Medicinal Properties of Cannabinoids, Terpenes, and Flavonoids in Cannabis, and Benefits in Migraine, Headache, and Pain: An Update on Current Evidence and Cannabis Science

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Background.—Comprehensive literature reviews of historical perspectives and evidence supporting cannabis/cannabinoids in the treatment of pain, including migraine and headache, with associated neurobiological mechanisms of pain modulation have been well described. Most of the existing literature reports on the cannabinoids Δ^9-tetrahydrocannabinol (THC) and cannabidiol (CBD), or cannabis in general. There are many cannabis strains that vary widely in the composition of cannabinoids, terpenes, flavonoids, and other compounds. These components work synergistically to produce wide variations in benefits, side effects, and strain characteristics. Knowledge of the individual medicinal properties of the cannabinoids, terpenes, and flavonoids is necessary to cross-breed strains to obtain optimal standardized synergistic compositions. This will enable targeting individual symptoms and/or diseases, including migraine, headache, and pain.

Objective.—Review the medical literature for the use of cannabis/cannabinoids in the treatment of migraine, headache, facial pain, and other chronic pain syndromes, and for supporting evidence of a potential role in combatting the opioid epidemic. Review the medical literature involving major and minor cannabinoids, primary and secondary terpenes, and flavonoids that underlie the synergistic entourage effects of cannabis. Summarize the individual medicinal benefits of these substances, including analgesic and anti-inflammatory properties.

Conclusion.—There is accumulating evidence for various therapeutic benefits of cannabis/cannabinoids, especially in the treatment of pain, which may also apply to the treatment of migraine and headache. There is also supporting evidence that cannabis may assist in opioid detoxification and weaning, thus making it a potential weapon in battling the opioid epidemic. Cannabis science is a rapidly evolving medical sector and industry with increasingly regulated production standards. Further research is anticipated to optimize breeding of strain-specific synergistic ratios of cannabinoids, terpenes, and other phytochemicals for predictable user effects, characteristics, and improved symptom and disease-targeted therapies.

Key words: cannabis, cannabinoids, marijuana, CBD, cannabidiol, THC, Δ9-tetrahydrocannabinol, migraine, headache, terpenes, flavonoids

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INTRODUCTION

Migraine affects approximately 18% of women and 6% of men in the United States (US) and Europe, and more than 10% of the world's population, accounting for approximately 700 million migraineurs worldwide.[1] It is estimated that there are 38 million migraineurs in the United States, accounting for 12% of the US population, and that 1in 4 households have someone with migraine. In 2016, migraine was determined to be the 2nd leading cause of all global disability, and the 2nd leading cause of all neurological disease burden.[2] These estimates have increased from prior estimates of migraine as the 6th leading cause of all global disability, and headache disorders as the 3rd leading cause of disability worldwide.[3] Migraine accounts for 50% of all neurologic disability and costs more than $20 billion per year with 113 million lost workdays annually.[4] Furthermore, chronic pain in general is the largest contributor to years lived with disability globally,[5] and is associated with tremendous negative impacts on social, economic, and personal function.

Migraine treatment is divided into acute and preventive therapy. Most existing preventive therapies are adopted from anti-epileptic, antidepressant, and antihypertensive medications. However, many of these medications are not well tolerated, resulting in poor compliance. OnabotulinumtoxinA is currently available for treatment of chronic migraine, and calcitonin gene related peptide (CGRP) antagonists, and neuromodulation devices are either available or in late-stage development for both acute and preventive migraine therapies. The most frequently used acute migraine medications include analgesics such as nonsteroidal anti-inflammatories (NSAIDs) and triptans.[6,7] Unfortunately, although the only medication class developed solely for migraine, 25% of patients do not respond to triptans.[8] Furthermore, only one-third of patients taking a triptan are pain-free at 2 hours, and only 17%-25% remain pain-free over

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the next 24 hours.[9,10] This confers a large unmet need for additional migraine specific medications in both the acute and preventive treatment of migraine.

New migraine specific medications are desperately needed. Data have shown that cannabinoids appear to work uniquely and synergistically within the inherent pathways of migraine and pain, including triptan mechanism of action pathways.[11–17] Comprehensive literature reviews of historical perspectives and neurobiological mechanisms of action of cannabis/cannabinoids in the treatment of pain, including migraine and headache, have been performed.[11–14,18,19] This paper should be considered an extension of those publications.

This paper has 3 primary goals. The first is to summarize the most recent evidence for the use of cannabis/cannabinoids in migraine and headache treatment. Second, to review the current literature regarding the use of cannabis/cannabinoids in chronic pain disorders, since these data likely extrapolate to headache disorders given overlapping neurobiological pathways of pain. Third, to explore the growing evidence for the use of cannabis to help with the opioid epidemic, as cannabis use has been associated with lowering opioid mortality and has shown benefit in detoxification from opioids.

Cannabis science is a rapidly evolving science with accumulating evidence for various therapeutic purposes. This science no longer revolves around use of generic unspecified cannabis strains with undefined content of Δ^9-tetrahydrocannabinol (THC), cannabidiol (CBD), and other phytochemicals. There are now strict and sterile production procedures with the goal of optimizing the breeding of cannabis strains and strain standardization with specific compositions of the major cannabinoids, THC and CBD, as well as minor cannabinoids and other important phytochemicals, particularly terpenes and flavonoids. Although most of the existing cannabis science literature focuses primarily on the major cannabinoids, THC and CBD, the minor cannabinoids, terpenes, and flavonoids have generally been ignored. Evidence suggests that these constituents, especially cannabinoids and terpenes, play significant roles in influencing one another and working synergistically. This results in a wide range of user effects, benefits, and side effects between strains with varying ratios of these components. The synergy and interactions between these cannabis compounds are referred to as the "cannabis entourage effects."[20,21] This paper will review the literature regarding the analgesic, anti-inflammatory, and other medicinal benefits of major and minor cannabinoids, primary and secondary terpenes, and flavonoids found in cannabis.

Because of the increasing evidence of cannabinoid efficacy in the treatment of pain and a combined number needed to treat (NNT) of 3.4, the Canadian Pain Society revised their consensus statement in 2014 to recommend cannabinoids as a third-level therapy for chronic neuropathic pain.[22] In 2017, The US National Academies of Sciences, Engineering, and Medicine published a statement that the use of cannabis for the treatment of pain is supported by well-controlled clinical trials and that there is substantial evidence that cannabis is an effective treatment for chronic pain in adults.[23]

In most medicinal cannabis registries, the most commonly reported reason for cannabis use by patients is chronic pain of some form. The first study using objective data for assessing national medicinal cannabis consumption came from data from a nationwide registry of all patients with a medical cannabis prescription in the Netherlands between 2003 and 2010.[24] The registry monitored 5540 patients use of 4 different cannabis strains of varying THC and CBD content and their use of co-medications. Notably, 53.6% of all users across each strain were also using some form of pain medication (nonopioid 40.5%, weak opioid 21.8%, strong opioid 21.2%) as the most common type of co-medication. It is likely that these people were using medicinal cannabis for some form of pain.

Another study evaluated the reasons why 348 patients in the waiting area of a Michigan medicinal cannabis certification clinic were seeking medicinal cannabis. Of all patients (recertification and 1st time applicants), 87% were using medicinal cannabis for severe or chronic pain relief (91% in 1st time applicants).[25] Chronic pain was observed as the most common reason for the use of medicinal cannabis across most other registries as well.[26–34]

THE ENDOCANNABINOID SYSTEM AND PAIN

The neurobiological pathways of cannabinoids and pain, including migraine, were detailed and summarized previously.[11–17] The endocannabinoid system involves the central and peripheral nervous system. It is involved in inflammatory and pain processes, and plays a role in a multitude of regulatory physiological processes across virtually every organ system.[35–40] The endocannabinoid system appears to work both independently and synergistically, binding other molecular targets within major endogenous pain circuitry systems, including inflammatory, endorphin/enkephalin, vanilloid/transient receptor potential cation channel subfamily V (TRPV), subfamily A (TRPA), subfamily M (TRPM), and a class of nuclear receptors/transcription factors called the peroxisome proliferator-activated receptors (PPAR).[41] The efficacy of cannabinoids in the treatment of chronic neuropathic pain is partly attributed to the endocannabinoid system modulation of the descending supraspinal inhibitory pathways. These pathways are often impaired in chronic pain syndromes.

The activities of the endocannabinoid system revolve around the presynaptic G protein-coupled cannabinoid 1 (CB1) and 2 (CB2) receptors, which inhibit adenylate cyclase activity.[42] There is a presumed third cannabinoid receptor, G protein-coupled receptor 55 (GPR55), termed CB3.[43] The primary endogenous cannabinoid receptor ligands (endogenous cannabinoids; endocannabinoids) are arachidonic acid derivatives synthesized "on demand," and include N-arachidonoylethanolamine (anandamide, or AEA), a primary mediator of endocannabinoid signaling, and 2-arachidonoylglycerol (2-AG).[36,44–46] The endocannabinoids, as well as the phytocannabinoids found in cannabis, bind to and activate the CB1 and CB2 receptors with variable affinities.[47–49] AEA and 2-AG are released from the postsynaptic neuron terminals and travel retrograde across the synaptic cleft to presynaptic neuron terminals, where they bind the CB receptors.

The CB1 receptor is the most abundant G protein-coupled receptor in the brain and one of the most abundant in both the peripheral and central nervous system.[47] CB1 receptors are expressed primarily on presynaptic peripheral and central nerve terminals, and to a lesser degree on peripheral organs. They are found extensively in the anatomical pain pathways including the periaqueductal gray (PAG) matter, rostral ventrolateral medulla, dorsal primary afferent and substantia gelatinosa spinal cord regions, spinal interneurons, peripheral nerves/nociceptors, as well as other brain regions such as the amygdala, cerebral cortex, hippocampus, substantia nigra pars reticulata, basal ganglia, globus pallidus (internal and external segments), and molecular layer of the cerebellum.[35,50–53] CB1 receptors mediate the behavioral and psychotropic effects of cannabinoids, including the "high" felt with some cannabis strains, activated by THC. Retrograde signaling receptor activation of the CB1 receptors leads to opening of potassium channels, hyperpolarization of the presynaptic terminal, closing of calcium channels, and inhibition of the release of stored inhibitory and excitatory neurotransmitters, including glutamate, 5-hydroxytryptamine (5-HT) (serotonin), acetylcholine, gamma-aminobutyric acid (GABA), noradrenaline, dopamine, D-aspartate, and cholecystokinin at both inhibitory and excitatory synapses.[35,36,38,46,52,54–56] Exogenous and endogenous cannabinoids are also known to modulate pain pathways involving opioid, serotonin, and N-methyl-d-aspartate (NMDA) receptors through other indirect mechanisms.[57]

The CB2 receptors are concentrated primarily in the peripheral tissues and immune cells where they influence the release of cytokines, chemokines, and cell migration including neutrophils and macrophages, and to a lesser degree in the nervous system.[52,58,59] The CB2 receptors are primarily concentrated in the peripheral tissues, especially cells of the immune system, but can be found in lower concentrations in some brain regions including the PAG and some neuronal subpopulations of astrocytes, microglia, and oligodendrocytes.[60–62] CB2 receptors may also contribute to pain relief by dopamine release modulation.[63,64]

CANNABIS AND CANNABINOIDS IN MIGRAINE, HEADACHE, AND FACIAL PAIN

The medical literature regarding treatment of headache, migraine, and facial pain disorders shows supporting evidence for cannabis/cannabinoids in the treatment of chronic headaches,[65–68] migraine including chronic migraine,[13,14,39,66,69–82] medication overuse headache,[83] cluster headache,[82,84–86] idiopathic intracranial hypertension,[87] and multiple sclerosis (MS) associated trigeminal neuralgia.[88] At the time of this writing, this majority of supporting literature consists primarily of case series, case studies, case reports, surveys, clinical/anecdotal reports, and one retrospective analysis. To date, there are no placebo-controlled studies of cannabis for headache disorders, although there is a multicenter (29 sites), double-blind, placebo-controlled study evaluating efficacy and safety of a synthetic THC, dronabinol, in a metered dose inhaler for the treatment of migraine with and without aura that has been completed, but results not published at the time of this writing (May 2018).[89] There are only two prospective trials containing a control group evaluating the use of cannabinoids in the treatment of headache disorders.[82,83]

The first of these two prospective trials was a randomized, double-blind, active-controlled crossover trial in two separate 8 week intervals involving 30 patients (26 completed) with treatment refractory medication overuse headache (MOH) with daily analgesic intake for at least 5 years who had failed at least 3 detoxification attempts. Patients completed a course of either ibuprofen 400 mg or nabilone 0.5 mg daily for 8 weeks, followed by a 1-week washout, and then a second 8 weeks of the other medication. Results showed that nabilone 0.5 mg daily, a synthetic cannabinoid, was superior in reducing daily analgesic intake, pain intensity, level of medication dependence, and improved quality of life in these patients.[83] There was no differentiation of the underlying type of daily headache that led to the medication overuse headache; chronic migraine versus chronic tension-type headache versus other forms of chronic daily headache. In addition, MOH has been attributed to overuse of NSAIDs, including ibuprofen, at more than 10 days per month.[90] Therefore, the significance of these results is uncertain, because taking daily ibuprofen may sustain MOH, rather than help it. Furthermore, there is a possibility that the improvement seen in the control daily ibuprofen group crossing over to nabilone could be due to cessation of the ibuprofen.

