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Cannabidiol in patients with treatment-resistant epilepsy: an open-label interventional trial



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Summary

Background Almost a third of patients with epilepsy have a treatment-resistant form, which is associated with severe morbidity and increased mortality. Cannabis-based treatments for epilepsy have generated much interest, but scientific data are scarce. We aimed to establish whether addition of cannabidiol to existing anti-epileptic regimens would be safe, tolerated, and efficacious in children and young adults with treatment-resistant epilepsy.

Methods In this open-label trial, patients (aged 1–30 years) with severe, intractable, childhood-onset, treatment-resistant epilepsy, who were receiving stable doses of antiepileptic drugs before study entry, were enrolled in an expanded-access programme at 11 epilepsy centres across the USA. Patients were given oral cannabidiol at 2–5 mg/kg per day, up-titrated until intolerance or to a maximum dose of 25 mg/kg or 50 mg/kg per day (dependent on study site). The primary objective was to establish the safety and tolerability of cannabidiol and the primary efficacy endpoint was median percentage change in the mean monthly frequency of motor seizures at 12 weeks. The efficacy analysis was by modified intention to treat. Comparisons of the percentage change in frequency of motor seizures were done with a Mann-Whitney *U* test.

Results Between Jan 15, 2014, and Jan 15, 2015, 214 patients were enrolled; 162 (76%) patients who had at least 12 weeks of follow-up after the first dose of cannabidiol 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 Dravet syndrome and 31 (19%) patients had Lennox-Gastaut syndrome. The remaining patients had intractable epilepsies of different causes and type. Adverse events were reported in 128 (79%) of the 162 patients within the safety group. Adverse events reported in more than 10% of patients were somnolence (n=41 [25%]), decreased appetite (n=31 [19%]), diarrhoea (n=31 [19%]), fatigue (n=21 [13%]), and convulsion (n=18 [11%]). Five (3%) patients discontinued treatment because of an adverse event. Serious adverse events were reported in 48 (30%) patients, including one death—a sudden unexpected death in epilepsy regarded as unrelated to study drug. 20 (12%) patients had severe adverse events possibly related to cannabidiol use, the most common of which was status epilepticus (n=9 [6%]). The median monthly frequency of motor seizures was 30·0 (IQR 11·0–96·0) at baseline and 15·8 (5·6–57·6) over the 12 week treatment period. The median reduction in monthly motor seizures was 36·5% (IQR 0–64·7).

Interpretation Our findings suggest that cannabidiol might reduce seizure frequency and might have an adequate safety profile in children and young adults with highly treatment-resistant epilepsy. Randomised controlled trials are warranted to characterise the safety profile and true efficacy of this compound.

Funding GW Pharmaceuticals, Epilepsy Therapy Project of the Epilepsy Foundation, Finding A Cure for Epilepsy and Seizures.

Introduction

Derivatives from the cannabis plant, *Cannabis sativa*, have long been used as a treatment for many disorders, from anorexia to pain.¹ Anecdotal reports suggest that cannabis extracts can reduce seizures.^{2–4} Cannabis contains more than 80 phytocannabinoids and, although little is known about the potential therapeutic effects of most of these molecules, two compounds—tetrahydrocannabinol and cannabidiol—have garnered the most attention based on their abundance in the plant.

Tetrahydrocannabinol, the major psychoactive cannabinoid, has been shown to have both anticonvulsant and proconvulsant effects in animal studies of seizures.⁵ The potential medical use of whole-plant cannabis

extracts, particularly in children with a developing brain, is limited by the psychoactive properties and the adverse effects associated with long-term tetrahydrocannabinol use. The potential adverse effects of tetrahydrocannabinol-containing drugs in adolescents include cognitive impairment and chronic psychiatric disturbances.⁶ The potential toxic effects of tetrahydrocannabinol and other cannabis constituents have not yet been studied in younger children (<12 years) who might be more vulnerable than adolescents to these and other potential adverse effects.

In the past few years, enormous interest has been generated by social and news media about the beneficial effects of non-purified medical marijuana, with high

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Research in context

Evidence before this study

Anecdotal evidence has long suggested that cannabis might have a role in control of epileptic seizures. We searched PubMed for English-language studies published between Nov 1, 1970, and Oct 15, 2015, with the search terms “cannabidiol and epilepsy” and “cannabis and epilepsy”. Our search identified several preclinical studies, from the 1980s to the past few years, of the effect of cannabidiol on electrical convulsant and chemoconvulsant models. Four small randomised studies of cannabidiol-based preparations showed an absence of serious side-effects, and two of these studies suggested some efficacy, but all studies were too small to provide definite answers. We additionally found two papers that used parental surveys of the effect of non-purified preparations of cannabis-based products for paediatric epilepsy.

