Cannabinoid therapy in epilepsy

Santoshi Billakota[a], *Orrin Devinsky*[b], *and Eric Marsh*[c,d,e]

Purpose of review
To review the history, pharmacology, and clinical science of cannabidiol (CBD) in the treatment of epilepsy.

Recent findings
Phase III randomized controlled trials and prospective open label trials have provided efficacy and safety data for the use of CBD in pediatric onset severe epilepsies. The product that was studied in the vast majority of these published trials, Epidiolex (>99% of CBD and <0.10% Δ9-tetrahydrocannabinol (THC); GW pharmaceuticals, Cambridge, UK), has now been FDA approved based on this published data.

Summary
Identification of CBD, Δ9-THC, and the endocannabinoid system in the mid-20th century has led to advancement of cannabis-based therapies for epilepsy. Based on clinical trial data, Epidiolex is the first CBD medication approved by a national regulatory agency (US Food and Drug Administration for Dravet and Lennox Gastaut syndrome). Approval of CBD as a treatment for these rare and severe pediatric-onset epilepsy syndromes is an important milestone, but the complete spectrum of use of cannabis-derived products, and the use of CBD for other epilepsy syndromes remains to be determined.

Keywords
cannabinoid, cannabis, epidiolex, epilepsy, seizure

INTRODUCTION

History

Cannabis is a plant in the Cannabaceae family. Its two species, *sativa* and *indica*, have been utilized for more than 10 000 years for medicinal, spiritual, recreational, and other purposes. Chinese pharmacopeia documents medical use of cannabis nearly 4700 years ago. Sumerians used cannabis to treat seizures over 3800 years ago [1–3]. Following his trip to India in 1841, O'Shaughnessy introduced Cannabis Indica's anticonvulsant effects to Western medicine. Founders of English epileptology, including Reynolds and Gowers, reported on *C. indica's* positive effects on seizure control [4].

In the mid-20th century, cannabidiol (CBD) and Δ9-tetrahydrocannabinol (THC) were isolated and synthesized. By 1990s, the endogenous cannabinoid system (ECS) was identified [5▪]. Between 1949 and 1990, four small, underpowered placebo-controlled studies assessed cannabinoids to treat epilepsy but methodologic problems contributed to inconsistent results [1,6]. Preclinical and clinical science of cannabis-based therapies has advanced over the past decade, multiple open-label and three randomized placebo-controlled trials (RCT) have since been published. The present review focuses on CBD and THC – as potential epilepsy therapies, with most clinical data available on CBD.

PHARMACOLOGY

Basic science

The precursor cannabigerol-type (CBG) is metabolized to produce eight classes of cannabinoids: CBG; CBD; THC and Cannabinol (CBN); Cannabichromene (CBC); Cannabielsoin (CBE); iso-THC, cannabicyclol (CBL), and cannabicitran (CBT). CBD and THC are the prominent compounds in the plant.

[a]NYU Langone Comprehensive Epilepsy Center and NYU Langone School of Medicine, New York, New York, [b]Saint Barnabas Institute of Neurology and Neurosurgery, Livingston, New Jersey, [c]Division of Child Neurology, Children's Hospital of Philadelphia, [d]Department of Neurology and [e]Department of Pediatrics, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, Pennsylvania, USA

Correspondence to Santoshi Billakota, MD, 223 East 34th St, New York, NY 10016, USA. Tel: +1 646 558 0800; fax: +1 646 754 9800; e-mail: santoshi.billakota@nyulangone.org

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KEY POINTS

- The present review focuses on CBD and THC – as potential epilepsy therapies, with most clinical data available for CBD.
- Since 2014, multiple open-label and three randomized placebo-controlled trials (RCT) have been published using a purified cannabis extract that contains more than 99% of CBD and less than 0.10% Δ9-THC (Epidiolex, GW Pharmaceuticals, Cambridge UK) to test efficacy of CBD for pediatric-onset severe epilepsies.
- Based on these studies, Epidiolex is the first CBD medication approved by a national regulatory agency [US Food and Drug Administration for Dravet and Lennox Gastaut syndrome (LGS)].

