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Therapeutic Potential of Cannabis, Cannabidiol, and Cannabinoid-Based Pharmaceuticals

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Δ^9-THC · CBD · Medical marijuana · Cannabis · Cannabinoids · Pharmacology · Therapeutics

Abstract
Background: There is a growing interest in the use of cannabis (and its extracts), as well as CBD oil (hemp extracts containing cannabidiol), for therapeutic purposes. While there is reason to believe that cannabinoids may be efficacious for a number of different diseases and syndromes, there exist limited objective data supporting the use of crude materials (CBD oil, cannabis extracts, and/or cannabis itself). ***Summary:*** In the present review, we examined data for pure cannabinoid compounds (dronabinol, nabilone, and CBD), as well as partially purified medicinal cannabis extracts (nabiximols), to provide guidance on the potential therapeutic uses of high-THC cannabis and CBD oil. In general, data support a role for cannabis/cannabinoids in pain, seizure disorders, appetite stimulation, muscle spasticity, and treatment of nausea/vomiting. Given the biological activities of the cannabinoids, there may be utility in treatment of central nervous system disorders (such as neurodegenerative diseases, PTSD, and addiction) or for the treatment of cancer. However, those data are much less compelling. ***Key Message:*** On balance, there are reasons to support the potential use of medical cannabis and cannabis extract (Δ^9-THC-dominant or CBD-dominant), but much more careful research is required.

Background

There are a growing number of US states and nations that have legalized the use of at least some components of *Cannabis sativa* for medicinal purposes. Despite this increase in the therapeutic use of these substances, evidence-based data regarding their clinical utility remain incomplete [1]. For the physician, this is a potential barrier to the understanding and recommendation of these treatments [2]. Here, we therefore summarize data supporting cannabis (high Δ^9-THC containing cannabis (marijuana) and low Δ^9-THC containing cannabis [hemp]), its extracts, and isolated cannabinoid compounds as treatments for human disease.

It is important to note that many cannabinoids, including Δ^9-THC, exhibit their physiological and pharma-

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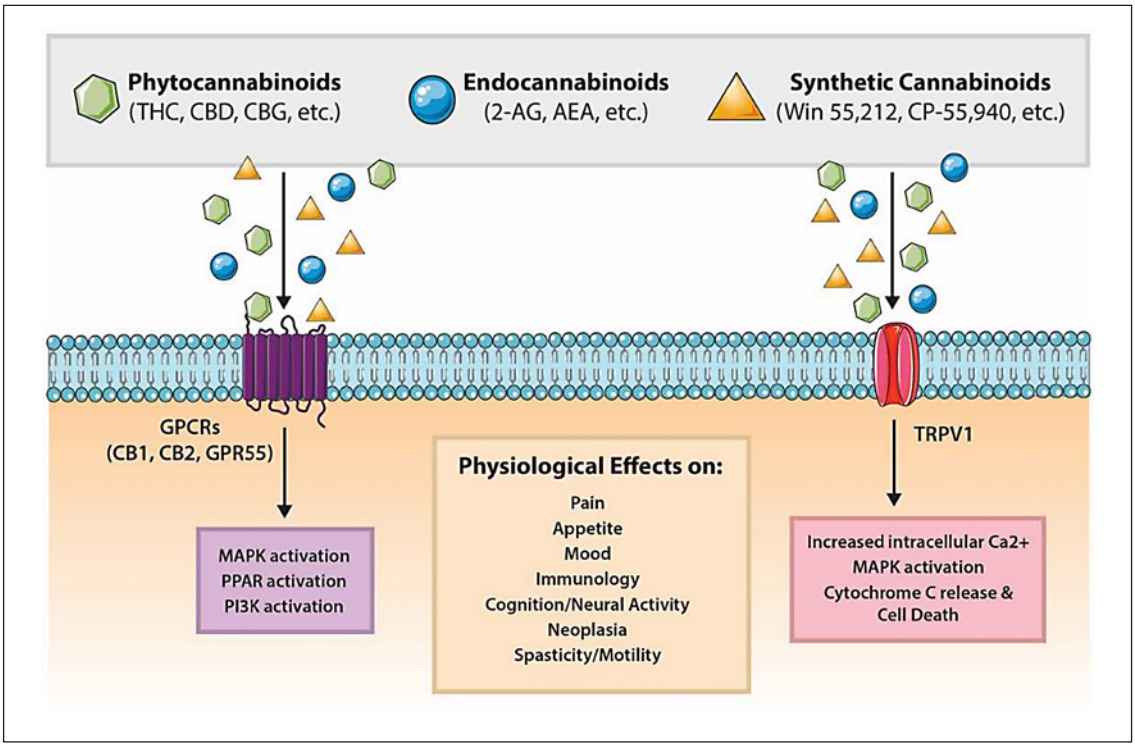

Fig. 1. Cannabinoid signaling pathways and effects. Regardless of the type of cannabinoid ligand (phytocannabinoid, endocannabinoid, or synthetic), these compounds primarily interact with GPCR proteins, such as the CB1 and CB2 receptors and GPR55, or with TRP, such as TRPV1, to induce a cellular response. The pathways activated vary based upon receptor activation and have physiological effects on pain, appetite, mood, and many other effects within the body.

cological effects by engaging the endogenous cannabinoid (endocannabinoid) system (Fig. 1). However, some cannabinoids such as CBD, have low binding affinity for these endogenous receptors and, instead, act outside of the endocannabinoid system [3–6]. The first described endocannabinoid, N-arachidonoylethanolamine (AEA), also known as anandamide, is synthesized from membrane phospholipid precursors [7–9]. Anandamide is a partial agonist at the cannabinoid receptor type 1 (CB1) and cannabinoid receptor type 2 (CB2) receptors at high nanomolar concentrations, a potent partial agonist at the G protein-coupled receptor 55 (GPR55) receptor, and a low-affinity full agonist at the transient receptor potential cation channel subfamily V (TRPV1) calcium channel (Table 1). Additionally, other TRP channels are also known to serve as receptors for cannabinoid ligands along with members of the PPAR, adrenoceptor, and serotonin families of receptors [6, 10–14]. 2-Arachidonoylglycerol (2-AG), the most abundant endocannabinoid, is synthesized from arachidonic acid-containing phosphatidylinositol 4,5-bisphosphate (PIP_2) [15–17]. Furthermore, 2-AG is more efficacious at the CB1, CB2, and GPR55 receptors than AEA; however, with the exception of GPR55 (where it is potent), this molecule has a lower affinity for the cannabinoid receptors than its counterpart (Table 1). Finally, lest we give the impression that the system is simple, it is important to note there are a number of additional putative endocannabinoids [18–21]. Perhaps, the most nuanced aspect of endocannabinoid structure and function is the fact that in contrast to traditional neurotransmitter signaling, the endocannabinoids are synthesized by the target cells (or neighboring support cells such as glia and astrocytes) and released (on demand) as neuromodulators to inhibit presynaptic activity [22, 23]. Cannabinoids also have functions outside the nervous system, and some of these activities will be discussed throughout this review, but a recent review by Lowe and colleagues [24] details these aspects. Detailed considerations of the biosynthesis, degradation, and pharmacology of the endocannabinoids can be found in a number of excellent recent reviews [23, 25, 26]. Additionally, cannabinoids from cannabis can modulate the