Added value of this study

This multicentre study provides the first prospectively collected data of cannabidiol use in patients with epilepsy. Our findings provide the first estimates of safety, tolerability, and efficacy of this compound in children and young adults with treatment-resistant epilepsy.

Implications of all the available evidence

By comparison with previous studies, which could not obtain robust conclusions, our study is the first to provide evidence that cannabidiol might be an effective treatment option for children and young adults with intractable epilepsy. Randomised controlled trials are warranted to characterise the safety profile and true efficacy of this compound.

ratios of cannabidiol to tetrahydrocannabinol, in children with treatment-resistant epilepsies, especially Dravet syndrome.⁷⁻⁹ Preclinical evidence showing the anti-convulsant properties of cannabidiol in animals supports this focus on preparations with high cannabidiol content.^{5,10} Furthermore, two of four previous trials in humans suggested modest benefits in seizure control¹¹ and good tolerability, with patients experiencing mild or no side-effects. However, these trials were all too small (between nine and 15 patients) to adequately assess efficacy.

Insufficient preclinical and clinical data, in addition to anecdotal reports from the past few years, have intersected with a need for more effective therapies for treatment-resistant epilepsy, which has created a demand for access to cannabidiol-based treatments by patients and families. As such, many US states have approved the use of medical marijuana for children and adults with epilepsy. Unfortunately, few well designed and conducted safety or efficacy studies of cannabidiol have been done in humans. However, safety data are available for cannabidiol-containing compounds in adults with pain and multiple sclerosis-related spasticity.¹² A pooled analysis of randomised trials of Sativex (GW Pharmaceuticals, London, UK), an oromucosal spray containing cannabidiol and tetrahydrocannabinol in a 1:1 ratio, showed no serious adverse events.¹³ Common mild or moderate adverse events included oral pain, dizziness, diarrhoea, nausea, oral mucosal disorder, bad taste, dry mouth, fatigue, heading, and somnolence.¹³ Because these compounds contain tetrahydrocannabinol, which is responsible for many of these effects, fewer adverse effects of cannabidiol alone are expected, and those that do occur (such as somnolence) are expected to be less severe. However this hypothesis remains undefined in a paediatric epilepsy population.

Given the scarcity of safety and efficacy data for cannabidiol use in children and young adults with severe

epilepsy, and the intense interest from our patients' families in obtaining cannabis, we did this study to test whether cannabidiol as an add-on treatment to conventional anti-epileptic drugs would be safe, tolerated, and efficacious in children and young adults with highly treatment-resistant epilepsy.

Methods

Study design and patients

We did this prospective, open-label, expanded-access trial at 11 independent epilepsy centres in the USA (appendix p 1). Inclusion criteria for entry into the physician-sponsored, expanded-access programmes varied dependent on site-specific protocols. However, patients at all sites were aged 1–30 years, had intractable childhood-onset epilepsy, had four or more countable seizures with a motor component per 4 week period, and were receiving stable doses of antiepileptic drugs for at least 4 weeks before enrolment. If patients were undergoing dietary treatment (eg, ketogenic or modified Atkins diet), the ratio of fat to carbohydrate and protein needed to be stable for 4 weeks before entering the study; similarly, in individuals with a vagus nerve stimulator, settings had to be stable for 4 weeks. Because each of the 11 study sites applied for their own investigational new drug registration for the expanded-access programme, there was some variability in eligibility criteria between centres. Specifically, some patients were taking more than four antiepileptic drugs (up to seven drugs in a few patients) and some patients did not have seizures with a prominent, sustained, and countable motor component. The appendix lists numbers of participants enrolled at each site.

Study-wide exclusion criteria included previous or current treatment with cannabis-based therapy. Most sites also excluded patients with baseline liver, renal, or haematological laboratory abnormalities, or initiation of felbamate or vigabatrin within 6 months of the first clinic visit. The institutional review boards at each study site

See Online for appendix

approved the study. Parents or patients provided written informed consent, and assent according to patients' physical and mental capability.

