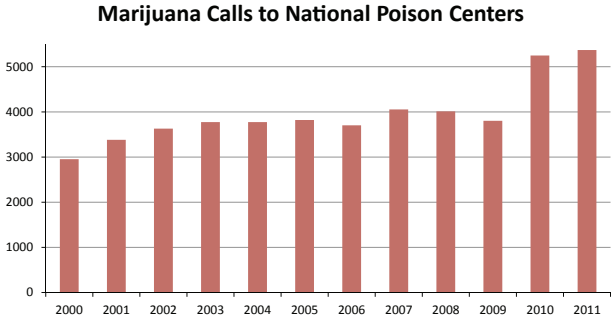

Figure 2. Telephone calls to national poison control centers pertaining to marijuana exposures.[89]

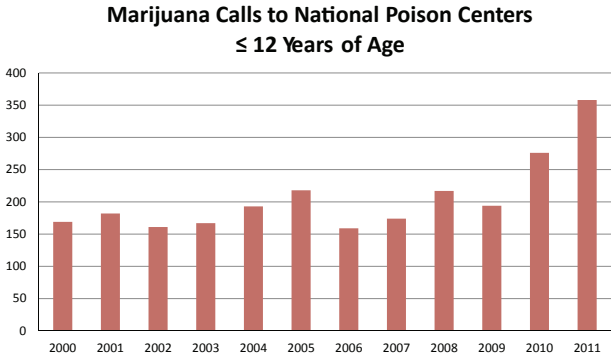

Figure 3. Telephone calls to national poison control centers pertaining to marijuana exposures in children aged 12 years or younger.[89]

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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