Current Status and Prospects for Cannabidiol Preparations as New Therapeutic Agents

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States and the federal government are under growing pressure to legalize the use of cannabis products for medical purposes in the United States. Sixteen states have legalized (or decriminalized possession of) products high in cannabidiol (CBD) and with restricted Δ^9-tetrahydrocannabinol (Δ^9-THC) content. In most of these states, the intent is for use in refractory epileptic seizures in children, but in a few states, the indications are broader. This review provides an overview of the pharmacology and toxicology of CBD; summarizes some of the regulatory, safety, and cultural issues relevant to the further exploitation of its antiepileptic or other pharmacologic activities; and assesses the current status and prospects for clinical development of CBD and CBD-rich preparations for medical use in the United States. Unlike Δ^9-THC, CBD elicits its pharmacologic effects without exerting any significant intrinsic activity on the cannabinoid receptors, whose activation results in the psychotropic effects characteristic of Δ^9-THC, and CBD possesses several pharmacologic activities that give it a high potential for therapeutic use. CBD exhibits neuroprotective, antiepileptic, anxiolytic, antipsychotic, and antiinflammatory properties. In combination with Δ^9-THC, CBD has received regulatory approvals in several European countries and is currently under study in trials registered by the U.S. Food and Drug Administration in the United States. A number of states have passed legislation to allow for the use of CBD-rich, limited Δ^9-THC–content preparations of cannabis for certain pathologic conditions. CBD is currently being studied in several clinical trials and is at different stages of clinical development for various medical indications. Judging from clinical findings reported so far, CBD and CBD-enriched preparations have great potential utility, but uncertainties regarding sourcing, long-term safety, abuse potential, and regulatory dilemmas remain.

Key Words cannabidiol, cannabis, drug development, medical marijuana, Δ^9-tetrahydrocannabinol.
(Pharmacotherapy 2016;36(7):781–796) doi: 10.1002/phar.1780

For many centuries, *Cannabis sativa*, along with other subspecies and varieties—*C. sativa, C. indica,* and *C. ruderalis*—was used in the treatment of epilepsy.[1] Preparations from the flowers and resins of cannabis have been in use in China for about 5 millennia, especially for the management of fever, malaria, constipation, absent-mindedness, menstrual disorders, gout, rheumatism, and pain.[2] Arabs have used cannabis for similar medicinal purposes since medieval times. Before aspirin was popularized, cannabis was a common pain remedy in Western medicine in the 1800s.[1] Its indications have broadened to include glaucoma, nausea and vomiting, insomnia, anxiety, epilepsy, and muscle spasms.[3]

Conventionally, cannabis preparations containing the dried crushed flowering tops and

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leaves of the plant are called marijuana. Since 1970, marijuana has been listed as a Schedule I drug in the United States under the Controlled Substances Act, a classification that indicated it as a substance with high abuse potential and with no currently accepted medical use. This initial criminalization of marijuana may have been driven by social and political considerations and not simply due to health or safety reasons. However, the ensuing years have witnessed the appearance of several research publications suggesting the potential of cannabis for therapeutic benefits in certain pathologic conditions. This has led to growing pressures for legalization of marijuana for medical use in the United States, with some successes recorded. Currently, 25 states and the District of Columbia have passed relatively broad so-called medical marijuana laws, thus generally making the medical use of cannabis legal under their state laws.

Although cannabis has been suggested to possess potential medical benefits in the management of pain, spasticity in neurodegenerative disease, anorexia and wasting syndromes, psychiatric disorders, and epilepsy, concerns relating to abuse and other deleterious consequences of smoking marijuana have limited progress in medical utility.[4] Cannabis is known to be addictive, and cannabis withdrawal—the experience of psychological and physiologic symptoms after discontinuing heavy and prolonged marijuana use—is a serious concern. Having been able to largely identify the compounds responsible for the psychoactivity of cannabis, the therapeutic potential of the nonpsychoactive compounds is being explored.[5] The major psychoactive component of cannabis is Δ^9-tetrahydrocannabinol (Δ^9-THC), whereas cannabidiol (CBD) is the major and most widely studied of the other constituents. Higher Δ^9-THC-to-CBD ratios are associated with more prominent psychoactivity (euphoric, relaxant, and anxiogenic effects), whereas low ratios of Δ^9-THC to CBD seem to be more sedating.[5] Although CBD is the desired medical form of cannabis, utilization of extracts of the plant material generally yields varying ratios of CBD to THC. Many states have passed legislation for restricted THC content to minimize the potential abuse liability and adverse effects. Extracts available from cannabis contain variable THC amounts depending on the variety used in the preparation.

Two U.S. Food and Drug Administration (FDA)-approved drugs derived from cannabis have already been developed based on Δ^9-THC. The first was dronabinol, which is pure Δ^9-THC in an oil-filled soft gelatin capsule. The second was nabilone, a synthetic analog of Δ^9-THC. Other new pharmaceuticals are in various levels of development, with an attempt to harness the therapeutic benefits of cannabinoids while minimizing or eliminating adverse effects.

CBD has shown beneficial anticonvulsant properties through novel mechanisms not involving the classic cannabinoid receptors, and many of the adverse effects of Δ^9-THC appear to be absent.[6] A significant amount of preclinical data and supporting anecdotal evidence are available in humans regarding the effectiveness of cannabinoids in the treatment of epilepsy and especially severe seizure syndromes in children refractory to other antiepileptic drugs. This has led to the passage of legislation aimed at relaxing restrictions on certain preparations of cannabis extracts that are low in Δ^9-THC and high in CBD by a number of states.

This review provides a brief orientation to CBD and its pharmacology, and it assesses the current status and prospects for CBD and CBD-rich preparations for medical use.

Cannabis and Phytocannabinoids

Cannabis is the only genus of the family Cannabaceae, and according to many authorities, it comprises a single but variable species, *Cannabis sativa*. Its taxonomy is controversial. Although some authors designate *sativa*, *indica*, and *ruderalis* as subspecies or varieties, others propose *indica* and/or *ruderalis* as distinct species.[7] These have distinct morphologic characteristics and habitats. *Cannabis* has been classified more conveniently into CBD, intermediate, and Δ^9-THC chemotypes corresponding, respectively, to higher, equal, and lower constituent CBD:Δ^9-to-THC ratios. Thus *C. indica*, with a higher CBD:Δ^9-to-THC ratio, typifies the CBD chemotype and is medically preferred, whereas *C. sativa* is seen as a typical Δ^9-THC chemotype.

Cannabis contains more than 500 identified phytochemical constituents, of which at least 104 are cannabinoids. The term *phytocannabinoids* is used to distinguish the naturally occurring plant-derived cannabinoids from the endocannabinoids, which are naturally occurring lipid-derived neurotransmitters found in the human body.[8, 9]

CBD was first isolated from marijuana extract in 1940, but no further major study was reported on it for the next 25 years.[8] Its exact

chemical structure was elucidated in 1963.[10] Initial studies on cannabinoids concentrated on Δ^9-THC following the discovery of its responsibility for the psychotropic activity of smoked cannabis.[11]

The marijuana plant varies in its concentration of cannabinoids depending on a variety of factors including the plant part, time of harvest, and the particular subspecies or strain. In the plant material, both Δ^9-THC and CBD are in their acid forms, which are inactive (Figure 1). During the smoking process, these acids are converted to the active forms of Δ^9-THC and CBD.[5]

Cannabinoid Receptors and the Endocannabinoid System

It was found that Δ^9-THC mimics the endogenous cannabinoid neurotransmitters by binding to two G-protein–coupled cell membrane receptors, referred to as the cannabinoid type 1 (CB_1) and type 2 (CB_2) receptors, to exert its pharmacologic effects.[11]

Although the CB_1 receptors are found primarily in the brain and in several peripheral tissues, the CB_2 receptors are mainly concentrated in immune and hematopoietic cells.[12] CB_1 receptors are located at presynaptic junctions where they are involved in the regulation of ion channels and modulation of the release of dopaminergic, γ-aminobutyric acid (GABA), glutamatergic, serotoninergic, adrenergic, and cholinergic neurotransmitters.[13] Although agonists at CB_1 receptors usually effect inhibition of neurotransmitter release in the affected cell, there may actually be an increased neurotransmitter release from adjacent neurons due to a lack of an inhibitory signal.[14]

Endocannabinoids were discovered that bind to these receptors and others under physiologic and pathologic conditions; these are a class of endogenously synthesized lipid-signaling molecules, whose prototypes are anandamide (*N*-arachidonyl ethanolamide) and 2-arachidonoyl glycerol (2-AG). The endocannabinoid system (ECS) thus consists of these endogenous ligands, the CB receptors, transporter proteins,

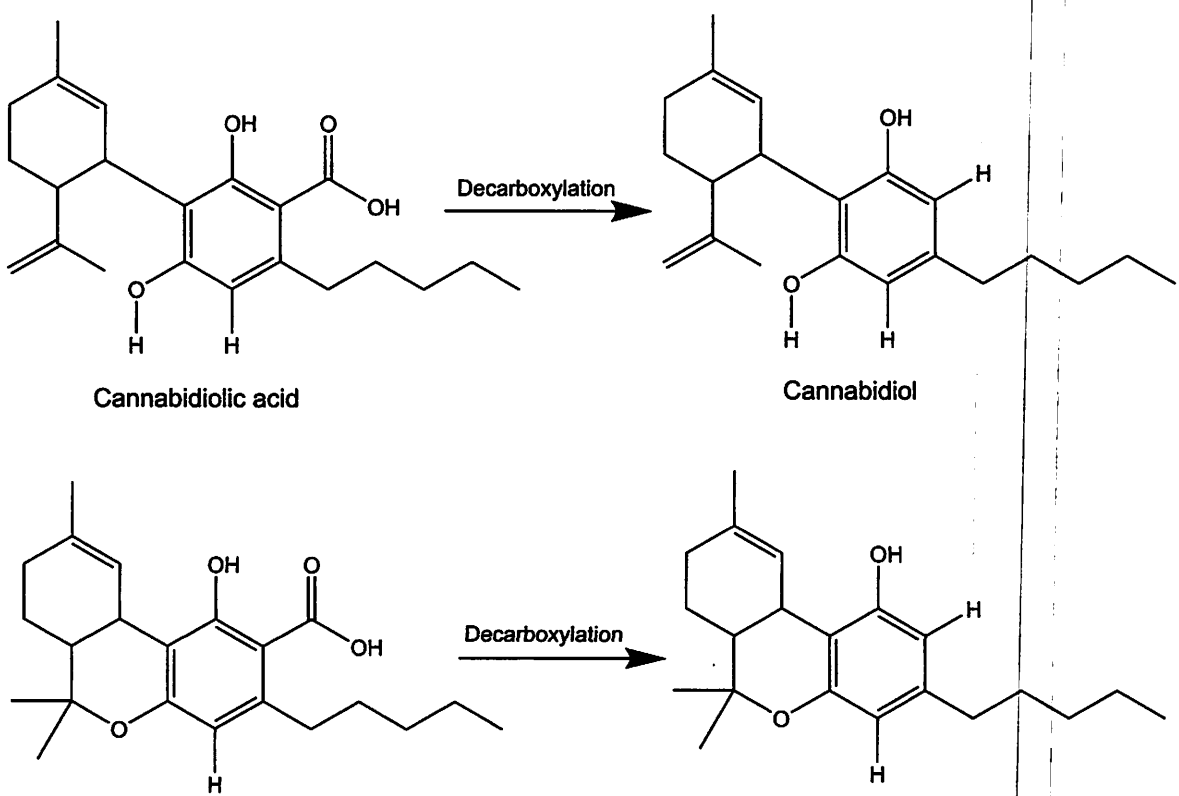

Figure 1. Structures of the naturally occurring cannabidiolic acid and Δ^9-tetrahydrocannabinolic acid, which are converted to cannabidiol and Δ^9-tetrahydrocannabinol on activation during smoking or in situ.

and synthetic and degradative enzymes. The ECS functionally impacts synaptic communication with direct modulatory effects on pain perception, eating, anxiety, learning, memory, and growth and development in the central nervous system, as well as motor control, immunocompetency, tumor cell proliferation, and inflammation.[15] The ECS can be dramatically modulated by a number of conditions such as stress, food intake, and behavioral manipulations. The endocannabinoids may also exert effects via non-CB receptors as well, such as through certain serotonin or vanilloid receptor subtypes.[12]

Pharmacology of Cannabidiol

CBD, unlike Δ^9-THC, does not activate the CB_1 and CB_2 receptors, which probably accounts for its lack of psychotropic activity. It exerts its pharmacologic effects through multiple mechanisms. At very low (nanomolar to micromolar) concentrations, it blocks the orphan G-protein–coupled receptor GPR55, the equilibrative nucleoside transporter, and the transient receptor potential of the melastatin type 8 (TRPM8) channel.[6] It enhances the activity of the serotonin $5\text{-}HT_{1a}$ receptor, the α_1 and α_3 glycine receptors, and the transient receptor potential of ankyrin type 1 (TRPA1) channel, with a bidirectional effect on intracellular calcium (in which case, it causes a slight increase in intracellular calcium under normal physiologic calcium conditions; in high-excitability conditions, it reduces intracellular calcium).[6]

At higher concentrations, CBD has been demonstrated to activate the nuclear peroxisome proliferator-activated receptor-γ (PPAR-γ) and the transient receptor potential of vanilloid types 1 (TRPV1) and 2 (TRPV2) channels.[12] It inhibits cellular uptake and fatty acid amide hydrolase–catalyzed degradation of *N*-arachidonoyl-ethanolamide.[12] CBD also has potent antioxidant properties, possibly due to its polyphenolic nature.

