CRITICAL REVIEW AND INVITED COMMENTARY

Cannabidiol: Pharmacology and potential therapeutic role in epilepsy and other neuropsychiatric disorders

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Summary

To present a summary of current scientific evidence about the cannabinoid, cannabidiol (CBD) with regard to its relevance to epilepsy and other selected neuropsychiatric disorders. We summarize the presentations from a conference in which invited participants reviewed relevant aspects of the physiology, mechanisms of action, pharmacology, and data from studies with animal models and human subjects. Cannabis has been used to treat disease since ancient times. Δ^9-Tetrahydrocannabinol (Δ^9-THC) is the major psychoactive ingredient and CBD is the major nonpsychoactive ingredient in cannabis. Cannabis and Δ^9-THC are anticonvulsant in most animal models but can be proconvulsant in some healthy animals. The psychotropic effects of Δ^9-THC limit tolerability. CBD is anticonvulsant in many acute animal models, but there are limited data in chronic models. The antiepileptic mechanisms of CBD are not known, but may include effects on the equilibrative nucleoside transporter; the orphan G-protein-coupled receptor GPR55; the transient receptor potential of vanilloid type-1 channel; the 5-HT_{1a} receptor; and the α3 and α1 glycine receptors. CBD has neuroprotective and antiinflammatory effects, and it appears to be well tolerated in humans, but small and methodologically limited studies of CBD in human epilepsy have been inconclusive. More recent anecdotal reports of high-ratio CBD:Δ^9-THC medical marijuana have claimed efficacy, but studies were not controlled. CBD bears investigation in epilepsy and other neuropsychiatric disorders, including anxiety, schizophrenia, addiction, and neonatal hypoxic-ischemic encephalopathy. However, we lack data from well-powered double-blind randomized, controlled studies on the efficacy of pure CBD for any disorder. Initial dose-tolerability and double-blind randomized, controlled studies focusing on target intractable epilepsy populations such as patients with Dravet and Lennox-Gastaut syndromes are being planned. Trials in other treatment-resistant epilepsies may also be warranted.

KEY WORDS: Cannabidiol, Cannabis, Tetrahydroacannabinol, Dravet syndrome, GPR55, Medical marijuana.

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Cannabis sativa and its sister species *Cannabis indica* have been used to treat epilepsy for centuries. Recent years have seen a resurgence in interest in the therapeutic potential of compounds derived from these plants. Specifically, the nonpsychoactive compound cannabidiol (CBD) has shown promise as an anticonvulsant with novel mechanisms of action and a favorable side-effect profile. Cannabinoid-based therapies are already approved for conditions as diverse as spasticity, nausea, and pain. An abundance of preclinical evidence and anecdotal human data support the use of cannabinoids in the treatment of epilepsy.

In this article, we survey the history of cannabis and its derivatives in the treatment of epilepsy from ancient times to the present day; review the clinical pharmacology of the neuroactive components of cannabis; summarize research into the potential of cannabinoids in other neurologic and psychiatric disorders; and discuss avenues for future clinical trials.

Cannabinoids: A Brief History of Their Medicinal Uses

The *Cannabis* genus of flowering plants mainly comprises the *sativa* and *indica* species. Indigenous to Central and South Asia, cannabis was used for millennia to produce hemp fiber for rope, clothing, bowstrings, and paper; for its seeds and seed oils; as livestock feed; and for medicine, religious ceremonies, and recreation. Hemp is now a worldwide crop used to make cordage, construction material, paper, and textiles, as well as for edible seeds, milk, and oil.

The two major neuroactive components in cannabis are the psychoactive Δ^9-tetrahydrocannabinol (Δ^9-THC) and the nonpsychoactive cannabidiol. We use nonpsychoactive to indicate a lack of psychotropic effects that produce a "high" similar to that of Δ^9-THC; however, CBD can have some antianxiety and other behavioral effects.[1] *Cannabis sativa* usually has higher Δ^9-THC:CBD ratios than *Cannabis indica*. *Sativa* strains often have more psychotropic effects, and are more stimulating, whereas *indica* strains are typically more sedating.[2] Δ^9-THC activates the endocannabinoid system, which consists of G-protein-coupled cannabinoid (CB) receptors, synthetic and degradative enzymes, and transporters. In the central nervous system, this system influences synaptic communication and modulates eating, anxiety, learning and memory, and growth and development.[3]

Medicinal preparations from the flowers and resin of *C. sativa* have been used in China since ~2,700 BCE to treat menstrual disorders, gout, rheumatism, malaria, constipation, and absent-mindedness.[4] In medieval times, Islamic physicians used cannabis to treat nausea and vomiting, epilepsy, inflammation, pain, and fever. Western medicine used cannabis widely in the 1800s; before aspirin, it was a common analgesic drug. More recently, cannabis has been used to treat glaucoma, pain, nausea and vomiting, muscle spasms, insomnia, anxiety, and epilepsy. Evidence for efficacy varies substantially for different indications, with the best data in painful HIV-associated sensory neuropathy,[5] chronic pain,[6] chemotherapy-induced nausea and vomiting,[7] and spasms in patients with multiple sclerosis.[8] Other medicinal uses for cannabis have been proposed (discussed later in this article), but none has been examined in well-controlled clinical trials.

Use in epilepsy in the modern era

In the late 19th century, prominent English neurologists including Reynolds[9] and Gowers[10] used cannabis to treat epilepsy (see Box 1). However, the use of cannabis for epilepsy remained very limited, and despite anecdotal successes, cannabis received scant or no mention from English-language epilepsy texts in the late 19th and early to mid-20th centuries.

Four controlled studies, mainly in the 1970s, examined the effect of CBD on seizures (Table 1, reviewed in Gloss & Vickrey[11]). However, although two of the studies found limited improvements, all four suffered from methodological flaws, including small sample size and, in some cases, inadequate blinding.

