Epilepsy & Behavior 70 (2017) 341–348

Contents lists available at ScienceDirect

Epilepsy & Behavior

journal homepage: www.elsevier.com/locate/yebeh

Review

Cannabinoids in treatment-resistant epilepsy: A review

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ARTICLE INFO

Article history:
Received 1 November 2016
Revised 7 November 2016
Accepted 7 November 2016
Available online 8 February 2017

Keywords:
Cannabidiol
Epilepsy
Dravet syndrome
Lennox-Gastaut syndrome

ABSTRACT

Treatment-resistant epilepsy (TRE) affects 30% of epilepsy patients and is associated with severe morbidity and increased mortality. Cannabis-based therapies have been used to treat epilepsy for millennia, but only in the last few years have we begun to collect data from adequately powered placebo-controlled, randomized trials (RCTs) with cannabidiol (CBD), a cannabis derivative. Previously, information was limited to case reports, small series, and surveys reporting on the use of CBD and diverse medical marijuana (MMJ) preparations containing: tetrahydrocannabinol (THC), CBD, and many other cannabinoids in differing combinations. These RCTs have studied the safety and explored the potential efficacy of CBD use in children with Dravet Syndrome (DS) and Lennox-Gastaut Syndrome (LGS).

The role of the placebo response is of paramount importance in studying medical cannabis products given the intense social and traditional media attention, as well as the strong beliefs held by many parents and patients that a natural product is safer and more effective than FDA-approved pharmaceutical agents. We lack valid data on the safety, efficacy, and dosing of artisanal preparations available from dispensaries in the 25 states and District of Columbia with MMJ programs and online sources of CBD and other cannabinoids. On the other hand, open-label studies with 100 mg/ml CBD (Epidiolex®, GW Pharmaceuticals) have provided additional evidence of its efficacy along with an adequate safety profile (including certain drug interactions) in children and young adults with a spectrum of TREs. Further, Phase 3 RCTs with Epidiolex support efficacy and adequate safety profiles for children with DS and LGS at doses of 10- and 20-mg/kg/day.

This article is part of a Special Issue titled "Cannabinoids and Epilepsy".

1. Introduction

Epilepsy is one of the most common chronic neurological disorders. Treatment-resistant epilepsy (TRE) arises from a failure to achieve sustained seizure remission after trials of at least two, appropriately selected antiepileptic drug (AED) regimens that are tolerated at therapeutic dosages [1]. Despite the introduction of many therapies, including drugs, neuromodulation, and surgical and dietary interventions, the burden of TRE remains enormous, affecting approximately 30% of patients [2–4]. Patients struggling with TRE suffer from both severe morbidity and markedly increased mortality [5–8]. Notwithstanding the new therapeutic measures, it remains unclear if the frequency of TRE cases has been reduced during the past two decades [4]. Even patients with 'treatment-responsive' epilepsy suffer from disabling side effects and breakthrough seizures under multiple settings (e.g. missed doses [9], sleep deprivation [10], and excess alcohol consumption [11]). For almost all patients diagnosed with epilepsy, quality of life (QOL) is adversely affected by both the disease and therapies used to control seizures, with devastating personal and substantial economic consequences [12].

All epilepsies can be treatment resistant, although seizures associated with the epileptic encephalopathies (e.g. Dravet Syndrome (DS) [13] and Lennox-Gastaut Syndrome (LGS)) [14], Febrile Infection-Related Epilepsy Syndrome (FIRES) [15], and epilepsy associated with Tuberous Sclerosis Complex (TSC) [16] are among the most refractory to medical therapies. For some (e.g. DS [17] and FIRES [18]), there are currently no U.S. Food and Drug Administration (FDA)-approved therapies. Further, by definition, available AEDs provide only limited success in controlling seizures in TREs. Although certain AEDs reduce seizure frequency in disorders such as DS [19] and LGS [20], there are limits to their safety and efficacy. This is especially relevant when these AEDS are used in multidrug regimens and at high doses. The repercussions of TREs are significant, especially as TREs starting in the first few years of life are associated with high rates of cognitive, behavioral, and motor delays [21]. Further, many believe that the burden of seizures and interictal epileptiform activity directly contribute to these neurodevelopmental delays.

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http://dx.doi.org/10.1016/j.yebeh.2016.11.012
1525-5050/

Table 1
Table 1 summaries findings from several surveys, case studies, case series, and placebo controlled trials related to isolated cannabinoids, oral cannabis extracts, and smoked cannabis use in the context of epilepsy.