Procedures

After enrolment patients had a 4 week pre-cannabidiol baseline period during which parents or caregivers kept prospective seizure diaries. They were asked to report countable, discrete seizures with a sustained (>3 s) motor component (henceforth referred to as motor seizures); seizure types include tonic-clonic, tonic, clonic, atonic, and focal seizures with prominent motor features. Although myoclonic jerks, absences, and non-motor complex partial seizures were counted, they were not considered part of the primary outcome because of difficulties in counting their frequency in this population with severe epilepsies. After the observation period, patients then received a 99% pure oil-based cannabidiol extract of constant composition (Epidiolex, GW Pharmaceuticals, London, UK), in a 100 mg per mL sesame oil-based solution (at study onset GW Pharmaceuticals provided a 25 mg per mL solution, which was later discontinued) administered orally or by gastric tube.

Cannabidiol at a dose of 2–5 mg/kg per day divided in twice-daily dosing was added to the baseline antiepileptic drug regimen, then up-titrated by 2–5 mg/kg once a week until intolerance or a maximum dose of 25 mg/kg per day was reached. At some sites, the institutional review board and the US Food and Drug Administration (FDA) allowed an increase to a maximum dose of 50 mg/kg per day. For the first 3 months of cannabidiol treatment, efforts were made to keep concomitant doses of antiepileptic drug constant. However, in some cases, sedation after addition of cannabidiol led to decreases in those antiepileptic drugs, as clinically indicated. No concomitant antiepileptic drug was withdrawn during the study.

All seizures were recorded by parents or caregivers on paper diaries and reviewed by the study team at each clinic visit. Tolerability and adverse effects were assessed every 2 weeks by use of the Liverpool Adverse Events Profile¹⁴ or the Pediatric Epilepsy Side Effects Questionnaire,¹⁵ depending on age. Additional variables measured prospectively in patient diaries were use of rescue medications, episodes of status epilepticus, and emergency room visits or hospital admissions. Laboratory studies for haematology, electrolytes, liver and kidney function, and concentrations of antiepileptic drugs and cannabidiol were done at baseline, and after 4, 8, and 12 weeks of cannabidiol treatment, or more frequently depending on the site-specific protocol.

Outcomes

The primary endpoint was to establish the safety and tolerability of cannabidiol, and the primary efficacy outcome was median percentage change in the mean

monthly frequency of motor seizures at 12 weeks. Mean monthly seizure frequency was calculated at each 4 week visit as (number of seizures since last visit)/(days since last visit) × 28. Median percentage change was calculated because patients had a wide range of seizure frequencies. Percentage change in seizure frequency for each patient was calculated as:

$$\text{post-cannabidiol seizure} = \frac{\text{seizure frequency week 4 visit} + \text{seizure frequency week 8 visit} + \text{seizure frequency week 1}}{3}$$

$$\% \text{ change seizure frequency} = \left(\frac{\text{post-cannabidiol seizure} - \text{baseline seizure frequency}}{\text{baseline seizure frequency}} \right) \times 100$$

Motor seizures can be more reliably counted by observers than subjective (impaired awareness) or transient (myoclonic jerks) events in children and young adults, most of whom had a degree of intellectual disability or epileptic encephalopathy. Thus, this endpoint was chosen in view of concern about potential parental bias due to media attention and desire for the patient to receive cannabidiol. For the secondary efficacy analysis we assessed the median percentage change in other seizure types, including tonic, atonic, tonic-clonic, focal non-motor, and total seizures. We also examined the response rate for all seizure types, defined as patients whose reduction in mean monthly seizure frequency was greater than 50%, 70%, or 90% over the study observation period. Response rate was calculated from individual patient percentage reductions. Because of the long titration phase for cannabidiol, we also examined the median percentage change in seizure frequency during the final 4 weeks of the observation period.

Statistical analysis

The study sample size was not predetermined, but based on patient enrolment at the study sites. Comparisons of the percentage change in frequency of motor seizures were done with a Mann-Whitney *U* test. Cannabidiol is a potent inhibitor of CYP3A4 and CYP2C19 (the P450 isozyme for the clearance of N-desmethyloclobazam, the long-acting active metabolite of clobazam) in addition to other CYP isozymes,¹⁶ with the potential to increase serum concentrations of background antiepileptic drugs and their active metabolites.^{17,18} Therefore, in a post-hoc analysis, we explored whether potential pharmacokinetic or pharmacokinetic interactions between cannabidiol and other antiepileptic drugs could potentiate antiseizure effects. We did a multiple logistic regression analysis as part of our post-hoc analysis to investigate the association

between background clobazam and valproate use and 50% rate of response to cannabidiol, with adjustments for age, sex, and the total number of background antiepileptic drugs. Additional post-hoc analysis was done to examine the association between maximum cannabidiol dose and frequency of adverse events and reported somnolence with Spearman's correlation. The efficacy analysis was by modified intention to treat. We did analyses with IBM SPSS (version 22).