One epidemiologic study of illicit drug use and new-onset seizures found that cannabis use appeared to be a protective factor against first seizures in men.[12] The adjusted odds ratio (OR) was 0.42 for every cannabis use and 0.36 for cannabis use within 90 days of hospitalization. No effect was observed in women. The authors suggested that cannabis is protective of both provoked and unprovoked seizures, for men.

Cannabinoid Pharmacology and Mechanisms of Action

C. sativa produces more than 80 terpenophenolic compounds called cannabinoids, which are present in varying relative proportions depending on the strain.[13,14] Isolation and characterization of these highly lipophilic compounds led to studies that found that psychotropic effects are due to Δ^9-THC (Fig. 1), which is produced from the corresponding acid derivative following heating. CBD (Fig. 1) was isolated in 1940 and its structure was elucidated in 1963,[15] whereas Δ^9-THC was isolated and characterized in 1964, and for the next 30 years, most chemical and pharmacologic research focused on Δ^9-THC because of its psychotropic activity and the associated sociopolitical ramifications. However, it was not until the late 1980s that Δ^9-THC was found to bind to two G-protein-coupled cell membrane receptors, consequently named the cannabinoid type 1 (CB_1) and type 2 (CB_2) receptors, to exert its effects. Thereafter, anandamide and 2-arachidonoylglycerol, CB_1 and CB_2 endogenous ligands, were identified in animals and

named endocannabinoids.[16] CB_1 receptors are found primarily in the brain but also in several peripheral tissues. CB_2 receptors are mainly found in immune and hematopoietic cells, but can become upregulated in other tissues.

BOX 1

Russell Reynolds and William Gowers on Cannabis for Epilepsy

Cannabis indica, which was first recommended in epilepsy by Dr. Reynolds, is sometimes, though not very frequently, useful. It is of small value as an adjunct to bromide, but is sometimes of considerable service given separately. It may be noted that the action of Indian hemp presents many points of resemblance to that of belladonna; it is capable of causing also delirium and sleep, first depression and then acceleration of the heart, and also dilates the pupil. The cerebral excitement is relatively more marked, and the effect on the heart and pupil much less than in the case of belladonna.[71]

John K., aged 40, came under treatment in 1868, having suffered from fits for 25 years. They occurred during both sleeping and waking, at intervals of a fortnight. There was a brief warning, vertigo, then loss of consciousness, and tonic and clonic spasm followed by some automatism;–"acts strangely and cannot dress himself." The attacks ceased for a time on bromide, but recurred when he discontinued attendance. He came again in October, 1870; scruple doses of bromide of potassium three times a day had now no effect, and the fits, at the end of 4 months' treatment, were as frequent as ever. Ext. cannabis indicae gr. (~9.8 g), three times a day, was then ordered; the fits ceased at once, "a wonderful change" the patient declared. He had no fit for 6 months, and then, having discontinued attendance, the fits recurred, but were at once arrested by the same dose of Indian hemp. He continued free from fits for some months, until, during my absence, bromide was substituted for the Indian hemp; the fits immediately recurred, and he left off treatment. He returned to the hospital in 6 months' time, and on Indian hemp passed 2 months without an attack. In the third month another fit occurred, and the patient again ceased to attend, and did not return.[10]

Although Δ^9-THC is the main psychoactive agent found in cannabis, other cannabinoids contribute to the plant's medicinal properties.[17] Studies in experimental models and humans have suggested antiinflammatory, neuroprotective, anxiolytic, and antipsychotic properties.[14,18] Unlike Δ^9-THC, CBD does not activate CB_1 and CB_2 receptors, which likely accounts for its lack of psychotropic activity. However, CBD interacts with many other, non-endocannabinoid signaling systems: It is a "multitarget" drug. At low micromolar to sub-micromolar concentrations, CBD is a blocker of the equilibrative nucleoside transporter (ENT), the orphan G-protein-coupled receptor GPR55, and the transient receptor potential of melastatin type 8 (TRPM8) channel. Conversely, CBD enhances the activity of the 5-HT_{1a} receptor, the $\alpha 3$ and $\alpha 1$ glycine receptors, the transient receptor potential of ankyrin type 1 (TRPA1) channel, and has a bidirectional effect on intracellular calcium.[14,19] At higher micromolar concentrations, CBD activates the nuclear peroxisome proliferator-activated receptor-γ and the transient receptor potential of vanilloid type 1 (TRPV1) and 2 (TRPV2) channels while also inhibiting cellular uptake and fatty acid amide hydrolase–catalyzed degradation of anandamide.[14,18] Finally, CBD's polyphenolic nature (Fig. 1) makes it a potent antioxidant.

CBD may also potentiate some of Δ^9-THC's beneficial effects as it reduces the psychoactivity of Δ^9-THC to enhance its tolerability and widen its therapeutic window.[20] CBD can counteract some of the functional consequences of CB_1 activation in the brain,[21] possibly by indirect enhancement of adenosine A1 receptors activity through ENT inhibition. This may partly explain why users of cannabis preparations with high CBD:Δ^9-THC ratios are less likely to develop psychotic symptoms than those who consume preparations with low CBD:Δ^9-THC ratios.[22] The botanical drug nabiximols, which contains equal amounts of Δ^9-THC and CBD, relieves spasticity and pain in multiple sclerosis more effectively than Δ^9-THC alone, possibly because CBD's effects allow patients to tolerate higher amounts of Δ^9-THC. CBD may also supplement the antispastic effects of Δ^9-THC (e.g., via local potentiation of glycine signaling, inhibition of endocannabinoid degradation, or retardation of demyelination through antiinflammatory, antioxidant, and antiexcitotoxic mechanisms).

