Review article

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The role of cannabinoids in epilepsy treatment: a critical review of efficacy results from clinical trials

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ABSTRACT – CBD was shown to have anti-seizure activity based on *in vitro* and *in vivo* models. However, several reports of small series or case reports of the use of cannabis extracts in epilepsy yielded contradictory results and the efficacy of cannabis use in patients with epilepsy have also been inconclusive. In 2013, the first Phase 1 trial for a purified form of CBD (Epidiolex/Epidyolex; >99% CBD), developed by GW Pharma, showed some efficacy signals and subsequently, a comprehensive program on the efficacy and tolerability of this compound for the treatment of drug-resistant epilepsies was initiated. Results of these trials led to the FDA and EMA approval respectively in 2018 and 2019 for the treatment of seizures associated with two rare epilepsies: Lennox-Gastaut syndrome (LGS) or Dravet syndrome (DS) in patients two years of age and older. Thus, CBD became the first FDA-approved purified drug substance derived from cannabis and also the first FDA-approved drug for the treatment of seizures in DS. We detail the clinical studies using purified CBD (Epidiolex/Epidyolex), including the first open interventional exploratory study and Randomized Control Ttrials for DS and LGS.

Key words: cannabidiol, clinical trial, Dravet syndrome, Lennox-Gastaut syndrome

The use of natural cannabinoids in the treatment of epilepsy was reported in ancient Greek and Arabic medical texts. During the 1850s and 60s there were numerous reports in the medical literature describing the effectiveness of cannabis in the treatment of several medical conditions, including epilepsy. In the 1980s and 90s, several reports of small series or case reports of the use of cannabis extracts in epilepsy yielded contradictory results (Cunha *et al*., 1980; Ames and Cridland, 1986; Trembly and Sherman, 1990). More recent reports of the efficacy of cannabis use in patients with epilepsy have also been inconclusive (Gross *et al*., 2004; Hamerle *et al*., 2014). A limitation of all of these studies was that the composition of the extracts used was not available, and likely highly variable including the concentrations of CBD in the extracts. However, CBD was

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shown to have anti-seizure activity based on *in vitro* and *in vivo* models (Jones *et al*., 2010; Devinsky *et al*., 2014).

A new interest in the clinical use of CBD enriched cannabis extracts in the treatment of pharmacoresistant epilepsies was prompted by media reports of efficacy in children with Dravet syndrome (DS) and surveys of parental evaluation of CBD efficacy from Colorado, USA, where medical cannabis was available for medical prescriptions (Porter and Jacobson, 2013).

In 2013, the first Phase 1 trial for a purified form of CBD (Epidiolex; >99% CBD), developed by GW Pharma, was initiated. Subsequently, a comprehensive program on the efficacy and tolerability of this compound for the treatment of drug-resistant epilepsies was initiated. Results of these trials led to the FDA approval of this formulation of purified CBD on June 25, 2018: "*Epidiolex is indicated for the treatment of seizures associated with Lennox-Gastaut syndrome (LGS) or DS in patients two years of age and older*". Thus, CBD became the first FDA-approved purified drug substance derived from cannabis and also the first FDA-approved drug for the treatment of seizures in DS. More recently, Epidyolex was also approved by the European Medicines Agency as treatment for DS and LGS in combination with clobazam treatment.

This paper will detail the clinical studies using purified CBD (Epidiolex), including the first open interventional exploratory study and RCTs for DS and LGS:

– Drug-resistant epilepsy in childhood and young adults (2-30 years old): an expanded access program in the USA (Devinsky *et al*., 2016);

– Dravet syndrome: two RCTs (GWCARE 1 et 2) (Devinsky *et al*., 2017);

– Lennox-Gastaut syndrome: two RCTs (GWCARE 3 and 4) (Thiele *et al*., 2018; Devinsky *et al*., 2018a);

– Dravet syndrome: an open-label extension study (GWCARE 5) (Devinsky *et al*., 2019).

Prospective open interventional study (Devinsky *et al*., 2016)

This open-label interventional trial recruited children and young adults with drug-resistant, childhood-onset epilepsies. This design was organized as a large exploratory study in patients with drug-resistant epilepsies fulfilling the following inclusion criteria: age 1-30 years, pharmacoresistant childhood-onset epilepsy, more than four countable seizures with a motor component over a four-week period, and a stable therapy regimen (AEDs, ketogenic diet, VNS) for at least four weeks prior to enrolment.