Role of the funding source

GW Pharmaceuticals had no role in study design, data analysis, data interpretation, or writing of the report, or in the decision to submit the paper for publication. GW Pharmaceuticals collated the data that were collected at each site, and had a role in data collection at one site, for which data were sent directly to OD and DF for analysis. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between Jan 15, 2014, and Jan 15, 2015, 214 patients were enrolled in expanded-access programmes at the participating institutions (figure 1). 162 (76%) patients were included in the safety analysis, including 11 (7%) patients who stopped cannabidiol before 12 weeks. 137 (64%) patients met our inclusion and exclusion criteria for efficacy analysis, including ten patients who discontinued treatment during the 12 week observation

period and were included in the analysis with the last observation carried forward (figure 1). Reasons for withdrawal included allergy to the sesame oil vehicle, hepatotoxicity, excessive somnolence and poor efficacy, gastrointestinal intolerance, worsening seizures, and hyperammonemia (figure 1). Additionally, 25 (15%) patients included in the safety analysis were not included in the efficacy analysis (figure 1). Table 1 shows the baseline clinical and demographic characteristics of patients in the safety and efficacy analysis groups. The most common epilepsy syndromes treated were Dravet syndrome and Lennox-Gastaut syndrome (table 2, appendix p 2).

Titration to a maximum dose of 50 mg/kg per day was done in 48 (30%) patients, 23 of whom received a dose of more than 25 mg/kg per day during the 12 week observation period; only 19 patients were receiving >25 mg/kg per day at the week 12 visit. The maximum dose at the 12 week visit was 41 mg/kg per day. Five (3%) patients were titrated to 50 mg/kg per day during the 12 weeks, but their dose was reduced before the week 12 visit. The mean cannabidiol dose at 12 weeks was 22.9 mg/kg (SD 9.1) in the safety analysis group and 22.7 mg/kg (8.5) in the efficacy analysis group.

Adverse events were reported in 128 (79%) of the 162 patients within the safety group. Events reported in

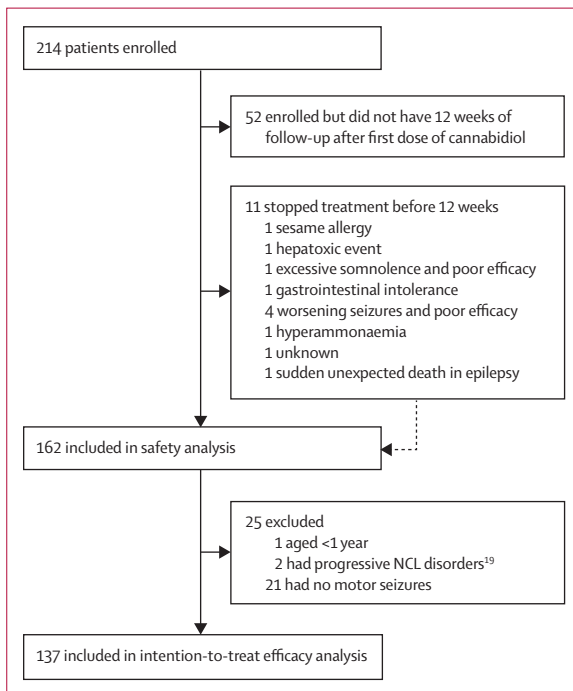


Figure 1: Trial profile
NCL=neuronal ceroid lipofuscinosis.