Study	Compound	Study Type	N	Efficacy	Toxicity
Isolated cannabinoids					
Davis & Ramsey [26]	THC isomers	Case series of institutionalized children with intellectual disability and epilepsy treated for 3–7 weeks	5	1 seizure-free, 1 almost seizure-free	None reported
Mechoulam & Carlini [27]	CBD 200 mg/day	Prospective, placebo controlled trial in adults with treatment resistant epilepsy over 3 months	4 Rx 5 PB	2 subjects in CBD arm seizure-free, 1 with partial improvement No report of baseline seizure measurement	None reported
Cunha et al. [28]	CBD 200-300 mg/day	Prospective, placebo controlled trial in teenagers/adults with treatment resistant convulsive seizures (at least 1 per week) with 8–18 weeks of exposure	8 Rx 7 PB	4 subjects in CBD arm seizure-free, 1 in placebo arm No blinded assessments, one unexplained cross-over	Somnolence, Gastric discomfort
Ames & Cridland [29]	CBD 200-300 mg/day	Prospective placebo controlled trial in institutionalized adults with intellectual disability and epilepsy over 3 weeks	6 Rx 6 PB	No difference between groups	None reported
Trembly & Sherman [30]	CBD 300 mg/day	Prospective randomized, double-blind placebo controlled crossover study in adults with treatment resistant epilepsy; 6 months treatment and placebo	12	No difference between CBD and placebo	None reported
Devinsky et al. [31]	Purified oral 100 mg/ml CBD extract	Prospective open label trial in children and young adults with severe childhood onset epilepsy for 12 weeks	214	137 (64%) in efficacy (12 weeks): 36.5% median reduction in weekly convulsive seizure rate	Somnolence, diarrhea, decreased appetite, fatigue, convulsion, status epilepticus
Oral cannabis extracts					
Gowers [25]	*Cannabis indica* extract, 32 mg/day	Case report of a 40-year-old man with focal epilepsy resistant to bromides	1	Seizure-free for 6 months followed by recurrence with cannabis extract discontinuation. Resumed seizure control with resumption of cannabis use several months later.	None reported
Porter & Jacobson [32]	CBD/THC extracts of varying composition/dose CBD up to 28 mg/kg/day and THC up to 0.8 mg/kg/day	Survey among participants in a Facebook group for parents of children with TRE	19	16 (84%) reported improvement with CBD/THC, 2 (11%) became seizure-free	Drowsiness, fatigue, decreased appetite
Maa & Figi [33]	Oral cannabis extract, high ratio of CBD:THC	Case report of a 5-year-old girl with DS	1	>90% reduction in generalized tonic-clonic seizure frequency and ability to reduce background drugs	Somnolence, fatigue
Gedde & Maa [34]	Oral cannabis extract, high ratio of CBD: THC	Survey of parents whose children with TRE used the extract	11	100% had reduction in motor seizure frequency; 8/11 with complete or near complete seizure control	Somnolence, unsteadiness
Press et al. [35]	Oral cannabis extracts	Retrospective case series of children with refractory epilepsy at one center in Colorado	75	25 (33%) reported a >50% reduction in seizure frequency	Somnolence, fatigue, increased seizures. Rare: developmental regression, status epilepticus
Tzadok et al. [36]	CBD enriched cannabis extracts	Retrospective case study of children and adolescents with intractable epilepsy at five Israeli pediatric epilepsy centers	74	66 (89%) reported a reduction in seizure frequency: 13 (18%) 75–100% reduction, 25 (34%) 50–75% reduction, 9 (12%) 25–50% reduction, and 19 (26%) <25% reduction	Somnolence, fatigue, gastrointestinal disturbances, irritability. 5 patients discontinued use.
Smoked cannabis					
Keeler & Reifler [37]	Cannabis	Case report of 20-year-old man with refractory tonic-clonic seizures who was seizure-free	1	Cluster of seizures following a period of marijuana use	Increased seizures
Consroe et al. [38]	Cannabis	Case report of 24-year-old man with refractory generalized epilepsy	1	Patient became nearly seizure-free when he started daily cannabis use	None reported
Ellison et al. [39]	Cannabis	Case report of a 29-year-old man with refractory focal epilepsy	1	Suppression of complex partial seizures and exacerbation of seizures with withdrawal	None reported
Mortati et al. [40]	Cannabis	Case report of a 45-year-old man with cerebral palsy and refractory focal epilepsy	1	>90% reduction in nocturnal seizures and tonic-clonic seizures	None reported
Gross et al. [41]	Cannabis	Survey of active users seen at a single tertiary epilepsy center	28	19 (68%) reported improvement in seizure severity, 15 (54%) reported improvement in frequency	None reported
Hamerle et al. [42]	Cannabis	Survey of cannabis users seen at one tertiary epilepsy center	310 (13 active users; 297 ex-users)	2 active users reported improvement in seizures; 7 ex-users reported worsening of seizure frequency/severity	Increased seizures

TRE – treatment–resistant epilepsy; DS – Dravet Syndromes; Rx – active cannabis-based therapy; PB – placebo; CBD – Cannabidiol; THC – Tetrahydrocannabidiol.
(Modified with permission from Friedman & Devinsky, NEJM 2016 – reference [35])*.
Note that content of cited compounds has not been verified.

Therefore, earlier and more complete seizure control can be associated with improved outcomes.

Documented medicinal use of *Cannabis Sativa* in the treatment of anorexia, pain, and other disorders extends back nearly five millennia [22]. Cannabis therapy for epilepsy was recorded on Sumerian tablets dated to 3800 years ago [23]. In the late 19th century, British and U.S. physicians reported cases in which *Cannabis indica* extracts reduced seizures [23–25]. The modern scientific era of cannabis studies was ushered in by Mechoulam and colleagues in the 1960s with the isolation, structure elucidation, and synthesis of THC (the main psychoactive compound in cannabis) and CBD (the main non-psychoactive compound in cannabis), and the isolation and identification of the endogenous brain cannabinoids (anandamide and 2-arachidonoyl glycerol) that stimulate brain cannabinoid (CB1) receptors. Mechoulam and Carlini also pioneered the first trial of CBD for TRE (Table 1). Several surveys and small series have reported use of cannabis products and derivatives among adults with epilepsy, who reported improved seizure control [40,41].

Among the hundreds of phytocannabinoids in cannabis, THC and CBD are the most abundant and extensively studied. Multiple animal studies have demonstrated that THC has mainly anti-convulsant effects, but other studies have failed to document similar findings, and rarely, pro-convulsant effects have been observed [43] (Table 2). Adverse effects (AEs) of THC in adolescents and adults include cognitive impairment and chronic psychiatric disturbances [46]. Currently, there are no adequate safety studies of THC use in children.

There has been growing interest generated by social media and traditional news sources about artisanal marijuana strains with high ratios of CBD:THC and their effects in controlling seizures in children with TREs, especially DS [32,33,47]. CBD has had documented anti-convulsant effects in multiple pre-clinical animal models [43,48]. In addition, two of four older human trials suggested modest benefits in seizure control (reviewed in [49]) with good tolerability (Table 1); both were previously reviewed [49,50].

At the time of this publication, an unprecedented movement, largely by lay individuals, has led to approval of MMJ by 25 states and the District of Columbia, for disorders that include TRE in all jurisdictions [51]. (At the time of this publication, November 8, 2016 MMJ ballot measures passed in Arkansas, Florida, and North Dakota. The subsequent legislation related to those approved measures has yet to be enacted.). These laws have decriminalized use for approved medical disorders or symptoms, provided for access, and allowed a variety of strains and various ingestion means [52]. At the same time, 17 states have passed limited access laws, which set maximum THC and minimum CBD requirements for heavily restricted products under extremely limited medical circumstances (limited only to TRE for some states) (Table 3) [51]. Consequently, most Americans live in a state with some form of MMJ legislation. Societal benefits of MMJ are supported by some association studies; however, scientific evidence of remains scant. Rising use of MMJ correlated with reductions in Medicare Part D expenditures of 165 million in 2013 [71] and decreased opioid overdoses between 1999 and 2010 in states with MMJ programs [72]. However, it is unclear if this effect persists given the widespread rise of opioid use and fatalities plaguing the United States of late. Despite the growing ubiquity of MMJ for patients with TRE in the United States, we lack any prospective RCTs on the safety or efficacy of cannabis products containing both CBD and THC.