After enrolment, patients had a four-week baseline period in which parents kept a seizure diary. After this observational period, Epidiolex was added to the patients' current regimen at 2-5 mg/kg/d, divided twice daily, then increased by 2-5 mg/kg/d every week until intolerance or until a dose of 25-50 mg/kg/d was reached.

The primary objective was to establish the safety and tolerability of CBD, and the primary efficacy endpoint was median percentage change in the mean monthly frequency of motor seizures at 12 weeks. Efficacy was examined based on modified intention-to-treat analysis.

Between January 15, 2014, and January 15, 2015, 214 patients were enrolled; 162 (76%) patients who had at least 12 weeks of follow-up after the first dose of CBD were included in the safety and tolerability analysis, and 137 (64%) patients were included in the efficacy analysis.

In the safety group, 33 (20%) patients had DS and 31 (19%) patients had LGS. The remaining patients had different drug-resistant epilepsies with variable syndromes and aetiologies including patients with *CDKL5* mutations, tuberous sclerosis complex, and myoclonic atonic epilepsy.

Tolerability and safety data were obtained for 162 patients (76%). Of this group, 78% showed adverse events (AEs), with somnolence in 25%, decreased appetite in 19%, diarrhoea in 19%, and fatigue in 13%. Serious AEs were reported in 20%, with status epilepticus, diarrhoea, and weight loss being the most common. Serious AEs (status epilepticus and diarrhoea plus weight loss) led to treatment discontinuation in 3% of patients.

For the efficacy analysis, the median reduction of motor seizures reached 36.5% over the 12-week treatment period, with five patients free of motor seizures. Reduction was >50% in 39%, >70% in 21%, and >90% in 9%. The median reduction was higher for patients with DS, who reached 49.8% reduction. Patients with atonic seizures (32 patients) showed a significant response, as 56% had >50% reduction in seizures and 16% became seizure-free (Devinsky *et al*., 2016).

Dravet syndrome (DS)

DS is an infantile-onset epilepsy presenting in a previously normal child before the age of 15 months (and often before one year of age) with prolonged, typically febrile and hemiclonic, seizures evolving into status epilepticus. Patients progressively develop other seizure types a few months after the onset including myoclonic, focal, and generalized tonic-clonic seizures, accompanied by developmental plateauing. DS is a highly pharmacoresistant epilepsy with poor developmental outcome including psychiatric disorders and disorders of behaviour, gait, sleep, and speech.

Prior to these trials, only one drug had completed a RCT for DS during its development (Diacomit*, Biocodex) and was registered in Europe in 2014 and in the USA in 2019, in association with clobazam. Other drugs showed variable degrees of efficacy on seizure reduction in patients with DS but were reported mostly in retrospective studies, and less in prospective studies. These treatments included topiramate, zonisamide, the ketogenic diet, and bromide. The treatment approach in different countries varies depending upon medication availability. Patients with DS are usually on polytherapy and seizure control is rarely achieved (De Liso *et al*., 2016). Thirty-two patients with DS were included in the first open-label CBD interventional trial; as described above, patients with DS showed a median decrease in motor seizures of 49.8% showing a higher response in this group compared to 36.5% median reduction of motor seizures in the trial at large, over the 12-week treatment period. This exploratory study provided a promising "signal" (Chiron *et al*., 2013) to continue further development of CBD for patients with DS and LGS.

Randomized controlled trial for DS (GWPCARE1) (Devinsky *et al*., 2017)

This study included patients with DS aged two to 18 years, with confirmation of a diagnosis made by the epilepsy study consortium. For eligibility, patients had to be inadequately controlled by at least one current drug and have ≥four convulsive seizures (tonic-clonic, tonic, clonic, or atonic seizures) during the four-week baseline period.

Exclusion criteria included: use of any other cannabis derivative within three months prior to entering or during the study, presence of a progressive diagnosed medical illness, evidence of impaired hepatic function on laboratory testing, and known or suspected hypersensitivity to cannabinoids or any of the excipients of the investigational medicinal products.