	Safety analysis group (n=162)	Efficacy analysis group (n=137)
Sex		
Female	82 (51%)	70 (51%)
Male	80 (49%)	67 (49%)
Age (years)	10.5 (0.9–26.2)	10.5 (1–22.2)
Background antiepileptic drugs	3 (0–7)	3 (0–7)
Total daily treatments	3 (1–7)	3 (1–7)
Receiving vagal nerve stimulation	17 (10%)	14 (10%)
On a ketogenic diet (%)	13 (8%)	12 (9%)
Receiving clobazam (%)	85 (52%)	69 (50%)
Receiving valproate (%)	48 (30%)	41 (30%)
Seizure types		
Focal	60 (36%)	42 (31%)
Monthly frequency	16.3 (4.0–55.5)	14.0 (3.0–53.0)
Tonic	66 (41%)	65 (47%)
Monthly frequency	36.0 (5.0–88)	40.0 (5.0–88.0)
Atonic	32 (20%)	32 (23%)
Monthly frequency	14.5 (7–39.0)	14.5 (7.0–39.0)
Tonic-clonic	92 (57%)	89 (65%)
Monthly frequency	10.0 (3.5–22.5)	10.0 (4.0–25.0)
Motor	138 (85%)	137 (100%)
Monthly frequency	29.5 (11.0–96.0)	30.0 (11.0–96.0)
Total seizures	162 (100%)	137 (100%)
Monthly frequency	60.5 (19.6–151)	60.0 (22.0–131.8)

Data are n (%), median (range), or median (IQR).

Table 1: Baseline characteristics

more than 5% of patients were somnolence, decreased appetite, diarrhoea, fatigue, convulsions, appetite changes, status epilepticus, lethargy, changes in concentrations of concomitant antiepileptic drugs, gait disturbance, and sedation (table 3, appendix p 3). Most adverse events were mild or moderate and transient. Serious adverse events were reported in 48 (30%) patients, including one death—a sudden unexpected death in epilepsy regarded as unrelated to study drug. Serious adverse events deemed possibly related to cannabidiol use were recorded in 20 patients and included status epilepticus, diarrhoea, pneumonia, and weight loss (table 3). None of the cases of status epilepticus were associated with preceding reductions in doses of background antiepileptic drugs or cannabidiol. There were no clinically significant changes in white or red blood cell counts or renal function. Five (3%) patients had mild to moderate thrombocytopenia; one (1%) patient had severe thrombocytopenia ($8 \times 10^9/L$) that resolved when valproate was stopped. 11 (7%) patients had elevated liver function tests; most were mild but one patient had a significant increase in transaminases (recorded as hepatotoxicity) leading to discontinuation of cannabidiol (figure 1). All patients with hepatic or platelet abnormalities were also taking valproate. One (1%) patient, also taking valproate, developed hyperammonaemia, which led to cannabidiol discontinuation (figure 1).

A post-hoc analysis showed that cannabidiol dose at week 12 was not correlated with the number of reported adverse events overall (Spearman's rho -0.014 , $p=0.37$). Additionally, there was no correlation with cannabidiol dose and reported somnolence and related side-effects

(eg, fatigue) at week 12 (Spearman's rho 0.029 , $p=0.34$). However, patients who were taking more than 15 mg/kg per day cannabidiol were more likely to report diarrhoea or related side-effects (eg, weight loss) than those taking doses less than 15 mg/kg per day (three [9%] of patients receiving a low cannabidiol dose vs 40 [31%] of 128 patients receiving a high dose; odds ratio [OR] 4.5, 95% CI 1.4–19.6). 43 (51%) of the 85 patients also taking clobazam reported somnolence or fatigue, whereas only 16 (21%) of the 77 patients not taking clobazam reported somnolence (OR for somnolence 3.87, 95% CI 1.9–7.9).

Baseline median monthly frequency of motor seizures was 30.0 (IQR 11.0–96.0) and decreased to 15.8 (5.6–57.6) over the 12 week treatment period (figure 2). The median change in monthly motor seizures from baseline was -36.5% (IQR -64.70 to 0). Five (4%) patients were free of all motor seizures during the 12 week treatment period (figure 3).