The second prospective trial was an abstract presented at the 3rd Congress of the European Academy of Neurology (EAN) in Amsterdam in June 2017.[82] The authors evaluated the use of cannabinoids as both a prophylaxis and acute treatment for both chronic migraine and chronic cluster headache. Patients were given a combination of 2 compounds; one contained 19% THC and the other contained a combination of 0.4% THC + 9% CBD. In phase 1, determination of the effective dose was performed with a group of 48 chronic migraine volunteers starting with an oral dose of 10 mg of the combination and titrated up. Doses less than 100 mg produced no benefit. Oral doses of 200 mg administered during a migraine attack decreased acute pain intensity by 55%. This dose was used in phase 2.

In phase 2, chronic migraine patients (n = 79) were randomly assigned to 3 months prophylaxis treatment with either amitriptyline 25 mg per day or THC + CBD 200 mg per day in a 200 mL 50% fat emulsion. Chronic cluster headache patients (n = 48) were randomly assigned to 1 month of prophylaxis treatment with either verapamil 480 mg per day or THC + CBD 200 mg per day in a 200 mL 50% fat emulsion. For acute pain attacks, additional dosing of THC + CBD 200 mg was allowed in both groups. In the migraine patients, the THC + CBD 200 mg prophylaxis led to a 40.4% improvement versus 40.1% with amitriptyline. In the cluster headache patients, the THC + CBD 200 mg prophylaxis provided minimal to no benefit. Additional acute THC + CBD 200 mg dosing decreased pain intensity in migraine patients by 43.5%. This same result was seen in cluster headache patients, but only if they had a history of migraine in childhood. In cluster headache patients without a previous history of childhood migraine, the additional THC-CBD 200 mg abortive treatment provided no benefit as an acute treatment.

There has been one retrospective study of cannabis use in the treatment of migraine, and it was strongly positive, although limitations exist.[74] In this study, the investigators reviewed charts of 121 adults from 2 medical marijuana specialty clinics in Colorado. These patients had the primary diagnosis of migraine and had been recommended by a physician for acute and/or preventive treatment with medicinal cannabis. There were 7 patients using only for daily prophylaxis, 4 patients using only for acute treatment, and 110 patients using for both acute and preventive management. The primary outcome was the mean number of migraines per month at initial vs follow-up visits. The mean number of migraines per month dropped from 10.4 to 4.6 ($P < .0001$). Overall, 103 (85.1%) patients reported a decrease in frequency of migraines per month, 15 (12.4%) reported the same number of migraines per month, and 3 (2.5%) had an increase in the number of migraines per month.

CANNABIS AND CANNABINOIDS IN CHRONIC PAIN

Despite the lack of prospective studies in migraine and headache, there are many well-designed prospective placebo and active controlled trials conferring benefit of cannabis/cannabinoids in the treatment of various chronic pain disorders, as summarized in Table 1. Although not all-inclusive, Table 1 includes most of these pertinent studies, in addition to the limited migraine studies. These studies were comprised of cannabis that was smoked, oromucosal cannabis extracts, or synthetic cannabinoids. Most studies involve varying amounts of THC, some with THC + CBD, but there are no trials of CBD alone.

In 2009, a systematic review and meta-analysis of 18 double-blind randomized controlled trials that compared any cannabis preparation to placebo among subjects with chronic pain determined that cannabis treatment is moderately efficacious for treatment of chronic pain.[134]

In 2011, a systematic review of 18 well designed randomized controlled trials evaluating cannabis/cannabinoids for treatment of chronic noncancer pain in 925 enrolled patients showed that 83% (15/18) of the trials confirmed cannabis/cannabinoids had statistically significant positive analgesic effects.[135] There were a total of 615 enrolled patients in these trials with statistically significant positive outcomes. Initially, there were 22 studies identified, but 4 of them were excluded because pain outcomes were not specifically examined, the number of participants was low, or there was a duplicated study group. The 15 studies that showed positive outcomes included neuropathic pain,[91–94,103,136] fibromyalgia,[122] rheumatoid arthritis,[105] and mixed chronic pain.[104,110,111,118,119,123,124] There was an additional study included in this review that evaluated oromucosal cannabis extracts in central neuropathic pain from brachial plexus root avulsion.[112] The cannabis preparations provided statistically significant reductions in pain and sleep disturbance, but fell short of the target hypothesis goal, so that study was not included as a positive study in this systematic review.

In 2013, a systematic review of 38 well designed randomized controlled trials evaluating cannabis/cannabinoids in the treatment of pain in 2,423 enrolled patients showed that 71% (27/38) of the trials confirmed cannabis/cannabinoids had statistically significant positive analgesic effects.[35] On further analysis of the 27 positive studies, 2 of them were not comparison studies, but rather open label extension studies[107,108] that followed their correlating initial randomized studies that were published separately.[104,137] Another study showed that dihydrocodeine was a better analgesic than nabilone and thus, a negative study, although a small number of patients did respond well to nabilone.[138] Two of the studies were separate publications of the same study sample and data, with additional

Table 1.—Studies Demonstrating Positive Analgesic Effects of Cannabis/Cannabinoids in Chronic Pain Syndromes

Agent	Control	Population	Enrolled / completed	Trial design	Results
Smoked cannabis (2.5%, 6%, 9.4% THC in 25 mg single inhalations/doses) tid × 5 days of each cycle, followed by 9 day washout[91]	Placebo	Chronic post-traumatic or postsurgical neuropathic pain with allodynia or hyperalgesia	23/21	Randomized, double-blind, placebo controlled, crossover trial for 8 weeks (4 treatment periods, each lasting 2 weeks)	25 mg inhalation of 9.4% THC tid × 5 days significantly reduced pain intensity + improved sleep. Mean daily pain intensity was lower among cannabis groups
Smoked cannabis (1-8% THC) titrated to tolerance day 1 followed by 4 days at tolerated dose, with 4 treatments per day separated by 90-120 minutes[92]	Placebo	HIV-associated distal sensory predominant polyneuropathy (DSPN)	34/28	Randomized, double-blind, placebo-controlled, crossover trial for 7 weeks	Significant pain reduction in all completers. NNT 3.5 for at least 30% pain reduction
Smoked cannabis (3.5%, 7% THC), 9 puffs per session[93]	Placebo	Chronic central and peripheral neuropathic pain (CRPS type I, spinal cord injury or MS, diabetic neuropathy, focal nerve injury)	38/32	Randomized, double-blind, placebo-controlled, crossover trial in three 6-hour sessions with 3-21 day intervals between sessions	Significant decrease in pain with both doses. 3.5% and 7% THC produced equal anti-nociception. Secondary outcomes of pain unpleasantness and global impression of change also improved with cannabis
Smoked cannabis (3.56% THC weighing average 0.9g/cigarette), 1 cigarette tid x 5 days[94]	Placebo	HIV sensory neuropathy	55/50	Randomized, double-blind, placebo-controlled trial	Smoking 1st cannabis cigarette reduced chronic pain ratings (AUC) 72% vs 15% placebo, compared with the last cannabis cigarette at 51% vs 5% placebo. Significant reduction in pain with median reduction of 34% (placebo 17%). 52% in cannabis group had ≥ 30% pain reduction (24% placebo). NNT for > 30% pain reduction 3.6
Smoked cannabis (4% THC weighing average 0.8g/cigarette), 1 cigarette/d × 3 days[95]	Placebo	Spasticity pain in MS	37/30	Randomized, double-blind, placebo-controlled, crossover trial for 17 days	Statistically significant reduction of both spasticity and pain. Cannabis reduced pain scores on the VAS by 5.28 points more than placebo
Smoked cannabis (low dose 2%, medium dose 4%, high dose 8% THC)[96]	Placebo	Healthy volunteers evaluated for pain and cutaneous hyperalgesia induced by intradermal capsaicin	19/15	Randomized, double-blind, placebo-controlled, crossover trial	Significant decrease in capsaicin induced pain with 4% (medium dose) and significant increase in pain with 8% (high dose) THC by 45 minutes after cannabis exposure. No effect seen with 2% (low dose). Authors suggested lower doses may decrease pain, while higher doses may increase pain
Smoked cannabis (3.55% THC)[97]	Placebo	Healthy volunteers who were regular marijuana users evaluated for dose dependent anti-nociception of marijuana, and whether pretreatment with naltrexone modulated this effect	13/5	Randomized, double-blind, placebo-controlled trial. Users participated in 3 sessions at least 3 days apart, each of which had 4 controlled smoking bouts per session, spaced at 40 minute intervals	Marijuana produced significant dose-dependent anti-nociception. Addition of naltrexone did not significantly influence marijuana dose-effect curves
Vaporized cannabis (low dose 1.29% THC, medium dose 3.53% THC), 8-12 puffs per session[98]	Placebo	Neuropathic pain (peripheral neuropathy, nerve injury, CRPS 1, spinal cord injury)	39/39	Randomized, double-blind, placebo-controlled, crossover trial consisting of three 6-hour treatment sessions. 3-14 day intervals between sessions	Significant improvement in pain and patient-rated global impression of change. 30% pain reduction in: 57% low dose 1.29% THC, 61% medium dose 3.53% THC, 26% placebo. NNT for 30% pain reduction: 3.2 for 1.29% THC vs. placebo, 2.9 for 3.53% THC vs placebo, 25 for 3.53% THC vs 1.29% THC. (Comparable anti-nociception between low and medium doses)
Vaporized cannabis (low (1% THC), medium (4% THC), high (7% THC)) dose by weight; cannabidiol <1%. At a weight of 400 mg of cannabis per administration, dosing therefore was controlled at 0, 4, 16 or 28 mg THC per dosing session[220]	Placebo	Short-term efficacy and tolerability of inhaled cannabis for treatment-refractory painful diabetic neuropathy	16/16	Randomized, short-term, placebo-controlled, four-period, cross-over study. Four-hour sessions separated by 2 weeks	Significant pain improvement with cannabis in placebo vs low ($P = .031$), medium ($P = .04$), high doses ($P < .001$). Also, significant improvement in high vs low and medium doses (both $P < .001$), but significant negative effect (impaired neuropsychological test performance) of the high dose
Vaporized cannabis[99]	N/A	Patients with chronic pain, on a regimen of twice-daily doses of sustained-release morphine or oxycodone	21/21	Participants admitted for 5-day inpatient stay. Inhaled vaporized cannabis in the evening of day 1, three times a day on days 2-4, and in the morning of day 5	Pain significantly decreased (average 27%) after addition of vaporized cannabis. Concluded that vaporized cannabis augments the analgesic effects of opioids without significantly altering plasma opioid levels. The combination may allow for opioid treatment at lower doses with fewer side effects
Novel portable thermal-metered-dose inhaler (tMDI) for cannabis: single 15.1 ± 0.1 mg dose of cannabis[100]	N/A	Chronic neuropathic pain	8/8	Single-dose, open-label study	Significant 45% reduction in pain intensity 20 minutes post inhalation ($P = .001$), turning back to baseline within 90 minutes