Table 2
Table 2 highlights known drug interactions with THC for each respective Cytochrome P450 enzyme listed.

CYP enzymes	Known drug interactions with THC
CYP 1A2 [44,45]	If on second-generation antipsychotics (especially olanzapine and clozapine), the immediate cessation of smoking THC has the potential to cause antipsychotic toxicity. (Enhanced clearance of drugs metabolized by CYP 1A2 is possible with smoking THC).
CYP 2C9 [45]	Inhibitors of this enzyme may cause an increase in THC levels (genetically low metabolizers have elevated THC levels).
CYP 2A6 [45]	Does not seem to be clinically affected by THC
CYP 3A4 [45]	Does not seem to be clinically affected by THC; inhibitors of this enzyme may increase THC levels while inducers may decrease THC levels.

CYP – Cytochrome P450 enzyme; THC – Tetrahydrocannabidiol.

The following studies report on physician-sponsored open-label studies as well as Phase 3 RCTs sponsored by GW Pharmaceuticals using Epidiolex (100 mg/ml CBD). For the open-label studies, GW Pharmaceuticals provided the study drug and administrative support at all sites, and research funding at some sites. In the case of the sponsored RCTs, GW Pharmaceuticals provided the study drug, oversight, and funding.

2. Cannabidiol in treatment-resistant epilepsy

Given the preclinical studies and anecdotal reports of children with DS and other severe pediatric epilepsies whose seizures responded to CBD, a collaboration between a group of clinical investigators and GW Pharmaceuticals developed to explore the safety and efficacy of CBD in patients with childhood-onset TRE [31,41–43,46]. All of the trials reported below used Epidiolex (100 mg/ml CBD).

2.1. Cannabidiol in patients with TRE: an open-label interventional trial [31]

Eleven independent United States-based investigator-initiated expanded access open-label studies assessed the safety and efficacy of CBD in TRE. The aggregated cohorts consisted of 214 patients (aged 1–30 years) with severe, intractable, childhood-onset TRE. All patients were taking stable doses of AEDs for 4 weeks before starting CBD as add-on therapy. Following a 4-week baseline period, patients were initiated on oral CBD (2–5 mg/kg per day in twice daily dosing); this dose was increased gradually until intolerance or a maximum dose of 25 mg/kg or 50 mg/kg per day (as determined by each study site's IRB) was reached.

Sufficient data on safety and tolerability were available in 162 patients; 33 with DS, 31 with LGS, and the rest with other TREs. Adverse events (AEs) that occurred in >10% of patients included somnolence (25%), reduced appetite (19%), diarrhea (19%), fatigue (13%) and convulsion (11%). Twenty patients (12%) reported severe adverse events (SAEs) during the study, but it was difficult to determine if the events were related to CBD use. Five cases (3%) discontinued use because of an AE. Sufficient data on efficacy was available in 137 patients. The primary efficacy measure was the reduction in median monthly motor seizure frequency. The mean monthly seizure frequency was calculated using the seizure incidence as recorded by patients and caregivers in paper seizure diaries. The median monthly frequency of motor seizures was reduced by 36.5% (interquartile range (IQR): 0–64.7) from the baseline frequency of 30.0 (IQR: 11.0–96.0) to 15.8 (IQR: 5.6–57.6) over the course of the treatment period.

Clobazam is predominantly metabolized by CYP3A4 and CYP2C19, and CBD potently inhibits CYP3A4 and CYP2C19 enzymes [19]. Consequently, a pharmacokinetic interaction is suspected between clobazam and CBD, as patients taking clobazam and CBD have experienced increased sedation. This study noted somnolence or fatigue in 51% of the 85 patients taking clobazam and CBD, compared to 21% of 77 patients treated with another AED (OR for somnolence 3.87, 95% CI 1.9–7.9) [31]. An open-label study found that the mean increase in nordesmethyl CLB (nCLB) levels was 500 ± 300% (95% CI [+90–610%] at 4 weeks [73]. Further, an increased responder rate of 70% and more frequent somnolence or fatigue in patients taking clobazam was noted in 6 of 13 patients [73]. Lastly, an abstract noted excessive sedation in 7 of 33 patients taking clobazam and CBD, as well as increased median changes in serum levels of clobazam (8.3% [range: −64 to 478%, N = 17]),

Table 3
Table 3 summarizes available information about limited access laws implemented in their respective states as of the time of this publication.

