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.

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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), glutama tergic, 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,

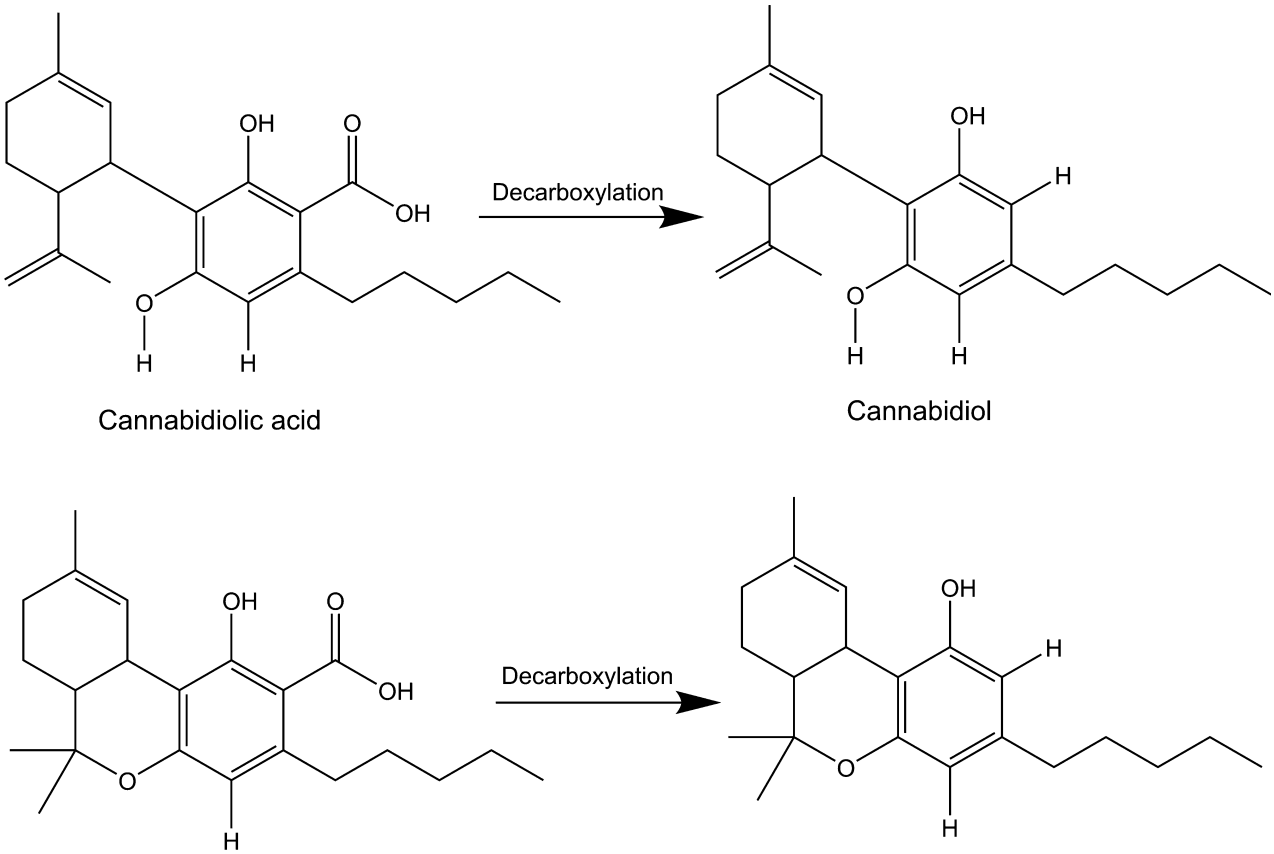

Figure 1. Structures of the naturally occurring cannabidiolic acid and Δ^9-tetrahydrocannabinolic acid, which are converted to cannabidiol and Δ^9-tetrahydrocannabinol on activation during smoking or in situ.

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-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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