Current Concepts Review

The Current Evidence for Marijuana as Medical Treatment

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- At present, the growth of public and political support for the use of marijuana as a medical treatment is outpacing the growth of scientific evidence.
- Despite limited evidence, marijuana-based compounds (including cannabidiol) are promoted as alternatives to opioid pain medication in the treatment of ongoing bodily pain for which people seek care.
- Clinical research on the medical applications of marijuana-based compounds is limited by federal regulations, and most commercially available products are not available to researchers for study.

At the time of writing, the use of marijuana as medical treatment was legal in 33 states in the U.S. and is on the ballot in an increasing number of states each election cycle. There are various anecdotal reports in the popular press about the efficacy of cannabis and its derivatives for neuropathic pain, intractable seizures, arthritis, and a number of other ailments, and enthusiasm for expanded use of marijuana as treatment is growing[1]. Medical sales of marijuana totaled nearly $9 billion in 2017 and were expected to exceed $20 billion annually by 2020[2]. The rapid popularity growth of marijuana as a treatment for medical conditions is reminiscent of the rise of opioids as a treatment for pain in the 1990s[3]. In the absence of scientific evidence, advocacy groups, testimonials, and political pressure—fueled by a multibillion dollar industry—contributed to the rise of the opioid epidemic in the United States[3,4]. We should allow the existing evidence to guide our next steps with respect to cannabis.

As a result of widespread marketing and widely shared anecdotal reports, we and our colleagues are frequently asked by patients, family members, and friends to provide guidance on the use of cannabis, or its derivatives, in the treatment of musculoskeletal conditions and/or postoperative orthopaedic surgical pain. As such, it is important that the orthopaedist has a basic understanding of the evidence regarding medical applications of cannabis and its derivatives.

The purposes of this review article are to educate orthopaedic surgeons on the history and pharmacology of marijuana as medical treatment; to provide an overview of selected literature (Fig. 1) with an emphasis on the role of marijuana in treating musculoskeletal pain from injury, surgery, or disease; and to discuss potential orthopaedic applications. Additionally, we explore the known side effects of marijuana and the current data regarding the societal impacts of legal marijuana in "early adopter" states such as Colorado and Washington.

A Brief History of the Use of Marijuana as Treatment

Evidence suggests that humans have been using the cannabis plant for medicinal purposes for >5,000 years[5]. Marijuana first appeared in the United States Pharmacopeia (USP) in 1850, with indications ranging from insanity to cholera[6]. During the Prohibition era, the U.S. government began regulating and restricting the use of marijuana. The Marihuana Tax Act of 1937 imposed heavy taxes on marijuana sales and dramatically reduced medical and recreational marijuana use[6]. Then, in 1942, marijuana was removed from the USP. The Controlled Substances Act, which was passed in 1970, listed marijuana as a Schedule-I drug (the same classification as heroin) with "no currently accepted medical use and a high potential for abuse."[7] Advocates for the use of marijuana as medical treatment have petitioned for the rescheduling of marijuana, arguing that its