Post-hoc analysis showed variability in responses of individual seizure types to cannabidiol treatment; the median change in total seizures was -34.6% (IQR -66.7 to -9.8), with the greatest reduction occurring in patients with focal seizures ($n=42$; -55.0% , IQR -97.3 to -4.4) or

	Safety analysis group (n=162)	Efficacy analysis group (n=137)
Dravet syndrome	33 (20%)	32 (23%)
Lennox-Gastaut syndrome	31 (19%)	30 (22%)
Other	27 (17%)	24 (18%)
Unknown	14 (9%)	8 (6%)
Minimal brain dysfunction	13 (8%)	10 (7%)
CDKL5 mutation	8 (5%)	8 (6%)
Tuberous sclerosis complex	6 (4%)	3 (2%)
Aicardi syndrome	6 (4%)	5 (4%)
Epilepsy with myoclonic absences	5 (3%)	3 (2%)
Myoclonic-astatic epilepsy (Doose syndrome)	5 (3%)	5 (4%)
Febrile infection-related epilepsy syndrome	3 (2%)	1 (<1%)
dup15q disorders	3 (2%)	3 (2%)
Ohtahara syndrome	2 (1%)	2 (<1%)
Neuronal ceroid lipofuscinosis	2 (1%)	0
Jeavons syndrome	2 (1%)	1 (<1%)
Down syndrome	1 (<1%)	1 (<1%)
Autoimmune	1 (<1%)	1 (<1%)

Data are n (%).

Table 2: Epilepsy syndromes and underlying causes

	Safety analysis group (n=162)
Adverse events (reported in >5% of patients)	
Somnolence	41 (25%)
Decreased appetite	31 (19%)
Diarrhoea	31 (19%)
Fatigue	21 (13%)
Convulsion	18 (11%)
Increased appetite	14 (9%)
Status epilepticus	13 (8%)
Lethargy	12 (7%)
Weight increased	12 (7%)
Weight decreased	10 (6%)
Drug concentration increased	9 (6%)
Treatment-emergent serious adverse events*	
Status epilepticus	9 (6%)
Diarrhoea	3 (2%)
Weight decreased	2 (1%)
Convulsion	1 (<1%)
Decreased appetite	1 (<1%)
Drug concentration increased	1 (<1%)
Hepatotoxicity	1 (<1%)
Hyperammonaemia	1 (<1%)
Lethargy	1 (<1%)
Unspecified pneumonia	1 (<1%)
Aspiration pneumonia	1 (<1%)
Bacterial pneumonia	1 (<1%)
Thrombocytopenia	1 (<1%)

Data are n (%). One patient might have had more than one serious adverse event.
*Reported by the investigator to be possibly related to cannabidiol use.

Table 3: Adverse events and treatment-emergent serious adverse events

atonic seizures (n=32; -54.3%, -91.5 to 25.7), followed by tonic seizures (n=65; -36.5%, -71.8 to 22.6) or tonic-clonic seizures (n=89; -16.0%, -60.1 to 35.3). Two (2%) patients were free of all seizure types over the entire 12 weeks.

The titration of cannabidiol dose was slow and there was variability between patients, which meant many patients had not stabilised their dose until half way through the 12 week observation period. Thus, we also analysed changes in seizure frequency during the final 4 weeks of observation only. During this period 15 (11%) patients were free of all motor seizures and nine (7%) patients were free of all seizures during this period. The appendix shows the percentage change in monthly frequency of all other seizure types.

Analysis of the secondary endpoint of responder rates showed that 54 (39%) patients had a reduction of 50% or

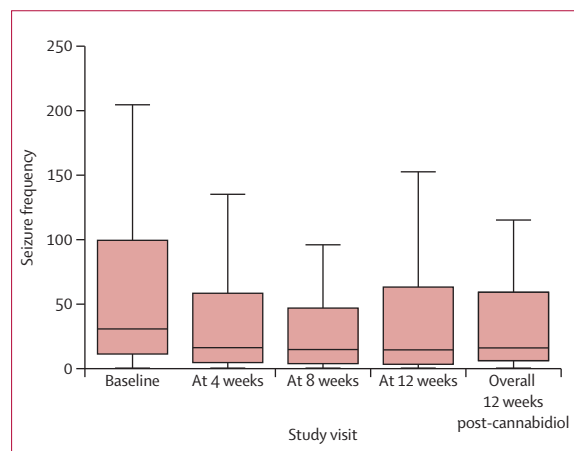


Figure 2: Monthly frequency of motor seizures in patients in the efficacy analysis group (n=137)

Boxplots show median values, with 25th and 75th percentiles. The whiskers denote the 25th percentile - 1.5 × IQR and the 75th percentile + 1.5 × IQR.