CBD oral solution (100 mg/ml) or placebo was added to current AEDs starting at 2.5 mg/kg/day and titrated to 20 mg/kg/day over two weeks. The dose of 20 mg/kg/d was set by an independent drug safety monitoring committee based on pharmacokinetic and safety data from an initial part of this study (Part A) evaluating doses of 5, 10, and 20 mg/kg/day. The titration period was followed by a 12-week dose-maintenance period. The total treatment duration was 14 weeks, comprising the two-week titration period plus the 12-week treatment period.

The primary endpoint was the median percentage change in convulsive seizure frequency from the four-week baseline period compared to the 14-week treatment period among patients who received CBD, compared with placebo. The secondary endpoint measures included: the Caregiver Global Impression of Change (CGIC), assessed on a Likert-like scale; the number of patients with at least 25%, 50%, 75% and 100% reduction in convulsive seizure frequency; the duration of seizure subtypes assessed by the caregiver (decrease, no change, or increase in average duration); sleep disruption, assessed on a numerical rating scale from 0 to 10; the change in score on the Epworth Sleepiness Scale; score based on the Quality of Life in Childhood Epilepsy questionnaire; score based on the Vineland Adaptive Behaviour Scales (second edition); the number of hospitalizations due to epilepsy; the number of patients with emergence of new seizures types compared to baseline period; and the use of rescue medication.

The safety profile of CBD was assessed on the basis of the number, type, and severity of AEs as well as the Columbia Suicide Severity Rating Scale (for patients ≥six years of age, when appropriate), vital signs, electrocardiographic variables, laboratory safety variables, and physical examination variables; safety end points were monitored at each visit. The palatability of the trial agent was assessed by caregivers on a 5-point scale, ranging from "liked it a lot" to "did not like it at all".

This study recruited in 33 study centres in the US and Europe. Over all centres, 177 patients were screened and 120 were randomized. The median age at inclusion was 9.7 years (range: 2.5-18.0) in the CBD group and 9.8 years (range: 2.3-18.4) in the placebo group. Patients in both groups had previously been treated with a median of four AEDs (0-26 for the CBD group and 0-14 for the placebo) and were currently on a median of three AEDS (1-5) for both groups. Seizure number in the four-week baseline period did not differ significantly, with 12.4 (6.2-28) seizures in the CBD group and 14.9 (7-36) in the placebo group.

The median reduction in seizure frequency was significantly higher in the CBD group during both the total treatment period (39% *vs*. 13%; p=0.01) and maintenance period (41 *vs*. 16%, p=0.002). Based on the CGIC scale, 37 of 60 caregivers (62%) judged their child's overall condition to improve in the CBD group, compared with 20 of 58 caregivers (34%) in the placebo group (p=0.02). There was no significant difference in sleep scores or QoL scales, moreover, no worsening was reported.

The adverse-event profile of CBD in this trial was similar to that seen in the open-label interventional study, including somnolence (36% in the CBD group *vs*. 10% in the placebo group), loss of appetite (28% *vs*. 5%), and diarrhoea (31% *vs*. 10%). Of the 22 patients in the CBD group in whom somnolence was reported, 18 were taking clobazam, compared with five of six patients in the placebo group. AEs led to a dose

reduction in 10 patients in the CBD group, with complete resolution in eight patients and partial resolution in one patient; in the remaining patient, the AE (loss of appetite) was ongoing. There were few dose adjustments of concomitant antiepileptic drugs during the trial. Abnormalities of hepatic aminotransferase levels occurred only in patients taking valproate, and all resolved spontaneously or with a dosage decrease.
Serious AEs were more common in the CBD group than in the placebo group (16% *vs*. 5%), and AEs led to withdrawal in eight patients in the CBD group compared with one in the placebo group.

Lennox Gastaut syndrome (LGS)

Randomized controlled trial 1 for LGS (GWPCARE3) (Thiele *et al.*, 2018)