Table 1.—*(Continued)*

Agent	Control	Population	Enrolled / completed	Trial design	Results
Smoked, vaporized, edible, topical cannabis formulations.Mean monthly doses: smoked 1.59 oz, vaporized 2.64 oz, edible 2.59 oz, topical 2.73 oz (Specific strains and/or amounts/ratios of cannabinoids within products not consistently documented.)[74]	N/A	Adults with primary diagnosis of migraine, recommended medical cannabis for migraine treatment or prophylaxis by a physician	121/121	Retrospective observational chart review of 2 medical marijuana specialty clinics in Colorado	Migraine frequency decreased from 10.4 to 4.6 per month ($P<.0001$) with medical cannabis. Reasons for use: Migraine daily prophylaxis only (7 patients), acute treatment only (4 patients), both acute and preventive (110 patients) 103 (85.1%) reported a decrease in frequency of migraines/month, 15 (12.4%) had same number of migraines/month, 3 (2.5%) had increase in number of migraines/month
Standardized herbal cannabis (12.5% ± 1.5% THC). Median daily dosage 2.5g/d (range = .1-13.4; interquartile range = 1.5-3.0). 58 (27%) used smoking as only route of administration, 130 (61%) used a combination of smoking, oral, and vaporization, and 17 (8%) consumed cannabis orally only[101]	Chronic pain patients who were not cannabis users	Chronic non-cancer pain. Primary outcome: serious adverse events and non-serious adverse events. Secondary safety outcomes included pulmonary and neurocognitive function and standard hematology, biochemistry, renal, liver, and endocrine function. Secondary efficacy parameters included pain and other symptoms, mood, and quality of life	431/330	Prospective cohort study with a 1-year follow-up conducted in 7 clinical centers. Six clinical visits (1, 2, 3, 6, 9, and 12 months after baseline) and 3 telephone interviews (1, 2, and 3 weeks after the baseline visit) were scheduled for patients in the cannabis group; 2 clinical visits (6 and 12 months after baseline) and 5 telephone interviews (1, 2, and 3 weeks, 3 and 9 months after baseline) were scheduled for control patients	Concluded that cannabis at average doses of 2.5g/d may be safe as part of a carefully monitored pain management program when conventional treatments have failed. Significant reduction in average pain intensity over 1 year in cannabis group (change = .92) but not in control group (change = .18). After adjusting for confounders, greater reduction in pain observed among cannabis users than controls (difference = 1.10). No difference in risk of serious adverse events between groups. Medical cannabis users were at increased risk of non-serious adverse events which were mild to moderate. No differences in secondary safety assessments. Neurocognitive function improved in both groups. After adjusting for tobacco smoking and other covariates, no significant change in slow vital capacity, functional residual capacity, and total lung capacity over 1 year among cannabis users. Cannabis users had a mean 50-mL decrease in FEV1 and a mean 1% decrease in the FEV1/FVC ratio, and increase in non-serious respiratory adverse events such as bronchitis
Cannabis: smoking (11%), oral (46%) and combined (43%)[102]	Fibromyalgia patients who were not cannabis users	Fibromyalgia patients who were cannabis users	56/56	Observational study comparing 100-mm VAS scales (VAS) before and at 2 hours of cannabis consumptions, 36-item Short Form Health Survey (SF-36), Fibromyalgia Impact Questionnaire (FIQ), Pittsburg Sleep Quality Index (PSQI)	After 2 hours of cannabis use, VAS scores showed statistically significant ($P<.001$) reduction of pain and stiffness, enhancement of relaxation, and increase in somnolence and feeling of well being. The mental health component summary score of the SF-36 was significantly higher ($P<.05$) in cannabis users than in non-users
Standardized oromucosal tincture spray (Sativex®; 0.1 mL sublingual spray = THC 2.7 mg:CBD 2.5 mg) with additional cannabis-based compounds (minor cannabinoids, terpenes, flavonoids)[103]	Placebo	Peripheral neuropathic pain with allodynia	125/105	Randomized double-blind, placebo-controlled, parallel design trial. 5 weeks plus open label extension option	Max dose 8 sprays/3 hours (THC 21.6 mg:CBD 20 mg), or 48 sprays/24 hours (THC 129.6 mg:CBD 120 mg). Mean daily sprays 10.9 (THC 29.4 mg:CBD 27.3 mg). Significantly less pain with Sativex® with mean pain decrease 22% (placebo 8%); 26% had 30% reduction (NNT 8.6) (placebo 15%); 20% had 50% reduction (NNT 8.5) (placebo 8%). Sativex® group also had significant benefit in sleep, allodynia, pain disability index. Open label extension showed initial pain relief was maintained without dose escalation for 52 weeks
Standardized oromucosal tincture spray (Sativex®; 0.1 mL sublingual spray = THC 2.7 mg:CBD 2.5 mg) with additional cannabis-based compounds (minor cannabinoids, terpenes, flavonoids)[104]	Placebo	Central neuropathic pain in MS	66/64	Randomized double-blind, placebo-controlled, parallel design trial. Treatment phase over 4 weeks	Max dose 8 sprays/3 hours (THC 21.6 mg:CBD 20 mg), or 48 sprays/24 hours (THC 129.6 mg:CBD 120 mg). Mean daily sprays 9.6 (THC 25.9 mg:CBD 24 mg). Significant reductions in pain and sleep disturbance with Sativex®. NNT 3.7
Standardized oromucosal tincture spray (Sativex®; 0.1 mL sublingual spray = THC 2.7 mg:CBD 2.5 mg) with additional cannabis-based compounds (minor cannabinoids, terpenes, flavonoids)[105]	Placebo	Rheumatoid arthritis	58/54	Randomized double-blind, placebo-controlled, parallel design trial. Treatment phase over 5 weeks	Mean daily sprays 5.4 (THC 14.6 mg:CBD 13.5 mg). Significant improvements in pain on movement, pain at rest, quality of sleep
Standardized oromucosal tincture spray (Sativex®; 0.1 mL sublingual spray = THC 2.7 mg:CBD 2.5 mg) with additional cannabis-based compounds (minor cannabinoids, terpenes, flavonoids)[106]	Placebo	Peripheral neuropathic pain with allodynia	246/173	Randomized, double-blind, placebo-controlled, parallel design trial. Treatment phase over 14 weeks	Max dose 8 sprays/3 hours (THC 21.6 mg:CBD 20 mg), or 24 sprays/24 hours (THC 64.8 mg:CBD 60 mg). Mean daily sprays 8.9 (THC 24 mg:CBD 22.3 mg). 34 patients in active treatment group had 30% or greater reduction in pain vs 19 in placebo (statistically significant). Also, statistically significant improvement in sleep

Table 1.—*(Continued)*

Agent	Control	Population	Enrolled / completed	Trial design	Results
Standardized oromucosal tincture spray (Sativex®; 0.1 mL sublingual spray = THC 2.7 mg:CBD 2.5 mg) with additional cannabis-based compounds (minor cannabinoids, terpenes, flavonoids) [107]	N/A	Central neuropathic pain in MS	63/34 completed >1 year; 28 completed full 2 year extension	Uncontrolled open label, 2-year extension trial for long term efficacy and tolerability. This followed a prior randomized double-blind, placebo-controlled, parallel design trial[94] which lasted 5 weeks (4 weeks treatment)	Mean NRS-11 pain scores in final week of initial randomized trial: 3.8 (5.0 placebo). In 28 subjects completing full 2-year open label extension, mean NRS-11 in final week: 2.9. Mean sprays per day by all patients after 1 year: 6.1 (THC 16.5 mg:CBD 15.3 mg), and 6.5 (THC 17.6 mg:CBD 16.3 mg) at 2 years. No evidence of tolerance
Standardized oromucosal tincture spray (Sativex®; 0.1 mL sublingual spray = THC 2.7 mg:CBD 2.5 mg) with additional cannabis-based compounds (minor cannabinoids, terpenes, flavonoids)[108]	N/A	MS associated pain, spasms	137/79 (92 followed for at least 1 year). These 137 patients (out of 160) were those whom felt benefit from Sativex in the initial randomized trial	Open label extension study assessing long-term efficacy. This followed a prior 6 week randomized double-blind, placebo-controlled, parallel design trial[95] which ended with a 4 week open label trial. (10 weeks total for initial study)	Sativex appeared to provide maintenance of symptom relief over the long term. Results showed that MS patients receiving symptom relief in the 1st 10 weeks maintain that relief over an extended time without needing an increased dose. Also, suddenly stopping Sativex did not cause any withdrawal syndrome, but MS symptoms did return over 5-10 days. Mean duration of study participation 434 days for patients remaining on treatment (79), and 225 days for patients who stopped (58). Mean sprays per day: 11 (THC 30 mg:CBD 28 mg). No evidence of tolerance
Standardized oromucosal tincture spray (Sativex®; 0.1 mL sublingual spray = THC 2.7 mg:CBD 2.5 mg) with additional cannabis-based compounds (minor cannabinoids, terpenes, flavonoids). Evaluated low dose (1-4 sprays/day), medium dose (6-10 sprays/day), high dose (11-16 sprays/day)[109]	Placebo	Adjunct to opioid-refractory cancer pain	360/263	Multicenter, randomized, double-blind, placebo-controlled, parallel group, graded-dose study for 5 week treatment periods	Secondary responder analysis of average daily pain was statistically significant for Sativex vs placebo overall, and specifically in the low and medium dose groups. Low dose group achieved 26% improvement in pain compared with baseline. However, primary endpoint of 30% pain reduction was not significant for Sativex. Significant sleep improvement with low dose, and non-significant sleep benefit with medium dose
Standardized oromucosal 0.1 mL sublingual tincture spray of cannabis-based compounds (minor cannabinoids, terpenes, flavonoids) and:a) THC 2.5 mg + CBD 2.5 mgb) 2.5 mg THC alonec) 2.5 mg CBD alone[110]	Placebo	Chronic pain	34/24	Initial 2-week open label period followed by 8-week randomized, double-blind, placebo-controlled, single-patient crossover trial. Subjects randomly received each of the 3 medications and placebo for two separate 1-week periods	Significant reduction in pain. and quality of sleep. Extracts that contained THC showed most benefit. Dose ranges varied between 1 and 8 sprays for a single dose
Standardized oromucosal 0.1 mL sublingual tincture spray of cannabis-based compounds (minor cannabinoids, terpenes, flavonoids) and: a) THC 2.5 mg + CBD 2.5 mg; b) 2.5 mg THC alone; c) 2.5 mg CBD alone[111]	Placebo	Neurogenic symptoms in spinal cord injury (4), MS (18), brachial plexus injury (1), limb amputation (1)	24/20	Randomized, double-blind, placebo-controlled, single-patient crossover trial in 2 week study periods	CBD significantly improved pain. THC significantly improved pain, muscle spasm, spasticity, and appetite. THC:CBD combination significantly improved muscle spasm and sleep. Max permitted dose 120 mg/24 hours
Standardized oromucosal 0.1 mL sublingual tincture spray of cannabis-based compounds (minor cannabinoids, terpenes, flavonoids) and THC 2.7 mg:CBD 2.5 mg (Sativex®) vs THC 2.7 mg[112]	Placebo	Neuropathic pain from brachial plexus avulsion	48/45	Randomized, double-blind, placebo-controlled, 3 period crossover trial in 2 week treatment periods. Followed by open label extension study of Sativex® (36/45; 83% entered)	Max dose 8 sprays/3 hours (THC 21.6 mg:CBD 20 mg), or 48 sprays/24 hours (THC 129.6 mg:CBD 120 mg). Statistically significant reductions in pain and sleep disturbance, but not to full 2 point reduction defined in study hypothesis. NNT for Sativex® 9, NNT for THC only 7.7
Standardized oromucosal 0.1 mL sublingual tincture spray of cannabis-based compounds (minor cannabinoids, terpenes, flavonoids) and THC 2.7 mg:CBD 2.5 mg (Sativex®) vs THC 2.7 mg only[113]	Placebo	Adjunct to opioid-refractory cancer pain	177/144	Multicenter, randomized double-blind, placebo-controlled, parallel design trial over 2 weeks	Primary endpoint of change from baseline mean pain numerical rating score statistically significant in favor of Sativex. 43% (greater than half) of Sativex group had >30% pain reduction compared to placebo (21%). Associated odds ratio statistically significant. The THC only group showed a non-significant improvement in pain. Sativex group had reduced breakthrough opioid dosing. Max dose 8 sprays/3 hours (THC 21.6 mg:CBD 20 mg), or 48 sprays/24 hours (THC 129.6 mg:CBD 120 mg). Average 8-12 sprays/d (22-32 mg THC, 20-30 mg/d CBD)