THC, but not other cannabinoids, acts via the body's endocannabinoid system (ECS). The ECS consists of G protein–coupled (GPR) cannabinoid receptors (CB_1R and CB_2R) and the endogenous agonists of these receptors, the lipids anandamide (ANA) and 2-arachidonoylglycerol (2-AG). The CB_1Rs are coded by CNR1 (chromosome 6) and expressed primarily in the central nervous system (CNS), but also in endocrine glands, reproductive organs, muscle, fat, and liver [7]. CNS CB_1Rs are activated by ANA and 2-AG, and act to modulate presynaptic neurotransmitter release and alter excitability via GPR-coupled pathways. CB_2Rs are encoded by CNR2 gene (chromosome 1) and activated by 2-AG. CB_2Rs are GPR coupled and modulate downstream activity in immune cells to modulate inflammation and in CNS microglia, vascular cells, and also brainstem and basal ganglia neurons at lower concentrations [2,8].

Mechanism of action

Both THC and CBD have anticonvulsant properties in animal models. The THC effect results from stimulation of CB_1R [9▪,10–12]. The anticonvulsant mechanism(s) of action of CBD is not fully understood [9▪] as it has mild antagonistic effects at CB_1R and CB_2R [10]; thus, its anticonvulsant effect is independent of these receptors. Multiple mechanisms may contribute to CBD's anticonvulsant effect – most notably its antagonism of lipid-activated GPR55, which is expressed in excitatory and inhibitory synapses which modulate excitability and synaptic plasticity [13–14]. Other mechanisms include being an agonist at several TRP cation channels (A1, V1–3, V4) [15–18], an agonist at the $5\text{-}HT_{1A}$ receptor, [19–21] an inhibitor of adenosine reuptake at voltage-dependent anion channel 1 (VDAC1) [22], and inhibition of diverse voltage-dependent currents from sodium, potassium, and other channels [9▪,23–25], inhibition of sodium channels, indirect modulation of ECS by blocking ANA uptake and hydrolysis (increasing its availability to activate CB_1R [13]), and antioxidant and anti-inflammatory effects [18,25,26▪].

Clinical science

Formulations

Epidiolex is the first CBD medication approved by a national regulatory agency [US Food and Drug Administration for Dravet syndrome and Lennox Gastaut syndrome (LGS)]. Various cannabis preparations are available worldwide. Multiple countries (e.g. Canada, Amsterdam, Israel) and more than 30 US states have approved medical cannabis programs with products containing CBD and THC in varying ratios. However, few of these preparations are produced with good manufacturing practice (GMP) standards, although some companies have begun to manufacture under those guidelines (e.g. Tilray, Canopy Growth, Bedrocan). Current scientific data does not support safety and efficacy of 'over-the-counter' medical cannabis and hemp products.

Pharmacokinetics

CBD is highly lipophilic and protein bound, with low water solubility. Following oral intake, CBD undergoes significant hepatic first-pass metabolism and is rapidly distributed to brain and adipose tissue [27]. Like other cannabinoids, CBD is metabolized in the liver by cytochrome P450 (CYP450). Circulating metabolites of CBD are 7-COOH-CBD and 6-OH-CBD [28]. Anticonvulsant effects of CBD metabolites remain undefined.

Orally administered CBD has variable absorption [29,30]. Both C_{max} and $AUC_{0\text{-}inf}$ increase when CBD is consumed with high fat meal or vehicle (e.g. coconut oil capsule) versus fasting states. Even with an oil-based CBD suspension (e.g. sesame oil-based suspension of Epidiolex), absorption increases significantly with a fatty meal [31]. In humans, serum levels of CBD and its metabolites are linearly related to dose over a clinically relevant dose range but with high individual variability. Peak concentrations occur nearly 2 h after oral administration in animal pharmacokinetic studies [32]. CBD $T_{1/2}$ in humans was initially estimated as 31 h after smoking and

24 h after intravenous injection [32]; however, more recent studies suggest it may be up to 56–61 h [22].

CBD is most commonly given as an oil suspension or oil-filled capsule. Other forms include transdermal (e.g. Zynerba Pharmaceuticals, Devon, PA, USA [33]), nasal, and sublingual applications. Human data on these various preparations are limited, but rodent studies show intranasal formulations were absorbed within 10 min with a bioavailability of 34–46%, and transdermal gels plasma concentrations achieved steady state after an average of 15.5 h [34]. Many new forms of delivery are being developed, including liposomes, micelles, and nanostructured lipid carriers [34,35].