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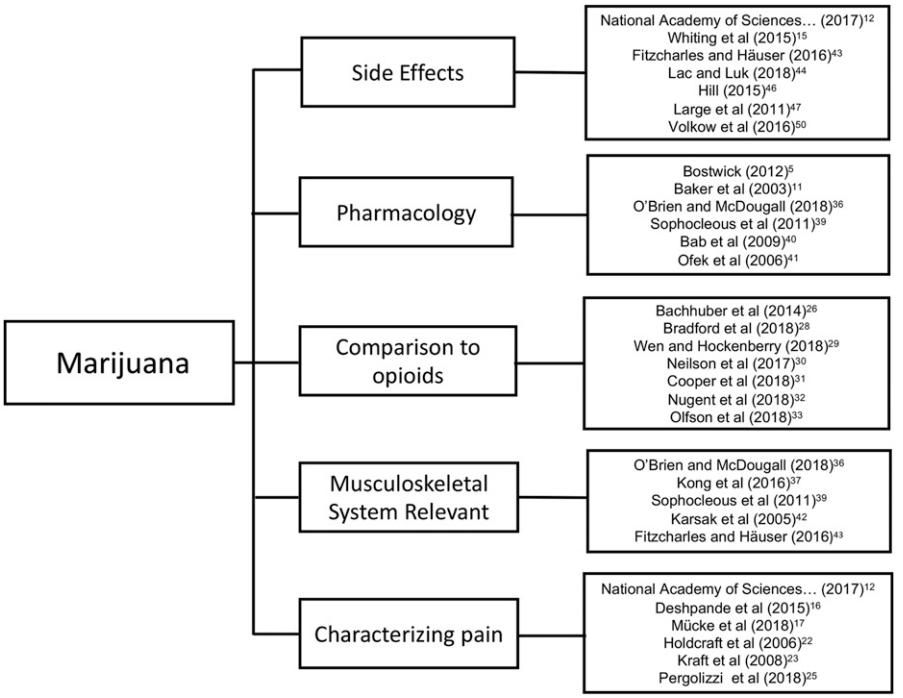

Fig. 1

Existing literature on medical marijuana organized by topic: side effects, pharmacology, comparison with opioids, musculoskeletal system-relevant, and characterizing pain.

current classification impedes the study of therapeutic applications. Presently, marijuana remains a Schedule-I substance. Despite this classification, research on medical applications of marijuana and marijuana-derived compounds continues. The U.S. Food and Drug Administration (FDA) approved the use of dronabinol—a synthetic form of tetrahydrocannabinol (THC), the active ingredient in marijuana—in 1985 as an antinausea medication for patients on chemotherapy and later as an appetite stimulant for acquired immunodeficiency syndrome (AIDS)-related anorexia[8]. More recently, the FDA approved an oral cannabidiol (CBD) compound for the treatment of rare forms of childhood epilepsy (Lennox-Gastaut and Dravet syndromes)[8]. Together, these 3 indications are the only FDA-approved medical uses of marijuana or its derivatives (Table I). There are no FDA-approved uses of marijuana for orthopaedic conditions.

Pharmacology of *Cannabis sativa* and the Endocannabinoid System

The active ingredients in marijuana are THC and CBD[9,10]. To date, >100 other compounds—termed *cannabinoids*—have been

TABLE I Comparison of THC and CBD, the Active Ingredients in Marijuana, with Regard to Psychoactive Effects, Targets in Body, Body System Expression, Potential Implications, and FDA-Approved Indications

Ingredient	Psychoactive?	Target in Body	Body System*	Potential Implications	FDA-Approved Indications
THC	Yes	CB1 receptor and CB2 receptor	CNS, immune, and skeletal	Memory, coordination, motor function, inflammatory and/or immune response, pain signaling, cardiovascular and psychiatric effects, bone remodeling, and cartilage formation	Antinausea treatment for patients on chemotherapy and for treatment of AIDS-related anorexia
CBD	No	Varied: ion channels, enzymes, and receptors	Varied and/or unknown	Varied and/or unknown	Seizures in children

*CNS = central nervous system.

isolated from the marijuana plant, and the effects of these cannabinoids on the human body are an area of active investigation[10]. THC is responsible for the well-known psychoactive effects of marijuana (i.e., the "high"), whereas CBD has no known psychoactive effects (Table I).

THC exerts its effects via 2 receptors, cannabinoid receptor 1 (CB1) and cannabinoid receptor 2 (CB2) (Table I)[9-12]. These receptors, along with several known endogenous ligands, comprise the endocannabinoid system in humans[11]. CB1 is widely expressed throughout the human body, but its highest density is in the central nervous system (CNS); CB2 exists primarily in the immune system (Table I)[11]. THC binds CB1 and CB2 with high affinity, whereas CBD has low affinity for these receptors and exerts its effects via interactions with a diverse set of ion channels, enzymes, and receptors throughout the body[11].