Table 1.—*(Continued)*

Agent	Control	Population	Enrolled / completed	Trial design	Results
Standardized oromucosal 0.1 mL sublingual tincture spray of cannabis-based compounds (minor cannabinoids, terpenes, flavonoids) and THC 2.7 mg:CBD 2.5 mg (Sativex®).[114] Max dose 12 sprays/24 hours	Placebo	Central neuropathic pain in MS	339/297	Multicenter (33 sites) phase III, 14 weeks parallel group randomized controlled double-blind trial, followed by 14 week open label extension	Statistically significant decrease in pain (>30% improvement from baseline) vs placebo at 10 weeks (P=.046), while at 14 weeks lower pain scores persisted for treatment group but not statistically significant. Secondary endpoints of mean change from baseline in Pain Numerical Rating Scale (NRS) (P=.028) and sleep quality NRS (0.015) both statistically significant in favor of treatment group
Oral cannabis extract (THC 2.5 mg bid titrated to effect/tolerability to a max 25 mg daily + CBD 0.8-1.8 mg)[115]	Placebo	Muscle stiffness and pain in MS	279/224	Randomized, double-blind, placebo-controlled, phase III trial over 12 weeks	Cannabis extract gave significant improvement in muscle stiffness (almost twice compared to placebo), pain, sleep, and spasms. Only 47% titrated up to THC 25 mg daily dose, most averaged 10 mg or 15 mg daily
Oral cannabis extract (Cannador) 5, 10, or 15 mg THC + variable CBD. THC:CBD ratios were 1:0.3 for the 5-mg dose (THC 5 mg:CBD 1.5 mg) and 1:0.5 for the 10 mg (THC 10 mg:CBD 5 mg) and 15 mg (THC 15 mg:CBD 7.5 mg) doses[116]	N/A	Postoperative patients requiring overnight patient-controlled analgesia with morphine	20/20	Multicenter randomized controlled dose-escalation trial. Pain relief, pain intensity, and side effects recorded over 6 hours	Rescue analgesia requested by 100% of patients receiving 5 mg, 50% of patients receiving 10 mg, and 25% of patients receiving 15 mg Cannador. NNT to prevent 1 rescue analgesia request for the 10-mg and 15-mg doses, relative to 5 mg, were 2.0 and 1.3, respectively. Overall, 10 mg was optimal dose in providing pain relief without serious side effects
Dronabinol 2.5 mg bid vs oral cannabis extract (THC 2.5 mg:CBD 1.25 mg and <5% other cannabinoids) bid. Dosing weight based; 30-49kg: 4 capsules daily, 50-69kg: 6 capsules daily, 70-89kg: 8 capsules daily, >89kg: 10 capsules daily[117]	Placebo	MS associated spasticity and pain	630/611	Multicenter, randomized, double-blind, placebo-controlled, parallel design trial for 15 weeks	Significant improvements in pain (Dronabinol: 50%, Cannabis extract: 57%, placebo: 37%) and spasticity (Dronabinol: 60%, Cannabis extract: 61%, placebo: 46%) reported by patients subjectively, although no improvement on spasticity by objective Ashworth scale
Dronabinol 10 mg vs 20 mg daily[118]	Placebo	Chronic non-cancer pain on opioids	30/29	Phase I: Randomized, single-dose, double-blinded, placebo-controlled, crossover trial, over three 8 hour visits. Phase II: Extended 4 week open-label multi-dose titrated trial as add-on to baseline opioid use	Phase I: Significant decrease in pain intensity with both 10 mg and 20 mg once daily doses.Phase II: Significant decrease from baseline pain scores
Dronabinol 5 mg bid[119,120]	Placebo	Central pain in MS	24/24	Randomized, double-blind, placebo-controlled, crossover trial in 3 week treatment periods	Significant reduction in pain. NNT for 50% relief 3.5. On quality of life scale, bodily pain and mental health indicated benefit
Dronabinol 20 mg vs morphine 30 mg vs Dronabinol-morphine 20 mg-30 mg[121]	Placebo	Healthy volunteers undergoing experimental pain tests (heat, cold, pressure, single and repeated transcutaneous electrical stimulation)	12/12	Randomized, double-blind, placebo-controlled, crossover trial in 8-hour study periods	Dronabinol-morphine statistically significant pain improvement compared to placebo and additively effective compared to morphine alone in repeated mode electrical stimulation. A slight additive analgesic effect was seen with Dronabinol-morphine in the single mode electrical stimulation compared to morphine alone. Dronabinol alone did not significantly reduce pain, and caused hyperalgesia in cold and heat tests, which was completely neutralized by Dronabinol-morphine. No analgesic effect in the pressure and heat test with Dronabinol or Dronabinol-morphine
Nabilone 0.5-1 mg. Titration from 0.5 mg qhs to 1 mg bid over 4 weeks[122]	Placebo	Fibromyalgia	40/33	Randomized, double-blind, placebo-controlled, parallel design trial	Significant decrease in both anxiety and pain at 4 weeks on 1 mg bid
Nabilone 1 mg[123]	Placebo	Spasticity related pain in upper motor neuron syndrome	13/11	Randomized, double-blind, placebo-controlled, crossover trial in 4 week treatment periods	Significant decrease in spasticity related pain with Nabilone 1 mg/day, but no significant decrease in spasticity itself
Nabilone 0.25-1 mg[124]	Placebo	Chronic musculoskeletal spinal pain (although "headache" was also monitored)	30/21	Randomized, double-blind, placebo-controlled, crossover trial in 4 week treatment periods followed by 16 week medication switch with free choice of study drugs	Significant decrease in spinal pain with Nabilone. Also noted significant decrease in headache intensity, increase in headache-free days, and increase in quality of life. In medication switch period, number of subjects favoring Nabilone was > 4x higher than those favoring placebo
Nabilone 0.5 m g daily[83]	Ibuprofen 400 mg daily	Medication overuse headache (MOH)	30/26	Randomized, double-blind, active-controlled, crossover trial in 8 week treatment periods	Nabilone superior in reducing daily analgesic intake, pain intensity, level of medication dependence, and improve quality of life

Table 1.—*(Continued)*

Agent	Control	Population	Enrolled / completed	Trial design	Results
Nabilone 0.5 mg bid titrated to 1-2 mg bid over initial 4 week phase. Dose achieved continued for next 5 week phase.[125]	Placebo	Diabetic neuropathy	Phase 1: 34/37Phase 2:25/26 (1 placebo dropped out due to lack of efficacy)	Randomized, double-blind, placebo-controlled, parallel design trial with 4 week single blind flexible dose phase, followed by 5 week double blind maintenance phase for subjects receiving >30% pain improvement in initial single blind phase (26/37)	Nabilone significantly more effective at improving pain, sleep, and anxiety. 11/13 (Nabilone) vs 5/13 (placebo) had 30% or greater reduction in pain in second double blind phase; 26/37 received >30% pain improvement in initial single blind phase
Nabilone 1 mg bid adjunct to Gabapentin[126]	Placebo	MS neuropathic pain	15/14	Randomized, double-blind, placebo-controlled, parallel design trial for 9 weeks (4 week titration, 5 week maintenance)	Significant improvement in pain and patient-rated global impression of change with addition of Nabilone
Oral THC 10 mg, 20 mg vs codeine 60 mg, 120 mg[127]	Placebo	Cancer pain	36/34	Randomized, double-blind, placebo-controlled trial	Analgesia of THC 10 mg comparable to codeine 60 mg, and THC 20 mg comparable to codeine 120 mg. Analgesic effect of THC 20 mg was statistically significant compared to placebo, but this was outweighed by sedation
Oral THC 5 mg, 10 mg, 15 mg, 20 mg[128]	Placebo	Cancer pain	10/10	Randomized, double-blind, placebo-controlled trial	Significant trend toward progressive relief of pain with increasing THC doses. Pain relief with THC was significantly higher than placebo at high dose levels of 15 mg and 20 mg. Low doses of 5 mg and 10 mg showed a trend toward greater pain relief than placebo. Analgesic effect of THC developed gradually and was prolonged. Sedation outweighed benefit at 20 mg
Oral THC daily dose of 2.5-15 mg, with a weekly increase of 2.5 mg if tolerating[129]	N/A	Fibromyalgia	9/4	Treatment over 3 month period	Electrically induced pain was significantly attenuated after doses of 10-15 mg THC ($P < .05$). Daily recorded pain levels were significantly reduced ($P < .01$)
Oral THC 5 mg vs codeine 50 mg[130]	Placebo	Spasticity and pain due to spinal cord injury	1/1	Single case, randomized double-blind, placebo-controlled trial. The 3 options were applied in a randomized pattern 18 times in a single patient and compared	THC and codeine both had an analgesic effect compared to placebo, but only THC showed a significant benefit on spasticity
Combination of 2 compounds; one 19% THC and the other 0.4% THC + 9% CBD 200 mg doses of this compound combination in a 200 mL 50% fat emulsion was studied as prophylaxis, as well as additional acute dosing[82]	Amitriptyline 25 mg daily in chronic migraine prophylaxis group Verapamil 480 mg daily in chronic cluster prophylaxis group	Prophylaxis and acute treatment in both chronic migraine and chronic cluster headache	Phase 1: 48/48 chronic migrainePhase 2:79/79 chronic migraine48/48 chronic cluster	Phase 1: dose finding to determine effective acute dosing in 48 chronic migraine volunteers starting with an oral dose of 10 mg of cannabinoid combination and titrated up Phase 2: Chronic migraine randomly assigned to 3 months prophylaxis treatment with 25 mg/day Amitriptyline or THC+CBD 200 mg/day. Chronic cluster randomly assigned to 1 month prophylaxis with Verapamil 480 mg/day or THC+CBD 200 mg/day. For acute pain attacks, additional dosing of THC+CBD 200 mg was allowed in both groups	Phase 1: Doses < 100 mg THC-CBD produced no benefit. With 200 mg THC-CBD, acute migraine pain intensity decreased by 55% Phase 2: THC+CBD 200 mg prophylaxis led to a 40.4% improvement vs 40.1% with Amitriptyline in migraine group, but no benefit in cluster group. Additional acute THC+CBD 200 mg dosing decreased pain intensity in migraine patients by 43.5%. This same result was seen in cluster headache patients, but only if they had a history of migraine in childhood. In cluster headache patients without a previous history of childhood migraine, the additional THC-CBD 200 mg treatment provided no benefit as an acute treatment
Synthetic nitrogen analog of tetrahydrocannabinol (NIB). 1st trial compared NIB 4 mg with codeine 50 mg. The 2nd trial compared NIB 4 mg with secobarbital 50 mg[131]	Placebo	Advanced cancer pain	1st trial: 30/26 2nd trial: 15/15	2 consecutive randomized, double-blind, placebo-controlled, crossover trials. 3 successive days on each treatment in each trial	1st trial: NIB superior to placebo and equivalent to codeine 50 mg 2nd trial: NIB superior to both placebo and secobarbital 50 mg
Ajulemic acid (AJA), or CT3: synthetic analog of the THC metabolite THC-11-oic acid. 20 mg bid x 4 days, then 40 mg bid x 3 days[132,136]	Placebo	Chronic neuropathic pain with hyperalgesia and allodynia	21/19	Randomized, double-blind, placebo-controlled, crossover 5-week trial in two 7-day treatment periods	Significant improvement in pain intensity 3 hours after AJA. Mechanical hypersensitivity also showed a strong tendency toward decreasing sensitivity in the AJA group, but not statistically significant. NNT for 30% pain relief were 2.14 for 1st treatment group and 5.29 for 2nd treatment group

outcomes data reported in the second study.[132,136] There was a total of 1889 enrolled patients in the trials with statistically significant positive outcomes in 56 studies identified initially, but 18 of them were excluded because they did not specifically examine pain outcomes, instead examining spasticity, cramps, or other global measure of benefit. The 27 studies showing positive outcomes included experimentally induced pain in healthy volunteers,[96,97,121] cancer-related pain,[113,131] chronic neuropathic pain with hyperalgesia and allodynia,[93,103,132,136,138] chronic pain in fibromyalgia,[122] chronic pain in rheumatoid arthritis,[105] chronic pain in MS,[104,107,108,117,119,120] chronic pain from chronic upper motor neuron syndrome/spasticity,[111,123,130] unspecified chronic noncancer pain,[110,118,124] and chronic neuropathic pain from HIV, complex regional pain syndrome (CRPS), trauma, or surgery.[91,92,94]

In 2015, the same authors of the 2011 systematic review[135] published an updated systematic review of additional randomized controlled trials evaluating cannabis/cannabinoids in the treatment of chronic noncancer pain.[139] They found 11 additional well designed randomized controlled trials evaluating 1135 enrolled patients, of which 64% (7/11) of the trials demonstrated statistically significant analgesic effects of cannabis/cannabinoids compared to controls. There was a total of 672 enrolled patients in these trials with statistically significant positive outcomes. The 7 studies showing positive outcomes included reduction in daily analgesic intake, pain intensity, and level of dependence in medication overuse headache,[83] diabetic neuropathy,[125] MS pain, muscle stiffness and spasticity pain,[95,115,126] neuropathic pain associated with allodynia,[106] and neuropathic pain.[98] There was an additional study included in this review that evaluated a THC/CBD oromucosal cannabis spray in central neuropathic pain in MS.[114] It showed a statistically significant reduction in pain compared to placebo at 10 weeks, but not at 14 weeks, so it was not included as a positive study in this systematic review.