CBD has proven beneficial in experimental models of several neurologic disorders, including those of seizure and epilepsy (see below),[17] as have other cannabinoids such as cannabichromene (CBC) and the propyl homologs of Δ^9-THC and CBD (respectively, Δ^9-tetrahydrocannabivarin [Δ^9-THCV] and cannabidivarin [CBDV]). Δ^9-THCV exhibits high affinity for cannabinoid receptors and acts as a neutral CB_1 antagonist and partial CB_2 agonist with efficacy in an animal model of Parkinson's disease.[23] CBC influences adult neural stem cell differentiation by reducing generation of new astrocytes potentially involved in neuroinflammation.[24] CBDV and, to a far smaller extent, Δ^9-THCV produce anticonvulsant effects in animal models of epilepsy, likely via non-CB_1/CB_2 mechanisms. Like CBD, these compounds interact with TRPV1, TRPV2, TRPA1, and TRPM8 channels, but their molecular pharmacology and mechanisms of action are less well understood.

Cannabinoid Effects in Preclinical Models of Seizure and Epilepsy

Whole cannabis or extracts

Preclinical studies, mainly in the 1970s, studied the effects of cannabis on seizure and epilepsy. In a rat max-

Table 1. Clinical trials of cannabidiol in epilepsy

Study	Treatments (subjects per group)	Duration	Outcome	Toxicity	Limitations
Mechoulam and Carlini, (1978)[72]	TRE – CBD 200 mg/day (4) TRE – Placebo (5)	3 months	CBD: 2 seizure free; 1 partial improvement; 1 no change	None	No baseline seizure frequency, no definition of improvement; unclear if AEDs were changed; small N/limited power; not truly randomized-blinded; unknown if groups were matched
Cunha et al. (1980)[73]	TRE-TLE CBD (7) [a] TRE-TLE Placebo (8)[a,b]	200–300 mg/day for 3–18 weeks	Last visit: 4 CBD, 1 placebo	Somnolence	Not clearly blinded, since one patient transferred groups and doses were adjusted in CBD, but no mention of this in placebo group and CBD group received had longer average treatment
Ames and Cridland (1986)[74]	IDD-TRE CBD (?6)[c] IDD-TRE Placebo (?6)[c] × 4 weeks	CBD 300/day × 1 week; 200/day × 3 weeks	No difference between CBD v. Placebo	Somnolence	This was a letter to the editor and details are lacking
Trembly and Sherman (1990)[75]	TRE (?10 or 12)[d]	3 months baseline; 6 months placebo: Randomized to either 6 months placebo v. CBD 100 t.i.d.; then crossover for 6 months on alternative treatment	No change in seizure frequency or cognitive/ behavioral tests	None	Only truly double blind study. Unclear why sample size differed in two reports. Data reported is incomplete

TRE, treatment-resistant epilepsy; TLE, temporal lobe epilepsy; IDD, intellectual/developmental disability.
[a]Frequent convulsions for ≥1 year; – 1 GTCSz per week.
[b]One patient transferred from placebo to treatment after 1 month.
[c]12 subjects were divided into two groups, but distribution uncertain.
[d]Abstract and subsequent book chapter have different N's (10 and 12).