The primary known function of the endocannabinoid system is neurotransmission regulation[11]. The pattern of CB1 receptor expression in the CNS—primarily basal ganglia, hippocampus, and cerebellum—implicates a role in memory, coordination, and motor function[11,13]. CB1 receptors are also found in the dorsal afferent spinal cord, which is important in pain signaling[11,13]. CB2 receptors are primarily expressed on immune cells—B-cells, natural killer cells, monocytes, and others—and may play a role in modulating the inflammatory and immune response[11,14]. On the basis of their widespread distribution throughout the nervous system and the immune system, cannabinoid receptors have potential as therapeutic targets for a host of medical conditions.

Medical Applications of Cannabis

The most commonly touted medical applications of marijuana and other cannabinoids are for treating epilepsy, glaucoma, nausea, mood and sleep disorders, and bodily pain related to neuropathy, cancer, or neurogenic spasticity; however, data supporting the use of marijuana for these conditions are limited in quality and quantity[15]. The potential role of marijuana in the treatment of bodily pain of various etiologies has gained traction, particularly within the context of the ongoing opioid epidemic in the United States.

Marijuana and Pain

Marijuana is purported to reduce pain via its effects on the central and peripheral nervous systems, although the exact mechanism of action is unknown[5,15]. Much of the literature to date has examined the effect of cannabis and cannabinoids on neuropathic pain caused by a lesion or disease involving the somatosensory system, such as multiple sclerosis, AIDS-human immunodeficiency virus (HIV), or spinal cord injury, with limited research on pain related to trauma or surgery. A summary of selected relevant evidence relating to cannabis and pain is provided in Table II. Whiting et al. conducted a systematic review of the literature in 2015 and found a mix of moderate and low-quality evidence to support the use of cannabinoids for neuropathic pain compared with placebo, but few studies in that review compared cannabinoids with standard forms of pain alleviation therapy[15]. A 2015 systematic review and 2018 Cochrane review found limited support for the use of marijuana or cannabinoids in patients with neuropathic pain, yet a 2017 report by the National Academies of Sciences, Engineering, and Medicine reviewed the same literature and concluded that there was "substantial evidence" in support of cannabis as a treatment for daily pain for which people seek care[12,16,17]. These differing interpretations of similar data sets are troubling and may be related to the concept of clinical importance versus statistical significance. Whiting et al. found a decrease in pain of 0.46 on a visual analog scale (VAS) of 0 to 10 points, which was similar to that reported by Stockings et al. (a 3-point reduction on a 100-point VAS)[15,18]. For context, the minimal clinically important difference (MCID) is approximately 19 to 23 points on a 100-point VAS for pain improvement after total joint replacement and 23 points for nonspecific daily pain present for >30 days[19,20]. While some patients may experience an improvement in their pain symptoms in response to cannabinoids, this response may not be clinically important.

The data regarding the use of cannabinoids for pain related to injury or surgery are similarly murky (Table II). Holdcroft et al. conducted a nonblinded, nonrandomized, dose-escalation study assessing the effect of an oral cannabis extract containing THC and CBD on postoperative pain[21]. The authors found a dose-dependent reduction in postoperative pain among patients taking a single dose of cannabis extract for postoperative pain; however, all patients requested some form of additional rescue pain medication and the trial was stopped early because of a serious vasovagal episode experienced by 1 patient in the high-dose cannabis extract arm. On the contrary, in a small, double-blinded crossover study, Kraft et al. found that the same cannabis extract studied by Holdcroft et al. had no effect compared with the placebo (diazepam) on the perception of pain in healthy female volunteers subjected to various painful stimuli[22]. Using methods similar to those of Kraft et al., Wallace and colleagues found that lower doses of inhaled marijuana decreased pain in 15 healthy volunteers with prior self-reported marijuana use; however, paradoxically, it significantly increased pain intensity at higher doses[23]. A major limitation of the studies by Kraft et al. and Wallace et al. is the inability to properly blind participants to treatment allocation because of the psychomotor effects of THC. It is likely that subjects were able to deduce their treatment allocation, which introduces bias. Neither study noted an assessment of blinding among subjects, and both studies identified substantial psychomotor effects in the THC-treated subjects. In a 2018 review on the topic, Pergolizzi et al. found evidence to support the use of cannabinoids in the treatment of neuropathic pain, but they did not find any advantage of cannabinoids over nonopioid analgesics for pain related to injury or surgery[24].