Table 1. Cannabinoid pharmacology: a compilation of experimental displacement, GTPγS binding, and cytoplasmic (Ca^{++}) assay data provides a relative measure of the affinity and efficacy properties of various cannabinoid molecules for major endocannabinoid system receptors

Compound	CB1		CB2		TPRV1		FABP1 (liver)	GPR55	
	affinity, nM	efficacy	affinity, nM	efficacy	affinity, nM	efficacy	affinity, nM	potency, nM	efficacy
Synthetic full agonist									
R-(+)-WIN55212	Ki: 1.89–123 [238]	E_{max}: 101% [239]	Ki: 0.28–16.2 [238]	E_{max}: 97% [239]	Ki: –	E_{max}: –	Ki: –	EC_{50}: >30,000 [239]	E_{max}: –
Major endocannabinoids (partial agonists)									
AEA	Ki: 239.2 [240]	E_{max}: 66% [239]	Ki: 439.5 [240]	E_{max}: 58% [239]	Ki: 1,660–2,504 [241]	E_{max}: 100% [242]	Ki: 111 [243]	EC_{50}: 18 [239]	E_{max}: 73% [239]
2-AG	Ki: 4.4–472 [238]	E_{max}: 92% [239]	Ki: 11.2–1,400 [238]	E_{max}: 87% [239]	Ki: –	E_{max}: –	Ki: 61 [243]	EC_{50}: 3 [239]	E_{max}: 99% [239]
Major phytocannabinoids (agonists/inverse agonists/antagonists)									
Δ^9-THC	Ki: 25.1 [240]	E_{max}: 61% [239]	Ki: 35.2 [240]	E_{max}: 67% [239]	Ki: –	E_{max}: –	Ki: 1,000 [243]	EC_{50}: 8 [239]	E_{max}: 92% [239]
CBD	Ki: 2,210.5 [240]	E_{max}: none [244]	Ki: 2,860 [240]	E_{max}: −15 [245]	Ki: 3,600 [172]	E_{max}: ∼91% [172]	Ki: 167 [243]	IC_{50}: 445 [239]	E_{max}: antagonist [239]
Synthetic inverse agonist									
Rimonabant	Ki: 1.8–12.3 [238]	E_{max}: −48% [246]	Ki: 514–13,200 [238]	E_{max}: −17 [245]	Ki: –	E_{max}: –	Ki: 2,000 [243]	EC_{50}: –	E_{max}: antagonist [239]

These data were taken irrespective of tissue location. For this paper, the efficacy of CBD at TPRV1 was calculated from the available data as a percent relative to capsaicin, an exogenous molecule that has been found to activate this receptor at comparable affinity and efficacy to the endogenous ligand, AEA.

degradation and metabolism of endocannabinoids adding further complexity to this system [27].

In addition to the endocannabinoids, there are two other sources of cannabinoids comprising the phytocannabinoids (produced by members of the plant genus *Cannabis*) and the synthetic cannabinoids (compounds generated in the laboratory that can interact with cannabinoid receptors). Regarding the phytocannabinoids, the two most abundant and well-studied are Δ^9-tetrahydrocannabinol (Δ^9-THC) and cannabidiol (CBD).

There are a number of excellent reviews that describe the endocannabinoid system (ligands and receptors) as well as the phytocannabinoids from *Cannabis* sp. [28–31]. So, rather than reviewing that information here, we will focus our attention on the medical conditions, disorders, and diseases for which cannabis has potential to be of therapeutic use. Furthermore, the enzymes that degrade the endocannabinoids, such as fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase (MAGL), are also important targets for the development of novel therapeutics [32–34].

Cannabis/Phytocannabinoids

While *Cannabis* has been used medicinally for millennia, there has been a renewed pharmacotherapeutic interest in cannabis and phytocannabinoids following the discovery of the endogenous receptors and the role of this system in the human body [35–38]. All phytocannabinoids arise from the central precursor cannabigerolic acid (CBGA), and the highest concentrations of these compounds are primarily found within the flower portion of the female part of the plant [14, 39, 40]. In most cultivars of *Cannabis*, the two most common cannabinoids are THC and CBD, although over 100 cannabinoids are produced by the plant [40, 41]. The biological properties of these cannabinoids vary greatly; for example, Δ^9-THC has been shown to have appetite stimulating and antinausea effects, while CBD has been shown to reduce seizures and have anti-inflammatory properties [41–43]. Other major classes of compounds (e.g., flavonoids, stillbenoids, alkaloids, lignans, and terpenoids) are thought to provide synergism with phytocannabinoids in what has been termed

an "entourage effect"; however, the mechanism of this synergism is not understood, and the existence of the "entourage effect" remains controversial [44–46].

Medical Cannabis: Extracts and Routes of Administration

Individual countries and selected states within the USA have legalized cannabis or *C. sativa* extracts for medical use, and several have also legalized recreational use. Medicinal cannabinoids may be administered in a variety of forms: smokable, oral (tablet), oral (edibles containing cannabis extract), oral (oils), oromucosal (oil/lozenge), vaporizable, sublingual, rectal, transcutaneous, and intravenous [47, 48]. The most popular method, inhalation of combusted plant material (smoking), provides patients with a fast onset of action, the ability to self-titrate doses, and a much higher peak serum concentration relative to most of the other routes of administration. However, this peak quickly drops, and smoking is associated with impairment and abuse potential [47]. Additionally, due to the adverse effects that are associated with smoking, variability in individual smoking dynamics, and the variability in cannabinoid composition within different *Cannabis* cultivars, smoking cannabis material is not a favorable route of administration for therapeutic applications [47, 49].