A systematic review and meta-analysis published in *JAMA* in 2015 evaluated 79 trials involving cannabis/cannabinoids for medicinal use (28 in chronic pain) and concluded that there was moderate-quality evidence to support their use for the treatment of chronic pain and spasticity. Compared with placebo, cannabis/cannabinoids were associated with reduction in pain, greater average reduction in numerical scale pain assessment, and average reduction in the Ashworth spasticity scale.[140] A second 2015 *JAMA* medical literature review included 6 trials involving 325 patients examining chronic pain, 6 trials involving 396 patients investigating neuropathic pain, and 12 trials involving 1600 patients focusing on MS.[141] They conclude that the use of marijuana for chronic pain, neuropathic pain, and spasticity due to multiple sclerosis is supported by high-quality evidence. A third systematic review in 2015 assessing the effectiveness of cannabis extracts and cannabinoids in the management of chronic nonmalignant neuropathic pain in 13 trials also suggested that these therapies may provide effective analgesia in conditions that are refractory to other treatments.[142]

The FDA approved 188 novel drugs for 206 indications based on 448 pivotal efficacy trials between 2005 and 2012.[143] The median number of pivotal trials per approved indication was only 2, although 74 indications (36.8%) were approved on the basis of only one pivotal trial. There were 4 drugs approved without any pivotal efficacy trial. Nearly all trials were randomized, double-blinded, and used either a placebo or an active comparator. The median number of patients enrolled per indication among all pivotal trials was 760. Another review of the new drugs available in the last 30 years showed that more than 35% of them had a direct natural origin, and that number rose to over 60% when taking into account all drugs whose structure was based from a natural pharmacophore.[144,145] Taking this into account, the number of studies and amount of evidence for the use of cannabis/cannabinoids in the treatment of pain continues to grow, and thus it is now considered a plausible option. The Canadian Pain Society now recommends cannabinoids as a third-level therapy for chronic neuropathic pain.[22] The US National Academies of Sciences, Engineering, and Medicine now states that cannabis use for the treatment of pain is supported by well-controlled clinical trials with substantial evidence that it is an effective treatment for chronic pain in adults.[23]

CANNABIS AND CANNABINOIDS IN THE OPIOID EPIDEMIC

Given the supporting evidence of cannabis/cannabinoids in pain management, some advocate for using them as a replacement for opioids. Substituting cannabis for alcohol, illicit drugs, and/or prescription medication has been observed in cross sectional surveys that suggested a harm reduction role in their use, along with implications for abstinence-based substance use treatment strategies.[146–148] The "opioid-sparing effect" of cannabinoids has been well described with extensive supporting evidence showing synergy between cannabis and opioids that results in decreased opioid dose requirements.[99,149] CB1 receptors are 10 times more concentrated then mu-opioid receptors in the brain, and cannabinoid receptors co-localize with opioid receptors in many regions involved in pain circuitry including the dorsal horn of the spinal cord. This results in synergistic augmentation of the analgesic opioid effects and decreased opioid dose requirements.[99,150–160] The interaction is suspected to be from pharmacodynamic mechanisms, since studies have

shown cannabis use did not affect blood levels of oxycodone or morphine.[99,151] Cannabinoid receptor agonists raise endogenous opioid peptide release, and chronic THC use increases endogenous opioid precursor gene expression in supraspinal and spinal structures involved in pain perception.[99,151,161,162]

In a study of chronic pain patients on a daily regimen of morphine or oxycodone, the addition of vaporized cannabis augmented the analgesic effect of opioids.[99] Pain significantly decreased (average 27%) after the addition of vaporized cannabis, and there was no effect on plasma opioid levels. Another large meta-analysis showed that 17 of 19 preclinical studies provided good evidence of synergistic effects from opioid and cannabinoid co-administration, and that the median effective dose (ED50) of morphine administered with THC is 3.6 times lower than the ED50 of morphine alone.[149] The ED50 for codeine administered with THC was 9.5 times lower than the ED50 of codeine alone. In summary, the authors stated that preclinical studies provide robust evidence of the opioid-sparing effect of cannabinoids.[149]

States with medicinal cannabis laws have a 24.8% lower mean annual opioid overdose mortality rate compared with states without medicinal cannabis laws.[163] There is an association between the implementation of medicinal cannabis laws and opioid mortality. In each year following the implementation of the law, the rates of overdose mortality declined, a trend that continued over time: year 1 (–19.9%; $P = .002$), year 2 (–25.2%; $P = .01$), year 3 (–23.6%; $P = .04$), year 4 (–20.2%; $P = .02$), year 5 (–33.7%; $P = .008$), and year 6 (–33.3%; $P < .001$).

The reduction of opioid dosing when used in combination with cannabis/cannabinoids reduces side effects and allows for easier detoxification and weaning due to less of a tolerance and withdrawal from opiates, and rekindling of opiate analgesia after prior dosages have worn off.[159] Because of the cannabis-opioid synergistic interactions as suggested by available data, cannabis has been suggested as a tool in the opioid detoxification and weaning process.[148,164–166] Some pain specialists have suggested the use of medicinal cannabis in addition to or as a replacement for opiates to help reduce overdose mortality and morbidity associated with opiate use.[167]

In a prospective study, chronic pain patients who used cannabis had improved pain and functional outcomes as well as a significant reduction in opioid use.[168] Medical cannabis use was associated with decreased opiate use, improvement in quality of life, and better side effect profile in a retrospective cross-sectional survey of chronic pain patients.[169]

Unfortunately, most chronic pain management programs have rules and "opioid contracts" mandating patients to be free of cannabis/cannabinoid use for enrollment and ongoing treatment. Given the abundance of evidence-based medicine and research on cannabinoid-opioid synergy, these policies seem quite outdated and should be re-evaluated. Patients using cannabis/cannabinoids may inadvertently be assisting their own detox and weaning from opiates. Chronic pain management programs should harness this potential benefit within their treatment program and use it to their patients' advantage.

THE CANNABINOIDS

Over 540 phytochemicals, 18 different chemical classes, and more than 100 different phytocannabinoids have been described in cannabis.[21,145] Phytocannabinoids accumulate and are concentrated in the secretory cavity of the glandular trichomes, primarily in female flowers and aerial parts of the plant.[145] Phytocannabinoid levels in hempseeds and hempseed oil are very low, as the seed and the stem contain only trace amounts of THC or CBD.[170,171] This point is important to those purchasing "CBD oil" and "hemp oil" seed-based products because the phytocannabinoid levels are subtherapeutic. Cannabinoid acids are found as the primary metabolite precursors to the cannabinoids in raw and live cannabis and have no psychotropic qualities. These acidic phytocannabinoids are decarboxylated by heat (such as from smoking or vaporizing), UV exposure, and prolonged storage to form the active cannabinoids. The predominant cannabinoid acids are tetrahydrocannabinolic acid (THCA) that is converted to Δ^9-tetrahydrocannabinol (THC), cannabidiolic acid (CBDA) that is converted to cannabidiol (CBD), cannabinolic acid (CBNA) that is converted to cannabinol (CBN), cannabigerolic acid (CBGA) that is converted to cannabigerol (CBG), cannabichromenic acid (CBCA) that is converted to cannabichromene (CBC), tetrahydrocannabivarin acid (THCVA) that is converted to tetrahydrocannabivarin (THCV), and cannabidivarinic acid (CBDVA) that is converted to cannabidivarin (CBDV).[145,172,173]

THC is a major cannabinoid and the most researched in cannabis. It is the primary source of the psychoactive side effects of cannabis. THC is a partial agonist at CB1 and CB2 receptors with preferential binding to CB1, and is also an agonist at the PPAR-γ and TRPA1 receptors.[49] Other reported mechanisms include 5HT3A antagonism, glycine receptor activation enhancement by allosteric modification, reducing elevated intracellular calcium levels from TRPM8 activity (cold and menthol receptor 1 [CMR1]), elevating calcium levels by TRPA1 or TRPV2, and stimulating G protein receptor 18 and other nuclear receptors.[173–182] Its actions at the CB1 receptor account for its psychoactive effects, thought to be mediated to some extent by modulation of both glutamate and GABA systems.[49,62,183–185]

NMDA mechanisms play a significant role in secondary and tertiary hyperalgesia in chronic pain syndromes such as fibromyalgia and chronic migraine.[186] THC reduces NMDA responses by 30-40% with associated antioxidant neuroprotective effects,[187–189] inhibits CGRP activity,[190] blocks capsaicin-induced hyperalgesia,[191] decreases 5HT reuptake, increases cerebral 5HT production, and inhibits 5HT release from platelets. All of these mechanisms could certainly influence trigeminovascular migraine circuitry.[14–16,161]

THC has well documented analgesic and anti-inflammatory benefits including arthritic and inflammatory conditions,[49,127–130,187,192–216] is 20 times more anti-inflammatory than aspirin, and twice as anti-inflammatory as hydrocortisone. [217] THC enhances analgesia from kappa opioid receptor agonist medications.[155,160,218,219] Intrathecal and intraventricular administration of THC produces analgesia similar to opioids.[204] THC also stimulates production of beta-endorphin and increases proenkephalin mRNA levels in brainstem regions involved in pain processing.[158,159,162]

There are numerous positive studies in various chronic pain syndromes showing a benefit of THC with smoked or vaporized cannabis and comparing different percentages of THC.[220,91–102] Unfortunately, percentages of other cannabinoids including CBD and other important compounds such as terpenes were not assessed in most of these trials. Because of the known entourage effects of cannabis[20,21] and the influence of the activity of cannabinoids and terpenes on one another, it is unclear if these study results are due to THC alone or due to the contribution of other undefined cannabinoids and terpenes.