Drug–drug interactions

CBD and THC inhibit liver enzymes CYP2C19 at low levels and CYP3A4 at high levels; 2C19 inhibition is most clinically relevant. These hepatic enzymes metabolize some antiseizure drugs (ASDs) and are induced by phenytoin, carbamazepine, and topiramate, and are inhibited by valproate [1]. Among the four CBD RCTs, the only significant interaction was an increase in N-desmethyl clobazam metabolite levels without significant changes in clobazam (parent drug) levels [36▪▪,37▪]. One open label CBD study demonstrated interactions with several ASDs taken by 81 children and adults, with elevations in clobazam, N-desmethyl clobazam, rufinamide, and topiramate levels were in all ages, with elevations of clobazam and N-desmethylclobazam above upper therapeutic range. Increased zonisamide and eslicarbazepine and levels in adults were also observed [9▪]. The role of elevated N-desmethyl clobazam levels in improved seizure control remains uncertain [9▪,38▪▪,39]. CBD may increase the international normalized ratio (INR) in patients on warfarin [40]. Low-dose CBD (40 mg) does not affect THC metabolism [19].

Elevated transaminases may occur in patients taking CBD alone, but more often when CBD is taken with concomitant valproate, in patients with elevated transaminase levels prior to CBD initiation, and those who receive higher CBD doses (i.e. 20 vs. 10 mg/kg/day). Serum transaminase elevations usually occur in the first 2 months after CBD initiation, but can occur to 18 months after initiation. Resolution occurred with discontinuation of CBD and/or concomitant valproate in about two-thirds of all cases [40].

Human tolerance and abuse potential studies

Recreational cannabis can cause acute psychoactive symptoms such as relaxation, euphoria, or anxiety, but can also cause transient depersonalization and rarely, psychosis [41,42]. Chronic use may impair perception, memory, and other cognitive functions, especially in individuals who initiate chronic use in adolescence [43]. Withdrawal from cannabis can present with tremulousness, insomnia, gastrointestinal problems, and delirium [42]. In animals, long-term exposure to THC can lead to downregulation and internalization of CB1Rs, causing tolerance [5▪] with THC withdrawal producing anxiety responses [44]. In animals, CBD does not produce withdrawal or tolerance and its antagonist effect on CB1Rs may reduce THC psychoactivity, tolerance, and withdrawal effects [5▪].

Animal abuse data show CBD itself does not produce rewarding effects. In a human abuse potential study, CBD given to nondependent adult recreational drug users at doses of 750, 1500, and 4500 mg showed little or no subjective pleasurable effects compared to placebo. There was no desire for repeat dosing, unlike dronabinol (synthetic THC; a CB_1R agonist), or lorazepam [45]. In a dependence study, administration of CBD 1500 mg/day in adults for 28 days did not produce symptoms of withdrawal over a 6-week assessment period starting 3 days after discontinuation. These suggest that CBD, unlike THC, is unlikely to produce physical dependence [41,46].

EPILEPSY

Preclinical

Animal models of seizures and epilepsy

For a recently approved antiseizure medication, less preclinical work exists then would be expected, but this is likely because of the long history of human use of Cannabis. Early studies done in rats in the 1970s reported that CBD was effective against a few seizure models [i.e. audiogenic focal seizure models, maximal electroshock (MES) generalized seizures, electrically kindled limbic seizures, and GABA antagonists] [47–49]. Not all early studies were positive using similar models [50,51]. More recent work found positive effects on different seizure models, both *in vitro* and *in vivo*, with minimal toxicity [52,53]. The NIH funded Epilepsy drug screening program provided the most recent evidence of anticonvulsant efficacy for CBD in different acute seizure models [54,55]. As CBD was approved for Dravet syndrome, a recent study confirmed in a mouse with a *Scn1a* mutation that CBD is effective [56].

The above preclinical epilepsy models validate CBD as an antiseizure medication. The mechanism by which CBD works is more elusive. A variety of

mechanisms have been proposed [45] and data are supporting its effect on GPR55 [13,14,57] and a direct sodium channel modulation [48]. The effect of CBD on serotonin receptor (mainly 5-HT1a) is of uncertain relevance to its antiseizure effect 17–19 [58]. Other potential antiseizure mechanisms include an agonist at several TRP cation channels (A1, V1-3, V4)15–16 [17,19,23,54,59,60].

Overall, the preclinical data support the clinical data, but further work elucidating the mechanism(s) of CBD is needed.

Clinical

Early case studies and epidemiological reports

Early epidemiological reports and surveys on cannabis and epilepsy were limited to caretaker surveys and small case series suggesting that CBD can reduce seizures [9▪,10,61,62]. Limited underpowered trials were also reported without conclusive results. These studies and clinical observations, together with preclinical studies, called for gold standard clinical trials [6].