The ability of CBD potentially to reduce the psychoactivity of Δ^9-THC, thereby revealing other beneficial effects of Δ^9-THC, was also reported.[16] By inhibiting the Δ^9-THC-induced activation of CB_1, CBD reduces the propensity for psychotic symptoms when cannabis users consume preparations with high CBD:Δ^9-to-THC ratios.[16] This may relate to the ability of CBD to modulate the cytochrome P450 (CYP) 2C–dependent metabolism of Δ^9-THC to the more psychoactive 11-hydroxy derivative. At high doses, CBD may also interfere with the CB_1-mediated effects of Δ^9-THC and its 11-hydroxy metabolite.

Pharmacokinetics of Cannabidiol

CBD has been delivered by oral administration, by inhalation (smoking), and through vaporization. Traditionally delivered through inhalation as a constituent of smoked cannabis, CBD is effectively taken up in the lungs by the circulating blood. Aerosolized CBD has been reported to yield rapid peak plasma concentrations in 5–10 minutes and ~31% bioavailability.[17] The need for specialized equipment and patient cooperation with administration limit the development and promotion of this delivery route.

Oral delivery of an oil-based capsule formulation of CBD has been assessed in humans. Probably due to its poor aqueous solubility, the absorption of CBD from the gastrointestinal tract is erratic, and the resulting pharmacokinetic profile is variable. Bioavailability from oral delivery was estimated to be 6% due to significant first-pass metabolism.[18] Bioavailability from oral-mucosal and sublingual routes are less variable but similar to oral delivery.

Following a daily administration of CBD 10 mg/kg in 15 neuroleptic-free patients for 6 weeks, one group reported a weekly mean CBD plasma level ranging from 5.9–11 ng/ml.[19]

CBD is rapidly distributed into the tissues with a high volume of distribution of ~32 L/kg.[20] It may preferentially accumulate in adipose tissues due to its high lipophilicity. It is highly bound to plasma proteins and circulating blood cells.[18] CBD undergoes CYP3A- and CYP2C-dependent phase I metabolism to 7-hydroxy-CBD, which is further metabolized and excreted, more in feces and to a lesser extent in urine. CBD has an estimated terminal half-life of 18–32 hours and a clearance of 57.6–93.6 L/hour.[18]

Although clinical studies on the ability of CBD to interact with other drugs have not been conducted exhaustively, CBD has shown potent inhibitory activity against CYP2C, CYP2D6, and CYP3A isoforms in preclinical studies, raising concerns of drug–drug interactions with other substrates of the enzymes.[21, 22]

In a drug–drug interaction study between CBD and clobazam, a CYP2C19 substrate, 25 children with refractory epilepsy were

administered CBD and clobazam concurrently.[23] CBD caused a greater than 60% and a 500% increase in mean plasma levels of clobazam and its major metabolite, *N*-desmethylclobazam, respectively, after 4 weeks. Because most commercially available antiepileptic drugs are metabolized through the CYP pathways, drug interactions with CBD may be expected. CYP3A4 inducers such as phenytoin and carbamazepine may also induce the metabolism of CBD. CBD is generally well tolerated, with an acceptable safety profile at therapeutic dosages.

Potential Therapeutic Utility of Cannabidiol in the Treatment of Epilepsy

Epilepsy is a neurologic disorder associated with abnormal electrical activity in the brain and marked by sudden and recurrent episodes of sensory disturbance, loss of consciousness, or seizures. Epilepsy costs the United States ~$15.5 billion annually.[24] About 4–10% of children experience at least one seizure within their first 16 years of life,[4] and ~150,000 children experience a seizure in their first year of life, and of these, 30,000 develop epilepsy.[23] About 30% of children with epilepsy have intractable seizures.[24] Intractable seizures are those that cannot be controlled with at least two epilepsy drugs for 18 months–2 years, or control has been attained but with serious drug adverse effects.[24]

In Western medicine, cannabis was reported to have been used in the treatment of epilepsy by prominent English neurologists in the late 19th century.[25] Cannabis preparations were widely available in the United States during this period and were advertised as remedies for a number of disorders.[26] The published reports on use in epilepsy, however, did not popularize cannabis as a suitable medication for this disorder, despite anecdotal success.

CBD is the only phytocannabinoid, other than Δ^9-THC, to have been investigated in preclinical and clinical studies for anticonvulsant effects. In rodent models, CBD blocked maximal electroshock as well as pentylenetetrazole-induced generalized seizures.[25]

Five controlled clinical trials have been published on the use of CBD in patients with epilepsy. In a placebo-controlled study of four patients administered CBD 200 mg/day for 3 months in 1978, two patients became seizure free, one partially improved, and the fourth had no improvement.[27] Although no toxicity was reported, the study was flawed by the small sample size, unclear design as to blinding, and the description of what constituted the partial improvement.

In a related study in 1980, 15 patients with "secondarily generalized epilepsy with temporal focus," randomly divided into a treatment group and a placebo group, were given CBD 200–300 mg/day or placebo.[28] The patients continued their pretrial regimen of antiepileptic medications prescribed by their doctors, although the drugs no longer helped in the control of their symptoms. CBD was tolerated in all patients, with no signs of toxicity. Of the eight in the treatment group, four were reported to be almost free of episodes of convulsion throughout the trial, whereas three others showed partial clinical improvement. CBD was ineffective in one patient. Apart from the small sample size, the report of clear improvement in one of the patients in the placebo group may limit the conclusions reached from the study.

In a third study conducted in 1986, CBD 200–300 mg/day for a month reported no significant differences between the treatment and placebo groups.[29] Similarly, a 6-month double-blind study administering CBD 100 mg 3 times/day did not result in any changes in seizure frequency or cognitive and behavioral improvement.[30]

In a more recent study, a multicenter interventional trial was aimed at establishing the safety, tolerability, and efficacy of CBD in patients with severe, intractable childhood-onset treatment-resistant epilepsy.[31] The authors recruited 214 patients. Only 3% of patients in the safety assessment group discontinued treatment because of an adverse event. A ~37% median reduction in monthly motor seizures was reported.

These limited clinical reports coupled with a long history of use and safety profiles make CBD a candidate for antiepileptic drug development. The limited availability of effective antiepileptic drugs in certain groups of seizure sufferers is also a good reason to explore CBD as an alternative.

Cannabis for the Treatment of Dravet and Lennox-Gastaut Syndromes

Dravet syndrome, also known as severe myoclonic epilepsy of infancy, is a form of intractable epilepsy that develops in infancy and continues

into childhood.[32] Although not a hereditary condition, it is most often caused by a genetic mutation affecting the brain ion (especially sodium) channels. The first seizures that appear during infancy are usually associated with fever and are tonic-clonic. Early seizures usually last more than 2 minutes and can even result in status epilepticus (a seizure lasting longer than 30 minutes). Current treatment includes drugs and alternative forms of treatment, such as vagus nerve stimulation and a ketogenic diet.[33]

Lennox-Gastaut syndrome is a severe form of epilepsy that develops in children ~4 years of age.[34] Seizure types include tonic, atonic, atypical absence, and myoclonic. Patients may experience developmental delays, behavioral disturbances, and impaired intellectual functioning. Lennox-Gastaut syndrome can be caused by a head injury or a central nervous system infection, but 30–35% of cases have no known cause.[35] Patients may respond to conventional antiepileptic drugs initially but may later develop tolerance or have uncontrollable seizures.[35]

Stiripentol, an aromatic allylic alcohol that allosterically modulates the $GABA_A$ receptor, is the only compound to have been assessed through a controlled clinical trial with clear advantage over placebo and was awarded orphan drug designation for the treatment of Dravet syndrome by the European Medicine Agency in 2001 and by the FDA in 2008.[36]

Due to some clinical and anecdotal evidence supporting cannabinoids, specifically CBD as a potential therapy for epilepsy, coupled with the failure of the conventional antiepileptic drugs to manage Dravet and Lennox-Gastaut syndromes effectively, many patients have turned to medical marijuana. Given the need for more effective therapy that is better tolerated, patients with Dravet syndrome and Lennox-Gastaut syndrome are potentially good candidates for CBD trials.

In many states in the United States and in several countries, supporting legislation has been enacted to allow the exploration of CBD for medical use. In this regard, Epidiolex, a purified cannabinoid that comes in a liquid form containing CBD and no THC, currently undergoing clinical trials in the United States, is being developed by GW Pharmaceuticals (Salisbury, UK).[37] It has been granted orphan drug status by the FDA for the treatment of Dravet and Lennox-Gastaut syndromes.

Other Potential Medical Uses of Cannabidiol

Cannabidiol has been assessed for potential therapeutic uses in other neurologic and psychiatric disorders, some of which may be associated or coexist with epilepsy.

Neonatal hypoxic-ischemic encephalopathy (NHIE), resulting from perinatal asphyxia, is one clinical condition that CBD may potentially treat. Therapeutic hypothermia is the only available therapy for asphyxiated infants and provides neuroprotection only in patients with mild NHIE.[38]

Although cannabis smoking has been identified as a risk factor for schizophrenia, several components of cannabis are being suggested to have potential therapeutic benefits in the management of psychiatric disorders. It has been reported that cannabis-associated psychosis is less prevalent in smokers of cannabis containing higher CBD-to-THC ratios.[39] CBD improves cognitive function and may be potentially beneficial in patients with schizophrenia for whom cognitive impairment is a major deficit.[40] CBD has been shown in laboratory-based and clinical studies to alleviate symptoms of schizophrenia.[41]

A controlled clinical trial that compared CBD and amisulpride, a standard antipsychotic drug, for 4 weeks in 33 patients with acute schizophrenia reported similar clinical outcomes, with CBD showing a better resolution of negative symptoms and fewer side effects.[41] In addition, CBD lacks the extrapyramidal symptoms associated with amisulpride.[41] In a case study of one schizophrenic patient administered CBD 1200 mg/day, symptoms improved after a few weeks.[42] Ten years later, the same authors reported mild symptom improvement in one of the three treatment-resistant schizophrenic patients who was enrolled in an inpatient study and administered increasing doses of CDB 40–1280 mg/day for 4 weeks.[43] In another study, six patients with Parkinson disease who had psychosis for at least 3 months were administered CBD 150 mg/day for 4 weeks in addition to their usual therapy.[44] Significant improvement was reported in the symptoms of psychosis and Parkinson disease.

CBD has also been investigated for potential benefits in the management of anxiety disorder. In rodent models, CBD showed positive results in conditioned fear, aversion to open space, conflicts tests, restraint stress, and other measures of anxiety disorder.[45] In humans, CBD reversed

the anxiety-inducing effects of Δ^9-THC in healthy volunteers and demonstrated anxiolytic effects in patients with social anxiety disorder.[46]

A number of clinical trials are currently underway around the world with CBD, alone or in combination with Δ^9-THC. Table 1 summarizes those trials registered with ClinicalTrials.gov.

An example of such a trial, whose results have been published, is the use of CBD-containing products to treat cannabis withdrawal. In this two-site double-blind randomized trial conducted in Australia, cannabis-dependent treatment seekers were administered a 6-day regimen of nabiximols, formulated to deliver maximum daily doses of 86.4 mg Δ^9-THC and 80 mg CBD. Relative to placebo, nabiximols attenuated cannabis withdrawal symptoms and improved patient retention in treatment, significantly reducing withdrawal-related irritability, depression, and cannabis cravings. The effect of nabiximols on long-term reductions in cannabis use following medication cessation, however, was not significantly different from that of placebo.[47]

In an observational prospective multicenter noninterventional study of nabiximols in patients with multiple sclerosis spasticity in a routine care setting in Germany, 74.6% of patients reported relief according to a specialist assessment.[48]

These findings and many more have continued to project CBD as a therapeutic option for a number of diseases. It is estimated that the results of the many ongoing clinical assessments will provide more evidence for possible clinical approvals for the medical use of CBD and CBD-containing preparations.

Current Legislation Status of Marijuana for Medical Use Across the United States

In the last several years, a number of states passed legislation for the legalization of marijuana possession; most of these are for medical purposes, a few for recreational use, and a steadily growing number have legalized, for treatment of seizures and select other disorders, certain cannabis-derived products rich in CBD but with restricted Δ^9-THC content. Figure 2 summarizes the legal status of cannabis products with regard to medical use as of June 2015. Twenty-five states along with the District of Columbia allow the use of marijuana for medical purposes. Four states (Colorado, Oregon, Washington, and Alaska) among these allow recreational marijuana use. But in addition, 15 states have "restricted THC" statutes. When not specifically mentioned as an indication for medical marijuana use, epilepsy is indirectly referred to in most states' legislation. Although these bills provide for legal status within the respective states, by federal law, these products are still illegal.The Department of Justice has opted to focus the Drug Enforcement Administration's (DEA) investigative and enforcement efforts regarding cannabis on more violent or dangerous activities associated with marijuana (use of firearms, gang activity, diversion, distribution to minors, cover for narcotics trafficking or other illegal activities, possession, or use on federal property). However, the DEA is currently not precluded from enforcing the federal statutes in states that have legalized marijuana. This has implications that are perhaps not widely appreciated. For example, no federal medical facilities (e.g., the Veterans Administration) can use so-called medical marijuana even if located in a legal state. No university or medical center such as those receiving federal research funding, even in states with medical marijuana laws, can treat patients or even conduct clinical research with these products without federal approvals; otherwise they may face prosecution and jeopardize their federal funding.