The oral route of administration overcomes many of the drawbacks of inhalation; tablets contain either purified extracts or synthesized molecules of known dosage, and serum concentrations remain relatively stable [47]. The dosing of orally administered cannabinoids is complicated by their extensive first-pass metabolism in the liver (approaching 95%) [47]. Therefore, other routes of administration that avoid this metabolism have been explored. In particular, oromucosal sprays, such as used for Sativex, allows for consistent, titratable dosing [50]. The above-described delivery methods are the two most widely utilized; however, other methods of cannabinoid delivery have been developed and have recently been reviewed by Bruni et al. [51]. In general, legal jurisdictions have either legalized the use of the intact plant materials (smoked or rendered edible) or provide for formulations of extracted cannabinoids/terpenoids (generally through supercritical CO_2 or organic solvent extraction) [52–54].

Medically Approved Cannabinoid Drugs

Given the function of the endocannabinoid system, there is intense interest in the use of exogenous cannabinoid drugs for the treatment or management of a large number of disparate diseases and disorders. However, despite the number of governments that permit whole-plant consumption for medical use, only a few cannabinoid drugs have been rigorously tested for safety, efficacy, and therefore approved for use at the national level by regulatory agencies, such as the Federal Drug Administration (FDA) and the European Medicines Agency (EMA).

Dronabinol (Marinol®)

Dronabinol (trade name Marinol®) is an orally administered and synthetically produced Δ^9-tetrahydrocannabinol (Δ^9-THC) [55, 56]. It was approved by the FDA in 1985 [57] for the treatment of anorexia and weight loss in patients with AIDS and for chemotherapy-induced nausea and vomiting (CINV) and is also approved by the EMA. This drug is classified as a schedule III substance, and the most frequently reported side effects include heart palpitations, asthenia, abdominal pain, and amnesia. A rare, but serious, side effect is depersonalization [57].

Nabilone (Cesamet™)

Nabilone (trade name Cesamet™) is an orally administered synthetic cannabinoid (structurally similar to Δ^9-THC, see Fig. 2) with similar CB1 receptor properties as Δ^9-THC [58]. This compound has been approved for the treatment of CINV by the FDA (in 1985, and again in 2016) and is also approved by the EMA. Due to its psychoactivity, nabilone is classified as a schedule II drug. The most frequently reported side effects are relatively minor and include orthostatic hypotension, dry mouth, drowsiness/vertigo, euphoria, dyspnea, and headache. Rare, but serious, side effects include psychosis [59].

Rimonabant (Acomplia®)

Rimonabant (trade name Acomplia®) is a potent synthetic CB1 receptor antagonist that was marketed in Europe (from 2006 to 2009) for the management of weight, dyslipidemia, and type II diabetes [60]. However, due to serious side effects, such as major depression, suicidal ideation, nausea, and upper respiratory tract infections, this drug was withdrawn from the market by the European Medicines Agency in 2009 [61, 62].

Nabiximols (Sativex®)

Sativex is an oromucosal spray of *C. sativa* plant extract that predominantly contains Δ^9-THC and CBD in near-equal amounts [63]. Sativex has been approved in Europe (in 2010) for the treatment of spasticity, and the most commonly reported side effects include dizziness,