CBD, the major nonpsychotropic active ingredient in cannabis, has been marketed as a treatment for a wide range of ailments. The compound has recently received FDA approval in the U.S. for the treatment of 2 seizure syndromes in children, but it has not been rigorously studied as a treatment for pain[8].

Cannabinoids have been celebrated in the lay press as a potential weapon against opioid overuse and abuse, but data from human studies to support this enthusiasm are limited. Widely cited epidemiological studies have suggested that

TABLE II Summary of Selected Literature on Marijuana Use for Acute and Chronic Pain Treatment*

Study	Level of Evidence	Study Design	Sample Size	Study Population	Intervention Details	Comparison Group	Outcome Measure	Results	Conclusion
Hill[45] (2015)	I	Systematic review of RCTs	28 studies and 2,321 patients	Chronic pain, neuropathic pain, and spasticity	Varied: nabilone, dronabinol, THC:CBD oromucosal spray, smoked cannabis, and OCE:THC	Varied: placebo and crossover	Varied: VAS, pain relief, 11-point box test, pain on movement, percent achieving 30% pain reduction, change in pain intensity, incontinence episodes, change in spasticity, change in muscle stiffness, pyschopathology, sleep disturbance, change in tremor index, etc.	Strongest level of evidence exists for use of marijuana and cannabinoids for chronic pain, neuropathic pain, and spasticity associated with multiple sclerosis; in general, this evidence is equivocal or weak	Medical marijuana has substantial health risks as well as many potential medical benefits
Nielsen et al.[29] (2017)	I	Systematic review and meta-analysis	19 preclinical and 9 clinical studies	Preclinical and clinical studies for which outcome was either analgesia or opioid dose; clinical studies were controlled studies and case series	Varied cannabinoids	Varied	Analgesia or opioid dose requirements	17 of 19 preclinical studies indicated that the effective dose of morphine administered in combination with THC is 3.6 times lower than morphine alone; the effective dose for codeine in combination with THC was 9.5 times lower than for codeine alone; 1 of 9 clinical studies provided very low-quality evidence of an opioid-sparing effect	Prospective high-quality controlled clinical trials are required to determine the opioid-sparing effect of cannabinoids
Mücke et al.[17] (2018)	I	Cochrane review of blinded RCTs	16 studies and 1,750 participants	Chronic neuropathic pain in adults	Varied cannabis: oromucosal spray combination of THC:CBD, nabilone, inhaled herbal cannabis, and dronabinol	Varied: placebo and dihydrocodeine	Pain relief, patient global impression of change, AEs, psychiatric disorders; number needed to treat for an additional beneficial outcome (NNTB); number needed to treat for an additional harmful outcome (NNTH)	Cannabis-based medicines were better than placebo for pain relief (NNTB, 20) and global improvement (NNTB, 11), reducing pain intensity, sleep problems, and psychological distress; more nervous system AEs (NNTH, 3) and psychiatric disorders (NNTH, 10); more people treated with cannabis dropped out of studies than those treated with placebo (NNTH, 25)	Potential benefits may be outweighed by potential harms; there is a lack of good evidence that any cannabis-derived product works for any chronic neuropathic pain

continued

TABLE II (*continued*)