In May 2014, the U.S. House of Representatives, by a 219–189 vote, passed legislation that would stop the DEA from targeting medical marijuana operations in states where it is legal.[49, 50] Proponents argue that the ultimate goal is to allow the states the final say on these medical matters. The bill was not taken up by the Senate. However, in March 2015, new legislation was introduced in both the House and Senate, and it will likely receive serious consideration during this Congress. The Compassionate Access, Research Expansion, and Respect States Act has several elements that would drastically impact the current landscape for medical use of cannabis-derived products, including the rescheduling of marijuana to Schedule II.[50] The Senate bill also calls for leaving medical marijuana regulation to the states, removing the potential for federal prosecution for those possessing marijuana for medical purposes, making marijuana available in federal medical facilities where cannabis has been decriminalized, reducing the barriers to research on marijuana, removing CBD from the listing of controlled substances, and allowing interstate commerce of CBD products. Many observers note that this

Table 1. Currently Registered Clinical Trials of Cannabis Products[a]

Condition	No. of trials	Status	No. of patients (age range, yrs)	Primary end point or results, if available	Formulation and dosage	Route of administration	Country
Anxiety	1	Not yet recruiting	~ 16 (≥ 18)	Change in anxiety symptoms via the Beck Anxiety Inventory	CBD tincture 4.68 mg/ml	Sublingual	United States
Bipolar disorder	1	Withdrawn	0 (19–60)	Bipolar symptom improvement	Cannabis extract of 1:1 ratio of THC to CBD	Oral spray	Canada
Bowel disease	1	Completed	20 (20–80)	Antiinflammatory effects	CBD in olive oil drops 5 mg twice/day	Sublingual	Israel
Cannabis use disorder	5	Various stages	168 (16–60) ~ 5 (18–65)	Reducing cannabis use Reducing cannabis withdrawal	CBD 200, 400, or 800 mg CBD 300 mg once on day 1, twice on days 2–5, and once on day 6	Oral Oral	United Kingdom Not provided
Cocaine dependence	1	Not yet recruiting	~ 110 (18–65)	Reduction in cocaine cravings	CBD 400 or 800 mg	Oral	Not provided
Diabetes mellitus	1	Completed (with results available)	62 (≥ 18)	Mean serum HDL level; all tests were 2 sided with 10% significance level; mean serum HDL level changes from baseline measures were as follows: CBD 5 mg + THCV 5 mg (0.00), CBD 100 mg + THCV 5 mg (0.04), CBD 100 mg + placebo (−0.04), THCV 5 mg + placebo (0.00), placebo alone (0.02); each was compared with placebo, and p values were as follows: CBD 5 mg + THCV 5 mg vs placebo (p=0.766), CBD 100 mg + THCV 5 mg vs placebo (p=0.424), CBD 100 mg + placebo vs placebo alone (p=0.412), THCV 5 mg + placebo vs placebo alone (p=0.668)	CBD 100-mg and 5-mg capsules, THCV 5-mg capsule, and placebo capsule	Oral	United Kingdom

(continued)

Table 1. (continued)

Condition	No. of trials	Status	No. of patients (age range, yrs)	Primary end point or results, if available	Formulation and dosage	Route of administration	Country
Dravet syndrome	6	Not yet recruiting	~ 86 (1–30)	Reduction in number of seizures	CBD liquid formulation; not more than 40 mg/kg/day, divided and given 12 hrs apart	Oral solution	Not provided
			~ 120 (2–18)	Reduction in number of seizures	Epidiolex (CBD in sesame oil with anhydrous ethanol with sweetener and strawberry flavoring); low dose (50% of high dose) or high dose of 100 mg/ml	Oral solution	The Netherlands
			~ 350 (≥ 2)[b]	Number of adverse effects seen	No more information given other than CBD	Not provided (assume oral)	Not provided
			~ 80 (2–18)	Treatment of seizure frequency	CBD 25 or 100 mg/ml dissolved in sesame oil and anhydrous ethanol with sweetener and strawberry flavoring	Oral solution	United States
			~ 30 (4–10)	Effectiveness in Dravet syndrome treatment and number of adverse effects	CBD 25 or 100 mg/ml dissolved in sesame oil and anhydrous ethanol with sweetener and strawberry flavoring; dosed at 5, 10, or 20 mg/kg/day	Oral solution	United States
			~ 150 (≤ 50)	Seizure reduction and overall medication response	Charlotte's web medical marijuana	Not provided (assume oral)	United States
Effects of CBD and THC in healthy subjects	6	Various stages	~ 75 (18–55)	Behavioral changes	CBD 5 mg + THC 0.035 mg/kg	Oral (CBD) and IV (THC)	United States
			20 (18–65)	Processing of emotional stimuli	THC 10 mg once or CBD 600 mg once	Oral	Germany
			20 (18–50)	Changes in blood oxygen level dependent responses and effects on memory	THC 10 mg once or CBD 600 mg once	Oral	Germany
			~ 60 (18–45)	Induction of psychotic symptoms	THC 20 mg and/or CBD 800 mg	Oral	Germany
			~ 60 (18–45)	Induction of psychotic symptoms	THC 20 mg and/or CBD 800 mg	Oral	Germany
Effects of CBD and smoking marijuana	1	Unknown (no status updates in ≥ 2 yrs)	~ 36 (18–50)	Physical and subjective effects of CBD when given with marijuana	CBD 0, 200, 400, or 800 mg of in combination with active or inactive marijuana cigarette	Oral (CBD) and inhalation (marijuana)	United States

(continued)

Table 1. (continued)

Condition	No. of trials	Status	No. of patients (age range, yrs)	Primary end point or results, if available	Formulation and dosage	Route of administration	Country
Fatty liver	1	Completed, has results	25 (≥ 18)	Mean % change from baseline in liver triglyceride levels; all statistical tests were 2 sided at a 10% significance level; CBD 200 mg showed a mean −0.68 change from baseline in liver triglycerides, CBD 400 mg showed a −0.28 change from baseline, CBD 800 mg showed a 0.65 change from baseline, and placebo showed a 6.36 change from baseline; each CBD dose (200, 400, and 800 mg) was compared with placebo and the respective p values were p=0.222, p=0.133, and p=0.302	CBD 200, 400, or 800 mg/day, or placebo	Oral	United Kingdom
GVHD	4	Various stages	~ 40 (≥ 18)	Resolution of GVHD	CBD dissolved in oil 10 mg twice/day up to 600 mg/day + i.v. or oral methylprednisolone 1–2 mg/kg/day	Oral	Israel
			~ 30 (≥ 18)	Prophylaxis of GVHD	CBD dissolved in oil 10 mg twice/day	Oral	Israel
			~ 10 (≥ 18)	Complete remission of GVHD	CBD 150 mg twice/day + i.v. methylprednisolone 2 mg/kg/day + a calcineurin inhibitor	Oral	Israel
			~ 10 (≥ 18)	GVHD prophylaxis	CBD 150 mg twice/day 1 wk before transplantation until 150 days posttransplantation with other transplant medications	Oral	Not provided
Infantile spasms	1	Not yet recruiting	~ 20 (6–36 mo)	Reduction in number of spasms	CBD 20–40 mg/kg/day in 2 divided doses	Oral solution	United States

(continued)

Table 1. (continued)

Condition	No. of trials	Status	No. of patients (age range, yrs)	Primary end point or results, if available	Formulation and dosage	Route of administration	Country
Lennox-Gastaut syndrome	4	Various stages	~ 86 (2–30)	Reduction in number of seizures	CBD, not more than 40 mg/kg/day in 2 divided doses	Oral solution	Not provided
			~ 120 (2–55)	Reduction in number of seizures	Epidiolex (CBD in sesame oil with anhydrous ethanol with sweetener and strawberry flavoring); low dose (50% of high dose) or high dose of 100 mg/ml	Oral solution	United States
			~ 80 (2–55)	Reduction in number of seizures	Epidiolex (CBD in sesame oil with anhydrous ethanol with sweetener and strawberry flavoring) 100 mg/ml	Oral solution	United States
			~ 350 (≥ 2)[b]	Number of adverse effects seen	No more information given other than CBD	Not provided (assume oral)	Not provided
Opiate addiction	3	Various stages	18 (21–65)	Control opioid cravings	CBD 400 or 800 mg + 0.5 + fentanyl 1 mcg/kg	Oral	United States
			~ 10 (21–65)	Control opioid cravings	CBD 400 or 800 mg	Oral	United States
			~ 45 (21–65)	Control opioid cravings	CBD 400 or 800 mg	Oral	Not provided
Pain	4	Various stages	~ 200 (18–60)	Control of postoperative pain	High-dose spray (THC 21.6 mg-to-CBD 20 mg) or low-dose spray (THC 10.8 mg-to-CBD 10 mg) with or without midazolam and/or acetaminophen	Oral spray	Israel
			~ 40 (≥ 50)	Reduction of osteoarthritic pain	100-mg capsule of varying doses (21.9% THC/0.8% CBD, 15% THC/5% CBD, 9% THC/9.5% CBD, 3.8% THC, 10% CBD, 0.6%THC/13% CBD, < 0.3% THC/< 0.3% CBD)	Oral	Canada

(continued)

Table 1. (continued)

Condition	No. of trials	Status	No. of patients (age range, yrs)	Primary end point or results, if available	Formulation and dosage	Route of administration	Country
Schizophrenia	8	Various stages	~ 74 (18–45)	Antipsychotic effects	CBD 200 mg, CBD 200 mg controlled release, or CBD 200 mg with amisulpride, olanzapine, quetiapine, or risperidone	Oral	Germany
			~ 150 (18–65)	Efficacy in acute, early-stage schizophrenia	CBD 300 mg twice/day vs placebo vs olanzapine	Oral	Denmark, Germany
			29 (18–65)	Effectiveness in acute schizophrenia treatment or schizophrenic psychosis	CBD 600-mg capsules	Oral	Germany
			42 (18–65)	Efficacy as an antipsychotic and treatment of side effects of schizophrenia and neuropsychological functioning	CBD 200 mg 3 times/day; amisulpride 200 mg 3 times/day for neuroleptic treatment	Oral	Germany
			36 (18–65)	Addition to antipsychotic medication vs placebo to treat cognitive dysfunction in schizophrenia	CBD daily over 6 wks; no further information given	Oral	United States
			~ 86 (18–65)	Different drugs to modify glucose regulation in the central nervous system for potential use in schizophrenia	URB597 10 mg/day orally for 5 days; intranasal insulin 160 IU daily for 5 days; CBD controlled release 320 mg/day orally for 5 days	Oral and intranasal	Germany
			88 (18–65)	Change in symptom severity of schizophrenia or related psychotic disorder	Epidiolex (oily solution containing 100 mg/ml of CBD dissolved in excipients, sesame oil, ethanol, sucralose, and strawberry flavoring); CBD 500 mg (5 ml) twice/day for 6 wks	Oral	United Kingdom, Poland, Romania
			~ 72 (18–65)	Efficacy in reducing schizophrenia severity	CBD 800 mg/day for 1 mo, then 2-wk washout, then placebo, or vice versa	Oral	Not provided

(continued)

Table 1. (continued)

Condition	No. of trials	Status	No. of patients (age range, yrs)	Primary end point or results, if available	Formulation and dosage	Route of administration	Country
Seizures	11	Various stages	~ 60 (1–17)	Pharmacokinetics of three different CBD doses in patients with resistant seizures	No information other than low-, medium-, and high-dose CBD	Oral solution	United States
			~ 232 (1–30)	Number of adverse effects	CBD dosed at a maximum of 40 mg/kg/day divided in 2 doses, separated by 12 hrs	Oral solution	United States
			~ 25 (2–25)	Number of seizures	CBD (GWP42003-P; assumed Epidiolex)	Not provided (assumed oral solution)	United States
			~ 20 (18–55)	Pharmacokinetic interactions with clobazam	Epidiolex (CBD dissolved in sesame oil and anhydrous ethanol with sweetener and strawberry flavoring); up to 20 mg/kg/day, divided into 2 doses	Oral solution	Not provided
			~ 20 (18–55)	Any interaction between Epidiolex and clobazam (phase II)	Epidiolex (CBD dissolved in sesame oil and anhydrous ethanol with sweetener and strawberry flavoring); up to 20 mg/kg/day, divided into 2 doses	Oral solution	Not provided
			Not provided (2–16)	Safety and efficacy of CBD in pediatric drug-resistant seizures	CBD 25 mg/kg/day titrated weekly as tolerated	Oral	United States
			Not provided (1–17)	Treatment of refractory epilepsy	CBD (Epidiolex) 2 mg/kg/day in 2 divided doses titrated to a maximum of 25 mg/kg/day	Oral solution	United States
			~ 40 (16–55)	Pharmacokinetics of Epidiolex with valproate or stiripentol	Epidiolex (CBD dissolved in sesame oil and anhydrous ethanol with sweetener and strawberry flavoring); maximum of 20 mg/kg/day in 2 divided doses with valproate or stiripentol	Oral solution	Not provided
			~ 300 (31 days –17 yrs)	Pharmacokinetics of CBD, THC, and other antiepileptic medications in epileptic pediatric patients	Not given (assumed Charlotte's web)	Not provided (assumed oral)	United States