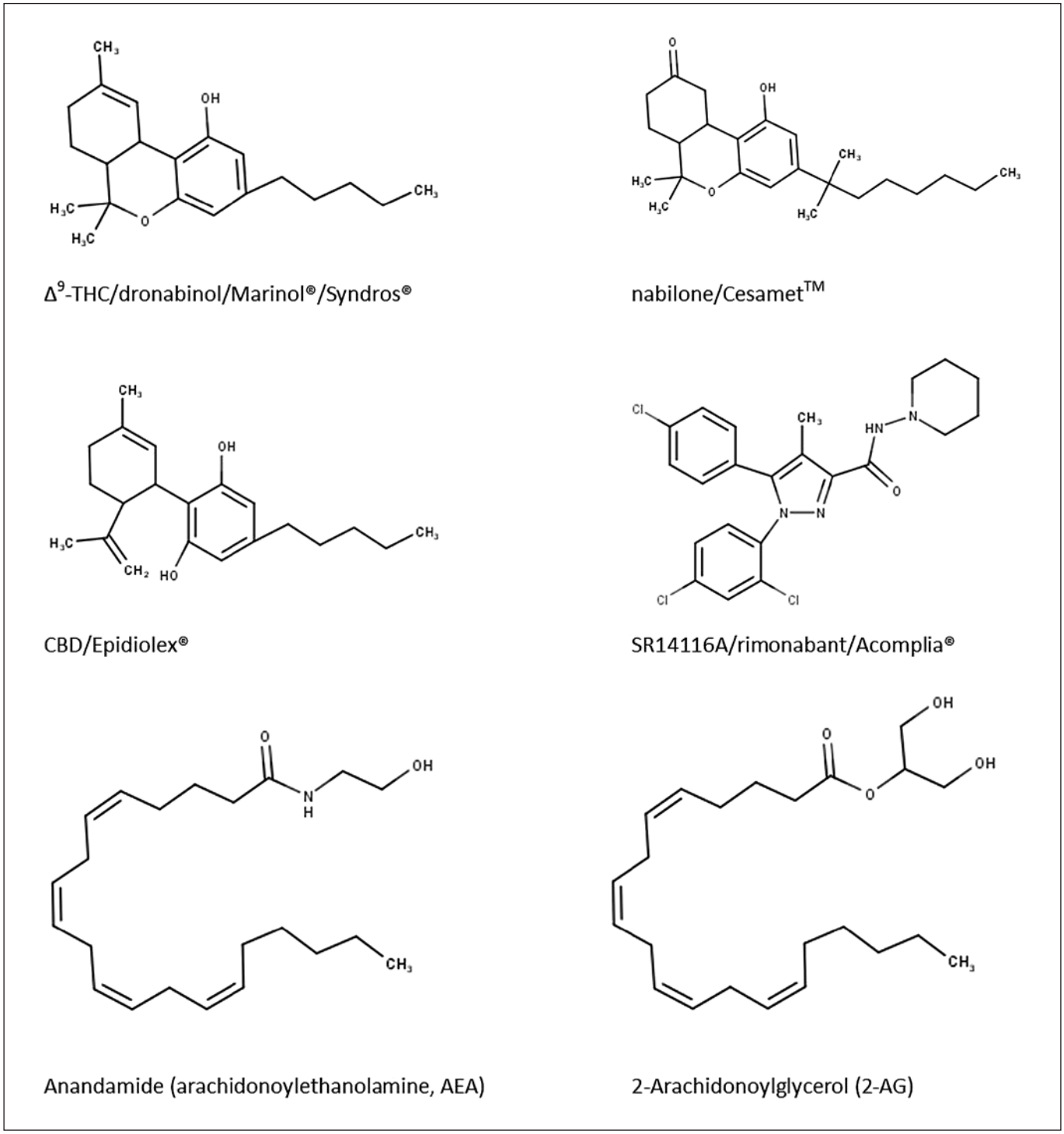

Fig. 2. Cannabinoid structures. Comparison of the structures for Δ9-THC, marketed under the prescription name dronabinol (trade name Marinol and Syndros), along with the prescription medication nabilone (trade name Cesamet), a Δ9-THC derivative. Other structures included cannabidiol, the active compound in the prescription Epidiolex, and the formerly approved cannabinoid receptor antagonist SR14116A (rimonabant/Acomplia). The bottom two structures are for the endogenous cannabinoids anandamide and 2-arachidonoylglycerol. Despite the lack of structural similarity, all of these compounds interact with cannabinoid receptors.

fatigue, blurred vision, vertigo, constipation, either appetite decrease or increase, and depression [63, 64]. Rare, but serious side effects, include palpitations, changes in blood pressure, and hallucinations [63]. Each spray contains approximately an equal ratio of CBD and Δ^9-THC (combined for 5 mg total).

Cannabidiol (Epidiolex®)

Cannabidiol (Epidiolex®) is a 98% pure plant-derived oral CBD solution [65]. It has been subject to extensive toxicology studies and is approved for the treatment of seizures associated with Lennox-Gastaut syndrome or Dravet syndrome in pediatric patients [65]. Epidiolex received FDA approval in 2018 [66] and is also approved by the EMA. As a highly purified preparation of CBD, this drug may be the closest analog to CBD oil when investigating the potential safety and therapeutic benefit of the latter agent. Side effects include hepatocellular toxicity, decreased appetite, diarrhea, drowsiness, and fatigue [66].

Cannabinoids and Disease

A detailed discussion of the endocannabinoid system and its potential utility in pharmacotherapy was presented in 2006; however, a plethora of new data have become available in recent years [21, 67]. Indeed, there are currently many ongoing clinical trials of Δ^9-THC, CBD, and other cannabinoids reported on the FDA ClinicalTrials.gov website. As of this writing, a search for CBD yielded 352 trials (including NCT04192370, NCT04729179, NCT04731116, and NCT04978428) and a similar search for Δ^9-THC found 322 trials (including NCT02792257, NCT03766269, NCT03560934, and NCT04734080). A review of the identified studies suggests novel avenues for the treatment of, or at least symptomatic control for, various disease states. For many diseases, there is growing evidence that suggests clinical potential for Δ^9-THC and/or CBD; however, there are few evidence-based, placebo-controlled studies for smokable and/or edible cannabis.

Chronic Pain

One therapeutic area for which medical cannabinoids may have the greatest potential is relieving chronic pain. The efficacy of cannabinoid treatments for neuropathy (nerve damage that results from disease, genetics, inflammation, or toxins) was assessed in a recent meta-analysis of eleven randomized controlled trials that used dronabinol (2.5–10 mg/day), nabilone (1–4 mg/day), and self-titrated Sativex-proportioned nabiximols (averaging 22.4 mg:20.8 mg Δ^9-THC:CBD/day). This meta-analysis found that selected cannabinoids elicit a significant reduction in pain in patients with neuropathy [68–70]. Nabilone was found to be the most effective treatment, while nabiximols were close behind in efficacy [70]. Δ^9-THC (dronabinol) by itself has been found to be ineffective for the treatment of neuropathic pain. However, emerging data may suggest a synergism between Δ^9-THC and opioid medications [70]. Interestingly, another key finding was that cannabinoid-induced pain reduction is greater in patients with peripheral neuropathic pain than it is in patients with centrally arising neuropathic pain [70]. A double-blind study found that smoked cannabis provided significant analgesia relative to a placebo in patients with HIV-induced neuropathic pain [71]. Beyond pain, a majority of the analyzed trials showed improvement in each of these side measures: quality of life, sleep, anxiety, and sensory profiles [70].

In chronic or intractable pain of non-neuropathic origin, a relatively prevalent condition that is frequently treated with opioids, nabilone was found to be ineffective for the alleviation of radiotherapy-induced pain and other quality of life measures in a double-blind study of cancer patients [72, 73]. On balance, a number of studies point to the utility of the synthetic nabilone [74–78]. Overall, trials using either Sativex or high CBD nabiximols for chemotherapy-induced pain produced nonsignificant, highly variable results [72]. Unfortunately, while these studies suggest that cannabis may have therapeutic potential, studies of nabilone will not be generalizable to phytocannabinoid mixtures.

Diseases of the Central Nervous System

Multiple Sclerosis

It is a progressive demyelinating disease [79, 80]. Patients with MS have been found to have changes in the expression of CB1 and CB2 receptors, and this may account for therapeutic potential of cannabis-derived products [81]. Sativex is approved in several countries for the treatment of spasticity associated with MS [82]. Additionally, Δ^9-THC alone was found to be ineffective in the management of this condition by the multi-year CUPID study [83]. Beyond spasticity, nabiximols treatment has also been found to be effective in alleviating multiple sclerosis-induced pain in multiple studies [84–86].

Epilepsy

A chronic condition of recurrent seizures often presents in childhood and arises out of abnormal excitation-

inhibition balance of neurons in the brain [87]. Cannabinoids may act as neuroprotective agents and may also reduce inflammatory responses in patients with epilepsy [88, 89]. Clinically, cannabidiol seems to have greater efficacy than whole-plant cannabis for the treatment of epileptic seizures as case reports and surveys have described smoked cannabis as having both pro- and anti-convulsant properties [90]. However, in regard to CBD itself, two recent open-label studies of similar design (i.e., patients with treatment-resistant epilepsy received doses of oral CBD for 3 months as an adjunctive therapy to their current anti-epileptic medications) found similar results: a responder rate of about 50% and a reduction in weekly seizure frequency of a little under 50% [91, 92]. Despite great variation between individuals within each study, these results were mirrored in patients with different root causes of their seizures, such as Dravet syndrome and tuberous sclerosis complex [91–93]. Interestingly, cannabidiol seems to be synergistic with clobazam, and individuals with baseline cognitive and behavioral problems showed improvement in these areas, in a seizure reduction independent manner, as well [91, 92]. Additionally, other trials that used lower doses of CBD or shorter lengths of time for treatment have had mixed results [90]. In 2018, CBD (branded as Epidiolex) received FDA approval for treatment of selected intractable seizure disorders in children, approval by the EMA followed in 2019.