There have been multiple studies confirming benefit in various chronic pain syndromes with an oral-mucosal spray called nabiximols (Sativex),[103–115,117,137,221–231] which has been approved in 30 countries. This is a tincture of cannabis made from cannabis plants rather than a synthetic form.[232] Each spray delivers a standardized dose of 2.7 mg THC and 2.5 mg CBD, along with additional cannabinoids, flavonoids, and terpenes in unmeasured small amounts. Despite the standardized THC:CBD ratio, the company doesn't mention what the actual concentrations of terpenes and other compounds are or how much variability exists. Similar to the smoked and vaporized studies, this missing information adds a layer of uncertainty as to what components are providing most of the benefit. Of note, one of these studies compared 3 varieties of this spray; 1:1 THC:CBD vs THC alone vs CBD alone. The spray that contained THC showed the most pain benefit.[110] Other cannabis extract studies of varying amounts of THC and CBD have also shown pain benefit.[115,116]

THC has potent anti-emetic benefits in adults[49,192,193,233–273] and children.[270,274–276] Migraine-associated nausea and vomiting would certainly be another therapeutic benefit. The antiemetic effects led to FDA approval for 2 synthetic forms of THC in the treatment of chemotherapy related nausea and vomiting, dronabinol,[277] and nabilone.[278] These 2 synthetic forms of THC have also been shown to have analgesic benefit.[81,83,84,117-126,279–282] There have been other benefits of THC reported also, including antioxidant and neuroprotective,[187,189,283–286] Alzheimer's disease,[287–291] amyotrophic lateral sclerosis (ALS),[292–296] MS,[104,106-108,114,115,117,137,197,221,224–231,297–299] autism,[300–304] Parkinson's,[305–312] Tourette's syndrome,[312–318] Huntington's disease/chorea,[319–321] depression,[322–324] posttraumatic stress disorder (PTSD),[325–329] sickle cell disease pain,[330,331] traumatic brain injury (TBI),[285,332–334] hypothermia,[335–339] duodenal ulcers,[340] anorexia and cachexia,[341–354] inflammatory bowel disease,[355–358] spinal cord injury,[359–361] antispasmodic, muscle relaxation, and spasticity,[130,229,298,299,362–366] antibacterial effects against methicillin-resistant *Staphylococcus aureus* (MRSA) strains,[367] anti-proliferative/pro-apoptotic against tumor cell lines of multiple organ systems including brain, breast, colon, and blood,[368–379] psoriasis,[380,381] bronchodilatation and asthma,[382–384] diabetes,[385] obesity,[386] glaucoma,[387–399] and as an antipruritic in cholestatic jaundice.[400]

CBD is the second major cannabinoid and has gained attention as a therapeutic agent over the past several years due to its lack of psychoactivity. In November 2017, The World Health Organization (WHO) announced that CBD in humans exhibits no evidence for abuse or dependence potential, and that there is no evidence of public health related problems associated with the use of pure CBD.[401] In January 2018, the World Anti-Doping Agency (WADA) removed CBD from their prohibited list, no longer banning use by athletes.[402]

CBD has much lower affinity for CB1 and CB2 receptors as compared to THC, and it acts as a noncompetitive CB1 and CB2 receptor antagonist.[403] This activity underlies its neutralizing actions on THC side effects such as anxiety, tachycardia, and sedation.[404–409] CBD seems to attenuate some of the negative side effects of THC when the CBD:THC ratio is at least 8:1 (± 11.1), but CBD may potentiate some of the THC side effects when the CBD:THC ratio is around 2:1 (± 1.4).[407,409] CBD was also shown to reduce cognitive and memory impairments that have been attributed to THC.[410] It is an inverse agonist at the CB2 receptor, which may contribute to its anti-inflammatory effects.[403]

CBD also interacts with a variety of ion channels, enzymes, and other receptors. [49,62,192,193,259,411] It inhibits AEA uptake and metabolism and acts as a TRPV1 agonist, similar to capsaicin, although without the noxious sides effects.[177–179,368,412] It acts as a positive allosteric modulator at α1 and α1β glycine receptors.[413] This has been suggested to play a role in chronic pain after inflammation or nerve injury, because glycine acts as an inhibitory postsynaptic neurotransmitter in the dorsal

horn of the spinal cord. CBD acts as a μ opioid receptor ligand and a positive allosteric modulator at μ and δ opioid receptors suggesting that it may enhance opiate effects.[49] CBD has additional actions that may account for its anti-inflammatory and analgesic effects including TRPA1 agonist, TRPV1 agonist, TRPM8 antagonist,[177–179] TRPV2 agonist by mediating CGRP release from dorsal root ganglion neurons,[414] T-type calcium^{2+} channel inhibitor,[415] suppresses tryptophan degradation (precursor to 5HT),[416] and phospholipase A2 modulator.[417] CBD has powerful analgesic and anti-inflammatory effects[49,142,187,192–194,196–199,209,330,403,411,418–437] mediated by both cyclooxygenase and lipoxygenase inhibition. In animal studies, its anti-inflammatory effect proved to be several hundred times more potent than aspirin.[217,438] There are other mechanisms by which CBD works in different pathways including 5-HT1A agonist,[49,439] regulator of intracellular calcium^{2+},[440,441] fatty acid amide hydrolase (FAAH; breaks down AEA) inhibition,[368] GPR55 antagonist,[43] adenosine uptake competitive inhibitor,[442] PPARγ agonist,[443] 5-lipoxygenase and 15-lipoxygenase inhibitors,[444] and antagonism of the abnormal-CBD receptor.[49,445]

There is medical evidence showing that CBD may be effective in treatment of a wide range of disorders[446] including epilepsy (particularly medically-refractory pediatric epilepsy syndromes),[49,447–472] Alzheimer's disease,[473–488] Parkinson's disease,[305,310–312,411,487–497] MS,[104,106-108,111,114,115,117,137,197,221,224–231,297,431–433,498–502] Huntington's disease,[321,485,503–505] ALS,[292,293,506] anxiety disorders including PTSD,[325,327,334,494,507–527] depression,[322,509,510,528–530] dystonia,[531,532] Meige's syndrome,[533] schizophrenia and psychosis,[493,509,534–545] stroke and hypoxic-ischemic injury,[478,546–554] antioxidant,[187,189,283] TBI,[552,553,555–558] spinal cord injury,[360,361] inflammatory disorders,[197,429–433,500] psoriasis,[380,381] rheumatoid arthritis,[421] a wide range of cancers across multiple organ systems including brain, blood, breast, lung, prostate, and colon,[262,368,369,379,446,559–582] graft vs host disease,[583] prion disease,[584] infection against MRSA,[367] inflammatory bowel diseases,[357,358,585–588] nausea,[259,589–591] appetite suppressant and weight loss,[592–594] bone formation, osteoporosis and fracture healing,[595–598] hepatic encephalopathy and cirrhosis,[599–603] cardiovascular diseases including hypertension, cardiomyopathy and myocardial ischemia,[426,604–609] and diabetic complications,[609–613] including diabetes-induced peripheral neuropathy.[434] There have been no studies evaluating pure CBD in the treatment of chronic pain or headache disorders to date.

The 2 main cannabinoid acids that have shown medicinal benefit are CBDA and THCA. CBDA is often obtained through consumption of raw cannabis juice and is a TRPA1 agonist,[177] TRPV1 agonist,[368] and TRPM8 antagonist.[177] This may reflect a potential role as an analgesic and anti-inflammatory[193,199,614] via selective COX2 inhibition. Other benefits include anti-proliferative/pro-apoptotic effects against breast, thyroid, glioma cancer cells,[368,561,615,616] and anti-nausea effects.[272,617]

THCA has anti-inflammatory[199] and anti-nausea effects.[618] It is a TRPA1 partial agonist,[177] and TRPM8 antagonist[177] which may reflect a potential role in analgesia. It has insecticidal effects,[619] potential anti-Parkinson's benefits,[305] and benefit in prostate cancer.[620] CBGA also has insecticidal effects.[619]

The most common minor cannabinoids include CBN, CBG, CBC, THCV, and CBDV. CBN is a product of THCA oxidation. As dried cannabis ages, THCA converts to CBNA, which then converts to CBN. Therefore, the older that dried cannabis is, the more CBN it contains. It has approximately 10% of the activity of THC and is a weak CB1 and CB2 partial agonist that binds stronger to CB2 than CB1.[49,173] It is the most sedative[621–625] of the cannabinoids, suggesting a potential role in insomnia and sleep disorders. Other benefits include anti-inflammatory,[105,217,417,626] analgesic,[203] anticonvulsant,[363,463,623,624] burn relief by TRPV2 agonism and mediation of CGRP release,[203,414] ALS,[506] antibacterial effects against MRSA strains,[367] promotion of bone formation,[595,627–629] appetite stimulant,[592] glaucoma,[388,630] and psoriasis.[380,381]

CBG is found in larger quantities in low THC cannabis strains, and especially in hemp strains. It is a CB1 and CB2 partial agonist,[49] CB1 antagonist,[631] TRPA1 agonist, TRPV1 agonist,[368] TRPV2 agonist, TRPV3 agonist, TRPV4 agonist and TRPM8 antagonist,[44,176–179,368] which may reflect a potential role in analgesia that has been described.[422] CBG is anti-inflammatory by phospholipase A2 modulation and reduction of PGE2,[105,417] and an inhibitor of AEA reuptake.[368] CBG has GABA uptake inhibitor effects,[632] and is a potent α2-adrenoreceptor agonist suggesting a potential role in α2-adrenoceptor-mediated analgesia.[631] CBG has antidepressant effects,[633] and a potent 5HT1A receptor antagonist that has been a proposed mechanism for potential antidepressant activity.[631] Benefits have been described for several issues including Huntington's disease,[634] as an appetite stimulant,[635] antibacterial effects against MRSA strains,[367] antifungal effects,[636] psoriasis,[381] inflammatory bowel disease,[637] anti-proliferative/pro-apoptotic against tumor cell lines of multiple organ systems,[178,179,368,638,639] glaucoma,[630,640] and potential benefit for detrusor overactivity and bladder pain.[641,642]

CBC is a potent TRPA1 agonist[177] that may reflect a potential role in analgesia, and a weak AEA reuptake inhibitor.[368] It interacts at TRPV1-4, and TRPV8 receptors.[643] Sedation, analgesic, and strong anti-inflammatory effects including superiority to phenylbutazone have been shown.[105,202,363,437,644–646] It may have antimicrobial effects against fungi and bacteria

including MRSA,[367,636,645] cytotoxicity in cancer cell lines,[368] antianxiety/antidepressant effects, promotion of neurogenesis,[322,647,648] potential use in inflammatory bowel disease,[649] and the ability to reduce THC intoxication symptoms.[650]

THCV is a propyl analog of THC. THCV antagonizes THC at the CB1 receptor at doses less than 3 mg/kg, is a CB1 agonist at doses greater than 10 mg/kg, and is also a CB2 partial agonist.[49,651,652] It increases GABA release, central nervous system inhibitory neurotransmission,[653] and has shown efficacy in experimental epilepsy models.[49,654] It has anti-nociception and anti-inflammatory effects.[49,655,656] Similar to synthetic CB1 antagonists, it causes decreased food intake, anorexia, and thus a potential weight loss treatment for obesity,[657–659] was effective in obesity-associated glucose intolerance,[660] and had beneficial effects on bone formation and fracture healing.[595,596]

Cannabidivarin (CBDV) is the propyl analog of CBD, but has an unknown mechanism of action. It has anticonvulsant activity in the hippocampus, comparable to felbamate and phenobarbitone,[456,654] and has bone formation and fracture healing benefits.[595,596]

TERPENES (TERPENOIDS)

The terpenes and terpenoids are major constituents of plant resins and essential oils, and are attributed to the pharmacological properties of many medicinal herbs, including cannabis. Terpenes are basic hydrocarbons as opposed to terpenoids that contain extra functional groups of a wide range of chemical elements. However, these terms are often used interchangeably in the literature. Terpenes form the largest group of phytochemicals.[145] Cannabis contains up to 200 different terpenes,[21] although this publication will focus on the primary and secondary terpenes which are generally present in the greatest concentrations. Terpenes are fragrant essential oils secreted by many different types of plants and herbs, including cannabis. They are the source of variable aromas, flavors, and other characteristics that help differentiate between cannabis strains.

They are lipophilic and have widely variable sites of action including neurotransmitter receptors, muscle and neuronal ion channels, G-protein receptors, enzymes, cell membranes, and second messenger systems.[21,661,662] Terpenes work both individually and synergistically with the cannabinoids for a variety of therapeutic effects. Terpenes may also increase the blood-brain barrier permeability, which led to a patent for a transdermal cannabinoid patch using a terpene as the permeation agent.[145,663] Terpenes may also influence the binding of THC to CB1 receptors, and interact with other neurotransmitter receptors that contribute to cannabinoid-mediated analgesia effects.[21,664] They have medicinal benefits including anti-inflammatory, analgesia, anxiolytic, antidepressant, anti-insomnia, skin penetration enhancement, cancer chemoprevention, antiviral, antibacterial, antifungal, anti-parasitic, and anti-hyperglycemic effects,[665] although it is important to note that the vast majority of these data come from preclinical studies involving animal models or in vitro studies. Some of the reported benefits attributed to individual terpenes come from studies evaluating whole essential oils or plants in which the specified terpene may be a predominant constituent. It is important to note that the therapeutic contribution from some of the other minor terpenes in some of these studies cannot be excluded. The most common primary terpenes found in cannabis are β-caryophyllene, myrcene, α-pinene, humulene, linalool, limonene, terpinolene, terpineol, ocimene, valencene, and geraniol. Some of the more common secondary terpenes in cannabis are α-bisabolol, nerolidol, caryophyllene oxide, phytol, borneol, δ-3-carene, terpinene, camphene, sabinene, cineole (eucalyptol), phellandrene, guaiol, isoborneol, cedrene, geranyl acetate, fenchol, camphor, menthol, isopulegol, cymene, citral, and citronellol.