(continued)

Table 1. (continued)

Condition	No. of trials	Status	No. of patients (age range, yrs)	Primary end point or results, if available	Formulation and dosage	Route of administration	Country
			~ 40 (16–55)	Number of adverse effects	Epidiolex (CBD dissolved in sesame oil and anhydrous ethanol with sweetener and strawberry flavoring); maximum of 20 mg/kg/day in 2 divided doses	Oral solution	Not provided
			Not provided (1–18)	Treatment of medication-resistant epilepsy	Epidiolex up to 25 mg/kg/day; may be increased to 50 mg/kg/day	Oral solution	United States
Sensory science	1	Recruiting	~ 36 (18–35)	Preference for sweet foods after THC, CBD, and placebo	No further details given other than THC, CBD, and placebo	Not provided (assume oral)	The Netherlands
Solid tumor	1	Not yet recruiting	~ 60 (≥ 18)	Tumor size based on computed tomography scans	No other information given other than pure CBD	Unknown	Not provided
Sturge-Weber syndrome	1	Recruiting	~ 10 (1 mo–30 yrs)	Change in seizure severity	Epidiolex 2 mg/kg/day titrated up to a maximum of 25 mg/kg/day	Not provided (assume oral solution)	United States
Tuberous sclerosis complex	2	Not yet recruiting)	~ 144 (2–65)	Change in number of seizures	Epidiolex 25 mg/kg/day vs 50 mg/kg/day vs placebo	Oral solution	Not provided
			~ 144 (2–65)	Occurrence of adverse effects	Epidiolex 100 mg/ml twice/day titrated to 25 mg/kg/day	Oral solution	Not provided

CBD = cannabidiol; GVHD = graft-versus-host disease; HDL = high-density lipoprotein cholesterol; THC = Δ^9-tetrahydrocannabinol; THCV = tetrahydrocannabivarin.
[a]Registered with ClinicalTrials.gov as of February 2016.

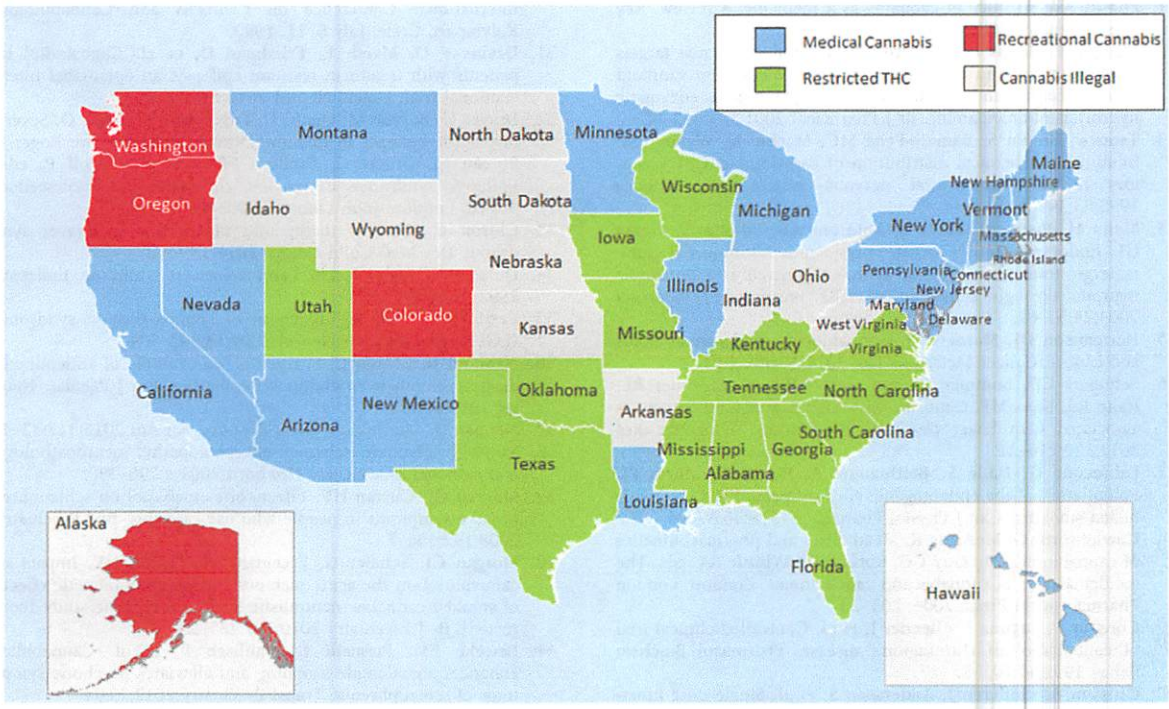

Figure 2. Status of current legislation on *Cannabis* for medical use across the United States (as of June 2015). At least five other states have legislation pending or special agreements to allow use of an Investigational New Drug Application–covered cannabidiol product. THC = tetrahydrocannabinol.

bill's careful language and broad bipartisan support give it a good chance of serious debate, and there is clearly a mounting public pressure, at least for some components of the legislation. Therefore, the overall state and federal legislative and enforcement landscape for cannabis-derived products may change dramatically in the coming months.

Conclusion

A long history of use, a good deal of experimental evidence, and a number of anecdotal and a few descriptive clinical studies point to the potential clinical utility of CBD in the management of seizures associated with epileptic syndromes. Growing pressure to make CBD preparations available for the treatment of severe cases of drug-resistant seizures has resulted in a wave of legislative activity around the country to ease restrictions on research and treatment. A large number of registered clinical trials are currently underway for several neurologic and behavioral disorders. If positive indications of therapeutic utility continue to accrue, interest in and understanding of the underlying mechanisms will certainly open new doors for pharmacologic management of these disorders and spawn new structural leads for central nervous system drug development.

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Comprehensive Review of Medicinal Marijuana, Cannabinoids, and Therapeutic Implications in Medicine and Headache: What a Long Strange Trip It's Been . . .

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Background.—The use of cannabis, or marijuana, for medicinal purposes is deeply rooted though history, dating back to ancient times. It once held a prominent position in the history of medicine, recommended by many eminent physicians for numerous diseases, particularly headache and migraine. Through the decades, this plant has taken a fascinating journey from a legal and frequently prescribed status to illegal, driven by political and social factors rather than by science. However, with an abundance of growing support for its multitude of medicinal uses, the misguided stigma of cannabis is fading, and there has been a dramatic push for legalizing medicinal cannabis and research. Almost half of the United States has now legalized medicinal cannabis, several states have legalized recreational use, and others have legalized cannabidiol-only use, which is one of many therapeutic cannabinoids extracted from cannabis. Physicians need to be educated on the history, pharmacology, clinical indications, and proper clinical use of cannabis, as patients will inevitably inquire about it for many diseases, including chronic pain and headache disorders for which there is some intriguing supportive evidence.

Objective.—To review the history of medicinal cannabis use, discuss the pharmacology and physiology of the endocannabinoid system and cannabis-derived cannabinoids, perform a comprehensive literature review of the clinical uses of medicinal cannabis and cannabinoids with a focus on migraine and other headache disorders, and outline general clinical practice guidelines.

Conclusion.—The literature suggests that the medicinal use of cannabis may have a therapeutic role for a multitude of diseases, particularly chronic pain disorders including headache. Supporting literature suggests a role for medicinal cannabis and cannabinoids in several types of headache disorders including migraine and cluster headache, although it is primarily limited to case based, anecdotal, or laboratory-based scientific research. Cannabis contains an extensive number of pharmacological and biochemical compounds, of which only a minority are understood, so many potential therapeutic uses likely remain undiscovered. Cannabinoids appear to modulate and interact at many pathways inherent to migraine, triptan mechanisms of action, and opiate pathways, suggesting potential synergistic or similar benefits. Modulation of the endocannabinoid system through agonism or antagonism of its receptors, targeting its metabolic pathways, or combining cannabinoids with other analgesics for synergistic effects, may provide the foundation for many new classes of medications. Despite the limited evidence and research suggesting a role for cannabis and cannabinoids in some headache disorders, randomized clinical trials are lacking and necessary for confirmation and further evaluation.

Key words: cannabis, hemp, headache, medical marijuana, cannabinoids, cannabidiol, CBD, delta-9-tetrahydrocannabinol, THC

The plant genus *Cannabis* is a member of the plant family Cannabaceae, and there are 3 primary cannabis species which vary in their biochemical constituents: *Cannabis sativa*, *Cannabis indica*, and *Cannabis ruderalis*.[1] In general, cannabis that has high levels of the psychoactive cannabinoid, delta^9-tetrahydrocannabinol (Δ^9-THC), and low levels of the non/anti-psychoactive cannabinoid, cannabidiol (CBD), is referred to as "marijuana." Cannabis that has high levels of CBD, and very low insignificant levels of Δ^9-THC, is referred to as "industrial hemp," or "hemp," and has no psychoactive effects. The botanical origin of cannabis is suspected to be from Western and Central Asia. It has been cultivated since ancient times in Asia and Europe, and spread to the New World in post-Columbian times.[2] Carbon dating has confirmed the use of cannabis fibers in the form of hemp back to 4000 BC.[3,4] Hemp has a long history of many past and current uses including textiles for clothing, industrial products, building materials (such as hempcrete), manufacturing, oil paints, solvents, fuel, paper, soaps, shampoos, cosmetics, food, and medicinal purposes, to name a few.

Historical records reveal that the use of cannabis once held a strong and prominent position in medicine. Various benefits of cannabis have been translated from Sanskrit and Hindi literature under many different names as early as 1400-2000 BC,[5,6] although its medicinal use was more thoroughly described in Indian *Ayurvedic* medicine and the plant cultivated as early as 900 BC.[2] The Greek physicians Claudius Galen (131-201 AD) and Pedanius Dioscorides (40-90 AD) described medicinal indications for cannabis.[7]

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Accepted for publication March 07, 2015.

Headache

Conflict of Interest: Owns stock in CEN-Biotech Inc., a publicly traded company.
Financial Support: None.

In 1839, Dr. William Brooke O'Shaughnessy introduced the Western world to the medicinal uses of *C. indica*, or "Indian hemp," after his time in Calcutta, India. He suggested its use in analgesia and as a muscle relaxant.[8-10] He was a physician and scientist who graduated from the University of Edinburgh, and a professor of chemistry at the Medical College of Calcutta.[11,12] Dr. Clendinning in London was one of the first Western physicians to treat migraine with cannabis in the 1840s,[11,13] and another London physician, Dr. R. Greene, was recommending daily doses of cannabis for the prophylaxis of migraine in 1872.[11,14]

The medicinal use of *C. indica* for both acute and preventive headache treatment was subsequently advocated by many prominent physicians through the 19th and early decades of the 20th centuries, including E.J. Waring, S. Weir Mitchell, Hobart Hare, Sir William Gowers, J.R. Reynolds, J.B. Mattison, and Sir William Osler.[4,8,9,15] Cannabis was included in British and American pharmacopeias for headache treatment during these early years.[4]

In 1887, Dr. S. Mackenzie published an article advocating for the use of marijuana twice daily for chronic daily headache, which was likely chronic migraine by description.[11,16] Dr. J.W. Farlow described the use of marijuana suppositories as having "few equals in its power over nervous headaches" in 1889.[11,17] In 1890, Sir John Russell Reynolds, the president of the British Medical Association and physician to the royal household, wrote a paper in *Lancet* reviewing 30 years of personal experience in prescribing cannabis to advocate for its legitimate medicinal uses for a wide variety of ailments, particularly migraine and neuralgia.[11,18]

In 1915, the father of modern medicine, Sir William Osler, advocated for cannabis use in migraine, which he published in his textbook *The Principles and Practice of Medicine*.[11] He stated that when treating migraine, "*Cannabis indica* is probably the most satisfactory remedy. Seguin recommends a prolonged course."[4,11,15]

Dr. E.C. Seguin, to whom Osler was referring, was a well-known neurologist and president of the New York Neurological Society, and a vocal proponent of cannabis for migraine at that time.[11] In 1916, Dr. Walter Ernest Dixon, who was a well-known professor of pharmacology at Kings' College and the University of Cambridge, described the therapeutic effects of smoked cannabis for headache treatment.[4]

The rising use of medicinal cannabis was eventually derailed by political factors in the United States (US) consisting of propaganda that cannabis was a drug of abuse used by minority and low-income communities, along with a campaign by Harry Anslinger and the Federal Bureau of Narcotics in the 1930s which attempted to associate psychosis, mental deterioration, addiction, and violent crimes to marijuana use. Other historians have stated that the purpose was to also reduce the size of the growing hemp industry, influenced by prominent businesspersons such as Andrew Mellon, and the Du Pont family, who were involved and invested heavily in competing industry including synthetic fibers such as nylon.[11,19-21] These claims and agenda led to the *Marihuana Tax Act of 1937*, despite the American Medical Association's strong opposition to this legislation.[4,22,23] This law imposed a heavy tax on anyone associated with cannabis and hemp for medicinal or industrial uses, with prison and large fines for those failing to comply.[11] In response to this ruling, Dr. Robert Walton published a comprehensive review of cannabis in 1938, and stated that legislation should not prohibit medicinal use and scientific investigation, referencing 12 significant authorities on its efficacy for migraine.[4]

The protest from the medical community could not overcome the political powers pushing for banning cannabis and associating it as a drug of abuse. In 1941, cannabis preparations were taken off the *United States Pharmacopoeia and National Formulary*.[4] Despite this removal, Dr. M. Fishbein, the editor of the *Journal of the American Medical Association*, still recommended oral preparations of cannabis over ergotamine tartrate for menstrual migraine in 1942.[4,24] A resurgence of recreational marijuana use occurred during the anti-establishment cultural phenomenon that developed in the US between the early 1960s and the early 1970s. This counterculture and time period left a lasting impression in many aspects. Unfortunately, one of those lasting impressions and stigma has been the association between the psychedelic hippie counterculture movement of that era and recreational marijuana use, rather than the longer and deeper history of medicinal use that existed long prior to that time period.