Clinical trials

Beginning in 2014 a series of studies using a purified cannabis extract that contains more than 99% of CBD and less than 0.10% Δ9-THC (Epidiolex, GW Pharmaceuticals Cambridge, UK) was used to test efficacy of CBD for pediatric-onset severe epilepsies. These studies led to approval of Epidiolex by the Food and Drug Administration (FDA) to treat seizures in Dravet syndrome and Lennox–Gastaut syndrome (LGS). Data regarding the treatment of other epilepsies exist from the many open-label prospective observational studies that have been completed and are ongoing since 2014.

The first open-label study of CBD (162 patients 1–30 years, with >12 weeks treatment) was published in 2016, in patients with severe, childhood-onset, treatment-resistant epilepsy (TRE) at 11 US epilepsy centers [63]. Oral CBD oil was dosed initially at 2–5 mg/kg per day and increased to a maximum dose of 25–50 mg/kg per day (center specific). The baseline median monthly frequency of motor seizures was 30.0 seizure per month, which was reduced to 15.8 seizures/month during initial 12-week treatment period. The median reduction in monthly motor seizures was 36.5%. Adjunctive CBD reduced median monthly convulsive and total seizures by nearly 50% at 12 weeks and similar improvements were observed throughout a 96-week follow-up period [63].

Other open-label studies of CBD have shown promising preliminary results. Seven patients with febrile infection-related epilepsy syndrome (FIRES) were treated with CBD during acute or chronic phase, with reduction in seizures in six patients and mean number of concomitant AEDs was reduced from 7.1 to 2.8 [64]. Among 18 patients with tuberous sclerosis treated with CBD for 3 months, weekly seizure frequency was reduced from a median of 22.0 to 13.3 and 50% had a more than 50% reduction in seizures [65]. Among 46 patients with CDKL5 deficiency, Aicardi Dup15q, and Doose syndromes treated with CBD for 3 months [66▪▪], median convulsive seizure frequency decreased from baseline by nearly 50% at week 12 and by 59% at week 48 ($n = 27$). Recently, one epilepsy center study reported their experience with open-label CBD for children and adults with TRE and demonstrated add-on CBD may be an efficacious long-term treatment option [67▪]. Among patients with brain tumor-related epilepsy three patients, two had a clinically beneficial reduction in seizures. This study showed a decrease in seizure severity (Chalfont Seizure Severity Scale) from 80.7 at baseline to 39.2 at 12 weeks ($P < 0.0001$) and in seizure frequency from a mean of 144.4 at entry to 52.2 at 12 weeks ($P = 0.01$) [68].

The most robust efficacy data for CBD and seizures come from three large randomized, placebo-controlled trials in Dravet syndrome and LGS [35,36▪▪,37▪,38▪▪]. All studies increased CBD over a 2-week titration. The first study of 120 patients with Dravet syndrome (NCT02091375) found that CBD at 20 mg/kg/day reduced median frequency of convulsive seizures per month from 12.4 to 5.9 versus placebo (decrease from 14.9 to 14.1) [36▪▪]. Adjusted median difference between the CBD and placebo groups in change in seizure frequency was −22.8 percentage points; $P = 0.01$). The percentage of patients who had at least a 50% reduction in convulsive-seizure frequency was 43% with CBD versus 27% with placebo (OR 2.00; $P = 0.08$). Patient's overall condition improved by at least one category on the seven-category caregiver global impression of change (CGIC) scale in 62% for the CBD versus 34% for the placebo group ($P = 0.02$). Total seizures were reduced with CBD ($P = 0.03$). Five percentage of patients on CBD became seizure-free versus none with placebo ($P = 0.08$). The second RCT included 171 patients with LGS treated with 20 mg/kg/day versus placebo (NCT02224690) [37▪]. Median percentage reduction in monthly drop seizure frequency from baseline was 43.9% in the CBD group and 21.8% in the placebo group; the estimated median difference between groups was −17.21 ($P = 0.0135$). The third RCT randomized

225 LGS patients to CBD 10 mg/kg/day, 20 mg/kg/day versus placebo (NCT02091375) [38▪▪]. Median percentage reduction in drop-seizure frequency was 41.9% in the 20 mg CBD group, 37.2% in the 10 mg CBD group, and 17.2% in the placebo group ($P = 0.005$ for 20 mg and $P = 0.002$ for the 10 mg CBD group vs. placebo group). In the CGIC, comparing baseline to last visit, an improvement was reported in 57% in the 20 mg group, 66% in the 10 mg group, and 44% in the placebo group ($P = 0.04$ for 20 mg and $P = 0.002$ for 10 mg group vs. placebo).