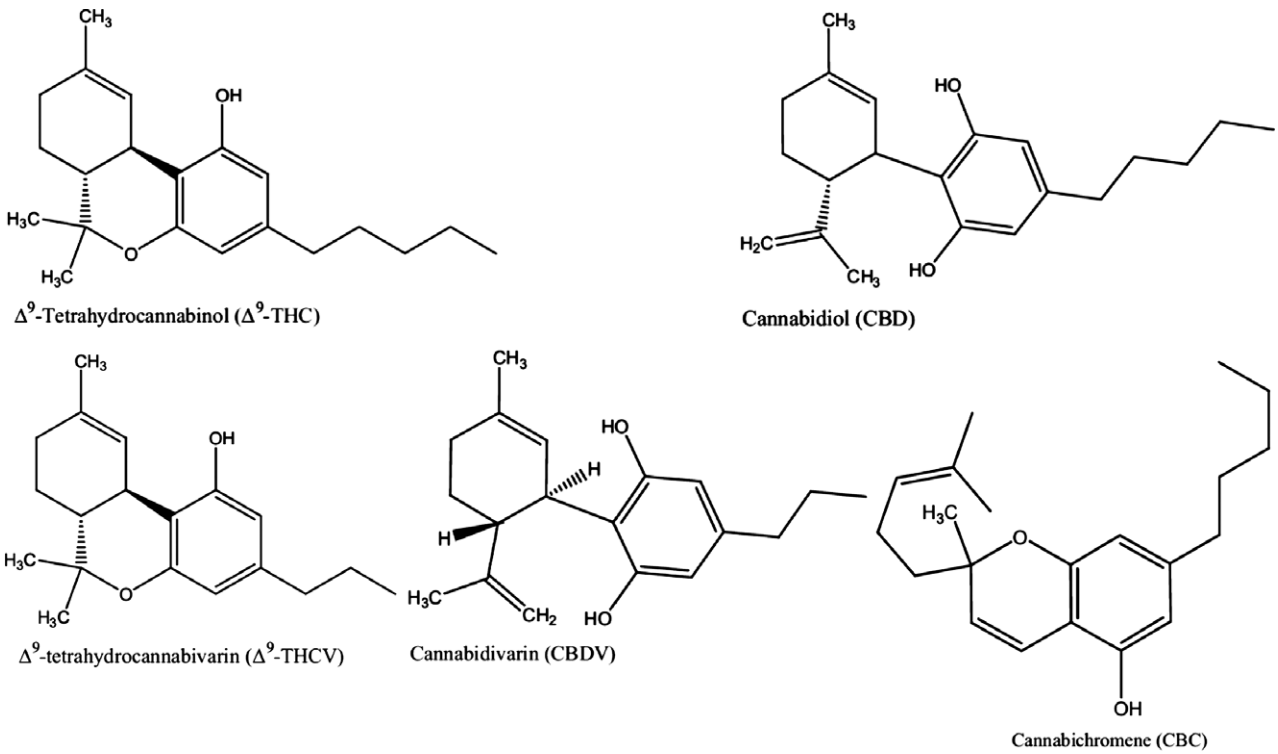

Figure 1.
Molecular structure of selected cannabidiols
Epilepsia © ILAE

imal electroshock study (MES), cannabis resin (17% Δ^9-THC content) was used with or without pharmacologic modulation of monoamines and catecholamines (which did not independently affect seizure parameters) to suggest that modulation of serotonergic signaling contributed to the anticonvulsant effects of cannabis.[25] However, because the non–Δ^9-THC cannabinoid composition of the cannabis was unknown, the potential contributions of other cannabinoid or noncannabinoid components were likewise unexplored.

In a dog model using a subconvulsant dose of penicillin (750,000 IU; i.v.), acute smoked cannabis (6 mg Δ^9-THC via tracheotomy) caused muscular jerks, whereas repeated treatment produced epileptiform activity in occipital and frontal cortices that generalized to tonic–clonic seizures.[26] Here, the authors suggested that Δ^9-THC either reduced seizure threshold or increased blood–brain barrier (BBB) permeability, although results of a related study did not support the latter hypothesis.[27]

Δ^9-Tetrahydrocannabinol

Many early studies on the effects of specific cannabinoids in preclinical models of seizures focused on Δ^9-THC and, later, synthetic CB_1 agonists. The results of these studies, which have been reviewed extensively elsewhere[28] and are summarized in Table 2, demonstrated mixed efficacy in acute seizure models in various species. In some models, Δ^9-THC reduced seizure frequency or severity, whereas in other studies there was no effect or even potentiation of convulsive effects. Similarly, synthetic CB_1 agonists have shown variable effects in seizure models. Finally, in some naive, seizure-susceptible rats and rabbits, Δ^9-THC actually provoked epileptiform activity.[29,30] Finally, some studies found dose-limiting toxicity and tolerance to the antiseizure effects with Δ^9-THC administration. These findings suggest that Δ^9-THC is not the sole cannabinoid responsible for the antiseizure effects of cannabis, and thus activation of CB_1 receptors with Δ^9-THC or synthetic agonists is unlikely to yield therapeutic benefit for patients with epilepsy.

Table 2. (A) Proposed molecular targets for plant cannabinoids investigated in animal models of seizure and (B) Cannabinoid efficacy in animal models of seizure and epilepsy

Cannabinoid	Molecular target(s)
(A)	
Δ^9-Tetrahydrocannabinol (Δ^9-THC)	CB1R, CB2R, TRPV1, TRPV2
Δ^9-Tetrahydrocannabivarin (Δ^9-THCV)	CB1, CB2, TRPV1, TRPV3, TRPV4
Cannabidiol (CBD)	ENT, GPR55, TRPV1, TRPV2, TRPV3, TRPA1, FAAH, TRPM8, adenosine, $5HT1_A$
Cannabidivarin (CBDV)	TRPV4, DAGLα
Cannabinol (CBN)	CB1R, TRPV4, TRPA1

Plant cannabinoid	Model	Efficacy
(B)		
Δ^9-Tetrahydrocannabinol (Δ^9-THC)	Generalized seizure (e.g., MES, PTZ, 6 Hz, 60 Hz, nicotine, and strychnine)	Y
	Temporal lobe epilepsy	Y
Synthetic CB1R agonists (e.g., WIN55-212)	Generalized seizure (MES, PTZ, amygdala kindling)	Y
	Partial seizure with secondary generalization (penicillin and maximal dentate gyrus activation)	Y
	Temporal lobe epilepsy	Y
	Absence epilepsy (WAG/Rij)	Mixed effect
Synthetic CB1R antagonists (e.g., SR141716A)	Generalized seizure (MES and PTZ)	N[a]
	Absence epilepsy (WAG/Rij)	N
	Partial seizures with secondary generalization (penicillin but not maximal dentate gyrus activation)	N[a]
	Epileptogenesis (juvenile head trauma but not kainic acid)	Y
Δ^9-Tetrahydrocannabivarin (Δ^9-THCV)	Generalized seizure	Y
Cannabidiol (CBD)	Generalized seizure (MES, PTZ, 6 Hz, 60 Hz, picrotoxin, isonicotinic acid, bicuculline, hydrazine, limbic kindling (electrical), and strychnine but not 3-mercaptoproprionic acid)	Y
	Temporal lobe convulsions/status epilepticus	Y
	Partial seizures with secondary generalization (penicillin but not cobalt)	Y
Cannabidivarin (CBDV)	Generalized seizure (MES, PTZ, and audiogenic)	Y
	Temporal lobe convulsions/status epilepticus	Y
	Partial seizures with secondary generalization (penicillin only)	Y
Cannabinol (CBN)	Generalized seizure (MES only)	Y

[a]Indicates a proconvulsant effect.

Cannabidiol and related compounds

CBD is the only non–Δ^9-THC phytocannabinoid to have been assessed in preclinical and clinical studies for anticonvulsant effects. In mice, CBD blocked MES-induced seizures in one study[31] but had no effect on pentylenetetrazol (PTZ)–induced or MES-induced seizures in another.[32] However, given the routes of administration used, the lack of efficacy in the latter study may reflect inadequate CBD levels, since several other reports (see subsequent text) have found CBD to be effective against both PTZ-induced and MES-induced seizures.