Amyotrophic Lateral sclerosis

It is a progressive neurodegenerative disease of upper and lower motor neurons [94]. CB2 has been found to be upregulated following postmortem examination of patients with ALS, primarily within the spinal cord and motor cortex. This, in conjunction with the anti-inflammatory and neuroprotective aspects of cannabinoids, makes them an appealing potential therapeutic for treating ALS [81, 95]. Experimental data have shown slight improvements in disease progression in mouse models of ALS with nabiximols treatment [82]. A double-blind crossover trial that provided Δ^9-THC to 27 patients with ALS found no significant improvement [96]. A recent systematic review found no change in cramp intensity/frequency for ALS patients following medical cannabis [43]. Another recent clinical case study found that an oral capsule containing equal parts Δ^9-THC and CBD reduced pruritus in a patient with ALS; however, other symptoms of the disease were not reduced [97]. A recent phase II study evaluating the efficacy of nabiximols for the treatment of spasticity in ALS patients found an improvement in spasticity in patients [98]. Yet, despite the lack of strong clinical study data, survey data show a patient preference for medicinal *C. sativa* over prescription medication due to subjective improvement in their symptoms [82].

Parkinson's Disease

It is a progressive neurodegenerative disease of the substantia nigra pars compacta dopaminergic neurons [99]. Cannabinoids have been shown to act through CB1 to regulate dopamine, and other neurotransmitters, at basal ganglia which may provide therapeutic benefit to patients with Parkinson's disease [100]. The clinical trials that have been performed have primarily investigated the efficacy of cannabinoids in limiting dyskinetic side effects of current therapies: 1 study, that tested nabilone, found a significant improvement in levodopa-induced dyskinesia while another, that tested a 2:1-Δ^9-THC:CBD ratio of nabiximols, failed to show an effect [101, 102]. A recent phase II trial found that nabilone was able to reduce troublesome nonmotor symptoms, such as olfactory loss, mood disorders, and cognition, in patients with PD [103]. Looking at the management of the disease itself, a double-blind study investigated the effects of pure nonpsychoactive CBD and found significant improvement in both intervention groups over the placebo in the activities of daily living and stigma categories on the Parkinson's Disease Questionnaire 39 (PDQ-39) [104]. Despite these individual findings, a recent systematic review found insufficient evidence for the use of cannabis to treat the motor symptoms associated with PD [100]. Additionally, animal models have shown cannabinoids to have antidyskinetic effects that are likely due to modulation of both the cannabinoid and TRPV receptors [105].

Huntington's Disease

It is a neurodegenerative disorder that is caused by the autosomal dominant inheritance of a mutated huntingtin (HTT) gene [106, 107]. An analysis of gene expression found a strong link between Huntington's disease and endocannabinoid system dysregulation: a mutated HTT gene is associated with the downregulation of CB1 and GPRR55 receptors and the endocannabinoid synthesizing NAPE-PLD enzyme, as well as the upregulation of the endocannabinoid degrading FAAH enzyme [108]. Clinically, neither nabiximols treatment nor CBD alone had any effect on symptom control in patients with Huntington's disease who were enrolled in double-blind studies [109, 110]. Furthermore, nabiximol treatment was found to raise peripheral CB2 receptor expression; however, it has no effect on the expression of other endocannabinoid system proteins [110]. In contrast to the nabiximols, a

double-blind trial, using nabilone, found this drug to be efficacious in reducing the involuntary movements associated with Huntington's disease, as well as the behavior and neuropsychiatric outcomes [111].

A small double-blind crossover study involving spinal cord injury found that nabilone treatment significantly improved spinal cord injury spasticity relative to placebo [112]. Another study has shown that nabilone significantly relieves spasticity-related pain, although this study did not find a significant decrease in spasticity [113]. In addition, other studies have shown variable results for nabilone in pain/spasticity [114, 115].

Post-traumatic Stress Disorder

Post-traumatic stress disorder is rooted in extreme emotional events [116]. Survey and cross-sectional data have shown that cannabis use can improve global PTSD symptoms, as well as providing a correlation between reduced PTSD severity and cannabis use [117]. These data are supported by a double-blind study of active-duty Canadian military personnel, for whom standard treatment was ineffective, in which nighttime doses of nabilone had a significant and beneficial effect on PTSD-related nightmare frequency [118]. Cannabinoids have also been found to be effective for reducing the anxiety, but not the depression that is associated with PTSD, as well as multiple other disorders [42].

Anxiety

One of the most common reported reasons patients take cannabis is to treat anxiety, and this is especially true for products high in CBD [119, 120]. A recent work has found a role for the endocannabinoid system in modulating mood, and, as such, cannabinoids may be of therapeutic benefit to reducing anxiety [121]. Preclinical models in mice have found that the cannabinoid agonist WIN 55,212 is able to reduce anxiety-like responses [122, 123]. Similar findings were also observed with an inhibitor of anandamide hydrolase, which leads to an increase in anandamide levels [122]. A double-blind, randomly controlled trial of 24 social anxiety disorder patients found that CBD at a dose of 600 mg when given 1.5 h before public speaking was able to significantly reduce anxiety when compared to healthy controls [124]. A search of Clinicaltrials.gov shows there are currently eight clinical trials underway to investigate the potential of CBD as an anxiety medication. Nabilone has also been shown to reduce anxiety in a small, placebo-controlled crossover study [125]. Importantly, Δ^9-THC has been shown to increase anxiety-like behavior in mice and rats [126, 127]. In a recent systematic review of twelve studies looking at anxiety onset, three found that cannabis use increased the odds of developing anxiety disorders [128]. Reports also indicate that high Δ^9-THC cannabis is more likely to induce anxiety symptoms in naïve patients [129, 130]. So, while some cannabinoids may have therapeutic utility in reducing anxiety, caution should be exercised regarding Δ^9-THC because the association between Δ^9-THC and anxiety is still unclear.