Study	Level of Evidence	Study Design	Sample Size	Study Population	Intervention Details	Comparison Group	Outcome Measure	Results	Conclusion
Deshpande et al.[16] (2015)	I	Systematic review	6 studies and 226 patients	Chronic noncancer pain	Varied cannabis: smoked or vaporized nonsynthetic, varied THC potency	Varied	Varied: pain, function, dose, AEs	Most studies included medical marijuana as adjunct to other concomitant analgesics (i.e., opioids and anticonvulsants); all short-term (max. 5 days); all noted significant pain relief with nonserious side effects; only half of the studies found clinically meaningful pain reduction (≥30%)	Evidence for use of low-dose medical marijuana in neuropathic pain in conjunction with traditional analgesics; however, trials had substantial limitations and variability; although well tolerated in the short term, the long-term effects of medical marijuana are unknown; generalizing use outside neuropathic pain is not supported
Whiting et al.[15] (2015)	I	Systematic review and meta-analysis	79 trials and 6,462 participants	Randomized clinical trials of cannabinoids for defined set of indications: nausea and vomiting due to chemotherapy, appetite stimulation in HIV-AIDS, chronic pain, spasticity due to multiple sclerosis or paraplegia, depression, anxiety disorder, sleep disorder, psychosis, glaucoma, or Tourette syndrome	Varied	Varied	Patient-relevant and/or disease-specific outcomes, activities of daily living, quality of life, global impression of change, and AEs	Most trials showed improvement in symptoms, but these did not reach significance in all trials; significant improvements were seen in a number of patients showing complete relief of nausea and vomiting, reduction in pain, and reduction in spasticity; there was an increased risk of AEs with cannabinoids	Moderate-quality evidence supports use of cannabinoids for chronic pain and spasticity; low-quality evidence suggests cannabinoids are associated with improvements in nausea and vomiting due to chemotherapy, weight gain in HIV, sleep disorders, and Tourette syndrome
Kraft et al.[22] (2008)	I	Randomized, double-blinded, placebo-controlled, crossover trial	18 healthy volunteers	Acute nociceptive pain	Oral cannabis: 20 mg total THC	Active placebo: 5 mg diazepam	Heat and electrical pain thresholds; secondary hyperalgesia	No effect on heat pain threshold; electrical threshold significantly lower compared with placebo; no effect on secondary hyperalgesia, flare, or spontaneous pain	No analgesic or antihyperalgesic activity of cannabis; cannabinoids are not effective analgesics for acute nociceptive pain
Wallace et al.[23] (2007)	I	Randomized, double-blinded, placebo-controlled, crossover trial	15 healthy volunteers	Acute pain	Smoked cannabis (2%, 4%, or 8% THC)	Placebo	Pain and hyperalgesia induced by capsaicin	No effect on pain at 5 min; significant decrease in pain at medium dose, but significant increase in pain at high dose at 45 min; no effect at low dose	There is a window of modest analgesia for smoked cannabis; lower doses decrease pain, while higher doses increase pain

continued

TABLE II (*continued*)

Study	Level of Evidence	Study Design	Sample Size	Study Population	Intervention Details	Comparison Group	Outcome Measure	Results	Conclusion
Cooper et al.[30] (2018)	I	RCT with crossover	18 healthy volunteers	Acute pain	Smoked cannabis (0.0 or, 5.6% THC), plus oxycodone (0, 2.5, or 5 mg)	Within-subject placebo	Analgesia during cold pressor test: times to report pain (threshold) and withdrawal from water (pain tolerance), abuse-related effects	Alone, 5 mg oxycodone increased pain threshold and tolerance ($p < 0.05$); cannabis and 2.5 mg oxycodone alone failed to elicit analgesia, but combined, they increased pain threshold and tolerance ($p < 0.05$); oxycodone did not increase subjective ratings associated with cannabis abuse or cannabis self-administration; combination of oxycodone and cannabis produced significant increase in oxycodone abuse liability ($p < 0.05$)	Cannabis enhances analgesic effects of subthreshold oxycodone, suggesting synergy; there was no increase in abuse liability of cannabis, but there was an increase in oxycodone abuse liability
Holdcroft et al.[21] (2006)	III	Dose escalation study	65 patients	Postop. pain	Oral cannabis: 5, 10, or 15 mg THC	Different doses of THC	Frequency and timing of rescue analgesia; pain relief at rest (VRS); pain intensity at rest and on movement (VRS); sedation, nausea, vomiting, and vital signs	Fewer patients requested rescue analgesia with increased dose (100% at 5 mg, 50% at 10 mg, and 25% at 15 mg); significant trend in time to rescue analgesia with dose ($p < 0.0001$); significant trends in decreasing pain intensity with escalated dose (p-0.01); increase in sedation and AEs with escalating dose ($p = 0.03$ and 0.002, respectively); study terminated for serious vasovagal AE in patient at 15 mg	Dose-related improvements in rescue analgesia requirements provide number needed to treat equivalent to other analgesics (2.0 at 10 mg and 1.3 at 15 mg)