State	Statute and provisions	Product Sources	Specific conditions and populations	Allowed products	Recognizes patients from other states
Limited access marijuana product laws					
Alabama [53]	SB 174-Allows U of AL-Birmingham to conduct effectiveness research using low-THC products to treat seizure disorders for up to 5 years. (**Non-operational as of April 2015**)	Only U of AL-Birmingham can dispense FDA-approved trial products (with permission)	Yes, debilitating epileptic conditions or life-threatening seizures	Extracts that are <3% THC	No
Florida [54]	CS for SB 1030-specifies that treatment information and outcomes will be collected and used for intractable childhood epilepsy research. (Amendment 2 approved as of November 8,2016, legislation pending.)	Yes, 5 registered nurseries across the state, by region which have been in business in FL for at least 30 years.	Yes, seizure disorders that chronically produce symptoms that can be alleviated by low-THC products (among others)	Cannabis with THC <0.8% and CBD >10% by weight	No
Georgia [55]	HB 1	Provision for University of GA system to develop a low THC oil clinical research program that meets FDA trial compliance.	Yes, seizure disorders (among others)	Cannabis oils with THC <5% and at least an equal amount of CBD	No
Iowa [56]	SF 2360-*Effective 7/1/14*	Doesn't define or provide in-state methods of access/production	Yes, intractable epilepsy	"CBD-a non-psychoactive cannabinoid" that contains <3% THC, no >32 oz, essentially free from plant matter	No
Idaho [57]	**Governor Vetoed 4/16/15**				
Kentucky [58]	SB 124-exempted CBD from the definition of marijuana and allows it to be administered by a public university or school of medicine in KY or clinical trial/expanded access program approved by the FDA.	Universities in KY with medical schools capable of conducting a research trial. Doesn't allow for in-state production of CBD product	Intractable Seizure disorders	No, only "CBD"	No
Louisiana [59]	SB 143	LA State University and the Southern University Agricultural Center have been granted the right of first refusal to be the licensed production facility. (If they pass, it goes to a competitive bid process)	Yes	"THC shall be reduced to the lowest acceptable therapeutic levels available through scientifically acceptable methods."	No
Mississippi [60]	HB 1231	Provided through National Center for Natural Products Research at the U of MI and dispensed by the Dept. of Pharm. Services at the U of MI Medical Center.	Yes, debilitating epileptic conditions or related illnesses	"CBD oil"-processed cannabis plant extract, oil or resin that contains no >15% CBD, or a dilution of the resin that contains at least 50 mg of CBD/mL, but not >0.5% THC."	No
Missouri [61]	HB 2238	CBD Oil Care Centers and cultivation and production facilities/laboratories	Yes, intractable epilepsy that has not responded to three or more other treatments	"Hemp extracts" ≤ 0.3% THC and >5% CBD by weight	No
North Carolina [62]	HB 1220	University research studies with a hemp extract registration card from the state DHHS or through another jurisdiction that allows removal of the products from the state.	Yes, intractable epilepsy	"Hemp extracts" <0.3% THC and >10% CBD by weight. Contains no other psychoactive substance.	No
Oklahoma [63]	HB 2154	No in-state production, products have to be imported. Federal approval would be needed for any formal distribution system.	Only minors with LGS, DS, also known as severe myoclonic epilepsy of infancy, or any other form of refractory epilepsy that is not adequately treated by traditional medical therapies	A preparation of cannabis <0.3% THC in liquid form	No
South Carolina [64]	S 1035	Must use CBD product from an approved source; including those approved by the United States FDA to be used for treatment of a condition specified in an investigational new drug application. -The principal investigator and any subinvestigator may receive CBD directly from an approved source or authorized distributor for an approved source for use in	LGS, DS, also any severe myoclonic epilepsy from infancy, or any other form of refractory epilepsy that is not adequately treated by traditional medical therapies	CBD or derivative of marijuana that contains 0.9% THC and >15% CBD, or ≥98% CBD and not >0.90% THC by volume that has been extracted from marijuana or synthesized in a laboratory.	No

Table 3 (*continued*)

State	Statute and provisions	Product Sources	Specific conditions and populations	Allowed products	Recognizes patients from other states
		expanded access clinical trials.			
Tennessee [65]	SB 2531-creates a four-year study of high CBD/low THC marijuana at TN Tech Univ./HB 197	Only products produced by TN Tech Univ. Patients may possess low THC oils only if they are purchased "legally in the United States and outside of TN," from an assumed medical cannabis state; however, most states do not allow products to leave the state. /Allows for legal defense related to having the product as long as it was obtained legally in the US or other medical marijuana state.	Yes, intractable seizure conditions/Yes, intractable seizure conditions	"Cannabis oil" with <0.9% THC as part of a clinical research study./"Cannabis oil" with <0.9% THC.	No
Texas [66]	SB 339	Yes, licensed by the Dept. of Public Safety	Yes, intractable epilepsy	"Low-THC Cannabis" with not >0.5% by weight of THC; and not <10% by weight of CBD.	No
Utah [67]	HB 105	Not clearly denoted, but allows higher education institutions to grow or cultivate industrial hemp.	Yes, intractable epilepsy that hasn't responded to 3 or more treatment options suggested by a neurologist	"Hemp extracts" with <0.3% THC by weight and at least 15% CBD by weight and contains no other psychoactive substances.	No
Virginia [68]	HB 1445	No in-state means of acquiring cannabis products.	Intractable epilepsy	Cannabis oils with >15% CBD or THC-A and <5% THC	No
Wisconsin [69]	AB 726	Physicians and pharmacies with an investigational drug permit by the FDA can dispense CBD. Qualified patients would also be allowed to access CBD from an out-of-state MMJ dispensary that allows for out-of-state patients to use their dispensaries as well as remove the products from the state. No in-state production or manufacturing mechanism provided.	Seizure disorders	Exception to the definition of prohibited THC by state law, allows for possession of "CBD in a form without a psychoactive effect." THC or CBD levels are not defined.	No
Wyoming [70]	HB 32-supervised medical use of hemp extracts. *Effective 7/1/2015*	No in-state production or purchase method defined.	Intractable epilepsy or seizure disorders	"Hemp extracts" with <0.3% THC and at least 5% CBD by weight.	No

CBD – Cannabidiol; THC – Tetrahydrocannabidiol; DS – Dravet Syndrome; LGS – Lennox-Gaustat Syndrome; FDA – Food and Drug Administration; MMJ – Medical Marijuana. (Adapted with permission from the National Conference of State Legislatures (NCSL) – reference [49]).

valproate (8.4% [range: −21–38%, N = 11]), and levetiracetam (9.8% [range: −23 –46%, N = 8]) [74]. Also, abnormalities in liver function studies are much more frequent among patients on valproate, suggesting pharmacokinetic (possibly via effects of CYP-2B) or pharmacodynamics interactions. Consequently, concomitant administration warrants extra vigilance.

2.2. CBD therapy in a state-sponsored treatment program [75]

Szaflarski and colleagues studied the safety and efficacy of CBD in a cohort of 51 patients (23 children; 28 adults) with TRE. Nearly half (49%) experienced a seizure reduction of ≥50%. Sustained improvement in seizure control was observed during the 6 months of study [76]. This group later studied CBD use in TRE patients in a dose assessment open-label expanded access study of 81 patients (42 children; 39 adults). Following a 3-month baseline period, patients were started at 5 mg/kg/day and incremental increases were made as tolerated every 2 weeks (5 mg/kg/day) to a maximum of 50 mg/kg/day. The CBD dose/seizure response was correlated with the seizure response to the dose, after factoring in the baseline seizure frequency. The 3-month model for all patients and the 3-month and 6-month models for pediatric patients showed that the seizure reduction associated with CBD at a dose of ~20–25 mg/kg/day was statistically significant. Among adult patients, there was a >25% reduction in 74% and >50% reduction in 56% of patients.

2.3. Cannabidiol for TRE in tuberous sclerosis complex (TSC) [77]

Tuberous sclerosis complex is a genetic disorder affecting the TSC1 or TSC2 genes that causes epilepsy in ~85% of patients, approximately two-thirds of whom develop TRE [78]. The safety and efficacy of CBD were studied in 18 TSC patients with TRE. Patients were taking 1–7 AEDs, consistently dosed, for 2-weeks, prior to the 4-week baseline period. They began with 5 mg/kg/day of CBD with weekly dose increases (5 mg/kg/day) as tolerated to a maximum dose of 50 mg/kg/day.