The anticonvulsant effects of CBD, Δ^9-THC, and other cannabinoids were also compared using a variety of standard seizure models by Karler and Turkanis.[33] Significant anticonvulsant effects against the MES test in mice were found for the following cannabinoids (approximate effective dose (ED_{50}) values in parentheses): CBD (120 mg/kg), Δ^9-THC (100 mg/kg), 11-OH-Δ^9-THC (14 mg/kg), 8β- but not 8α-OH-Δ^9-THC (100 mg/kg), Δ^9-THC acid (200–400 mg/kg), Δ^8-THC (80 mg/kg), cannabinol (CBN) (230 mg/kg), and Δ^9-nor-9α- or Δ^9-nor-9β-OH-hexahydro CBN (each 100 mg/kg). More recently, CBD has been shown to have antiepileptiform and anticonvulsant effects in in vitro and in vivo models. In two different models of spontaneous epileptiform local field potentials (LFPs) in vitro, CBD decreased epileptiform LFP burst amplitude and duration. CBD also exerted anticonvulsant effects against PTZ-induced acute generalized seizures, pilocarpine-induced temporal lobe convulsions, and penicillin-induced partial seizures in Wistar-Kyoto rats.[34,35]

Despite the convincingly anticonvulsant profile of CBD in acute models of seizure, there is less preclinical evidence for CBD's effects in animal models of chronic epilepsy. CBD exerted no effect on focal seizure with a secondary generalization produced by cobalt implantation,[36] although Δ^9-THC had a time-limited (~1 day) anticonvulsant effect. Model-specific effects were evident for CBD, which was effective in the MES and all of the γ-aminobutyric acid (GABA)–inhibition-based models, but was ineffective against strychnine-induced convulsions.[37] CBD has also been shown to increase the afterdischarge threshold and reduce afterdischarge amplitude, duration, and propagation in electrically kindled, limbic seizures in rats.[38]

As mentioned previously, CBDV, the propyl variant of CBD, also has significant anticonvulsant properties. Using the same in vitro models of epileptiform activity described earlier,[34] CBDV attenuated epileptiform LFPs and was anticonvulsant in the MES model in ICR mouse strain mice and the PTZ model in adult Wistar-Kyoto rats. In the PTZ model, CBDV administered with sodium valproate or ethosuximide was well tolerated and retained its own additive anticonvulsant actions. It also retained efficacy when delivered orally. In contrast, although CBDV exerted less dramatic anticonvulsant effects against pilocarpine-induced seizures, it acted synergistically with phenobarbital to reduce seizure activity. CBDV exerts its effects via a CB_1-receptor-independent mechanism.[39]

The mechanisms by which CBD and CVDV exert their antiseizure effects are not fully known, although several of the potential targets of cannabidiols described earlier may be involved. Via modulation of intracellular calcium through interactions with targets such as TRP channels,[40] G-coupled protein receptor protein 55 (GPR55), or voltage-dependent anion-selective channel protein 1 (VDAC1),[41] CBD and related compounds may reduce neuronal excitability and neuronal transmission. Alternatively, the antiinflammatory effects of cannabidiol, such as modulation of tumor necrosis factor alpha (TNFα) release,[42] or inhibition of adenosine reuptake[43] may also be involved in antiictogenesis. Careful pharmacologic studies are needed to further delineate mechanisms.

Other phytocannabinoids

Of the plant cannabinoids that have been identified, few have been investigated beyond early screening for affinity or activity at CB receptors. Δ^9-THCV, a propyl analog of Δ^9-THC, is a neutral antagonist at CB_1 receptors.[44] Δ^9-THCV exerts some antiepileptiform effects in vitro and very limited anticonvulsant effects in the PTZ model of generalized seizures.[45] Synthetic CB_1-receptor antagonists/inverse agonists have also been investigated in some models of acute seizure and, although partial or full CB_1 agonism produces largely anticonvulsant effects, neutral antagonism has very limited effects on seizure, and inverse agonism has either no effect or a limited proconvulsant effect (see Table 2). Finally, CBN exerted no effect upon chemically or electrically induced seizures in mice [32].

Cannabidiol Pharmacology in Humans

Studies of synthetic CBD and plant extracts, either isolated or in combination with Δ^9-THC, have likely provided sufficient human data on the pharmacology of CBD to proceed with dosing and efficacy trials for epilepsy. There are multiple potential routes of administration for CBD. The most common delivery form for CBD the inhaled route as a constituent of smoked cannabis used for recreational or medicinal purposes. This approach is obviously unsuitable for medicinal drug delivery but highlights the fact that the lungs are a very efficient mechanism for drug delivery. Studies that have examined delivery of CBD through aerosolization or vaporization using specialized devices have reported rapid peak plasma concentrations (<10 min) and bioavailability of ~31%,[46] although such an approach is limited by the need for specialized equipment and patient cooperation with administration.

CBD has been delivered orally in an oil-based capsule in some human trials. Because of low water solubility, absorp-

tion from the gastrointestinal system is erratic and leads to variable pharmacokinetics. Bioavailability from oral delivery has been estimated at 6% due to significant first-pass metabolism in the liver.[47] Oral-mucosal/sublingual delivery through sprays/lozenges has bioavailability similar to the oral route but less variability. Most of the data for oral-mucosal delivery comes from studies of nabiximols oral spray, which is a mixture of ~1:1 Δ^9-THC and CBD. Serial measurement of serum CBD levels in healthy volunteers after a single dose of nabiximols containing 10 mg each of CBD and THC has demonstrated a maximum concentration (C_{max}) of 3.0 ± 3.1 μg/L and maximum time (T_{max}) of 2.8 ± 1.3 h.[48] Transdermal approaches to CBD delivery have also been investigated, but due to CBD's high lipophilicity, special ethosomal delivery systems are needed to prevent drug accumulation in the skin, which are impractical and costly at this time.[49]

Distribution

The distribution of CBD is governed by its high lipophilicity ($K_{octanol\text{-}water}$ ~6-7), and a high volume of distribution (~32 L/kg) has been estimated, with rapid distribution in the brain, adipose tissue, and other organs.[46] CBD is also highly protein bound, and ~10% is bound to circulating red blood cells.[47] Preferential distribution to fat raises the possibility of accumulation of depot in chronic administration, especially in patients with high adiposity.