This RCT included patients aged 2-55 years with a diagnosis of LGS. LGS diagnosis was based on evidence of >one type of generalized seizure, including drop seizures for ≥six months with documented history of a slow (<3-Hz) spike-and-wave pattern on the EEG. Diagnosis was confirmed by the epilepsy study consortium.
Eligibility criteria included: refractory seizures on more than two AEDs, inclusive of previous and current treatment with at least one AED at the time of inclusion; eight or more drop seizures during the four-week baseline period provided that the patient presented with at least two seizures per week; and all medications and interventions for epilepsy (including the ketogenic diet and vagus nerve stimulation) stable for four weeks before screening.
Exclusion criteria were applied for any patient who: used any cannabinoid derivative within three months of entering the study or not abstaining from use during the study; presented a progressive diagnosed medical illnesses; was initially administered felbamate within the past 12 months; showed significantly impaired hepatic function on liver tests; and finally patients with known or suspected hypersensitivity to cannabinoids or any of the excipients of the investigational medicinal products.
CBD oral solution (100 mg/ml) or placebo was added to current AEDs starting at 2.5 mg/kg/day and titrated to 20 mg/kg/day over two weeks. This titration period was followed by a 12-week dose-maintenance period. The overall duration of the treatment period was 14 weeks; two weeks titration plus the 12 weeks of treatment.
The primary end point was the percentage of change from baseline in drop seizures over the 14-week treatment period. The secondary endpoints included the proportion of patients achieving a >50% reduction in drop seizures, the percentage of change in total seizure frequency, and finally the change from baseline in patient and caregiver global impression of change.
In this study, 171 patients were randomized (86 to CBD and 85 to placebo). The mean age was 15 years with 34% over 18 years. Patients included had previously tried a median of six AEDs and were currently taking a median of three. The median drop seizure frequency over the four-week baseline was 74.
During the 14-week treatment period, patients on CBD achieved a 44% median reduction in drop seizure frequency *vs*. 22% in the placebo group (primary end point; p=0.0135). In the same treatment period, patients had a 49% median reduction in non-drop seizures *vs*. 23% in the placebo group (p=0.004). Regarding the response for both seizure types (drop and non-drop), patients on CBD had a 41.2% median reduction in seizure frequency compared to 13.7% in the placebo group (p=0.0005).
In addition to seizure frequency reduction, in the CBD group, caregivers or patients were significantly more likely to report an improvement in condition (OR=2.54; p=0.0012).
A total of 86% patients in the CBD and 69% in the placebo group had AEs, with 78% rated as mild or moderate in the CBD group. The major treatment-emergent AEs were diarrhoea, somnolence, pyrexia, and decreased appetite.
A higher incidence of somnolence was observed in patients on AED regimens that included clobazam (CLB) compared with those without CLB for both the CBD (22% *vs*. 9% patients) and placebo (16% *vs*. 2% of patients) groups. In addition, in the CBD group, a higher incidence of elevated transaminases was observed in patients on antiepileptic drug regimens that included valproate compared to those without valproate (19% *vs*. 5%).

Randomized controlled trial 2 for LGS (GWPCARE4) (Devinsky *et al.*, 2018a)

This RCT was designed with the same inclusion and exclusion criteria as well as primary and secondary endpoints and the first LGS trial. The only difference with the previous study was the addition of a third arm consisting of CBD at a lower dose of 10 mg/kg/d.
A total of 225 patients were randomized; 76 to 20 mg/kg/day, 73 to 10 mg/kg/day, and 76 to placebo. The mean age was 15.3 (2.6-43.4 for the placebo group, and 15.4 [2.6-42.6] and 16 years [2.6-48] for the 10 and 20 mg/kg/day CBD groups, respectively). The number of drop seizures during the four-week baseline was 80.3 (47.8-148.0), 86.9 (40.6-190.0), and 85.5 (38.3-161.5) in the 20 mg/kg/d, 10 mg/kg/d, and placebo group, respectively.

The reduction in seizure frequency was 41.9% and 37.2% in the 20 and 10 mg/kg/d CBD group, respectively, *vs*. 17.2% in the placebo group, revealing a significant difference in both CBD arms relative to placebo (p=0.005 and p=0.002, respectively).
Somnolence, diarrhoea, and decreased appetite were the major treatment-emergent AEs. An increase in liver enzymes was predominantly found in patients with valproate.