*RCTs = randomized controlled trials, OCE = oral cannabis extract, AE = adverse event, VAS = visual analog scale, and VRS = verbal rating scale.

marijuana may decrease opioid use, although these findings are controversial[25-28]. Two studies using Medicare and Medicaid databases found that, in states with medical marijuana laws (MMLs), opioid prescriptions decreased after implementation of MMLs compared with prelegalization levels and that states with MMLs had lower opioid prescribing rates than those without MMLs[27,28]. Those studies concluded that marijuana may play a role in combating the opioid epidemic in the United States. One of the most widely cited studies found that, from 1999 to 2010, accidental opioid overdose deaths were nearly 25% lower in states with MMLs compared with states without MMLs[25]. However, this finding was not significant when overdose death rates of individual states were compared before and after marijuana legalization[25]. More recently, Shover et al. used the same data set and methodology as Bachhuber et al.[25] but extended the analysis period by 7 years[26]. They found a complete reversal of the correlation between MMLs and opioid overdose deaths. The authors concluded that the association

between MMLs and opioid overdose deaths was likely spurious and cautioned readers that claims to the contrary "should be met with skepticism."[26] On the basis of current data, no firm conclusions can be drawn regarding the effect of MMLs on opioid use and abuse at the state level.

There is strong preclinical evidence that coadministration of cannabinoids and opioids reduces the overall dose of opioids required for analgesia; however, this synergistic effect has not been as clear in human research[29]. Cooper and colleagues demonstrated a synergistic effect between smoked cannabis and oxycodone in a double-blinded, placebo-controlled crossover study of 18 human subjects[30]. The authors found that coadministration of cannabis and oxycodone increased participants' pain threshold during a cold-water immersion test compared with monotherapy with either cannabis or oxycodone. Interestingly, coadministration of marijuana and opioids increased participants' positive perception of the opioid drug and made them more likely to take the opioid again—the authors referred to this finding as increased "abuse liability."[30] The latter finding has been replicated in other studies showing that prescription opioid misuse was significantly higher among long-term opioid users who self-identified as using marijuana for the treatment of ailments[31,32]. Additionally, Rogers and colleagues found that the combined use of marijuana and prescription opioids had little effect on the pain experience of patients and was associated with increased levels of anxiety, depression, and substance abuse problems[33]. Among patients with traumatic musculoskeletal injuries, Bhashyam and colleagues found that self-reported recreational marijuana use during recovery from a musculoskeletal injury was associated with an increased total amount of prescribed opioids and longer duration of opioid therapy compared with patients with musculoskeletal injuries who did not use marijuana during recovery[34]. The available evidence on the effects of marijuana on opioid consumption is contradictory; enthusiasm for marijuana as a substitute, or even adjuvant, for narcotic pain medications should be tempered.