Metabolism and elimination

Like most cannabinoids, CBD is metabolized extensively by the liver, where it is hydroxylated to 7-OH-CBD by cytochrome P450 (CYP) enzymes, predominantly by the CYP3A (2/4) and CYP2C (8/9/19) families of isozymes. This metabolite then undergoes significant further metabolism in the liver, and the resulting metabolites are excreted in the feces and to a much lesser extent in the urine. The terminal half-life of CBD in humans is estimated at 18–32 h, and following single dose administration in chronic cannabis users, the clearance was 960–1,560 ml/min.[47]

Safety in humans

Multiple small studies of CBD safety in humans in both placebo-controlled and open trials have demonstrated that it is well tolerated across a wide dosage range. No significant central nervous system side effects, or effects on vital signs or mood, have been seen at doses of up to 1,500 mg/day (p.o.) or 30 mg (i.v.) in both acute and chronic administration.[50] Limited safety data exist for long-term use in humans, although there have been many patient-years of exposure to nabiximols following approval in many European countries and Canada. There is some theoretical risk of immunosuppression, as CBD has been shown to suppress interleukin 8 and 10 production and to induce lymphocyte apoptosis in vitro.[51,52]

It should be noted that the above studies were performed in adults. The pharmacokinetics and toxicity of CBD in children is not well understood.

Drug–drug interactions

Few data exist regarding drug interactions with CBD in humans, although there are some theoretical concerns that could have implications for its use in people with epilepsy (PWE). CBD is a potent inhibitor of CYP isozymes, primarily CYP2C and CYP3A classes of isozymes, in vitro and in animal models.[53] This is particularly important because many medications are substrates for CYP3A4. However, inhibition has typically not been observed at concentrations used in human studies.[53]

Repeated administration of CBD may induce CYP2B isozymes (CYP2B1/6) in animal models, which may have implications for PWE, because antiepileptic drugs (AEDs) such as valproate and clobazam are metabolized via these isozymes. Finally, because CBD is metabolized in a large part by CYP3A4, it is likely that common enzyme-inducing AEDs such as carbamazepine and phenytoin could reduce serum CBD levels.

CBD for Dravet and Lennox-Gastaut Syndromes

Several countries and U.S. states have liberalized their laws to allow individuals to access cannabis for medicinal use. Because of the historical and limited preclinical and clinical evidence for the efficacy of cannabinoids in general and CBD specifically, many patients have turned to medical marijuana when traditional AEDs have failed due to lack of efficacy or intolerable side effects. Perhaps most desperate of all for new therapies have been parents of children with severe early life epilepsy. Accounts of dramatic improvements with cannabis-based products with high CBD:Δ^9-THC (e.g., >20:1) ratios in the popular press have sparked a serious interest among epilepsy clinicians in pursuing the rigorous, scientific study of CBD. The use of cannabinoid-based therapies for the treatment of spasticity, pain, and anorexia has demonstrated to clinicians and pharmaceutical companies that it is possible to develop and commercialize cannabinoids for human disease. Exploring CBD treatments in populations that are increasingly turning to cannabis-based epilepsy therapies because of a lack of therapeutic alternatives and given that the lack of THC reduces the potential for adverse effects, this a promising avenue for clinical development. Preclinical testing in recently developed murine models of Dravet syndrome[54] could provide further support for the efficacy of CBD in this condition.

Planned trials for CBD in Dravet and Lennox–Gastaut syndromes

Among children with treatment-resistant epilepsy, those with early onset and severe epilepsies such as Dravet syndrome (DS) and Lennox-Gastaut syndrome (LGS) have the greatest neurodevelopmental problems, including intellectual disability and autism. In DS, which most often results from mutations in the *SCN1A* gene, healthy, developmentally normal children present in the first year of life, usually around 6 months, with convulsive status epilepticus (SE) frequently triggered by fever. Further episodes of SE, hemiclonic or generalized, tend to recur and, after the first year of life, other seizure types develop, including focal dyscognitive seizures, absences, and myoclonic seizures.[55] Seizures in DS are usually refractory to standard AEDs and, from the second year of life, affected children develop an epileptic encephalopathy resulting in cognitive, behavioral, and motor impairment. Outcome is generally poor, with intellectual disabilities and ongoing seizures in most patients.

Thus early and effective therapy for DS is crucial. More effective early control of epilepsy is associated with better developmental outcomes in children today than those who were treated 20–30 years ago. Currently, doctors know to avoid drugs that can worsen seizures (e.g., carbamazepine and lamotrigine) and to prescribe effective drugs (e.g., valproic acid, clobazam, topiramate, stiripentol) or dietary therapies (ketogenic or modified Atkins diet) earlier in the disease course. Stiripentol (STP) is the only compound for which a controlled trial has been performed in DS,[56] and it has showed a high rate of responders (71% responders on STP versus 5% on placebo). Stiripentol was awarded Orphan Drug Designation for the treatment of DS by the European Medicine Agency (EMA) in 2001 and by the U.S. Food and Drug Administration (FDA) in 2008.