Sleep

A common reason that individuals report using CBD oil is to help with sleep [131, 132]. However, there are currently few to no clinical data in humans that support the use of CBD for sleep. Studies in rats suggest that there is a correlation between CBD dose and increased percentage of sleep [133–135]. Additionally, chronic CBD exposure in adolescent rats leads to a decrease in wakefulness during the dark period [136]. Survey data from people using CBD to promote sleep have been highly variable, and this may be attributed to the high variability in the content and quality of CBD currently on the market [132]. In contrast, acute Δ^9-THC use is associated with increased total sleep time, while chronic Δ^9-THC use may lead to sleep disruption (possibly due to tolerance) [137]. Interestingly, withdrawal from Δ^9-THC is associated with an increase in vivid dreams and sleep disturbance [137]. Taken together, as with most diseases, more data are needed to make any conclusion on the benefit of cannabinoids for promoting sleep.

Opioid Use Disorder

The opioid crisis in North America has been one of the most pressing health issues of our time and continues to grow. Cannabis has been proposed to augment medication-assisted treatments such as methadone and buprenorphine. In particular, the noneuphorigenic cannabinoid CBD is viewed as having potential therapeutic use for the treatment of opioid use disorder (OUD); unfortunately, to date, only short pilot studies have been conducted, and therefore the effectiveness of this treatment remains unclear [138]. However, another recent study found that daily cannabis use was associated with lower opioid use during treatment of OUD [139]. These findings are in agreement with another study that found cannabis users show lower symptoms of withdrawal [140]. Epidiolex has recently been found to reduce cravings and anxiety in heroin-abstinent individuals [141]. Clearly, cannabis will not serve as an effective replacement for OUD individuals, but it may serve as a valuable addition

to traditional medication-assisted treatments (methadone, buprenorphine, and naltrexone) [141, 142]. Of course, substitution of one abused substance with another will not be well received by some healthcare providers.

Tourette's Syndrome

Tourette's syndrome is a neuropsychiatric disorder associated with verbal and physical tics. Additionally, many patients also suffer from comorbidities such as attention deficit/hyperactivity disorder, obsessive-compulsive behavior/disorder, anxiety, depression, and rage attacks [143]. Because of the anti-anxiety potential of cannabinoids and the high level of receptor expression in the striatum, cannabis may be a therapeutic for Tourette's [144]. To date, only two small, controlled trials have been conducted using dronabinol, and both studies found that dronabinol was able to reduce the number of tics with few adverse effects [145, 146]. There is currently a larger multicenter clinical trial being conducted to evaluate the effectiveness of nabiximols for the treatment of Tourette's syndrome, and data from this study will be highly valuable for validating the findings of the two smaller trials previously conducted [147].

Cancer and Cancer-Related Illness

Two major factors that diminish the quality of life in cancer patients are CINV and cancer cachexia, which is a state of weight and muscle loss that results from metabolic changes, chemotherapy, and inflammation [148, 149]. One aspect of cannabinoid signaling includes the establishment of an anti-emesis tone through the inhibition of serotonin signaling in the brainstem [150, 151]. Treatment with either dronabinol or nabiximols has been shown to be similarly efficacious for the treatment of CINV [42]. Data suggest that cannabinoid treatment may be superior to the anti-emetic drugs that are currently on the market [42]. Interestingly, nausea and vomiting that are induced by other factors, such as surgery, are not reduced by Δ^9-THC [152]. In regard to cancer cachexia, dronabinol treatment may increase appetite; however, its effect is inferior to other available treatments [153]. The lack of significance in these trials may be, in part, explained by the relatively low doses administered since smoked high-THC cannabis has been shown to increase caloric intake in healthy individuals [153]. A meta-analysis of four studies investigating the effects of dronabinol on weight gain in HIV-infected individuals found a mix of significant and nonsignificant increases in weight and appetite in these patients [42].

In addition to reducing nausea and increasing appetite in cancer patients, a number of cannabinoids have been identified that reduce cancer cell growth in vitro. These studies will be described in detailed in the following sections.

Gliomas and Glioblastomas

They are a group of highly invasive primary malignancies of the brain [154]. In regard to medicinal cannabinoids, there are very little clinical data on their utility. However, cell and animal studies, along with limited human trials, suggest that Δ^9-THC (perhaps modulated by CBD) may lower tumor vascularization, promote cell death, and limit metastasis [155–157].

Colorectal Cancer

It despite being easily treated by resection is highly heterogeneous and therefore at risk for drug resistance because of frequent epigenetic changes [158, 159]. Clinical data regarding treatment of this disease with cannabinoids also remain minimal; however, a significant association between increases in CB1 receptor expression in colorectal cancer samples, cancer stage, and prognosis has been observed [160–162]. Interestingly, cannabinoids may act synergistically, in a cannabinoid receptor-independent manner, with chemotherapeutics, such as 5-fluorouracil, in eliciting their antiproliferative action on colorectal cancers [163]. Our own recent findings suggest that cannabinoids may reduce colorectal cancer cell viability through a mechanism independent of CB1, CB2, GPR55, and TRPV1 [164].

Pancreatic, Lung, and Breast Cancers

They are leading causes of cancer-related death in the world [165]. Investigations have shown that synthetic cannabinoids inhibit pancreatic cancer growth through the promotion of autophagy [166]. Similar to colorectal cancer, however, CB1 receptor overexpression is associated with shorter survival [167]. Symptomatically, the deterioration of pancreatic cancer patient quality of life is largely due to pain, anxiety, sleep disturbance, and cachexia that may be mitigated by cannabinoids [42, 168]. Cannabinoid treatment for lung cancer is still in the preclinical stage; however, data from these experiments suggest a proapoptotic potential for CBD on cells from a primary lung tumor while increased AEA levels, achieved through FAAH inhibition, have been shown to inhibit EFGR signaling and induce apoptosis [169]. Breast cancer remains the primary cause of cancer-related death for women around the world [170, 171]. Modern treatment options,

which include chemotherapy, radiotherapy, and surgery, still diminish quality of life due to their adverse side effects [171]. As discussed with pancreatic cancer, cannabinoid treatment seems to help limit sleep disturbances and pain [42]. Therefore, medicinal cannabinoids may be used in conjunction with classical chemotherapeutics for the reduction of their side effects. Meanwhile, breast cancer is unlike pancreatic and colorectal cancers in that it is associated with increased levels of the CB2 receptor, rather than the CB1 receptor, and overexpressed levels of FAAH [169]. This may help to explain why multiple preclinical models of this cancer have shown that cannabidiol, an inverse agonist/antagonist at the CB2 receptor and an FAAH inhibitor, is effective at reducing breast cancer proliferation, invasion, and metastasis [172–174] (Table 1).