Marijuana and the Musculoskeletal System

There are a few potential applications of marijuana in the treatment of musculoskeletal conditions such as osteoarthritis and osteoporosis. At this point, data are limited and mostly preclinical. Cannabinoid receptors are widely expressed in bone, and endogenous cannabinoid ligands are present in bone at levels similar to those seen in brain tissue[35]. Preclinical studies have shown that the endocannabinoid system plays a role in the modulation of pain and disease progression in animal models of osteoarthritis[35-38]. In a mouse model of degenerative osteoarthritis, CB2 knockout mice had more severe osteoarthritis than control mice, and disease severity in knockout mice was reduced when a selective CB2 agonist was administered[37]. In cell culture, CB2 knockout chondrocytes produced fewer proteoglycans than wildtype chondrocytes, indicating an important role for the cannabinoid receptor in cartilage formation[37]. To our knowledge, there are no clinical studies evaluating the effect of cannabinoid receptor modulation on pain or disease progression in osteoarthritis. In human osteoarthritic chondrocytes, matrix metalloproteinase activity was inhibited by a synthetic cannabinoid that modified the CB2 receptor, indicating a potential chondroprotective role of the cannabinoid signaling pathway[36].

The endogenous cannabinoid system also plays a role in osteopenia and osteoporosis; CB2 receptor knockout mice have been shown to have low bone density and high bone turnover[39]. The mechanism by which CB2 modulates bone metabolism remains unclear, but there is sufficient preclinical evidence to indicate a role for the endocannabinoid system in bone remodeling[38-40]. In humans, polymorphisms in the CB2 receptor gene (CNR2) are highly associated with low bone mineral density[41]. While more research is needed, CB2 receptors may be therapeutic targets in the treatment or prevention of low bone mineral density and osteoarthritis. It is not clear how inhaled marijuana or CBD formulations affect osteoarthritis or bone mineral density in humans.

Adverse Effects of Cannabinoids

A number of the adverse effects of cannabinoids are widely known. Recreational and medical users inhaling marijuana or taking cannabinoid formulations containing THC are prone to a number of psychomotor effects including memory impairment, cognitive delay, and impaired coordination[12,42]. Among daily, heavy users, marijuana use has additionally been associated with cardiovascular events (e.g., tachycardia and hypotension), respiratory effects (e.g., chronic cough), and psychiatric effects (e.g., anxiety, paranoia, psychosis, suicidal ideation, and an amotivational syndrome characterized by decreased persistence, initiative, and overall self-efficacy)[12,42-44]. There is some evidence that in susceptible individuals, heavy cannabis use in adolescence may accelerate the onset of schizophrenia, although these findings are controversial[44-47]. Furthermore, the effects of marijuana use during pregnancy on perinatal outcomes and later childhood development are not well understood, but recent studies have shown an increasing prevalence of marijuana use during pregnancy and an association with preterm birth[48-50].

Long-term and heavy use also carries a risk of use disorder and dependence. Cannabis use disorder is an official diagnosis in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), defined in part by frequent marijuana use causing failure to fulfill major role obligations in private or professional life[51]. Approximately 12% of frequent cannabis users (i.e., those who use it ≥3 times per week) may experience a withdrawal syndrome—indicating chemical dependence—with symptoms such as anxiety, hostility, disordered sleep, and/or depressed mood, among others[52]. Addiction may be present in the heaviest users who continue to use cannabis despite adverse effects on their performance in school, relationships, and/or the workplace.

Adverse effects of other cannabinoids, such as CBD formulations or synthetic THC-CBD combinations have been reported; however, long-term effects of these agents are largely unknown[15]. One major hurdle to further understanding the effects of marijuana and cannabinoids on humans is the lack of

consistency between the strains of marijuana and cannabinoid products used in clinical research and those products available to the medical and recreational user. Because of federal regulation, only a limited number of cannabinoid products and marijuana strains are available to researchers in the U.S. through the National Institute on Drug Abuse (NIDA)[53]. While efforts have been made to increase the quantity and diversity of cannabinoids available for study, the products available to medical users and the general public far outnumber those available to researchers. It is difficult to make general statements regarding the safety and/or efficacy of cannabinoids for the treatment of medical conditions, as most cannabinoids available to the public have not been formally investigated.