In August 1970, the Assistant Secretary of Health, Dr. Roger O. Egeberg, wrote a letter recommending that marijuana be classified as a Schedule 1 substance, the same as heroin and lysergic acid diethylamide (LSD), and it has remained so since the passage of the Controlled Substances Act of 1970. His stated reasoning for this decision was:

> "Since there is still a considerable void in our knowledge of the plant and effects of the active drug contained in it, our recommendation is that marijuana be retained within Schedule 1 at least until the completion of certain studies now underway to resolve the issue."[25]

Therefore, marijuana was classified as a Schedule 1 substance, not because of scientific evidence, but due to a lack of existing scientific knowledge at that time.[25] The consequence of the Schedule 1 classification of cannabis has been detrimental to researching its benefits. This is because research on cannabis in the US remains illegal as a consequence of this classification. This has senselessly left the potential therapeutic applications of cannabis at a standstill for decades, despite possible benefits described through history with extensive anecdotal descriptions and scientific research, the fact that cannabis remained in the Western pharmacopoeia until 1941, and was prescribed for a multitude of symptoms including headache by many of the most prestigious physicians of those times.

The Drug Enforcement Agency (DEA) continues to refuse to take marijuana off the restricted "most dangerous" Schedule 1 classification, claiming it has "no accepted medicinal use," a statement that has no evidence-based medicine to support it. More evidence exists disproving and refuting those claims. The Schedule 1 classification impedes US federal funding for research, or even the legal ability to proceed with research. This has been the primary hurdle in conducting the large-scale medical research that is needed to obtain that necessary evidence-based medicine on the potential benefits, or lack thereof, of cannabis.

Hypocritically, despite the insistence of the Schedule 1 classification, the US Government, as represented by the Department of Health and Human Services, in 2001 filed a patent (US Patent #6,630,507) for cannabinoids that was awarded in 2003 for "cannabinoids as antioxidants and neuroprotectants."[26] This patent is a clear contradiction of the US Government's own definition for classification of a Schedule 1 drug having no medicinal benefit.

Another glaring contradiction to the Schedule 1 status of marijuana is the fact that the US Federal Drug Administration (FDA) has approved synthetic versions of the cannabinoid Δ^9-THC in the form of Dronabinol (Marinol®) and Nabilone (Cesamet®) for medicinal purposes. These observations further confirm that the cannabinoids found in cannabis are recognized by the government to be therapeutic with valid medicinal uses. However, the Schedule 1 status remains intact, stating that there is no accepted medical use of cannabis. Clearly, this Schedule 1 status needs to be reviewed and reclassified.

An attempt to reclassify marijuana to Schedule 2 failed in 1988, despite the DEA administrative law judge, Francis Young's, recommendation that marijuana be removed from Schedule 1 and made available for physicians to prescribe.[27-30] He reviewed evidence and testimonies from the scientific community and stated, "By any measure of rational analysis, marijuana can be safely used within a supervised routine of medical care," and its use was suggested for spasticity, paraplegia, and multiple sclerosis (MS), and as an anti-emetic, while its use for glaucoma was considered "reasonable."[4,28] The FDA reviewed the scheduling of marijuana in both 2001 and 2006, both times recommending that it should remain in Schedule 1. A federal judge is again reviewing whether reclassification is warranted at the time of this writing.

The only access to legal marijuana has been through the FDA's Investigational New Drug Program, which was closed by the Secretary of Health and Human Services in 1992, although the 13 patients in the program at that time were allowed to continue.[31,32] The only federally approved source of research-grade cannabis for that program, and still remaining, has been from a farm at the University of Mississippi. It has had contracts with the federal government since 1968, and has provided medicinal marijuana to a few patients. The program initially started in 1976 when a glaucoma patient sued the government on grounds that the cannabis was preventing his vision loss, and won.[32] Currently there are still 2 patients who receive monthly government supplied marijuana, one for multiple hereditary exostoses, a painful bone tumor disorder, and the other for glaucoma.[32] The program is still controlled by the National Institute on Drug Abuse (NIDA).

In 1995, Richard Smith, the editor of *British Medical Journal*, called for some marijuana legalization and decriminalization,[33] and the *Journal of the American Medical Association* also published a commentary in support of medical marijuana.[34] In November 1995, the *American Journal of Public Health*, the journal for the oldest and largest organization of healthcare professionals in the world, issued a resolution urging lawmakers to make medical marijuana accessible for research as an investigational new drug, and to make marijuana a legally available medicine to ill patients.[27] They further stated that, "cannabis/marijuana was wrongfully placed on the Schedule 1 of the Controlled Substances depriving patients of its therapeutic potential," and concluded that, "greater harm is caused by the legal consequences of its prohibition than possible risks of medicinal use."[27] In 1997, the British Medical Association published a book called *Therapeutic Uses of Cannabis* describing the many potential medical benefits of cannabinoids, and also concluded that cannabinoids may have potential use for patients with spastic neurological disorders such as spinal cord injury and MS, which are not well controlled with available drugs.[35]

Neurologist Dr. Ethan Russo received FDA support in conducting a study looking at the effects of smoked marijuana in the treatment of migraines in the late 1990s. However, his study was halted by the NIDA. He stated the following:

> *"My FDA-approved study on cannabis' ability to reduce migraine was stone-walled because NIDA holds a monopoly on the legal supply of cannabis for research, and they refused to provide it for my study. As a doctor and a citizen, knowing that researchers in other countries are researching and confirming new medical uses for cannabis all the time, such as its ability to protect the brain after head trauma or stroke, I am dismayed by policies that prevent us from fully utilizing the healing potential of this plant and preventing people from using the best medicine for their condition."*[36]

Many physicians are pushing for schedule reclassification of cannabis allowing medicinal cannabis for the treatment of a multitude of ailments, and allowing research. In a 2013 apology article retracting his previous anti-marijuana stance, Dr. Sanjay Gupta MD, CNN Chief Medical Correspondent, stated:

> *"Well, I am here to apologize. I apologize because I didn't look hard enough, until now. I didn't look far enough. I didn't review papers from smaller labs in other countries doing some remarkable research, and I was too dismissive of the loud chorus of legitimate patients whose symptoms improved on cannabis. Instead, I lumped them with the high-visibility malingerers, just*

looking to get high. I mistakenly believed the Drug Enforcement Agency listed marijuana as a Schedule 1 substance because of sound scientific proof. Surely, they must have quality reasoning as to why marijuana is in the category of the most dangerous drugs that have "no accepted medicinal use and a high potential for abuse." They didn't have the science to support that claim, and I now know that when it comes to marijuana neither of those things are true. It doesn't have a high potential for abuse, and there are very legitimate medical applications. In fact, sometimes marijuana is the only thing that works. We have been terribly and systematically misled for nearly 70 years in the United States, and I apologize for my own role in that.[25]

Dr. Gupta also noted that of more than 20,000 papers published in recent times, only 6% of the studies look at the potential benefits of cannabis, while all the rest investigate potential harm, leading to an inherent bias and a profoundly distorted view.[25]

A poll by WebMD/Medscape revealed that the majority of 1544 physicians from more than 12 specialties and 48 states said that medicinal marijuana should be legalized nationally, and agreed that it should be an option for patients.[37] The rapidly increasing anecdotal reports about its benefits and subsequent exodus of families being forced to move to Colorado for legal use of a special strain of marijuana called *Charlotte's Web*[38] to treat their children's refractory seizure disorders seems cruel and senseless, and has led to stronger calls for legal research and availability.

The Epilepsy Foundation has asked the DEA to relax its marijuana restrictions to allow for medical research to proceed, and in April 2014, the American Academy of Neurology published a consensus statement on the use of medical marijuana in neurologic disorders.[39] It was based on a systematic review of studies involving marijuana or synthetic cannabinoid treatment for symptoms of only MS, epilepsy, and movement disorders between 1948 and November 2013. In that consensus, they concluded that certain forms of medical marijuana, cannabinoids, and synthetic formulations can effectively treat some symptoms of MS, including spasticity, painful spasms, central pain, and overactive bladder, although efficacy was uncertain for the other neurologic conditions evaluated. They recommended that cannabinoids should be studied as other drugs are in order to continue seeking answers as to the potential benefits of marijuana use in patients who have neurologic illness, and if found to be effective, it should be prescribed. Most recently in January 2015, the American Academy of Pediatrics recommended that the government and DEA re-classify marijuana as a Schedule 2 drug to allow further research to be done on its therapeutic benefits.

In 1996, California was the first state to pass the Compassionate Use Act, which allowed the legal use of marijuana for medicinal purposes. Since then, at the time of this writing (March 2015), the number of states which have legalized medical marijuana is rapidly growing, currently at 23 (AK, AZ, CA, CO, CT, DE, HI, IL, ME, MD, MA, MI, MN, MT, NV, NH, NJ, NM, NY, OR, RI, VT, WA), in addition to Washington, DC. Furthermore, 10 states (AL, FL, IA, KY, MO, MS, SC, TN, UT, WI) have legalized CBD-only (CBD; extracted from cannabis) medical marijuana bills, and 4 states (AK, CO, OR, WA) and Washington, DC have successfully voted to legalize marijuana for both medical and recreational purposes. More states will be voting on upcoming election ballots for similar variable measures, increasing its availability for self-medication and/or physician-prescribed medication. Several Congress members introduced the "Charlotte's Web Medical Hemp Act of 2014 (H.R.)" to Congress on July 28, 2014. The bill proposes to exclude industrial hemp and CBD from the definition of marijuana in the Controlled Substances Act, so that patients can have legal access to CBD oil and therapeutic hemp.

THE ENDOCANNABINOID SYSTEM

A breakthrough in the understanding of how cannabis works in the brain occurred with the discovery of the endogenous cannabinoids and receptors,[40-44] which comprise the endocannabinoid system. The endocannabinoid system is widely distributed throughout the brain and spinal cord, and plays a role in many regulatory physiological processes including inflammation, appetite regulation, metabolism, energy balance, thermogenesis, neural development, immune function, cardiovascular function, digestion, synaptic plasticity and learning, pain, memory, psychiatric disease, movement, nociception/pain, psychomotor behavior, sleep/wake cycles, regulation of stress and emotion, and digestion.[45-50]

The endocannabinoid system consists of the cannabinoid 1 (CB1) and 2 (CB2) receptors, the endogenous cannabinoid receptor ligands (endogenous cannabinoids) N-arachidonoylethanolamine (anandamide, or AEA) and 2-arachidonoylglycerol (2-AG), as well as their degrading enzymes fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase, respectively.[40,46,51,52] The CB1 and CB2 receptors were cloned in 1990 and 1993, respectively.[53-55] The CB1 receptor is primarily expressed on presynaptic peripheral and central nerve terminals, and to a lesser degree on many other peripheral organs. This is in contrast to CB2 receptors, which are concentrated primarily in the peripheral tissues and immune cells where they influence the release of cytokines and cell migration, although are also present to a lesser degree in the nervous system.[56-58] Discovery of AEA, which notably is the ethanolamide of arachidonic acid, occurred in 1992,[40] and this is a primary mediator of endocannabinoid signaling, although a multitude of other endogenous mediators with "cannabinoid-like" effects continue to be discovered.[46,51,59-61]

The CB1 and CB2 receptors are both located pre-synaptically and modulate neurotransmitter release.[56] The endocannabinoids AEA and 2-AG, as well as the phytocannabinoids found in cannabis, bind to and activate (with variable affinities) the

pre-synaptic G-protein coupled CB1 and CB2 receptors.[62-64] Activation of these receptors leads to opening of potassium channels causing a hyperpolarization of the pre-synaptic terminal, and closing of calcium channels which inhibits release of stored inhibitory and excitatory neurotransmitters, including glutamate, acetylcholine, and dopamine when neuronal excitation is present.[48,52,65] Indirect effects on 5-hydroxytryptamine (5HT) (serotonin), N-methyl-D-aspartate (NMDA), opiate, and γ-aminobutyric acid (GABA) receptors allow endocannabinoids to modulate other networks.[66] AEA is a partial agonist at CB receptors, and binds with slightly higher affinity at CB1 compared with CB2 receptors, as does 2-AG.[46,53,67]