Open-label extension study (GWPCARE5) (Devinsky *et al.*, 2019)

Patients who completed GWPCARE1 Part A (NCT02091206) or Part B, or a second placebo-controlled trial, GWPCARE2 (NCT02224703) (data not published), were invited to enroll in a long-term open-label extension trial, GWPCARE5 (NCT02224573). GWPCARE5 is an ongoing open-label extension trial of add-on CBD in patients with DS who completed GWPCARE1 or GWPCARE2 and patients with LGS who completed treatment in one of two Phase 3 trials (GWPCARE 3 and GWPCARE4).
The first report of GWPCARE5 is the interim analysis for safety, efficacy, and patient-reported outcomes for patients with DS enrolled in this open study (Devinsky *et al*., 2019).
Patients entered this extension phase after the end of the maintenance period of 12 weeks. Investigators could decrease the dose of CBD and/or concomitant AEDs if a patient experienced intolerance or could increase the dose to a maximum of 30 mg/kg/d if thought to be of benefit by the physician. The data cut-off for this interim analysis was November 3, 2016.
The primary objective of this open-label extension was to evaluate the long-term safety and tolerability of adjunctive CBD treatment, based on treatment-emergent AEs (occurring at any time during the open-label extension, from enrolment through to follow-up visit), vital signs, 12-lead electrocardiograms, and clinical laboratory parameters. Secondary objectives were to evaluate the efficacy of CBD and patient-reported outcomes based on changes in the Subject/Caregiver Global Impression of Change (S/CGIC) scale.
By November 2016, at the time of cut-off analysis for GWPCARE5, 278 patients with DS from the completed GWCARE1 study and the ongoing GWCARE2 study had completed the original randomized trials, and 264 (95%) enrolled in this open-label extension.
Median treatment duration was 274 days (range: 1-512) with a mean modal dose of 21 mg/kg/d. Patients received a median of three concomitant antiepileptic medications. AEs occurred in 93.2% of patients and were mostly mild (36.7%) or moderate (39.0%). Commonly reported AEs were the same as those reported in the RCTs: diarrhoea (34.5%), pyrexia (27.3%), decreased appetite (25.4%), and somnolence (24.6%). Seventeen patients (6.4%) discontinued due to AEs. Twenty-two of 128 patients from GWPCARE1 (17.2%), all on valproic acid, had elevated liver transaminase, ≥three times greater than the upper normal limit.
In patients from GWPCARE1 Part B, median reduction from baseline in monthly seizure frequency, assessed in 12-week periods up to Week 48, ranged from 38% to 44% for convulsive seizures and 39% to 51% for total seizures. After 48 weeks of treatment, 85% of patients/caregivers reported improvement in the patients' overall condition based on the Subject/Caregiver Global Impression of Change scale.
This trial showed a good tolerance of long-term CBD treatment with an acceptable safety profile without new-emergent side effects. CBD led to a sustained and clinically meaningful reduction in seizure frequency in patients with treatment-resistant DS in this extension phase.

Conclusion

CBD has been shown to be effective, safe, and well tolerated as a treatment for DS and LGS. CBD (20 mg/kg/day) as an add-on to existing AEDs resulted in significantly greater reductions in total seizure frequency *vs*. placebo with a significant reduction of convulsive seizures *vs*. add-on placebo in patients with DS and drop seizures in patients with LGS. This efficacy was achieved on 20 mg/kg/d in DS and LGS trials but also on 10 mg/kg/d in one LGS trial.
CBD showed higher efficacy when associated with CLB. This synergy could be at least partially due to an increase in nor-CLB, the active compound of CLB, due an inhibition of Cyp2C19.
CBD treatment resulted in more AEs than placebo. Most common AEs were somnolence, diarrhoea, and decreased appetite. A higher risk of somnolence was associated with the combination of CBD and CLB, requiring dose adjustment (Devinsky *et al*., 2018b).
Abnormal hepatic aminotransferase levels were identified predominantly in patients taking concomitant valproate, suggesting an interaction in which CBD may potentiate a valproic acid-induced change in hepatic aminotransferase levels. A few patients exited the trial or the open-label extension study due to AEs.
Compared to placebo, caregivers were significantly more likely to report an improvement in overall condition for patients taking CBD, as measured on the CGIC scale.
The CBD expanded access program (Devinsky *et al*., 2016) suggests that CBD may have a wider spectrum of

efficacy beyond DS and LGS. Results from a randomized controlled trial of CBD in refractory epilepsy in tuberous sclerosis complex were recently released and showed similar efficacy and tolerability. These results along with further results from the expanded access program will help to establish the best guidelines for the use of CBD. □

Disclosures.
None of the authors have any conflict of interest to declare.

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