The median weekly seizure frequency from 22.0 (IQR 14.8–57.4) during baseline was reduced to 13.3 (IQR 5.1–22.1) after 3 months of CBD treatment. Additionally, after 3 months of CBD treatment, the median reduction in weekly seizure frequency was 48.8% (IQR 69.1% to 11.1%) and the 50% responder rate was 50%. One or more AEs occurred in 66.7% of patients; the majority were mild and transient. The most common were drowsiness (44.4%), ataxia, (27.8%), and diarrhea (22.2%). No SAEs were attributed to CBD.

2.4. CBD use in Febrile Infection-Related Epilepsy Syndrome (FIRES) [79]

Febrile Infection-Related Epilepsy Syndrome is a rare disorder in children causing severe TRE, the consequences of which are severe intellectual disability with persistent TRE or death [80,81]. There is no effective therapy for FIRES; however, the ketogenic diet has been the most

promising, to date [82]. Seven children with FIRES at 5 epilepsy centers with ongoing seizures despite multiple therapies received CBD in emergency or expanded investigational protocols during the acute or chronic phase of FIRES [15]. Seizure frequency and duration improved in 6 of the 7 patients. One patient died from multi-organ failure due to isoflurane. After CBD therapy, the number of concomitant AEDs was reduced from a mean of 7.1 to 2.8. Three patients were also on the ketogenic diet. Five patients were ambulatory and four were verbal at the time of reporting, which was an improvement from their baseline.

3. Epidiolex

GW Pharmaceuticals has sponsored four placebo RCTs for evaluation in DS, LGS, and TSC. In DS and LGS, populations, Epidiolex 20 mg/kg/day was compared to placebo. A dose-finding study was also conducted in a LGS population comparing Epidiolex 10 mg/kg/day, 20 mg/kg/day, and placebo. (Results are still pending from the TSC study.) Available preliminary results from the Phase 3 trials are summarized below. The described data will be presented at professional meetings and published in peer-reviewed journals. These results support the safety and efficacy findings of previous open-label studies in a rigorous double-blind placebo controlled trial methodology. Epidiolex was granted Orphan Drug and Fast Track Designations from the FDA for DS, LGS, and TSC.

3.1. Dravet phase 3 preliminary study results [83]

The study population consisted of 120 patients with DS who were taking a mean of 3 concomitant AEDs and whose seizures had not adequately responded to an average of 4 AEDs. The median baseline convulsive seizure frequency from the baseline period was 13 per month. Patients were randomized to receive either Epidiolex 20 mg/kg/day ($n = 61$) or placebo ($n = 59$) in addition to baseline AEDs.

The primary efficacy measure was the change in monthly convulsive seizure frequency during the 14-week treatment period generated by Epidiolex versus placebo. The median reduction was 39% in the Epidiolex group and 13% in the placebo group ($p = 0.01$). Among patients who reported AEs, 84% were mild or moderate. The most common AEs (>10% of Epidiolex-treated patients) were: somnolence, diarrhea, decreased appetite, fatigue, pyrexia, vomiting, lethargy, upper respiratory tract infection, and convulsion. The incidence of SAEs reported was 10 in the Epidiolex cohort and 3 in the placebo cohort, and 8 Epidiolex patients and 1 placebo patient discontinued treatment because of an AE.

3.2. RCT phase 3 preliminary study results in Lennox Gastaut syndrome [84]

Lennox-Gastaut Syndrome is another rare and severe childhood-onset epilepsy. The first LGS study enrolled 171 patients (2–55 years) with TRE who were randomized to CBD 20 mg/kg/day ($n = 86$) or placebo ($n = 85$) in addition to current AEDs. Patients were taking an average of 3 AEDs after prior trials with an average of 6 other AEDs. The median baseline drop seizure frequency for the population was 74 per month.

The primary efficacy measure was the percent change in the monthly frequency of drop (atonic, tonic and tonic-clonic) seizures during the initial 2-week titration and 12-week maintenance periods. The CBD group had a 44% reduction versus 22% in the placebo group ($p = 0.0135$). The differences generated by the administration of CBD and placebo occurred in the first month of therapy and persisted throughout the maintenance period. The most common AEs (>10% of CBD-treated patients) were: diarrhea, somnolence, decreased appetite, pyrexia, and vomiting. Adverse events were reported in 86% of CBD- and 69% of placebo-treated patients. Among AEs in CBD-treated patients, 78% were rated as mild or moderate. Serious adverse events occurred in 23% of CBD-treated patients (9 were considered treatment-related) versus 5% of placebo patients (1 was treatment-related). AEs led to discontinuation for 12 CBD patients and 1 placebo patient. All patients who completed the trial elected to continue into an open-label extension trial.

3.3. Dose-ranging phase 3 RCT in Lennox-Gastaut syndrome [85]

This study population consisted of 225 patients with LGS (2–55 years old) with TRE who were taking an average of 3 AEDs after prior treatment with an average of 7 other AEDs. Patients were randomized to one of three trial arms: Epidiolex 20 mg/kg/day ($n = 76$), Epidiolex 10 mg/kg/day ($n = 73$), or placebo ($n = 76$) in addition to their current AEDs. The median reduction in monthly drop seizures in the placebo group was 17% compared to Epidiolex 20 mg/kg/day of 42% ($p = 0.0047$) and Epidiolex 10 mg/kg/day of 37% ($p = 0.0016$).

Epidiolex was generally well tolerated, similarly to the two prior Phase 3 studies. Rates of AEs were: 84% in the 10 mg/kg cohort (89% mild or moderate), 94% in the 20 mg/kg cohort (88% mild or moderate) and 72% in the placebo group. The most common AEs (>10% in one of the Epidiolex-dose cohorts) included somnolence, decreased appetite, upper respiratory infection, diarrhea, pyrexia, vomiting, nasopharyngitis, and status epilepticus. Discontinuation of treatment due to AEs affected 1 patient in the 10 mg/kg/day Epidiolex group, 6 patients on 20 mg/kg/day group, and 1 patient on placebo. Serious adverse events occurred in 13 patients in the 10 mg/kg/day group (2 study drug-related), 13 patients in the 20 mg/kg/day group (5 study drug-related), and 8 patients in the placebo group (0 study drug-related). There were no deaths during the course of the study. Ninety-nine percent of patients who completed the trial elected to participate in an open-label extension trial.