LGS is a rare but devastating childhood epilepsy syndrome that can result from diverse etiologies, including structural, metabolic, and many genetic disorders; in many cases the cause is unknown. LGS presents in children ages 1 to 8 years; in most cases, onset is between the ages of 3 and 5 years. Most patients with LGS experience multiple refractory seizures every day despite multiple AEDs and nonpharmacologic treatment including ketogenic diet, vagus nerve stimulation, and epilepsy surgery. The prognosis remains poor with current therapies. Morbidity is significant: Head injuries are common, so that patients often must wear helmets; some patients have even become wheelchair-bound as a result of violent drop attacks.

Effective treatments for both DS and LGS are needed. A recent U.S. survey of 19 parents, 12 of whom had children with DS, explored the use of CBD-enriched cannabis therapy.[54] Of the 12 DS parental respondents, 5 (42%) reported a >80% reduction in seizure frequency. A single LGS parent responded and reported a >80% reduction in seizure frequency. Overall, parents reported improved alertness and lack of side effects apart from fatigue and drowsiness in some children. This may have been related to clinically significant levels of THC in some cannabis preparations used.

Patients with DS and LGS are potentially good candidates for a CBD trial given the need for more effective and better-tolerated therapies for these epilepsies, the high rate of seizure frequency, and the relative homogeneity of the specific syndromes. Several of the authors are currently initiating a study to determine the tolerability and optimal dose of CBD in children with DS and LGS. Inclusion criteria include a definite epilepsy syndrome diagnosis, ongoing seizures despite having tried two or more appropriate AEDs at therapeutic doses, and at least two seizures per week. To help improve the accuracy of seizure frequency reporting, seizures will be recorded with video–electroencephalography (EEG) to ensure that the seizure types documented by parents are confirmed by epileptologists. This is particularly important, since these syndromes may include some seizure types that are difficult to identify (e.g., atypical absence) or quantify (e.g., eyelid myoclonias); these will not be used as countable seizure types in the planned studies. We will focus attention on the most disabling seizure types: tonic, atonic, and tonic–clonic seizures. Based on the information obtained from these dose tolerability studies, we will then plan subsequent randomized, placebo-controlled, double-blind studies in DS and LGS. The ultimate goal is to determine whether CBD is effective in treating these epilepsies, with the hope of improving seizure control and quality of life. Although initial studies have been planned to focus on these severe childhood-onset epilepsies, there is no reason to believe based on available evidence that CBD would not be effective in other forms of treatment-resistant epilepsy.

Cannabinoids in Other Neuropsychiatric Disorders

Cannabidiol has been evaluated as a therapy for other neurologic and psychiatric conditions. Some of these disorders, such as neonatal hypoxic-ischemic encephalopathy, can be associated with seizures. Other disorders, such as anxiety and psychosis, are often comorbid conditions in PWE. Activity of CBD in conditions that may lead to epilepsy or coexist with epilepsy make it an attractive therapeutic compound because of its potential to affect the underlying epileptogenic process or target some of the additional disabling symptoms of the disease.

Neonatal hypoxic-ischemic encephalopathy

Perinatal asphyxia resulting in newborn hypoxic-ischemic encephalopathy (NHIE) occurs in 2–9/1,000 live births at term.[57] Therapeutic hypothermia is the only available therapy for asphyxiated infants[57] but only provides neuroprotec-

tion in infants with mild NHIE. Cannabinoids are promising neuroprotective compounds; they close Ca^{2+} channels and prevent toxic intracellular Ca^{2+} buildup and reduce glutamate release.[58] In addition, cannabinoids are antioxidants and antiinflammatory, modulate toxic NO production, are vasodilators, and show neuroproliferative and remyelinating effects. Acute hypoxic or traumatic brain injury is associated with increased brain endocannabinoid levels.[58]

In newborn rats, the CB receptor agonist WIN 55,212-2 reduces hypoxic-ischemic (HI) brain damage in vitro and in vivo by modulating excitotoxicity, nitric oxide toxicity, and inflammation, and enhances postinsult proliferation of neurons and oligodendrocytes.[58] However, long-lasting deleterious effects of overactivating CB_1 receptors in the developing brain are a potential disadvantage of WIN 55,212-2. By contrast, CBD is an attractive alternative because it lacks CB_1-receptor activity.[59] In the immature brain, CB_2 receptors are involved in CBD actions.[59,60] In forebrain slices from newborn mice deprived of oxygen and glucose, CBD reduced glutamate release, inducible nitric oxide synthase (iNOS), and cyclooxygenase 2 (COX-2) expression, cytokine production, and cell death.[59] In newborn pigs, CBD reduced HI-induced injury to neurons and astrocytes; reduced cerebral hemodynamic impairment, brain edema, and seizures; and improved brain metabolic activity.[60,61] CBD restored motor and behavioral performance in the 72 h after HI.[61] $5HT_{1A}$ and CB_2 receptors are involved in CBD neuroprotection at least in the first hours after HI.[60]

In newborn rats, post-HI neuroprotection by CBD is sustained long term, so that CBD-treated asphyxiated newborn rats behave similarly to controls in motor and cognitive tests 1 month after HI.[62] CBD is also associated with cardiac, hemodynamic, and ventilatory benefits.[60–62] Moreover, CBD is still neuroprotective when administered 12 h after the HI insult in newborn mice and shows synergistic neuroprotective effects with hypothermia in newborn pigs. All these data make CBD a promising candidate for studies of the treatment of NHIE.

Cannabinoids for psychiatric symptoms

Although epidemiologic evidence identifies cannabis smoking as a risk factor for schizophrenia, several cannabinoid components of the plant are emerging as potential treatments for psychiatric symptoms.

Psychosis

Current antipsychotics are partially effective against positive symptoms but do not successfully treat negative symptoms. These current drugs primarily block mesolimbic and mesocortical dopamine D2 receptors (D2R), a mechanism that is not thought to treat the underlying cause or neurochemical disorder.