Glaucoma

Glaucoma involves the degeneration of retinal ganglion cells, increased intraocular pressure (IOP), and eventual blindness [175]. Clinically, medicinal cannabinoids have been found to reduce IOP: a sublingual dose of 5 mg of Δ^9-THC significantly reduced IOP in a double-blind study of glaucoma. Moreover, topical administration of the synthetic cannabinoid, WIN55212-2 (a CB1/CB2 agonist), at doses of 25–50 μg, had a similar effect [176, 177]. Intravenous Δ^9-THC, Δ^8-THC, and 11-hydroxyl-Δ^9-THC, as well as oral nabilone, have also been found to effectively decrease IOP [178]. Yet, despite these encouraging findings, there is no evidence that cannabinoid treatments slow the progression of this disease [178]. Additionally, as the hypotensive effects of these treatments average only 3–4 h, compliance with repeated administration and cost are other concerns [178].

Inflammatory Bowel Disease

A wealth of survey data suggest that individuals with inflammatory bowel disease use these substances to medicate their symptoms [179]. Indeed, a recent review and a retrospective cohort study suggest that many IBD patients report the use of high-THC cannabis to specifically manage the pain associated with this medical condition [180, 181]. These survey data are supported by double-blind clinical data. A study provided steroid and immunomodulator nonresponsive patients with smoked Δ^9-THC twice a day and found a significant reduction in Crohn's Disease Activity Index scores [182]. These patients also had improvements in sleep and appetite, and about one-third of the patients in the intervention group were weaned off of steroid treatment [182]. Unfortunately, despite the symptomatic relief that cannabinoids provide, their prolonged use is strongly associated with a worse prognosis and the need for surgical treatment [183]. An examination of the US government's clinical trials website (https://clinicaltrials.gov) reveals that there are a number of ongoing trials of nabiximols for the treatment of inflammatory bowel disease.

Summary

While there are pharmacological reasons to believe that cannabinoids may have beneficial effects, there is insufficient clinical trial evidence to make definitive statements. Certainly, pure Δ^9-THC has been documented to be efficacious in appetite stimulation, treatment of nausea and vomiting, and amelioration of spasticity in multiple sclerosis, and CBD has been found to be effective for the treatment of pediatric seizure disorders. Major impediments to studying cannabis, cannabis extracts, and CBD oil are (1) the federal regulations of high-THC cannabis in the USA and (2) the lack of motivation on the part of major pharmaceutical companies to invest in clinical trials that will not produce a patent-protected prescription drug. In this regard, ongoing clinical trials on *Cannabis* extracts containing Δ^9-THC/CBD (and other cannabinoids, terpenoids, and phytochemicals; nabiximols) may serve as a surrogate marker for *Cannabis* in general.

Adverse Effects of Cannabinoids

According to the US Substance Abuse and Mental Health Services Administration, the proportion of developing adolescents (ages 12–17) in the USA who are current high-THC cannabis users has remained the same (at 7.4%) over the last decade [184]. However, this same study also notes a recent uptick in the use of this substance among older individuals. Therefore, if the connection between parental drinking and adolescent drinking holds true for other substances of abuse, this uptick may foreshadow later increases in illicit marijuana consumption among this particularly vulnerable population [185]. This is especially worrying as emerging evidence indicates serious contraindications for heavy cannabis use by adolescents [186]. Moreover, there is growing concern for the emergence of cannabis-induced hyperemesis syndrome, or uncontrolled vomiting, observed in both adolescents and adults [187, 188]. A further complication is the fact that there seems to have been a marketplace race (in jurisdictions with legalized recreational cannabis) to provide products with higher and higher Δ^9-THC levels and with lower and lower CBD [189, 190].

Adverse Effects on Cognition and Development

As described above, endocannabinoids have an important role in tempering neuronal excitability through modulation of the release of the GABA and glutamate neurotransmitters. The disruption of these processes, such as through exposure to high doses of exogenous cannabinoids prior to the age of sixteen, has been implicated in the arrest of cortical maturation due to the dysregulation of nerve connection potentiation and brain plasticity [191, 192]. When paired with research that links reduced mitochondrial activity with cannabis use and poor memory formation, these data serve to explain the drop of ~2–6 IQ points that has been observed from childhood to adulthood in persistent cannabis users [193, 194]. Notably, this drop in neuropsychological function is not fully reversed with cessation of the drug, and this was observed even when years of education, alcohol use, and other drug dependences were considered [193]. More acutely, in regard to memory, intravenous Δ^9-THC administration in the amount of 0.03 mg/kg, or about 2.4 mg for the average North American, inhibits the encoding of verbal information and significantly decreases immediate and delayed recall in a broad spectrum of ages [195, 196]. This dose is also sufficient for the development of cannabis euphoria, anxiety, impaired cognition, and schizophrenia-like symptoms that are associated with this drug [197]. In addition to IQ scores and memory, the effects of cannabis use on cognition have also been found to manifest themselves in a sex-dependent manner that is exacerbated by an earlier age of use: females seem to primarily exhibit decreases in episodic memory, while male subjects show poorer decision-making skills [198, 199].

Psychological Risk

Adolescent cannabis use has been associated with increased rates of psychological disorders. The age at which an individual first uses cannabis has been shown to have a significant correlation with the frequency and severity of lifetime manic, anxiety, and obsessive-compulsive symptoms [200]. This is especially true in what has been described as a "vulnerable minority" of early users who are genetically predisposed to cannabis-induced psychological harm – an effect that is seen even when controlling for symptoms before cannabis use [201]. Growing evidence suggests that normal genetic variation in a variety of different genes is serving to interact with cannabinoids to create behavioral problems, dependence, and increased impulsivity [202–205]. While correlation does not equal causation, and it may be possible that individuals with underlying psychoses are predisposed to use *Cannabis*, it has been hypothesized that individuals with these alterations may use these substances to self-medicate subthreshold symptoms and that this use then worsens their condition in a perpetuating cycle [203]. Mechanistically, another route by which these psychological disorders may be instigated by chronic cannabis use is through the upregulation of 5-HT_{2A} serotonin receptors by CB2 receptor activation [206].