4. Conclusions

After millennia of cannabis use for epilepsy, we are beginning to collect sound scientific evidence suggesting that CBD is effective in reducing convulsive seizures in DS and drop seizures in LGS. Open-label experiences with CBD support efficacy in a broader range of TRE, including those associated with TSC, FIRES, focal epilepsy, and other syndromes.

The safety and efficacy of THC – either alone or used in various ratios with CBD – remains undefined in children or adults with any epilepsy syndrome. Given the widespread and growing use of MMJ containing both CBD and THC, we believe that it is essential that safety and efficacy data from RCTs be sought to inform both patient and physician groups.

Disclosures

Orrin Devinsky reports that the Expanded Access Program and the Phase III Clinical Trials with Epidiolex have been supported by a grant from GW Pharmaceuticals and the Epilepsy Foundation/Epilepsy Therapy Project; no funds have been provided for salary support. He also receives funding support from NINDS/NIMH – R01 MH107396 02, U01 NS099705 01, R01 MH111417 01, U01 NS090415 and CDC – U48 DP 005008-01S4.

David Gloss is an evidence-based medicine consultant for the AAN.

Author contributions

Orrin Devinsky – Planning of study, Data collection, Data analysis, Writing, Editing

Brooke O'Connell – Data analysis, Writing, Editing

David Gloss – Data analysis, Editing

References

[1] Kwan P, Arzimanoglou A, Berg AT, Brodie MJ, Hauser WA, Mathern J, et al. Definition of drug resistant epilepsy: consensus proposal by the ad hock task force of the ILAE commission on therapeutic strategies. Epilepsia June 2010;51(6):1069–77.