Beta-caryophyllene (β-caryophyllene) is the more common of two forms of caryophyllene. It is found in cinnamon, cloves, black pepper, oregano, basil, rosemary, and hops. It has analgesic effects in inflammatory and neuropathic pain,[666] and has potent anti-inflammatory,[667–670] local anesthetic,[671] antioxidant,[672–674] anti-cancer,[672,675–678] and gastric cytoprotector effects.[679,680] Its anti-inflammatory effects occur via PGE-1,[681] with similar efficacy to indomethacin and etodolac,[682,683] and comparable to phenylbutazone.[681] β-caryophyllene is anti-fungal, anti-bacterial against *Staphylococcus aureus*,[684] anti-malarial,[685] beneficial in inflammatory bowel disease,[686] and anti-pruritic in contact dermatitis.[687] It is a selective CB2 agonist.[672,688,689] CB2 receptors have been implicated in anxiety and depression disorders, and caryophyllene has shown anxiolytic and antidepressant-like effects.[690] Research has also suggested that CB2 receptors play a major role in alcohol reward and the CB2 receptor system appears to be involved in alcohol[688] and cocaine[691] dependence and sensitivity via modulation of dopamine reward pathways. β-caryophyllene has been shown to reduce voluntary alcohol intake and attenuate ethanol-induced place preference and sensitivity in mice,[688] as well as decrease cocaine self-administration.[691] It may therefore represent a potential pharmacological target for the treatment of alcohol and cocaine abuse, and perhaps other abused substances in which the dopamine reward pathways are central to the pathophysiology. Trans-caryophyllene was shown to suppress hypoxia-induced neuroinflammatory responses,[692] and help regulate lipids.[693]

Myrcene is common in highly aromatic plants such as sweet basil, bay leaves, lemongrass, wild thyme, parsley, tropical fruits such as mango, and hops. It has potent anti-inflammatory, analgesic, and anxiolytic properties[694,695] and is used extensively in the cosmetics industry. The analgesic effects of myrcene were antagonized by naloxone suggesting an opioid-mediated mechanism.[695,696] It also has effects as a muscle relaxant, hypnotic, prominent sedation,[697] sleep aid,[698] and antioxidant.[699] It has significant anti-inflammatory effects[700] via prostaglandin E2[695] and anti-catabolic effects in human chondrocytes suggesting potential anti-osteoarthritic activity and the ability to halt, or at least slow down cartilage destruction and osteoarthritis progression.[701] It has also been shown to block hepatic carcinogenesis by aflatoxin in rats,[699] although there was concern of potential carcinogenesis in a separate rodent study.[702]

Alpha-pinene (α-pinene) accounts for the aroma of fresh pine needles, conifers, and sage, and is produced by many herbs such as parsley, rosemary, basil, and dill. It is the most commonly occurring terpene in nature.[703] It has shown antioxidant activity[704,705] and anti-inflammatory effects[706,707] in human chondrocytes suggesting potential anti-osteoarthritic activity,[708,709] as well as anti-inflammatory effects by PGE-1.[710] Anti-inflammatory effects in acute pancreatitis[711] and anti-nociception effects[712] have been demonstrated. It is an acetylcholinesterase inhibitor that may aid in memory and help to counter short-term memory loss associated with THC.[713–715] It has anti-fungal and broad-spectrum anti-bacterial effects[716–721] including against gram negative and positive bacteria such as *Staphylococcus aureus*, including MRSA.[684,722–724] Alpha-pinene has bronchodilator effects,[21,725] antiviral action[726] against anti-infectious bronchitis virus (IBV),[727] activity against herpes simplex virus-1 (HSV1) and severe acute respiratory syndrome (SARS),[728] and is an insect repellent.[703,729] It showed antiproliferative effects[678] and reduced melanoma tumor growth,[730] and has anti-cancer effects[717] against neuroblastoma cells[705] and in hepatic carcinoma cell lines.[731]

Humulene (α-caryophyllene) is an isomer of β-caryophyllene and plays a strong role in many of the distinguishing characteristics between different cannabis strains. It is found in herbs and spices such as hops, clove, basil, sage, ginger, spearmint, and ginseng as well as some fruits and vegetables. It has strong anti-inflammatory properties comparable to dexamethasone systemically, topically, and in allergic airway inflammation,[667–669,732,733] as well as anti-nociceptive and analgesic properties.[733] It has anti-cancer activity,[675,676,734] is anti-bacterial including activity against *Staphylococcus aureus*,[684] and insecticidal/larvicidal effects[735] have been documented. There are anecdotal reports that it causes weight loss and appetite suppression. Humulene was shown to increase the rate of Interleukin-8 (IL-8) secretion in human intestinal epithelial cells, but the significance is unclear.[736]

Linalool is found in many spices and flowers including lavender, citrus, coriander, rosewood, and laurels, birch trees, and is widely used in the cosmetics industry. It exhibits properties including anti-inflammatory and analgesic,[737–739] anti-nociception via activation of opioidergic and cholinergic systems,[737] anti-anxiety/stress,[740–743] sedation,[742,744–746] anti-depressant, modulation of motor movements and locomotion,[742] anti-bacterial, potent anti-leishmanial,[747] antimalarial,[748] anticonvulsant via anti-glutamatergic and GABA neurotransmitter systems,[749–753] anti-insomnia,[21] and antioxidant properties.[754] Its local anesthetic effects[755] were equal to procaine and menthol.[756] Analgesic effects have also been attributed to adenosine A_{2A} activity[757] and by ionotropic glutamate receptors including AMPA, NMDA, and kainate.[758] Linalool significantly decreased morphine opioid usage in gastric banding surgical patients following lavender inhalation vs placebo.[759]

Limonene is found in the rinds of all citrus fruits. It is the second most commonly occurring terpenoid in nature.[703] It is used in many household cleaners, perfumes, and foods. Studies have shown characteristics including anti-inflammatory,[701,706,760–762] analgesic,[763] antioxidant,[754,764,765] antidepressant and immunostimulating benefit,[763,766] anti-cancer against skin cancer, breast cancer, prostate cancer, other advanced solid tumors such as recurrent glioblastoma,[760,761,766–770] anti-bacterial, anti-fungal, and antimalarial,[748,764] and acts as insect repellent.[729] Limonene is active against acne,[771] dermatophytes,[764,772] and GERD.[773] It has been associated with bronchodilator effects in asthma.[760] It has also been shown to cause muscle relaxation and sleep in mice,[697] to be a powerful anxiolytic,[774–777] and reduced anxiety in patients with chronic myeloid leukemia.[778] Limonene has been shown to increase the metabolic turnover of dopamine in the hippocampus and serotonin in the prefrontal cortex and striatum, suggesting anxiolytic and antidepressant-like effects may occur by the suppression of dopamine activity related to enhanced serotonergic neurons, especially via 5-HT1A.[779]

Terpinolene is found in lilac, apples, nutmeg, cumin, conifers, tea tree, and sometimes used in perfumes, lotions, and soaps. It has shown anti-oxidant,[765,780,781] anti-bacterial and anti-fungal,[782,783] anti-cancer,[781,784] sedative,[785] and insecticidal[786] properties. It has also been suggested a potential treatment for heart disease by preventing low-density lipoprotein oxidation.[787]

Terpineol is found in pine trees, lilacs, eucalyptus, and lime blossoms, and used commonly in soap, perfume, and lotion. It reduced hyperalgesia in a chronic muscle pain fibromyalgia model presumably by affecting the opioid and

serotonergic receptors.[788] It has anti-inflammatory and analgesic actions,[788–790] antioxidant properties,[791]anti-proliferative and anti-cancer effects especially in small cell lung carcinoma,[678,792] antibacterial,[793,794] antifungal,[795] and antiviral[726] effects. It also has skin penetration enhancing effects,[796] airway smooth muscle relaxation in asthma,[797] vasorelaxation and blood pressure reduction effects,[798] and anxiolytic and sedative effects.[744,746]

Ocimene is found in many fruits and plants such as mango, mint, pepper, oregano, basil, parsley, orchids, hops, kumquat, pepper, and lavender. It has a sweet, fragrant, aroma that is used in perfumes. It has anti-inflammatory,[706] antifungal,[799] antiviral,[728] and antibacterial[800] benefits.

Valencene is found in Valencia oranges, grapefruit, tangerines, and other citrus fruits. It has anti-inflammatory effects,[801] insecticidal benefits,[802] and is a tick repellent.[803]

Geraniol is found in geraniums, rose, citronella, lemongrass, and is commonly added to perfumes. Its properties are anti-nociceptive,[804] anti-inflammatory,[805] antioxidant in inflammatory lung disease,[806] skin penetration enhancing effects,[807] antibacterial,[808–810] antifungal,[811,812] and antiparasitic.[813]

Alpha-bisabolol (α-bisabolol; levomenol) is produced by some plants such as the chamomile flower. It is used in making tea and in the cosmetics industry. It has anti-inflammatory effects in the skin,[814] as well as anti-nociceptive and neuroprotective benefit.[815] It was a pro-apoptotic agent for primary human acute leukemia cells[816] and glioma cells in both humans and rats,[817] breast cancer,[818] highly malignant human pancreatic carcinoma cell lines,[819] and anti-mutagenic/antioxidant.[820] Bisabolol has also shown protection against cisplatin-induced nephrotoxicity,[821] and successful treatment of visceral leishmaniasis.[822] It has also been shown be antibacterial,[823] and enhanced sensitization of *Staphylococcus aureus* to multiple antibiotic therapies.[824]

Nerolidol (trans-nerolidol) is found in many herbs and spices including ginger, jasmine, lavender, lemon grass, tea tree, oranges, and present in low levels in orange and other citrus peels. It has many applications in cooking and is approved by the US FDA as a food-flavoring agent. It has anti-insomnia and sedative properties,[825] anti-leishmanial activity,[826] anti-parasitic effects against *Babesia* parasites,[827] antifungal effects[828] against Microsporum gypseum,[829] anti-malarial effects,[748,830] and enhanced sensitization of *Staphylococcus aureus* and *Escherichia coli* to multiple antibiotic therapies.[824] It diminished large bowel adenomas[831] and enhanced skin penetration of 5-fluorouracil.[832]

Caryophyllene oxide is found in lemon balm, rosemary, lavender, cloves, hops, basil, oregano, black pepper, and eucalyptus, and often a metabolic byproduct of caryophyllene. It is used as a preservative in drugs, food, and cosmetics. It has analgesic and anti-inflammatory activity comparable to aspirin.[833] Carophyllene has anti-fungal[828] properties including onychomycosis comparable to sulconazole and ciclopiroxolamine,[834] insecticidal,[835] and anti-ischemic and anti-platelet aggregation properties.[836]

Phytol is a breakdown product of chlorophyl and tocopherol. It is found in green tea and wild lettuce. It has anti-insomnia and relaxing effects and has been postulated to increase levels of GABA through its inhibitory action on one of the GABA degradative enzymes, succinic semialdehyde dehydrogenase (SSADH).[837] It also prevented vitamin-A induced teratogenesis by converting retinol to a harmful metabolite.[838]

Borneol is found in camphor, rosemary, and mint. It has analgesic and anti-insomnia properties as well as bronchodilator and anti-septic effects.[839] It has a greater inhibitory potential on the nicotinic acetylcholine receptor than lidocaine, suggesting it could be an even more potent anesthetic.[840] Borneol has anti-inflammatory and analgesic effects,[841–845] insecticidal benefits,[846] anti-fibrosis properties,[847] wound-healing properties,[848] anti-cancer in a molecular relative (bornyl),[849] potentiator of cancer treatments,[850,851] enhancer for brain-targeting delivery systems,[852] and anticoagulant benefits[853] that were strong enough to prevent ischemic stroke in an animal model.[854]

Delta-3-carene (δ-3-carene) can be found in cedar, basil, pine, rosemary, and bell pepper, has shown anti-inflammatory effects,[710] and is known to dry out excess body fluids such as tears and mucus (well-known cannabis side effects of dry mouth and red eyes). It promotes bone growth and repair,[855] and has insecticidal and repellent qualities.[856–858]

Terpinene can be found in tea tree oil and some other plants. It is often used in the cosmetic and food industries. It is anti-inflammatory,[706,859] and has strong antioxidant properties.[860]

Camphene can be found in turpentine, camphor oil, citronella oil, ginger oil, cypress oil, and valerian. It is used as a food additive for flavoring and infused into topical creams and perfumes for fragrance. Camphene has antioxidant and analgesic effects[861] even when used topically,[843] antifungal action,[862] lowers cholesterol and triglycerides,[863] and acts as an antioxidant in inflammatory lung disease.[806] In traditional medicine it is often used as a topical treatment of bacterial and fungal infections, eczema, psoriasis, and athlete's foot.