Exposure to cannabis, Δ^9-THC, or other euphorigenic cannabinoids has been shown to induce psychotic symptoms in a high percentage (20–50%) of the population [207, 208]. These symptoms manifest as both positive (suspiciousness, grandiose delusions, fragmented thinking, etc.) and negative (emotional withdrawal, psychomotor retardation, blunted affect, etc.) and are observed shortly after exposure [207, 209, 210]. The addition of the noneuphorigenic cannabinoids, such as CBD, may blunt these psychotic symptoms, although the findings are highly variable between studies [210]. While these symptoms are generally transient and are resolved after the period of intoxication, there is a subset of individuals in which the symptoms persist after intoxication has ended. This is known as cannabis-induced acute persistent psychosis (CIAPP). Symptoms of CIAPP include hallucinations, amnesia, disorientation, paranoia, and depersonalization [207, 208]. While this psychosis persists after the initial intoxicating event, CIAPP resolves faster than schizophrenic episodes and does not usually reoccur unless there is a subsequent exposure to cannabis or cannabinoids [207, 208].

Another area of concern with the use of high-THC cannabis is a well-documented association between cannabis use and risk of psychosis. A meta-analysis of 10 studies identified a 4-fold increase in risk of psychosis among heavy users and a 2-fold increase in risk among average users [211]. Similarly, another meta-analysis found a significant relationship between exacerbated mania symptoms in patients with bipolar disorder and a 3-fold increase in mania symptoms in nonclinical patients [212]. The most common psychological illness associated with high-THC cannabis use is schizophrenia, and while this association is modest, it is also consistent across a number of studies and cohorts [207]. This link between cannabis use and schizophrenia has been demonstrated in longitudinal studies in populations from Sweden [213, 214], the Netherlands [201], Germany [215], and New Zealand [216]. Interestingly, the Swedish cohort showed that the risk for developing schizophrenia decreased as the follow-up time increased, suggesting that there is a genetic predisposition that cannabis use can exacerbate [207, 214]. Of note, in individuals that were pre-

viously diagnosed with CIAPP, 50% of those without a pre-existing condition were diagnosed with a schizophrenia-spectrum disorder after 8 years [207, 208]. Δ^9-THC has also been shown to worsen symptoms even in patients that are being treated and on a stable dose of antipsychotics [207]. Interestingly, CBD has been shown to have antipsychotic properties in both animal models and in selected studies in patients [217–220]. Importantly, other studies in patients failed to find consistent or marked improvements in patients suffering from schizophrenia [221, 222]. Taken together, while CBD may reduce the psychotic activities of Δ^9-THC, further work is needed to validate these findings.

Future Imperatives

Implications for Opioid Use

Cannabinoids have engendered interest as a tool in fighting the opioid epidemic. When cannabinoids are used in conjunction with opioid medications for the treatment of chronic pain, one study found a 64% decrease in opioid use [223]. Mechanistically, exogenous cannabinoids seem to elicit this effect through the tempering of opioid withdrawal symptoms. Moreover, as the opioid-sparing effect of cannabinoids was observed to be greater in patients with peripheral pain rather than central, the TRPV1 receptor is a possible mediator, as are common signal transduction pathways [223–225]. Exogenous cannabinoids have also been found to allosterically modulate multiple opioid receptors; this function may serve to lower the opioid dosage that is necessary to achieve their analgesic effect [226]. This idea is supported by the fact that although there is a 27% decrease in reported pain when these medications are used together, opioid plasma concentration pharmacokinetics do not significantly change after the administration of cannabinoids [227]. As a result, research should focus on the use of cannabinoids as adjunct therapies for pain management as a tool to reduce the overall use of opioids.

Difficulties Performing Research on Medical Cannabis

High-THC cannabis and its derivatives are regulated, in the USA (under the Controlled Substances Act of 1970), as a schedule I controlled substance. This is a classification that defines these drugs as having a high potential for abuse, no currently accepted medical use, and a lack of accepted safety for use under medical supervision [228]. This impedes research progress through reduced access and resistance to clinical trials – not to mention societal stigmas. Further complicating the study of medical cannabis is the diverse array of phytocannabinoids found in *C. sativa* that may work in concert in what has been termed the "entourage effect." Δ^9-THC and CBD, however, that contain largely different pharmacodynamics, are the most prevalent cannabinoid molecules found within *C. sativa* (Table 1). This has led to the development of medications that contain ratios of CBD and Δ^9-THC that differ from those found naturally (e.g., Sativex® [nabiximols]). Interestingly, CBD to Δ^9-THC ratios above what are found normally seem to attenuate and/or reverse the psychoactivity, euphoria, and impaired facial emotional processing that are caused by relatively higher amounts of Δ^9-THC [229–231]. Furthermore, noncannabinoid components of the *C. sativa* plant, such as terpenoids, may also modulate the bioactivity of the cannabinoids [46, 232].

A further difficulty in studying one of the most easily accessible forms of cannabis medication, CBD oils, is that there is currently little to no regulation on the labeling of these products. In fact, studies have found that some oils contain little to no CBD and that levels of Δ^9-THC are often higher than reported [233–235]. Additionally, we have shown that the content of the oils can alter the efficacy of the CBD in some situations, further complicating the ability to study these products [236]. While variations in terpene and cannabinoid content in oil are unavoidable due to cultivar variation and extraction methods, efforts should be made to ensure that the labels match the content, which will undoubtedly require regulation of this growing industry.

Future trials for any disease or medical condition should be performed using standardized variables for different formulations for testing efficacy and routes of administration. In a similar vein, changes in the expression of endocannabinoid system genes should also be better characterized in human subjects with these conditions to provide further insight into potential therapies. Other approaches, such as the inactivation of the FAAH and MAGL metabolic enzymes of the endocannabinoid system, are gathering much interest [237].

Finally, there is considerable disagreement between the scientific and lay communities on routes of administration. Much pressure is focused on use of combustible plant materials (with its attendant psychoactivity, potential entourage effects, and its diversion to recreational use). However, this approach prevents effective placebo studies (there is no "sham" condition as the euphoria associated with Δ^9-THC is obvious when administered in this way) or carefully controlled dose-effect studies. As a result, double-blind, placebo-controlled trials (the gold standard for evaluating efficacy) are very difficult, if not

impossible. Therefore, moving forward the field requires studies to evaluate carefully characterized extracts of compounds to better understand dosing, blood levels, and pharmacotherapeutic outcomes.

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