[2] Sharma S, Dixit V. Epilepsy – a comprehensive review. Int J Pharma Res Rev Dec 2013;2(12):61–80.
[3] Milby AH, Halpern CH, Baltuch GH. Vagus nerve stimulation in the treatment of refractory epilepsy. Neurother Apr 2009;6(2):228–37.
[4] Kwan P, Brodie MJ. Early identification of refractory epilepsy. New Eng J Med 2000; 342:314–9.
[5] Sillanpaa M, Shinnar S. SUDEP and other causes of mortality in childhood-onset epilepsy. Epilepsy Behav Aug 2013;28(2):249–55.
[6] Racoosin JA, Feeney J, Burkhart G, Boehm G. Mortality in antiepileptic drug development programs. Neurology Feb 27, 2001;56(4):514–9.
[7] Sillanpaa M, Shinnar S. Long-term mortality in childhood-onset epilepsy. N Engl J Med 2010;363(26):2522–9.
[8] Ryvlin P, Cucherat M, Rheims S. Risk of sudden unexpected death in epilepsy in patients given adjunctive antiepileptic treatment for refractory seizures: a meta analysis of placebo-controlled randomised trials. Lancet Neurol Nov 2011;10(11):961–8.
[9] Faught E, Duh MS, Weiner JR, Guerin A, Cunnington MC. Nonadherence to antiepileptic drugs and increased mortality: findings from the RANSOM study. Neurology 2008;71:1572–8.
[10] Friis ML, Lund M. Stress convulsions. Arch Neurol 1974;31(3):155–9.
[11] Gordon E, Devinsky O. Alcohol and marijuana: effects on epilepsy and use by patients with epilepsy. Epilepsia Oct 29, 2001;42(10):1266–72.
[12] Devinsky O. Cognitive and behavioral effects of antiepileptic drugs. Epilepsia 1995; 36(Suppl. 2):S46–65.
[13] Shumely S, Sisodiya SM, Gunning WB, Sander JW, Thijs RD. Mortality in Dravet syndrome: a review. Epilepsy Behav Nov 2016;64(A):69–74.
[14] Arzimanoglou A, Resnick T. All children who experience epileptic falls do not necessarily have Lennox–Gastaut syndrome… but many do. Epileptic Disord 2011; 13(Suppl. 1):S3–13.
[15] Kramer U, Chi C-S, Lin K-L, Specchio N, Mustafa S, Olson H, et al. Febrile infection-related epilepsy syndrome (FIRES): pathogenesis, treatment, and outcome. Epilepsia Aug 2011;52(11):1956–65.
[16] de Vries PJ, Whittemore VH, Leclezio L, Byars AW, Dunn E, Ess KC, et al. Tuberous sclerosis associated neuropsychiatric disorders (TAND) and the TAND checklist. Pediatr Neurol Jan 2015;52(1):25–35.
[17] Wirrell EC. Treatment of Dravet syndrome. Can J Neurol Sci 2016;43:S13–8.
[18] Gofshteyn JS, Wilfong A, Devinsky O, Bluvstein J, Charuta J, et al. Cannabidiol as a potential treatment for Febrile Infection-Related Epilepsy Syndrome (FIRES) in the acute and chronic phases. J Child Neurol Sep 2016;21 [pii:0883073816669450 Epub ahead of print].
[19] Chiron C, Dulac C. The pharmacologic treatment of Dravet syndrome. Epilepsia 2011 Apr;52(Suppl. 2):72–5.
[20] Glauser T, Kluger G, Sachdeo R, Krauss G, Perdomo C, Arroyo S. Rufinamide for generalized seizures associated with Lennox–Gastaut syndrome. Neurology 2008;70:1950–8.
[21] Mudigoudar B, Weatherspoon S, Wheless JW. Emerging antiepileptic drugs for severe pediatric epilepsies. Semin Pediatr Neurol May 2016;23(2):167–79.
[22] Russo EB. History of cannabis and its preparations in saga, science, and sobriquet. Chem Biodivers 2007;4:1614–48.
[23] Pereira P. The elements of materia medical and therapeutics. Philadelphia, PA: Lea & Blanchard; 1843.
[24] McMeens RR. Report of the Ohio state medical committee on Cannabis indica; 1860.
[25] Gowers W. Epilepsy and other chronic convulsive disorders. London: Churchill; 1881.
[26] Davis JP, Ramsey HH. Anti-epileptic action of marijuana-active substances. Fed Proc, Am Soc Exp Biol 1949;8:284.
[27] Mechoulam R, Carlini EA. Toward drugs derived from cannabis. Naturwissenschaften 1978;65:174–9.
[28] Cunha JM, Carlini EA, Pereira AE, Ramos OL, Pimental C, Gagliardi R, et al. Chronic administration of cannabidiol to healthy volunteers and epileptic patients. Pharmacology 1980;21:175–85.
[29] Ames FR, Cridland S. Anticonvulsant effect of cannabidiol. S Afr Med J Jan 4, 1986;69:14.
[30] Trembly B, Sherman M. Double-blind clinical study of cannabidiol as a secondary anticonvulsant. Presented at the Marijuana '90 international conference on cannabis and cannabinoids; July 8–11, 1990 [Kolympari, Crete]. [abstract].
[31] Devinsky O, Marsh E, Friedman D, Thiele E, Laux L, Sullivan J, et al. Cannabidiol in patients with treatment resistant epilepsy: an open-label interventional trial. Lancet Neurol Mar 2016;15(3):270–8.
[32] Porter BE, Jacobson C. Report of a parent survey of cannabidiol-enriched cannabis use in pediatric treatment-resistant epilepsy. Epilepsy Behav 2013;29:574–7.
[33] Maa E, Figi P. The case for medical marijuana in epilepsy. Epilepsia 2014;55:783–6.
[34] Gedde M, Maa E. Whole cannabis extract of high concentration cannabidiol may calm seizures in highly refractory pediatric epilepsies. In press at the 67th annual meeting of the American Epilepsy Society; December 6–10, 2013.
[35] Press CA, Knupp KG, Chapman KE. Parental reporting of response to oral cannabis extracts for treatment of refractory epilepsy. Epilepsy Behav 2015;45:49–52.
[36] Tzadok M, Uliel-Siboni S, Linder I, Kramer U, Epstein O, Menascu S, et al. CBD-enriched medical cannabis for intractable pediatric epilepsy: the current Israeli experience. Seizure 2016;35:41–4.
[37] Keeler MH, Reifler CB. Grand mal convulsions subsequent to marijuana use: case report. Dis Nerv Syst 1967;28:474–5.
[38] Consroe PF, Wood GC, Buchsbaum H. Anticonvulsant nature of marihuana smoking. JAMA 1975;234:306–7.
[39] Ellison JM, Gelwan E, Ogletree J. Complex partial seizure symptoms affected by marijuana abuse. J Clin Psychiatry 1990;51:439–40.
[40] Mortati K, Dworetzky B, Devinsky O. Marijuana: an effective antiepileptic treatment in partial epilepsy? A case report and review of the literature. Rev Neurol Dis 2007; 4:103–6.
[41] Gross DW, Hamm J, Ashworth NL, Quigley D. Marijuana use and epilepsy: prevalence in patients of a tertiary care epilepsy center. Neurology 2004;62:2095–7.
[42] Hamerle M, Ghaeni L, Kowski A, Weissinger F, Holtkamp M. Cannabis and other illicit drug use in epilepsy patients. Eur J Neurol 2014;21:167–70.
[43] Hill AJ, Hill TDM, Whalley BJ. The development of cannabinoid based therapies for epilepsy. In: Onaivi ES, Darmani NA, Wagner E, editors. Endocannabinoids: molecular, pharmacological, behavioral and clinical features. Bentham Science; 2013. p. 164–204.
[44] Zullino DF, Delessert D, Eap CB, Preisig M, Baumann P. Tobacco and cannabis smoking cessation can lead to intoxication with clozapine or olanzapine. Int Clin Psychopharmacol May 2002;17(3):141–3.
[45] Stout SM, Cimino NM. Exogenous cannabinoids as substrates, inhibitors, and inducers of human drug metabolizing enzymes: a systematic review. Drug Metab Rev Feb 2014;46(1):86–95.
[46] Volkow ND, Baler RD, Compton WM, Weiss SR. Adverse health effects of marijuana use. N Engl J Med 2014;370:2219–27.
[47] Gupta S. WEED. In: Gupta S, editor. CNN; 2013 The documentary is available through several sources at http://www.youtube.com.
[48] Devinsky O, Cilio MR, Cross H, Fernandez-Ruiz J, French J, Hill C, et al. Cannabidiol: pharmacology and potential therapeutic role in epilepsy and other neuropsychiatric disorders. Epilepsia 2014;55:791–802.
[49] Gloss D, Vickrey B. Cannabinoids for epilepsy. Cochrane Database Syst Rev 2014; 3:CD009270.
[50] Friedman D, Devinsky O. Cannabinoids in the treatment of epilepsy. N Engl J Med Sep 10, 2015;373(11):1048–58.
[51] National Conference of State Legislatures. State medical marijuana laws. [Accessed October 13, 2016] http://www.ncsl.org/research/health/state-medical-marijuana-laws.aspx; September 29, 2016.
[52] Choo EK, Emery SL. Clearing the haze: the complexities and challenges of research on state marijuana laws. Ann N Y Acad Sci 2016:1– [xxxx].
[53] Bill Status for SB174. The Alabama Legislature website. http://alisondb.legislature.state.al.us/alison/SESSBillStatusResult.ASPX?BILL=SB174&WIN_TYPE=BillResult. [Accessed Oct 26, 2016].
[54] CS/CS/SB 1030: Cannabis. The Florida Senate website. https://www.flsenate.gov/Session/Bill/2014/1030/?Tab=BillText. [Accessed Oct 26, 2016].
[55] 2015–2016 Regular Session – HB 1: Haleigh's Hope Act. Enact. Georgia General Assembly Legislation website. http://www.legis.ga.gov/Legislation/en-US/display/20152016/HB/1. [Accessed Oct 26, 2016].
[56] Senate File 2360. The Iowa Legislature: BillBook website. https://www.legis.iowa.gov/legislation/BillBook?ga=85&ba=SF2360. [Accessed Oct 26, 2016].
[57] Senate Bill 1146. State of Idaho USA Legislature website. https://www.legislature.idaho.gov/legislation/2015/S1146.htm. [Accessed Oct 26, 2016].
[58] SB124:14RS. Kentucky Legislature website. http://www.lrc.ky.gov/record/14rs/sb124.htm. [Accessed Oct 26, 2016].
[59] SB143 by Senator Fred H. Mills, Jr. Louisiana State Legislature website. https://www.legis.la.gov/legis/BillInfo.aspx?i=226928. [Accessed Oct 26, 2016].
[60] House Bill 1231. Mississippi Legislature. Regular session website. http://billstatus.ls.state.ms.us/2014/pdf/history/HB/HB1231.xml; 2014. [Accessed Oct 26, 2016].
[61] HB 2238. Missouri House of Representatives website. http://www.house.mo.gov/billsummary.aspx?bill=HB2238&year=2014&code=R. [Accessed Oct 26, 2016].
[62] House Bill 1220/S.L. 2014–53. NCGA North Carolina General Assembly website. http://www.ncleg.net/gascripts/BillLookUp/BillLookUp.pl?Session=2013&BillID=h1220. [Accessed Oct 26, 2016].
[63] Bill Information for HB 2154. Oklahoma State Legislature website. http://www.oklegislature.gov/BillInfo.aspx?Bill=hb2154. [Accessed Oct 26, 2016].
[64] A221, R229, S1035 Status Information. South Carolina General Assembly 120st session. [website] http://www.scstatehouse.gov/sess120_2013-2014/bills/1035.htm; 2013–2014. [Accessed Oct 26, 2016].
[65] SB 2531. Tennessee General Assembly website. http://wapp.capitol.tn.gov/apps/Billinfo/default.aspx?BillNumber=SB2531&ga=108. [Accessed Oct 26, 2016].
[66] Bill: SB 339. Texas Legislation Online: history website. http://www.capitol.state.tx.us/BillLookup/History.aspx?LegSess=84R&Bill=SB339. [Accessed Oct 26, 2016].
[67] H.B. 105 Plant Extract Amendments. Utah State Legislature website. http://le.utah.gov/~2014/bills/static/hb0105.html. [Accessed Oct 26, 2016].
[68] HB 1445 Cannabidiol oil and THC-A oil. Possession of marijuana. Virginia's Legislative Information System; 2015 [Session website] https://lis.virginia.gov/cgi-bin/legp604.exe?151+sum+HB1445. [Accessed Oct 26, 2016].
[69] Assembly Bill 726. Wisconsin State Legislature. [Wisconsin Legislature website] http://docs.legis.wisconsin.gov/2013/proposals/ab726; 2013–2014. [Accessed Oct 26, 2016].
[70] 2015 General Session. 63rd Legislature House Bills Index website. http://legisweb.state.**wy**.us/2015/bills/HB0032.pdf. [Accessed Oct 26, 2016].
[71] Bradford AC, Bradford WD. Medical marijuana laws reduce prescription medication use in Medicare part D. Health Aff July 2016;35(7):1230–6.
[72] Bachuber MA, Saloner B, Cunningham CO, Barry CL. Medical cannabis laws and opioid analgesic overdose mortality in the US, 1999–2010. JAMA Intern Med 2014; 174(10):1668–73.
[73] Geffrey AL, Pollack SF, Bruno PL, Thiele EA. Drug–drug interaction between clobazam and cannabidiol in children with refractory epilepsy. Epilepsia 2015; 56:1246–51.
[74] Friedman D, Cilio MR, Tilton N, Sullivan J, Hedlund J, Rosenberg E, et al. The effect of Epidiolex (cannabidiol) on serum levels of concomitant anti-epileptic drugs in children and young adults with treatment-resistant epilepsy in an expanded access program. Seattle, WA: American Epilepsy Society; 2014.
[75] Szaflarski JP, Bebin EM, Cutter G, DeWolfe J, Dure L, Gaston T, et al. Response to pharmaceutical grade cannabidiol in a state-sponsored treatment program. AES 70th annual meeting abstract: 194427; 2016.