In the central nervous system, CB1 activation inhibits neurotransmitter release of GABA, glutamate, serotonin, dopamine, acetylcholine, noradrenaline, cholecystokinin, and D-aspartate at both inhibitory and excitatory synapses.[46,58,68] The CB1 receptor is one of the most abundant G-protein coupled receptors in both the peripheral and central nervous system.[62] Notably, CB1 receptors are prominent not only in the anatomical pain pathways including the periaqueductal gray (PAG) matter, rostral ventrolateral medulla (RVM), dorsal primary afferent and substantia gelatinosa spinal cord regions, spinal interneurons, and peripheral nerves/nociceptors, but also in 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.[45,58,69,70] The cardiopulmonary centers in the brainstem are sparsely populated with CB1 receptors, which is why there is a lack of respiratory depression with the cannabinoids, as opposed to opiate receptors.[11]

The presence of CB1 receptors in this wide array throughout the central and peripheral nervous system provides the substrate for a multitude of potential therapeutic neurologic targets. The CB1 receptors are widely expressed throughout the rest of the body and organ systems, but this is beyond the scope of this review. 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 astrocytes, microglia, and oligodendrocytes.[39,71,72] AEA and other cannabinoid agonists have also been shown to have inhibitory effects on serotonin type 3 ($5HT_3$) receptors, which further suggests its role as an anti-emetic and in analgesia.[73]

The endocannabinoids are arachidonic acid derivatives synthesized "on demand" in the post-synaptic terminals from membrane phospholipid precursors in response to cellular metabolic needs, and there appears to be cross-talk between the eicosanoid and endocannabinoid pathways.[46,52,74-76] The CB1 receptor mediated anti-inflammatory effects of cannabinoids are suspected to be secondary to inhibition of arachidonic acid conversion by cyclooxygenase,[11,77] although CB2 receptor activation induces immunosuppression, which also reduces inflammation.[78]

THE PHYTOCANNABINOIDS

The plant genus *Cannabis* is within the plant family Cannabaceae. Three cannabis species are described: *C. sativa*, *C. indica*, and *C. ruderalis*, although there has been a long-standing debate among taxonomists regarding classification of these variants into species, so a biochemical method to classify cannabis variants is typically used.[1] As noted previously, cannabis that has high levels of the psychoactive cannabinoid, Δ^9-THC, and low levels of the non/anti-psychoactive cannabinoid, CBD, is generally referred to as "marijuana," while cannabis that has high levels of CBD and very low insignificant levels of Δ^9-THC is referred to as "industrial hemp," or "hemp."

The leaves and flowering tops of cannabis plants contain at least 489 distinct compounds among 18 different chemical classes, and contain at least 100 different phytocannabinoid compounds identified thus far, potentially holding therapeutic benefit individually, or in variable combinations.[79,80] The primary cannabinoids studied to date include Δ^9-THC, CBD, cannabinol (CBN), cannabigerol (CBG), and tetrahydrocannabivarin (THCV), although there are many others.[79,81-84] The percentage present of these and other cannabinoids vary depending on the cannabis strain, climate, soil, and techniques of cultivation, and these factors also account for the wide variability in medicinal benefits as well as side effects.[85,86] Delta^9-THC is the most studied and responsible for most of the physical, and particularly the psychotropic effects of cannabis.[87] All species contain the psychoactive component, Δ^9-THC, in variable amounts, although *C. sativa* contains the highest Δ^9-THC, while *C. ruderalis* contains the least.[1,78] The other cannabinoids including CBD, CBN, and CBG have little to no psychotropic properties,[87] which makes them very attractive for potential therapeutics.

Delta^9-THC was first isolated in 1964,[88] and is a partial agonist at both CB1 and CB2 receptors, but also acts at other non-CB receptors. Its actions at the CB1 receptor account for the psychoactive effects of cannabis, thought to be mediated to some extent by suppression of both glutamate and GABA release.[39,64,89-91]

CBD was isolated in 1963, lacks psychoactivity, and does not appear to bind to CB1 or CB2 receptors, but rather interacts with a multitude of various ion channels, enzymes, and other receptors that are felt to explain its potential analgesic, anti-epileptic, anti-nausea, anti-emetic, anti-inflammatory, anxiolytic, anti-psychotic, and anti-ischemic properties.[39,64,92-95] Its potential analgesic and anti-inflammatory effects are mediated by both cyclooxygenase and lipoxygenase inhibition, and its anti-inflammatory effect is several hundred times more potent than aspirin in animal studies.[84,96] Both CBD and Δ^9-THC also have strong anti-oxidant actions, more potent than α-tocopherol and ascorbate, and have been shown to reduce NMDA, α-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate, and kainate receptor-mediated neurotoxicities.[97,98]

CBN may have some immunosuppressive properties, and CBG may have some analgesic and anti-inflammatory properties as a partial agonist at CB1 and CB2, as well as actions as a $5HT^{1A}$ receptor antagonist and α2-adrenoceptor agonist.[94,99-103] It has also been suggested that THCV may have some anti-convulsant properties[104,105] by acting as a CB1 receptor antagonist and CB2 receptor partial agonist.[106,107]

Cannabinoids including Δ^9-THC have been shown to have anti-nociceptive effects in the PAG gray matter,[108] an area in the brainstem that has been suspected to play an integral role in migraine generation,[109] as well as involvement in both descending and ascending pain transmission.[108,110] CB1 receptors have also been shown to have a dense concentration in the hypothalamus.[56] Cannabinoid analgesic properties are mediated through CB1 receptors[111] in the brain, spinal cord, and peripheral nerves.[108,110,112-117] Studies suggest that the endogenous cannabinoid system may modulate anti-nociceptive effects in isolation, or through simultaneous potentiation of specific opioid receptors.[118-129] CB1 receptors are 10 times more concentrated then μ-opioid receptors in the brain, and cannabinoid receptors co-localize with opioid receptors in many regions such as the dorsal horn of the spinal cord, leading to synergistic augmentation of the analgesic opioid effects, with subsequent lower dose requirements of opioid therapy.[11,119,120,123,127,130-135] Administration of cannabinoid receptor agonists leads to endogenous opioid peptide release and chronic Δ^9-THC use increases endogenous opioid precursor gene expression in supraspinal and spinal structures involved in pain perception.[130] This interaction is suspected to be from pharmacodynamic mechanisms, since studies show marijuana use does not affect blood levels of oxycodone or morphine.[11,136]

Little is known about the potential therapeutic role of the extensive number of other compounds that cannabis contains, including flavonoids, terpenes, phenols, amino acids, vitamins, proteins, steroids, nitrogenous compounds, enzymes, glycoproteins, simple alcohols, hydrocarbons, ketones, aldehydes, fatty acids, simple esters and lactones, and pigments.[79,137] This makes it difficult to appropriately assess the potential beneficial contribution by each of these compounds in studies evaluating possible therapeutic uses of cannabis, since different strains have different ratios of Δ^9-THC, CBD, additional cannabinoids, and other compounds. Variable routes of administration add to this complexity. Ultimately, studying each isolated constituent is mandatory to determine each compound's individual therapeutic benefits. For example, the terpenes are thought to contribute to the distinctive differences in fragrance among cannabis strains, as well as the smoking qualities and character of the subsequent "high."[86] However, terpenes have a broad range of other actions including anti-inflammatory, anti-anxiety, anti-oxidant, anti-neoplastic, anti-bacterial, and anti-malarial properties.[86]

POTENTIAL MEDICINAL USES OF CANNABIS FOR HEADACHE

Literature review shows that medicinal marijuana and its derived cannabinoids have reported therapeutic benefit in an extensively wide area of medicine encompassing many specialties,[118,137,138] as compiled and referenced in Table 1. This is not an all-inclusive list, and it is important to remember that much of the included data are anecdotal, case based, or laboratory-based scientific research, although there are some randomized trials as well. One of the most documented uses of medicinal marijuana is in the treatment of pain, particularly chronic pain, and suppression of hyperalgesia and allodynia, with most studies involving endocannabinoids, Δ^9-THC, or synthetic cannabinoids.[58,139,140] The cannabinoid–opioid interactions and "opioid-sparing effect" of cannabinoids has attracted interest in medicinal marijuana for a possible alternative to narcotics with less potential for dependence, addiction, and abuse. These interactions also raise the question of a theoretical role in helping patients to wean down or off of opiates.

Components of the endocannabinoid system are found throughout the nervous system in supraspinal, spinal, and peripheral pain pathways. Both Δ^9-THC and CBD have analgesic properties, although they act through different mechanisms, and the psychotropic side effects of Δ^9-THC may be a limiting factor in its use.[141-144] Medicinal cannabis and its cannabinoid extracts increase pain thresholds[145] and possess analgesic properties.[66,146-149] Delta-9-THC doses of 15-20 mg have been shown to be comparable to the analgesic effects of codeine 60-120 mg.[150] Therapeutic uses of cannabis are reported in a wide range of chronic pain disorders as detailed and referenced in Table 1. A review of 38 published randomized controlled trials evaluating cannabinoids in pain management revealed that 71% (27) concluded that cannabinoids had empirically demonstrable and statistically significant pain-relieving effects, whereas 29% (11) did not.[45]

Given the pharmacology and reported therapeutic benefits of cannabis in pain medicine, it is only logical that this benefit may extend to the arena of headache medicine, including migraine. There is supporting literature for this, although it is primarily anecdotal and case based. Cannabinoids are active through CB1 receptors in areas of the brain and brainstem involved with migraine pathophysiology including the PAG (which may be a migraine generator area), rostral medulla, area postrema of the medulla, nucleus trigeminal caudalis,[49,151-156] and trigeminal ganglia.[11]

The endogenous endocannabinoid AEA modulates pain signaling in the central nervous system in various ways. AEA inhibits dural blood vessel dilation induced from neurogenic, calcitonin gene-related peptide (CGRP), electrical stimulation, capsaicin, and nitric oxide (NO) sources, and this effect is reversed by a cannabinoid antagonist.[40,153,154,157,158] AEA also activates the transient receptor potential vanilloid receptor on

Table 1.—Medicinal Uses Reported With Cannabis and Cannabinoids

Central Nervous System (CNS)
Chronic non-cancer pain:[45,58,136,140,150,267-289] chronic neuropathic pain,[136,139,277,287-301] phantom limb pain,[302] fibromyalgia,[300,303-307] rheumatoid arthritis,[308-311] chronic abdominal pain from inflammatory bowel diseases,[312-318] cancer-related pain (especially with potent opiate failure)[150,244,268,319,320]
Headache and facial pain: chronic headaches,[146,196] migraine,[49,192-196,321] cluster headache,[217,221,222] pseudotumor cerebri,[198] multiple sclerosis-associated trigeminal neuralgia[226]
Epilepsy[80,104,105,322-339]
Spasticity and related central pain and bladder dysfunction in multiple sclerosis[35,121,140,226,250,328,340-376] and spinal cord injury[121,140,328,340,341,362,377-382]
Additional multiple sclerosis associated symptoms: tremor,[343] pendular nystagmus suppression,[383] dystonia[345]
Reduce muscle cramps and fasciculations in amyotrophic lateral sclerosis (ALS),[384] and delay disease progression (ALS and MS)[385-387]
Reduce intracranial pressure in traumatic brain injury, aid in cerebral ischemia and neuro/excitotoxicity,[199-203,388] and regulation of neuroinflammatory response[372,373,389-391]
Tourette's syndrome[392-403]
Dystonic movement disorders,[399,404-408] oral dyskinesia[409]
Parkinson's disease; reduction of levodopa-induced dyskinesia,[399,410] and disease progression[411-414]
Huntington's disease[415-417]
Meige's syndrome[418]
Intractable hiccups[419]
Depression, anxiety, and mood disorders[143,144,203,266,290,376,420-437]
Post-traumatic stress disorder (PTSD)[242,438-448]
Neuroprotective antioxidants[97,98,201,202,391]
Alzheimer's; behavioral/agitation,[449-451] disease progression and cognitive symptoms[452,453]
Insomnia (majority in setting of pain relief)[242,277,290,297,303,306-308,314,346,347,349,362,377,379,435-437,454,455]
Fulminant hepatic encephalopathy[456]
Autism and autistic spectrum disorders[457-461]
General Medical Systems
Nausea and vomiting from chemotherapy in adults[93,276,462-497] and children[497-500]
Appetite stimulation in healthy subjects as well as cancer and AIDS-associated anorexia/cachexia syndrome ± altered chemosensory perception[143,162,203,435-437,455,463,482,497,501-519] and associated nausea[519-521]
Reducing intraocular pressure in glaucoma[204-216]
Gastrointestinal disorders (irritable bowel syndrome, inflammatory bowel disease, pain)[312-318,522-536]
Anti-cancer/neoplastic including breast, brain (glioma), lung, colon, skin cancer (melanoma), leukemia[489,537-568]
Asthma (oral or aerosol rather than smoked)[569-571]
Regulation and decrease of inflammation associated with autoimmune diseases[572-574]

trigeminal ganglion neurons, modulating the release of CGRP, and influencing vasomotor tone.[157,159]