CBD has antipsychotic properties.[18] It is active in both dopamine-based and glutamate-based laboratory models of schizophrenia symptoms, and the prevalence of cannabis-linked psychosis is lower when street cannabis contains higher proportions of CBD. In healthy humans, CBD reverses Δ^9-THC–induced psychotic symptoms and binocular depth inversion (an endophenotype of schizophrenia) and ketamine-induced depersonalization (a human glutamate model of psychosis).

One controlled clinical trial in acute schizophrenia compared CBD and a standard antipsychotic, amisulpride, in 33 patients over 4 weeks.[18] Both groups showed similar, highly significant improvements from baseline in the primary outcome measure (Positive and Negative Syndrome Scale (PANSS) total score), with some evidence of a better improvement of negative symptoms by CBD. CBD also demonstrated a significantly superior safety profile, lacking amisulpride's extrapyramidal symptoms, weight gain, and elevated serum prolactin. In addition, the antipsychotic effect of CBD was examined using a hair analysis to determine relative Δ^9-THC and CBD intake among 140 recreational ketamine users.[63] Smokers of cannabis low in CBD showed significantly more positive psychotic symptoms than both the Δ^9-THC-plus-CBD group and nonsmoking controls.

In functional magnetic resonance imaging (fMRI) studies, CBD alters brain function in the limbic and neocortical areas that show abnormalities in schizophrenia. In healthy subjects, the acute psychotomimetic effects of Δ^9-THC correlated significantly with attenuation of striatal activation during a verbal memory task, whereas CBD augments striatal activation in the same task.[64]

Cognitive impairment is a core deficit in schizophrenia, and preliminary evidence suggests that CBD may improve cognitive function.[65]

Anxiety disorders

CBD is anxiolytic in rodent models including conflict tests, conditioned fear, restraint stress, and aversion to open spaces.[66,67] In healthy humans, CBD reverses the anxiogenic effects of Δ^9-THC and reduces anxiety in a simulated public-speaking task.[68] Single photon emission computed tomography (SPECT) studies show blood-flow correlates such as decrease in left mesial temporal lobe perfusion.[69]

A more recent study in patients with social anxiety disorder confirmed an anxiolytic effect of CBD, and SPECT analysis showed that this was associated with alterations in blood flow in limbic and paralimbic brain areas.[70] A significant anxiolytic effect has also been demonstrated during emotional processing following exposure to neutral, mildly fearful, and intensely fearful visual cues using an objective measure of arousal (skin conductance response).[1] fMRI revealed that this effect correlated with decreased left amygdala activity, an effect opposite of that seen following Δ^9-THC treatment.

Addictive behavior

One of the main concerns about the use of cannabinoids as a treatment for medical conditions, including epilepsy, is the

risk for patients to develop an addiction to the compound or other drugs. There is evidence from rodent models of heroin and stimulant dependence that CBD actually reduces drug-seeking behavior and normalizes drug-induced neuronal abnormalities. In a study using cocaine-induced and amphetamine-induced place preference in rats, researchers gave the animals low doses of Δ^9-THC, CBD, or vehicle 30 min before an extinction trial. Δ^9-THC and CBD potentiated the extinction of stimulant-conditioned place-preference learning, without altering learning or retrieval.[62] Studies of cannabinoids on opioid-seeking behaviors found that Δ^9-THC potentiates heroin self-administration, whereas CBD inhibits cue-induced heroin-seeking behaviors for up to 2 weeks following administration.[67] CBD also normalized drug-induced changes in amino-hydroxy-methyl-isoxazolepropionic (AMPA) receptor 1 (GluR1) and CB_1 receptors within the nucleus accumbens. Together, these results indicate that CBD decreases cue-induced drug-seeking behaviors for up to 2 weeks after intake, suggesting a long-term impact on neural mechanisms relevant to drug relapse.

Data obtained from animal models of addiction have been shown to translate in humans in the few studies looking at these effects in clinical populations. Among 94 cannabis users whose samples were tested for CBD and Δ^9-THC content, smokers of higher CBD:Δ^9-THC samples showed lower attentional bias to drug stimuli and lower self-rated liking of cannabis stimuli than smokers of lower CBD:Δ^9-THC samples[57] CBD may have therapeutic effects on cannabis withdrawal[16] and nicotine dependence.[56]

Together, these preclinical findings and early clinical signals suggest that CBD should be evaluated more carefully as a potential agent to treat human addictive behaviors. In addition to data showing that CBD is not reinforcing on its own,[62] they also support its low addictive risk as a new intervention for epilepsy.

Conclusion

Cannabidiol has a wide range of biologic effects with multiple potential sites of action in the nervous system. Preclinical evidence for antiseizure properties and a favorable side-effect profile support further development of CBD-based treatments for epilepsy. Activity in models of neuronal injury, neurodegeneration, and psychiatric disease suggest that CBD may also be effective for a wide range of central nervous system disorders that may complicate the lives of individuals with epilepsy; a treatment for both seizures and comorbid conditions is highly desirable. Decades of prohibition have left cannabis-derived therapies in a legal gray area that may pose challenges for the evaluation and clinical development of CBD-based drugs for epilepsy and other disorders. However, a growing acceptance of the potential benefits of cannabis-derived treatments in many countries may ease the regulatory and bureaucratic path for clinicians and scientists to conduct well-designed studies of CBD. Much remains to be learned about CBD even as investigation moves into humans: We do not fully understand the targets through which this pleiotropic compound produces its antiseizure effects. Identifying these targets may also yield important insights into the mechanisms of seizures and epilepsy.

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O.D. has received an unrestricted medical education grant from GW Pharmaceuticals and funding from the Epilepsy Therapy Project for human trials of CBD. Dr Devinsky is involved in assessing the safety and tolerability, and is involved in planning randomized controlled trials of CBD supplied by GW Pharmaceuticals in patients with epilepsy.

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