Societal Impact of MMLs

Several studies detailing the societal effects of legalized recreational marijuana have been published[54-57], but few studies have examined the societal effects of MMLs alone. Issues of particular concern are crime rates, traffic deaths, and adolescent marijuana use. Colorado and Washington, 2 of the first states to allow both medical and recreational marijuana use, published their findings on the social impact of legalized marijuana in 2018 and 2016, respectively[54,55]. Colorado reported fewer marijuana-related arrests and court filings after legalization but noticed a fourfold increase in organized crime court filings. Regarding traffic violations, Colorado reported a 3% increase in the proportion of citations for driving under the influence (DUI) in which THC was identified as the impairing substance (15% in 2017 compared with 12% in 2014), but there was a decrease in the proportion of traffic fatalities in which the driver tested positive for the active THC metabolite, delta-9 THC (13% in 2016 versus 8% in 2017)[54]. Washington reported a 122% increase in the proportion of fatal traffic accidents involving a driver who tested positive for active THC; the greatest number of these drivers were from 16 to 25 years old[55]. In contrast to the report from Washington, an analysis of the U.S. Fatality Analysis Reporting System from 1985 to 2014 found that states with MMLs had fewer traffic fatalities than states without MMLs; however, in state-specific analyses before and after legalization, MMLs were inconsistently associated with a decrease in traffic fatalities[56]. Further study is needed to understand the effect of marijuana laws on traffic accidents and fatalities.

Use of marijuana by adolescents is a major concern for parents, pediatricians, and public health officials as the long-term effects of marijuana on the developing brain are unknown. Reports from Colorado, Washington, and a number of other states with MMLs have shown that—at least in the short term—marijuana use by adolescents has remained unchanged despite increased access for adults in states with MMLs[54,55,57]. Interestingly, adolescents in Washington reported declining perceptions of the risks associated with regular and 1-time use of marijuana after legalization. This may reflect an area where drug awareness campaigns can be better implemented[55].

As marijuana remains illegal at the federal level, states with medical and/or recreational marijuana laws are active participants in an ongoing social experiment. The true effects of legalized marijuana on society may not be known for many years. It is incumbent on state officials to maintain detailed public records and for researchers to continue studying the effects of MMLs on communities.

Overview and Recommendations

This review aimed to provide a summary of selected literature on the use of marijuana as a medical treatment and to highlight potential orthopaedic applications in order to provide a useful resource for the orthopaedist without expertise in this field. We did not conduct a systematic review or synthesis of the literature, as that was beyond the scope and purpose of this article. Several systematic reviews are cited as resources for interested readers.

Public support for the expanded use of marijuana as medical treatment is at an all-time high, and it is imperative that physicians have a basic understanding of the available literature. The growth of public and political support for medical use of marijuana seems to be outpacing the growth of scientific evidence. Companies marketing marijuana and cannabinoids to the public make lofty claims about the medical applications of their products, but many of those claims are not backed by research. Modulation of the widely distributed endocannabinoid system certainly holds promise for a number of medical conditions including neuropathic pain, osteoarthritis, and osteoporosis, among others, but additional high-quality studies are needed. Claims that marijuana and cannabinoids can reduce opioid consumption are not well supported by the evidence, and physicians should be aware that coadministration of marijuana and opioids may actually increase opioid use and abuse.

There are numerous known adverse effects of marijuana, but long-term effects on the medical consumer are unclear. Given the groundswell of public support for marijuana, further research is needed and federal regulations regarding marijuana and cannabinoid research should be modified to allow for practical study of available products. Researchers must continue to evaluate the societal effects of MMLs on the communities in which these laws have already been implemented; furthermore, expansion of legislation permitting medical use of marijuana must follow the evidence, not public opinion. ■

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