Modulation of serotonergic pain transmission is well established in migraine treatment, particularly with the mechanism of action of the triptans. Endocannabinoids interact with serotonergic neurons in the brainstem dorsal raphe to modulate pain mechanisms,[160,161] and AEA potentiates $5HT_{1A}$ and inhibits $5HT_{2A}$ receptors.[153,154] Cannabinoids have been shown to inhibit 5HT release from platelets during a migraine.[162] Endocannabinoids, via CB1 receptor activation, have anti-nociceptive effects by descending modulation of pain at the spinal level through PAG and RVM connections,[163-168] and modulation of descending cutaneous-evoked C-fiber spinal nociceptive responses from the brainstem regions including the ventrolateral PAG and RVM.[168,169] CB1 receptor activation inhibits dural trigeminovascular nociceptive responses.[158,170] When CB1 receptors are activated in the ventrolateral PAG, there is subsequent descending attenuation and modulation of dural-evoked nociceptive trigeminovascular processing and transmission, including Aδ-fiber and C-fiber responses, and basal trigeminal neuronal tone in the trigeminocervical complex.[171-174] Furthermore, variations in the *cnr1* gene on chromosome 6, which encodes for the CB1 receptor, in a region that has shown linkage with migraine, are associated with a greater risk of developing migraine.[175,176]

The CB1 activation pathways are notable, given that triptan activation of $5HT_{1B/1D}$ receptors in the ventrolateral PAG also leads to descending modulatory inhibition of dural nociceptive Aδ-fiber and C-fiber neuronal responses and basal trigeminal neuronal tone in the trigeminal nucleus caudalis, but not cutaneous responses.[177] Experimental studies show that in the ventrolateral PAG, the CB1 receptor-mediated trigeminovascular responses are modulated by the serotonergic system, particularly via the $5HT_{1B/1D}$ triptan receptor,[171] and other studies of neuropathic pain models have shown that serotonergic neuron firing in

the brainstem dorsal raphe are modulated by CB1 receptor activation.[160,161] Furthermore, $5HT_{1B/1D}$ antagonists inhibit CB1 responses in the ventrolateral PAG.[171] These findings show how serotonergic and endocannabinoid neurons in the brainstem can modulate the effects of either system as trigeminal or spinal nociceptive inputs are processed.[171] This suggests that the endocannabinoid neurotransmitter system is a potential target for treating migraine, and that triptans may help to break migraines by activating the brain's endocannabinoid system.[171]

Triptans are suspected to inhibit GABAergic and glutamatergic signaling in the PAG by preventing neurotransmitter release from nerve terminals as part of their mechanism of action.[178] Similarly, activation of CB1 receptors in the PAG and RVM also inhibit GABAergic and glutamatergic transmission by preventing release of neurotransmitters.[179,180] Triptan action may in part be secondary to modulation of endocannabinoidergic neurons in the brainstem, and descending control of trigeminovascular nociceptive transmission may occur through interactions between serotonergic and endocannabinoid receptor systems.[171] Pharmacological manipulation of the CB2 receptor suggests a potential therapeutic target for the treatment of migraine as well.[181]

The endogenous endocannabinoid AEA, the phytocannabinoid Δ^9-THC, and synthetic cannabinoids suppress glutamatergic neurotransmission via inhibitory modulation of the NMDA receptors, mediated by CB1 receptors.[153,154,182-186] Activation of CB1 receptors suppresses cortical spreading depression (CSD). This is suspected to be due to decreased glutamatergic transmission via inhibitory NMDA modulation, although modulation of NO, CGRP, or lipoxygenase and cyclooxygenase pathways are also possible contributors to the suppressive effect of cannabinoids on CSD.[183] Activation of CB1 receptors may stop migraine pain by inhibition of CSD and subsequent trigeminal neuronal activation.[183]

Endocannabinoid deficiency has been theorized as a possible cause for migraine and other chronic pain disorders, including chronic migraine and medication overuse headache.[187,188] Levels of AEA are decreased in the cerebrospinal fluid of individuals with chronic migraine compared with normal controls, while levels of CGRP and NO (normally inhibited by AEA) are increased.[153,189,190] Platelets of female migraineurs as opposed to male have also shown increased activity of the AEA-degrading enzyme FAAH, suggesting increased endocannabinoid degradation.[191] A widely recognized migraine trigger, nitroglycerin, increases activity of endocannabinoid degrading enzymes, leading to increased breakdown of endogenous endocannabinoids in the midbrain, where the PAG is located.[156]

Unfortunately, there have been no controlled clinical trials evaluating smoked or oral formulations of medicinal cannabis or prescription cannabinoids for either acute or prophylactic therapy in migraine or other headache disorders. A small case series of cannabis use for patients with pain included 3 subjects with chronic headaches that were relieved by smoking cannabis, with results similar or superior to ergotamine and aspirin.[146] Another small case series of 3 patients reported that abrupt cessation of chronic daily marijuana smoking was followed by migraine attacks, while subsequent remission of headaches was seen with resumption of episodic marijuana use in 1 of the patients.[192] It is not certain whether this suggests effective prevention by the marijuana or medication overuse headache with withdrawal headache upon cessation.

A case of a migraineur who had failed standard medical therapy, and ultimately received relief with small doses of smoked marijuana was reported.[193] Similarly, this author has encountered multiple patients with chronic migraine, and a similar history of failing all standard medical therapy, but receiving a significant positive response to smoked cannabis (usually admitted reluctantly) or synthetic cannabinoids.

One study suggested that cannabinoid compounds may provide benefit in migraine treatment due to platelet stabilization and inhibition of serotonin release.[194] A small survey of 54 patients in a drug treatment center reported that marijuana use was commonly used as a self-medication treatment for migraine.[195]

An anonymous standardized survey investigating reasons for self-medication with cannabis in Germany, Austria, and Switzerland was conducted by the Association for Cannabis as Medicine (Cologne, Germany).[196] There were 128 patient questionnaires evaluated, and of the many reported medical uses, 6.6% used cannabis for migraine, and 3.6% used it for headache. Another survey of 2480 patients of the Oakland Cannabis Buyer's Club revealed that 5% used it for migraine relief.[197]

Medicinal cannabis may have a role in headache disorders other than migraine as well. A case study reported a woman with pseudotumor cerebri would smoke a marijuana cigarette about once per week when her headache was more severe. She would have complete resolution of her headache within 5 minutes, and it would not recur that day.[198] This is interesting given other studies that suggest that cannabinoids may reduce intracranial pressure in traumatic brain injury,[199-203] as well as intraocular pressure in glaucoma.[204-216] The synthetic cannabinoid, Dexabinol, has no psychotropic activity, but blocks NMDA receptors, and suppresses production of tumor necrosis factor. In phase II trials in Israeli hospitals, it lowered intracranial pressure with a trend toward faster and better neurologic outcome.[199,203]

Cannabis has been reported to treat cluster headache. In a case report,[217] a 19-year-old male who was refractory to a multitude of preventive and abortive medications reported that smoking marijuana at the onset of a cluster headache attack would consistently give complete headache relief within 5 minutes of inhalation, and was the only thing that helped. Given the dramatic improvement with smoked cannabis, his physician decided to substitute the smoked cannabis with Dronabinol (Marinol®) 5 mg, a synthetic cannabinoid. Dronabinol taken at the onset of cluster headache consistently provided complete and rapid relief within 5-15

minutes. Notably, CB1 receptors have a dense concentration in the hypothalamus,[56] of which the posterior inferior ipsilateral hypothalamus has been suspected to be a site of activation in cluster headache.[218-220]

A survey of 113 patients with chronic cluster headaches in France found that 26% regularly consumed cannabis, although whether cannabis was used for treatment of cluster headache or only recreationally was not further evaluated.[221] In another study conducted in 2 French headache centers with a patient questionnaire evaluating marijuana use in cluster headache patients, 63/139 (45.3%) had a history of cannabis use, of which 27 patients (19.4% of total cohort) had used it to treat cluster headache attacks.[222] Efficacy was reported in 25.9%, variable or uncertain effects in 51.8%, and negative effects in 22.3%. Thus, in almost three quarters, the cluster headache subjects did not report efficacy. The authors noted the need for controlled trials with synthetic selective cannabinoids to show a more convincing therapeutic benefit.

Similar to cluster headache, this hypothalamic region is also activated during short-lasting unilateral neuralgiform headache attacks, including those with specific conjunctival injection and tearing,[223] paroxysmal hemicranias,[224] and hemicrania continua,[225] raising a theoretical question of whether refractory cases of these headache disorders may also be responsive to medical cannabis and the cannabinoids.

A trial of 112 patients with MS who smoked cannabis reported that 90% had significant chronic pain relief, and particularly 70% had relief of MS-associated trigeminal neuralgia.[226]

PHARMACOKINETICS

Cannabis can be used by smoked, vaporized, oral, oral mucosal, topical, or rectal routes of administration. The majority of cannabinoid metabolism occurs in the liver, with variable levels of different metabolites, dependent on the route of administration.[227-229] Health Canada (US FDA equivalent) published an excellent in-depth review of the pharmacokinetics and pharmacodynamics of cannabis, and it is recommended for more detailed discussion of these topics.[137]

Smoked cannabis results in the fastest onset of action, within minutes, due to the lipophilicity of Δ^9-THC, and results in higher cannabinoid blood levels and shorter duration of effects compared with oral routes.[227,228] When smoked, the psychotropic effects start within seconds to a few minutes, peak in 15-30 minutes, and wear off within 2-3 hours. Depending on efficiency and method of smoking, bioavailability of Δ^9-THC ranges from 2% to 56% based on puff duration, breath hold duration, and depth of inhalation, but typical use is predicted to be about 25-27%.[228,230-232]

Smoking cannabis by vaporization is a more recent technique of smoking cannabis, developed due to the fact that inhalation of a combustion product is an undesirable delivery system.[233] The goal of this technique is to suppress irritating respiratory toxins by heating cannabis to a temperature where active cannabinoid vapors form, but below the point of combustion where smoke and associated toxins are produced.[234] Vaporization may be advantageous to smoking due to less toxic byproducts such as tar, polycyclic aromatic hydrocarbons, carbon monoxide, and more efficient extraction of Δ^9-THC.[234-238] Plasma concentrations and effects are similar to those of smoking cannabis by standard methods, although absorption has been suggested to occur faster.[233]

Oral administration is associated with a slower onset of action with delayed psychotropic effects beginning in 30-90 minutes, slower peak at 2-3 hours, lower peak blood Δ^9-THC levels (5-6 times lower as compared with smoking[239]), and longer duration of action and effects lasting 4-12 hours, depending on dose and specific psychotropic effect.[227,230] Delta-9-THC is often ingested by adding it to foods such as brownies, oils, butters, cookies, and teas.

There are 2 synthetic pharmaceutical versions of oral Δ^9-THC available. The first is Dronabinol (Marinol®), which comes in 2.5 mg, 5 mg, or 10 mg Δ^9-THC tablets. It is typically used once to twice daily, and dose ranges vary from 2.5 to 40 mg/day.[240] It is Schedule III and approved by the FDA for nausea/vomiting associated with chemotherapy, and acquired immune deficiency syndrome (AIDS)-associated anorexia and weight loss.

The second is Nabilone (Cesamet®), which comes in 0.25, 0.5, and 1 mg Δ^9-THC tablets, and is used once to 3 times daily, with dose ranges varying from 0.2 to 6 mg/day.[241,242] It is Schedule II and FDA approved for nausea/vomiting associated with chemotherapy. These 2 medications contain only Δ^9-THC, without other cannabinoids such as CBD, which typically provides much of the analgesic effects of cannabis. Another oral formulation from the United Kingdom is called Epidiolex®. It has received Orphan Drug Designation from the FDA for the treatment of severe, drug-resistant epilepsy syndromes such as Dravet and Lennox-Gastaut syndromes, and is currently in clinical trials.

An oral mucosal formulation called Nabiximols (Sativex®) is available in the United Kingdom for spasticity in MS. It is also approved by Health Canada as an adjunct treatment for neuropathic pain in MS, and for moderate to severe cancer-related pain for patients who have failed the highest tolerated opiate dosing. In April 2014, the FDA granted Fast Track designation to Sativex® for the treatment of pain in patients with advanced cancer, who experience inadequate analgesia during optimized chronic opioid therapy, and it is currently undergoing phase III clinical trials in the US for this indication. It is also undergoing phase III trials in the US for MS spasticity. Each spray delivers a total dose of 2.7 mg Δ^9-THC and 2.5 mg CBD, along with additional cannabinoids, flavonoids, and terpenoids since it is a tincture of cannabis, made from cannabis plants rather than a synthetic form, and doses range from 1 to 16 sprays per day.[243,244] Peak plasma concentrations of the CBD and Δ^9-THC occur in 2-4 hours, although there is wide variation between patients in

peak blood levels, time to onset, and peak of effects.[243] Similar to the oral formulations, Δ^9-THC and cannabinoid blood levels are lower as compared with smoking, although Δ^9-THC blood levels are similar to Dronabinol.[243,245]

Topical transdermal formulations of cannabinoids exist in ointments, creams, and lotions, although there are no clinical studies evaluating these. However, some research has been done evaluating a dermal patch for delivery of synthetic cannabinoids with good permeation results, suggesting the utility for development of a transdermal therapeutic system.[246-248]

Rectal formulations have been studied, and blood concentrations of Δ^9-THC are dose and vehicle dependent.[249] The prodrug Δ^9-THC hemisuccinate is absorbed rectally rather than Δ^9-THC, and this in combination with decreased first-pass metabolism leads to higher bioavailability of Δ^9-THC (52-61%) as compared with the oral route.[249-253]

Intramuscular and intravenous Δ^9-THC has been evaluated in limited studies,[251,254] and the authors of 1 study involving monkeys suggested that intramuscular Δ^9-THC may be a useful alternative route of administration, since it is more completely bioavailable as compared with the oral route.[251]

ADVERSE EFFECTS OF CANNABIS

There are a multitude of variables that may influence the presence or severity of adverse effects with cannabis use, as well as benefits. The majority of information regarding adverse effects reported with cannabis use come from studies and case reports primarily evaluating recreational users, rather than from controlled therapeutic clinical studies. It is important to remember that none of the studies or reported adverse effects of cannabis specifically compare and take into account many potential variables. These include route of administration, patient age, concurrent medications being taken, patient comorbidities, standardized dosing, type of cannabis strain, ratio of the phytocannabinoids in the cannabis strain (particularly the CBD:THC ratio), sterility of cannabis growing conditions, cannabis analyzation for commonly encountered issues of toxins, pesticides, and fungal and bacterial microbial contaminants, among others.