Sabinene is found in various plants including marjoram, holm oak, juniper, Norway spruce, black pepper, nutmeg, and is a major component of carrot seed oil. It has benefits in digestion, antioxidant, inflammation, arthritis, soothing skin conditions,[707,864,865] and is anti-bacterial and anti-fungal.[721]

Cineole (Eucalyptol) is found in tea tree, rosemary, sweet basil, wormwood, tea trees, mugwort, bay leaves, common sage, and eucalyptus, and has historically been used as a topical to the gums and skin. It is one of the terpenes that is also

supported by several randomized placebo-controlled trials. According to the Natural Health Research Institute, it has been proven to improve memory and cognitive learning. Because of its cholinesterase inhibitory activity, it has potential for use in Alzheimer's disease,[715,866] and protection against amyloid beta-induced inflammation.[867] Cineole has anti-oxidative,[868] anti-inflammatory and analgesic properties,[869] and has been suggested as a potential long-term therapy in the prevention of COPD exacerbations and asthma control,[870–874] inflammatory bowel disease,[875] and acute pancreatitis.[876] It helps treat nasal and sinus inflammation and secretions in acute nonpurulent rhinosinusitis[877] and is used as a nasal decongestant and cough suppressant.[878] It is anti-fungal[879] including activity against onychomycosis,[880] anti-cancer,[881,882] antibacterial,[883] anti-tuberculosis,[884] insecticidal,[885,886] and inhibits cholesterol synthesis.[887]

Phellandrene is found in eucalyptus, water fennel, lavender, grand fir, and found in several herbs and spices including cinnamon, dill garlic, ginger and parsley. It has analgesic and anti-depressive effects.[763]

Guaiol is found in guaiacum and cypress pine. It has anti-inflammatory[683] and antimicrobial,[888] and insecticidal[889] benefits.

Isoborneol is found in mugwort and other plants. It has antioxidant effects that may be helpful in neurodegenerative diseases such Parkinson's disease that is associated oxidative stress.[890] It has anti-inflammatory,[845,891] antimicrobial,[892] and antiviral properties including a potent inhibitor of HSV1.[726,893]

Cedrene is found in cedar and has anti-cancer[894,895] antiparasitic,[896] and antifungal[897] properties.

Geranyl acetate is found in citronella, sassafras, roses, lemongrass, geranium, coriander, and carrot. It has antimicrobial,[898,899] antifungal, and anti-inflammatory properties.[900]

Fenchol is found in basil and is used in perfumes. It has antioxidant and antibacterial properties.[901]

Camphor comes primarily from the camphor tree, is easily absorbed through the skin, and produces a cooling sensation like menthol. It is used in inflammation-related disorders including sprains, rheumatism, muscle pains, and is antipruritic because of its local anti-inflammatory, anesthetic and analgesic properties.[902–904] Camphor desensitizes TRPV1 receptors more rapidly and completely than capsaicin, activates TRPV3, and inhibits TRPA1, correlating to its analgesic properties.[905] Camphor is used as a nasal decongestant and cough suppressant,[878] is an antioxidant,[902] has antibiotic properties,[906] and is antifungal against onychomycosis.[880] It has cholinesterase inhibitory activity, suggesting benefit in dementia and cognitive disorders.[715]

Menthol comes from corn mint, peppermint, or other mint oils. It is an analgesic used topically for inflammatory pain such as sprains, joint and muscle pains, and is antipruritic.[903] Central and peripheral analgesic mechanisms include activation of sensory neurons at the TRPM8 receptor,[907] selective activation of kappa-opioid receptors, inhibition of voltage gated sodium and calcium channels, and activation of GABA A receptors.[907–909] It is used as a nasal decongestant and cough suppressant,[878] is antifungal including activity against onychomycosis,[880] antibacterial, anti-cancer, and enhances the dermal penetration of pharmaceuticals.[910]

Isopulegol is a precursor to menthol. Its properties include anti-inflammatory and gastroprotective,[911] antidepressant and antianxiety,[912] and antioxidant and anticonvulsant properties.[913]

Cymene is found in cumin, thyme, coriander, and oregano. It has analgesic and anti-inflammatory properties including opioid system involvement, [914,915] antibacterial,[916] antifungal,[917] and is protective against acute lung injury.[918]

Citral is found in lemon balm, lemongrass, and citrus fruits. It has antioxidant,[754,919] antibacterial and antifungal,[920] muscle relaxation including gastrointestinal,[921] and sleep benefits.[697]

Citronellol is found in roses, geranium, sandalwood, lemongrass, chamomile, basil and lavender. It has shown promotion of wound healing, anti-cancer, anti-inflammatory, analgesic, and antioxidant benefits.[922,923] Citronellol has anti-hypertensive,[924] antifungal, and antibacterial effects.[925,926] It also acts as an insect repellent.

FLAVONOIDS

Cannabis also contains phenolic compounds (phenylpropanoids), one of which is called the flavonoids. These compounds normally act as antioxidants in plants and protect against oxidative stress.[145] They also contribute to the vibrant color in many fruits and vegetables. There have been about 20 different flavonoids identified in cannabis.[927] These include apigenin, luteolin, quercetin, kaempferol, cannflavin A, cannflavin B (unique to cannabis), β-sitosterol, vitexin, isovitexin, kaempferol, and orientin.[145] There have been correlations between dietary phenolic compound intake and reduced incidence of chronic diseases such as neurodegenerative diseases, cancers, and cardiovascular disorders.[928] Similar to terpenes, many of these compounds have also been shown to have anti-inflammatory, neuroprotective, and anti-cancer effects.[929] Apigenin has anxiolytic effects,[930] and inhibits TNF-α[931] which is involved in many inflammatory conditions. Cannflavin A and B have potent anti-inflammatory effects,[932] with Cannflavin A shown to inhibit PGE-2 30 times more potently than aspirin.[933]

β-sitosterol was shown to reduce topical inflammation by 65% and chronic edema by 41% in skin models.[934] Other phenolic compounds found in cannabis include the stilbenes, phenolic amides, and lignans.[145] There is much less research available on these various compounds at this time, and medicinal characteristics have yet to be differentiated.

CANNABIS STRAINS

Cannabis sativa strains are commonly described as energetic, uplifting, creative, euphoric, spacey, cerebrally focused effects, and better for day use. Cannabis indica strains are described as relaxing, calming, sedative, having full body effects such as "body buzz," and better for night use. These effects are not purely due to CBD:THC ratios according to research, as there are no significant differences in CBD:THC ratios between sativa and indica strains. These different subjective effects are most likely due to varying ratios of major cannabinoids, minor cannabinoids, terpenes and probably additional phytochemicals.[21,935–939] High CBD strains are sativa or indica strains that have been crossed with high CBD hemp strains (1:1 CBD:THC up to approximately 5:1 CBD:THC), while pure CBD strains (ratios of >10:1 CBD:THC up to approximately 50:1 CBD:THC) are considered hemp strains.[939]

Terpene concentration studies[940] show that "mostly indica" strains are often dominant in β-myrcene with limonene or α-pinene as the second most commonly present terpenes. "Mostly sativa" strains were more complex. Some strains were more dominant in terpinolene or α-pinene, while others were dominant in β-myrcene. Terpinolene or ocimene are the second most abundant terpenoids. Regardless, most strains used today are hybrids bred with specific and standardized ratios of THC, CBD, minor cannabinoids, and terpenes with a goal of targeting specific symptoms and predictable user effects. Cannabis science has evolved to classify strains not only based on THC and CBD compositions, but also based on minor cannabinoids, terpenes, and ultimately classified according to end-user effects and responses. In a recent study evaluating cannabis use patterns among medicinal cannabis patients who were treating for migraine and headache, hybrid strains were the most preferred. More specifically, "OG Shark," a high THC/THCA, low CBDA/CBD strain with β-caryophyllene followed by β-myrcene as the predominant terpenes, was the most preferred strain in these groups.[939] This could reflect the potent analgesic, anti-inflammatory, and anti-emetic properties of THC, along with documented anti-inflammatory and analgesic properties of β-caryophyllene and β-myrcene. Vaporizing and joint use were the most common primary methods of use, likely reflecting the need for a quick acting inhaled or nonorally ingested therapy in migraine attacks before severe pain and nausea and vomiting become prominent.

The health and medicinal benefits of many fruits, vegetables, whole grains, and other plant foods are the result of synergy between the various nutrients and bioactive compounds within the food rather than a single compound.[941] Similarly, cannabis exerts its medicinal effects via synergistic interactions between its cannabinoids, terpenes, flavonoids, and other compounds. To illustrate, in a rat model of neuropathic pain (thermal hyperalgesia), a controlled cannabis sativa extract containing multiple cannabinoids in a defined ratio along with other noncannabinoid compounds such as terpenes and flavonoids provided better and total relief of neuropathic pain compared to pure cannabinoids alone.[435]

CONCLUSIONS

The synergistic interactions between the many cannabis compounds are termed the "entourage effects." A variety of therapeutic benefits and effects reflect the cannabis entourage effects. Cannabis should be thought of as a broad category of medicines comprised of many different strains varying in their targets, responses, and side effects. This is synonymous to the broad category of antidepressants, comprised of many different medication classes varying in their neurotransmitter targets, responses and side effects.

There is growing evidence for therapeutic benefits of cannabis/cannabinoids in many diseases and symptoms, especially in the treatment of chronic pain with extension to migraine and headache, as well as a potential weapon in battling the opioid epidemic. More data are needed to determine what the most effective therapeutic ratios of cannabinoids, terpenes, flavonoids, and other compounds may be for these pain syndromes, as well as for other diseases and symptoms. These data will ultimately unveil optimal reproducible strain combinations to be bred for maximum predictable therapeutic efficacies.

CLINICAL HIGHLIGHTS

- There are numerous cannabis strains with variably unique and predictable characteristics, benefits, and side effects, depending on the ratios of cannabinoids, terpenes, flavonoids, and other phytochemicals working together synergistically.
- Many of the individual cannabinoids, terpenes, and flavonoids, have strong anti-inflammatory and analgesic properties that work individually and synergistically to provide the well-described analgesic benefits of cannabis/cannabinoids.
- The National Academies of Sciences, Engineering, and Medicine now state that the use of cannabis for the treatment

of pain is supported by well-controlled clinical trials with substantial evidence that cannabis is an effective treatment for chronic pain in adults. This benefit may extend to migraine and headache based on overlapping neurobiological mechanisms of pain and early research, although prospective studies are necessary.

- The well-documented opioid-sparing effect of cannabis/cannabinoids in conjunction with opioid use leads to lower opioid dose requirements, allowing for easier detoxification and weaning, and a potential tool against the opioid epidemic.
- Cannabis science is a rapidly growing new medical sector and industry involving sophisticated crossbreeding of specific strains for standardized compositions of cannabinoids, terpenes, and other phytochemicals, to target individualized diseases and/or symptoms including migraine and headache.

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