Efficacy of CBD in focal epilepsy has not been determined. One randomized placebo-controlled trial compared synthetic transdermal CBD with placebo in 188 adults with treatment-resistant focal epilepsy (STAR 1, ZYN002). Subjects were randomized to receive 195 mg of 4.2% CBD gel twice daily, 97.5 mg of 4.2% CBD gel twice daily, or placebo gel twice daily for 12 weeks. Median reduction of focal seizures during treatment period compared to baseline did not differ between groups. None of the secondary outcomes showed a significant difference [33].

Adverse effects

The safety profile of CBD was similar in open-label trials and RCTs with frequent mild to moderate adverse effects and rare serious side effects. In the 162 patient open-label trial, adverse events occurred in 79% of patients, including somnolence (25%), decreased appetite (19%), diarrhea (19%), fatigue (13%), and convulsion (11%). Severe adverse effects occurred in 1–7% of patients and included increased seizure frequency or severity, diarrhea, and weight loss. Adverse effects diminished after 12-weeks of exposure and stabilized thereafter, supporting tolerance to many of these effects. In the RCTs, the adverse event rates were similar to the first open-label trial. As the RCTs had specific dose groups, some side events were more common in the 20 than 10 mg/kg/day group (e.g. somnolence, drooling; decreased appetite, weight loss diarrhea, transaminitis). Transaminase elevation was most common among patients taking concomitant valproate with high dose (20 mg/kg/day) CBD or those who had elevated transaminases before starting CBD [39].

Antiseizure effects of tetrahydrocannabinol, cannabidavarin, and other cannabinoids

The effect of other cannabinoids in epilepsy is still not established. THC and cannabidavarin (CBDV) show antiseizure effects in animal models, although THC alone has not shown antiseizure effects in some studies [5▪,54]. A recent study was published using a combination of both, contained 100 mg/ml CBD and 2 mg/ml Δ9-THC that was dosed between 2 and 16 mg/kg/day in 20 patients with Dravet syndrome (Tilray; NCT02983695 [69▪]). In this study, mean CBD dose was 13.3 mg/kg/day (7–16 mg/kg/day) and 0.27 mg/kg/day of Δ9-THC (range 0.14–0.32 mg/kg/day). Median reduction in motor seizures was 70.6% ($P < 0.05$) and 63% of patients had a at least 50% reduction in motor seizures. There were significant improvements in quality of life and reductions in EEG spike activity. A randomized placebo-controlled trial compared CBDV versus placebo in focal epilepsy [31]. Both arms showed similar reductions in focal seizures of approximately 40%, with no significant difference between the groups. Further studies are needed to test efficacy of isolated cannabinoids other than CBD and the range of blended products that can be generated from the cannabis plant. For these studies, products made with GMP that are reliable and standardized are needed. This latter issue limits the use of products coming from on line providers and state dispensers until the quality of product is proven [70].

CONCLUSION

Overall, there are multiple phase III RCTs and prospective open label trials that provide efficacy and safety data for CBD for use in pediatric onset severe epilepsies. The product that was studied in the vast majority of these published trials, Epidiolex, has now been FDA approved based on this published data. Although efficacy of CBD for these seizure disorders is now known, there remain many open questions regarding the optimal delivery system for CBD, efficacy of other isolated cannabinoids, or the use of blended cannabinoid mixtures. The addition of CBD to the epileptologist and neurologist armamentarium for seizures is exciting, but the complete spectrum of use of cannabis derived products is still 'highly' questionable.

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Conflicts of interest

Santoshi Billakota has no conflicts of interest.
O.D. serves on the scientific and/or medical advisory boards, and has equity interest and/or receives compensation from Receptor Life Sciences, Privateer Holdings/Tilray, and Egg Rock Holdings/Papa & Barkley. He has

also been an investigator and consultant for GW Pharmaceuticals. He has also consulted for Zogenix. He also compensated serves on the scientific and/or medical advisory boards, and has equity interest and/or receives compensation from Tevard, Rettco, Engage Pharmaceuticals, Pairnomix, and Empatica.
E.M. has been local PI on GW pharma studies and his division has received funds for EAP studies. He has funding from the state of PA for EAP studies. He is a local PI for zogenix studies, Rett Syndrome Research Trust studies, Marinus pharma studies. He has been a consultant for Eisai pharma and Stoke Therapeutics. He has funding from the NIH for unrelated studies.

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