The importance of sterility and potential side effects from non-sterile growing environments is illustrated by a case of allergic bronchopulmonary aspergillosis due to microbial contamination from smoking moldy cannabis.[255] These variables will be extremely important in future studies, as there are suspected to be at least 100 different types of phytocannabinoids, and only a few of them have been studied and evaluated. Some (such as Δ^9-THC) cause psychoactive side effects, while others (such as CBD) have no psychoactive side effects, as previously discussed. Therefore, these reported adverse side effects are based on entirely non-standardized evaluations, similar to many of the anecdotal and case-based reports suggesting benefit. This is synonymous to evaluating adverse reactions in a random combination of the widely variable antidepressant medications, and then lumping all reported adverse effects into the same adverse effect profile for antidepressants as a general class. However, in reality, it is understood that different antidepressants have different pharmacologic properties and adverse reactions. Cannabis use as a medication should be thought of no differently. Therefore, these reported adverse side effects should not be assumed to be universal cannabis side effects, but need to be more appropriately correlated with specific phytocannabinoids, phytocannabinoid ratios, and the aforementioned variables as medical research moves forward. This is critical for evaluating adverse side effects, as well as therapeutic benefits.

Unfortunately, cannabinoid science and associated medical research is in its infancy, and these many variables and factors have yet to be evaluated and incorporated into research for more specific data regarding both benefits and adverse side effects. With that said, adverse reactions reported in the central nervous system and cardiovascular system are seen in Table 2, while adverse reactions in the respiratory system, gastrointestinal, reproductive, and immune systems are reported in Table 3.

Regarding cannabis dependency, the problem may be less significant compared with other substances. A study reported by the health arm of the National Academy of Sciences, The Institute of Medicine, showed that dependency occurs in 32% of tobacco users, 23% of heroin users, 17% of cocaine users, 15% of alcohol drinkers, and 9% of marijuana users.[256] Withdrawal symptoms following prolonged cannabis use have been reported to include anger, depressed mood, irritability, anxiety, restlessness, insomnia, strange dreams, weight loss, and decreased appetite. The question of cannabis overuse headache and withdrawal headache remains unstudied.[257-259]

To date, there has been no documented evidence of death exclusively attributed to cannabis overdose or use.[137] A recent comparative risk assessment to quantify the risk of death associated with commonly used recreational substances using the margin of exposure approach was conducted.[260] The *margin of exposure* is defined as a ratio between toxicological threshold (benchmark dose) and estimated human intake. This method uses the most recent guidelines for risk assessment of chemical substances, which also takes the population-based exposure into account. The toxicological margin of exposure approach validates epidemiological and social science-based drug ranking approaches. Results showed that alcohol was the deadliest substance, followed by heroin, cocaine, tobacco, ecstasy, methamphetamine, and lastly, cannabis. These results suggested that cannabis was approximately 114 times less lethal than alcohol, and reinforced similar results in comparative toxicology studies and drug safety rankings developed decades prior under different methodologies.[261,262]

The ratio between Δ^9-THC and CBD appears to be an important factor in relation to side effects based on currently available literature, and some cannabinoids such as CBD may modulate

Table 2.—Adverse Effects Reported With Use of Cannabis and Cannabinoids on Central Nervous and Cardiovascular Systems

Central Nervous System (CNS)	Adverse Effects Reported
Sedative	Somnolence, generalized CNS depression, additive with other CNS depressants, amotivational syndrome in chronic use[137,232,272,290-292,303,314,346,347,435,436,575-578]
Psychological	Euphoria ("high"), dysphoria, depersonalization, anxiety/panic attacks (primarily from Δ^9-THC and lessened by presence of CBD), aggravation of psychosis in those predisposed for or having psychotic disorders (however, a study of 10,000 psychiatric hospital admissions found no evidence that use of cannabis induced psychosis in previously asymptomatic patients,[578] and a recent study reported no correlation with high risk individuals and development of psychosis from cannabis use[579])[87,137,232,259,292,303,314,427,580-603]
Perception	Synesthesia (stimulation of 1 sense stimulates a totally different sense; hearing colors, seeing sounds, feeling/tasting sounds, etc.), distortion of sense of time and space, heightened sensory perception, misperceptions, hallucinations[137,259,488,594,597,604-607]
Motor function	Ataxia, weakness, disequilibrium, incoordination, dysarthria[84,137,232,291,605,608]
Psychomotor/cognitive function	Mental clouding, thought fragmentation, impaired memory, impairment in general cognitive performance (especially complex/demanding tasks), and driving may be impaired in occasional > chronic smokers (less as compared with alcohol, but increased in combination with alcohol),[137,314,605,609-627] possible impairment in neurocognitive brain development in users who begin at a younger age including adolescence[628,629]
Dependence	Physical and psychological dependence associated with chronic, heavy cannabis use[258,259,630-632]
Stroke	Limited and somewhat loosely associated case reports of stroke following recent use of smoked cannabis (one of which was cardioembolic from myocardial infarction)[137,633-636]
Cerebral blood flow	Increased with acute cannabis use, chronic use may decrease, variations exist between regions,[137,637,638] possible association with reversible cerebral vasoconstriction syndrome (RCVS),[639] and multifocal intracranial stenosis[636]
Other	Headache,[240,241,243,290,359,362] especially with withdrawal[640]
Cardiovascular	**Adverse Effects Reported**
Peripheral circulation	Conjunctival injection, vasodilatation, postural hypotension, supine hypertension,[137,144,490,577,635,637,641-643] and arteritis[644-647]
Heart rate	Tachycardia with acute use, but tolerance develops with chronic use[137,144,232,303,314,490,637,648-654]
Heart rhythm	Ventricular arrhythmia, atrial fibrillation, premature ventricular contractions[635,652,653,655-658]
Myocardial infarction (MI)	Possible increased risk of MI after acutely smoking cannabis, particularly with pre-existing cardiovascular disease, increased myocardial oxygen demand[137,642,653,659,660]

the activity of Δ^9-THC.[263] Delta^9-THC accounts for the vast majority of the psychotropic and physical side effects of cannabis.[87]

In contrast, as noted, CBD lacks psychoactivity, which is why the specialized bred high-CBD, low-THC strain of *Charlotte's Web*™ has become such a popular treatment for refractory childhood epilepsy.[38] CBD-mediated attenuation of Δ^9-THC side effects may be observed when the CBD:THC ratio is at least 8:1 (± 11.1),[264,265] while CBD may potentiate some of the THC side effects when the CBD:THC ratio is around 2:1 (± 1.4).[264] CBD has been shown to have anxiolytic effects in animals and humans by reducing the anxiety reaction induced by Δ^9-THC.[266]

There are no studies evaluating the therapeutic benefits correlating to varying cannabis strains or CBD:THC ratios, despite the wide spectrum of diseases and symptoms that the medical literature suggests cannabis is beneficial for. This is clearly a wide open area containing many potential therapeutic medical treatments for which research is desperately needed. Determining which cannabis strains and CBD:THC ratios are the most effective for specific diseases and symptoms, including acute and chronic pain should be a primary research focus.

There are an extensive number of variables that make it difficult for establishing standardized dosing schedules. Some of these variables include the complex cannabinoid pharmacology, potency of cannabis being used such as CBD:THC ratios, the large number of other compounds found in cannabis, different dosing regimens, different routes of administration, tolerance to cannabinoids, inter-individual differences in cannabinoid receptor structure, function, and density, as well as differences in cannabinoid metabolism.[137] Current dosing recommendations are highly individualized, relying significantly on titration.[231]

For new patients, it is recommended that waiting a few minutes between puffs of smoked/inhaled cannabis, and waiting 30-60 minutes between bites of cannabis-based oral products to monitor for effects or adverse symptoms is most prudent.[137] Based on peer-reviewed literature, the majority of patients using smoked or orally ingested cannabis for medical purposes have been observed to use between 10 and 20 g of cannabis per week, or approximately 1-3 g per day.[137] Detailed estimated dose amounts and percentages of Δ^9-THC between various routes of administration, including conversion factors between smoked and oral forms can be seen in Health Canada's publication of

Table 3.—Adverse effects Reported With Use of Cannabis and Cannabinoids on Respiratory, Gastrointestinal, Reproductive, and Immune Systems

Respiratory System	Adverse Effects Reported
Carcinogenesis	Cannabis smoke contains many similar chemicals as tobacco smoke, and cannabis smoke condensates may be more cytotoxic and mutagenic then tobacco smoke condensates,[137,661,662] although evidence linking cancer and cannabis smoke are conflicting and inconclusive[137,663-666]
Inflammation	Chronic cannabis smoking associated with histopathologic changes, cough, wheezing, bronchitis, and phlegm production[137,667-671]
Bronchial tone	Acute use of smoked cannabis causes bronchodilatation,[667,672-674] but long term heavy smoking may lead to increased obstruction and decreased lung function[137,667,670,671,675,676]
Gastrointestinal System	**Adverse Effects Reported**
General	Decreased secretion, decreased motility and gastric/colonic emptying, anti-inflammatory[137,312-315,535]
Pancreas	Pancreatitis has been reported with heavy acute and chronic daily use[137,677-680]
Liver	Possible increased risk of hepatic fibrosis/steatosis, particularly in patients with hepatitis C[137,681-686]
Reproductive System	**Adverse Effects Reported**
Females	Inconclusive and unclear as most data are from animal studies; dose-dependent stimulatory or inhibitory effects on sexual behavior,[137,687] possible ovulation suppression and menstrual cycle changes[137,688-690]
Males	Inconclusive as most data are from animal studies with limited human studies. With chronic and daily use, possibly decreased sperm count, morphology, and motility, anti-androgenic,[137,490,689,691-693] possible inhibitory sexual effects[220,304]
Immune System	**Adverse Effects Reported**
General	Complex and unclear with both suppressive and stimulatory actions reported[137,574,694,695]

Information for Health Care Professionals: Cannabis (marihuana, marijuana) and the cannabinoids.[137] There are no standard clinical guidelines in terms of contraindications for use of cannabis and cannabinoids, although Health Canada has outlined some suggestions, as modified and seen in Table 4.[137] The risk/benefit ratio needs to be evaluated in patients with certain medical conditions until further research becomes available to form more standardized guidelines.

CONCLUSIONS AND SUMMARY

The historical use of cannabis for medicinal purposes is described for numerous diseases. There is an abundance of support for its many medicinal uses as well as potential benefit in some forms of headache disorders, including migraine and cluster. With the majority of the US now legalizing medicinal cannabis and/or limited CBD-only use, it is important for physicians to be educated on the history and proper clinical use of cannabis, because patients will become increasingly aware of it as a potential treatment, including for chronic pain and headache disorders. Cannabis contains an extensive number of pharmacological and biochemical compounds, of which only a small fraction are understood, so many therapeutic uses likely remain undiscovered. Cannabinoids appear to modulate and interact at many pathways inherent to migraine, triptan mechanisms of action,

Table 4.—Suggested Contraindications and/or Precautions Requiring Evaluation of Risk/Benefit Ratio of Cannabis and Cannabinoids

Use with caution in patients with a history of substance abuse including alcohol, given abuse potential.
Use with caution in patients using sedative-hypnotics, alcohol, or other psychoactive drugs due to potential synergistic sedative effects.
Use with caution in severe renal or liver disease, including chronic hepatitis C (daily use not recommended due to potential for worsening steatosis severity).
Avoid use under the age of 18 due to potential for increased adverse effects on mental health during development and adolescence.
Avoid use while driving, operating heavy machinery, or performing other hazardous tasks or activities.
Avoid use with history of cannabinoid or smoke hypersensitivity.
Avoid use in patients with severe cardio-pulmonary disease due to risk for potential hypotension, hypertension, tachycardia, or syncope.
Avoid use of smoked cannabis in patients with pulmonary diseases including asthma and chronic obstructive pulmonary disease.
Avoid use in women who are pregnant or breastfeeding. Use with caution in women of childbearing age who are planning pregnancy or not using a reliable contraceptive.
Avoid use in patients with psychiatric disease, particularly schizophrenia, or a family history of schizophrenia.
Careful psychiatric monitoring is recommended for patients with mania or depression.

and opiate pathways, suggesting a potential synergistic or related benefit. Modulation of the endocannabinoid system through agonism or antagonism of its receptors, targeting its metabolic pathways such as inhibition of endocannabinoid-degrading enzymes, or combining cannabinoids with other analgesics for synergistic effects, may provide the basis for many new classes of medications. Despite the limited evidence and research suggesting a therapeutic role for cannabis and cannabinoids in some headache disorders, randomized clinical trials are necessary for confirmation and further evaluation.

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