[76] Szaflarski JP, Bebin E, Dewolfe J, Dure L, Gaston T, Harsanyi K, et al. Seizure response to cannabidiol in a state sponsored open-label program. AAN 2016 annual meeting abstract: 16-A-3735-AAN; 2016.
[77] Hess EJ, Moody KA, Geffrey AL, Pollack SF, Skirvin LA, Bruno PL, et al. Cannabidiol as a new treatment for drug-resistant epilepsy in tuberous sclerosis complex. Epilepsia Oct 2016;57(10):1617–24.
[78] Chu-Shore CJ, Major P, Camposano S, Muzykewicz D, Thiele EA. The natural history of epilepsy in tuberous sclerosis complex. Epilepsia Jul 2010;51(7):1236–41.
[79] Gofshteyn JS, Wilfong A, Devinksy O, Bluvstein J, Charuta J, Ciliberto MA. Cannabidiol as a potential treatment for Febrile Infection-Related Epilepsy Syndrome (FIRES) in the acute and chronic phases. J Child Neurol Sep 21, 2016 [pii: 0883073816669450. Epub ahead of print].
[80] Mikaeloff Y, Jambaque I, Hertz-Pannier L, Zanfirescu A, Adamsbaum C, Ploin P, et al. Devastating epileptic encephalopathy in school-aged children (DESC): a pseudo encephalitis. Epilepsy Res 2001;69(1):67–79.
[81] Sing RK, Joshi SM, Potter DM, Leber SM, Carlson MD, Shellhaas RA. Cognitive outcomes in febrile infection-related epilespy syndrome treated with the ketogenic diet. Pediatrics Nov 2014;134(5):e1431–5.
[82] Nabbout R, Mazzuca M, Hubert P, Peudennier S, Allaire C, Flurin V, et al. Efficacy of ketogenic diet in severe refractory status epilepticus initiating fever induced refractory epileptic encephalopathy in school age children (FIRES). Epilepsia 2010;51:2033–7.
[83] GW Pharmaceutical Announces Positive Phase 3 Pivotal Study Results for Epidiolex®(cannabidiol). GW Pharmaceuticals website. https://www.gwpharm.com/about-us/news/gw-pharmaceuticals-announces-positive-phase-3-pivotal-study-results-epidiolex; March 2016. [Accessed November 9, 2016].
[84] GW Pharmaceutical Announces Positive Phase 3 Pivotal Study Results for Epidiolex®(cannabidiol) in the Treatment of Lennox-Gastaut Syndrome. GW Pharmaceuticals website. https://www.gwpharm.com/about-us/news/gw-pharmaceuticals-announces-positive-phase-3-pivotal-trial-results-epidiolex; July 2016. [Accessed November 9, 2016].
[85] GW Pharmaceuticals Announces Second Positive Phase 3 Pivotal Trial for Epidiolex®(cannabidiol) in the Treatment of Lennox-Gastaut Syndrome. GW Pharmaceuticals website. https://www.gwpharm.com/about-us/news/gw-pharmaceuticals-announces-second-positive-phase-3-pivotal-trial-epidiolex; September 2016. [Accessed November 9, 2016].