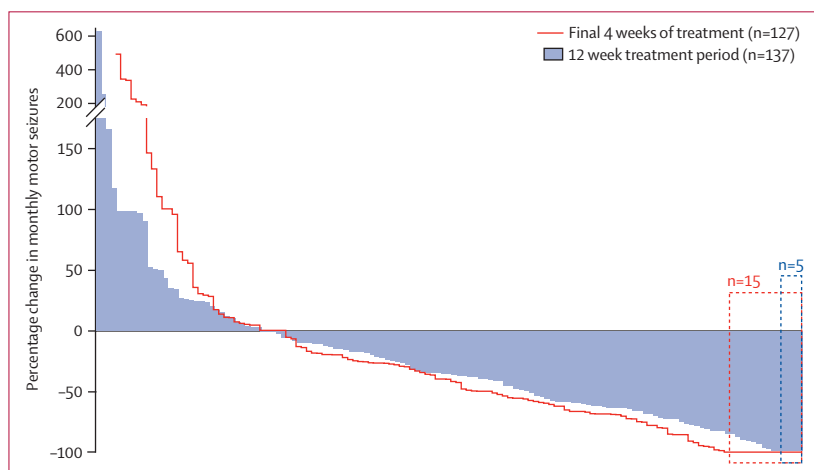


Figure 3: Percentage change in monthly frequency of motor seizures in patients in the efficacy analysis group (n=137)

Percentage changes for each patient are ordered from greatest increase to greatest decrease. The dashed boxes indicate patients who became free of that seizure type during the 12 week treatment period (blue) or the last 4 weeks of treatment (red).

more in motor seizures, whereas 29 (21%) had a reduction of 70% or more and 12 (9%) had a reduction of 90% or more. For all seizure types, 51 (37%) of patients had a reduction of 50% or more, 30 (22%) patients had a response of 70% or more, and 11 (8%) had a response of 90% or more. Of the 32 patients with atonic seizures, 18 (56%) patients had a reduction of 50% or more and five (16%) patients became seizure free of this seizure type. Of the 65 patients with tonic seizures, 26 (40%) patients had a reduction of 50% or more and seven (11%) patients became free of this seizure type and, for the 89 patients with tonic-clonic seizures, 30 (34%) had a reduction of 50% or more and eight (9%) became free of this seizure type.

Patients with Dravet syndrome or Lennox-Gastaut syndrome represented a large proportion of our cohort; therefore, we did a post-hoc analysis to establish whether these syndromes had an improved response profile. For patients with Dravet syndrome in the efficacy group (n=32), the median reduction in monthly motor seizures was 49.8% (IQR -64.3 to -12.4). 16 (50%) patients had a reduction of 50% or greater and one (3%) patient was free from motor seizures during the 3 months of treatment. We recorded a median reduction of 42.7% (IQR -64.6 to -20.6) in monthly total seizures for all seizure types and, during the last 4 weeks of treatment, four (13%) patients were free of motor seizures; these patients were also free of all other seizure types. Among patients with Dravet syndrome, we recorded a median change of -69.2% (IQR -100 to 3.2) in monthly tonic seizures (n=6), of -46.7% (-60.1 to 7.7) in monthly tonic-clonic seizures (n=29), and a reduction of -83.3% (-100 to -50.0) in non-motor focal seizures (n=10). For patients with Lennox-Gastaut syndrome (n=30), we recorded a median reduction of 36.8% (IQR -60.3 to -18.8) in motor seizures and 11 (37%) patients had a reduction in seizures of 50% or more, however no-one was seizure free after 3 months of treatment. The median change in total monthly seizures of all types was -35.5% (IQR -55.1 to -16.4). There was a median reduction of 68.8% (IQR -91.78 to 14.81) in patients with atonic seizures (n=14), and 44.0% (-68.5 to 14.8) in those with tonic seizures (n=21), but there was no reduction in tonic-clonic seizures in patients with Lennox-Gastaut syndrome (n=16). During the last 4 weeks of treatment, one (3%) patient was free of all seizures and three (21%) of 12 patients were free of atonic seizures. The percentage change in motor seizures did not differ significantly between patients with Lennox-Gastaut syndrome and those with Dravet syndrome (Mann-Whitney U 448.0, $p=0.65$), but this study was not designed or powered to make this determination.

Results of our post-hoc analysis assessing interactions between cannabidiol and antiepileptic drugs showed that, of the 70 patients in the efficacy group receiving clobazam, 36 (51%) had a reduction of 50% or more in motor seizures, compared with only 18 (27%) of the

67 patients not taking clobazam. Similarly, more patients taking valproate had a reduction of 50% or more in motor seizures than did those not taking valproate (22 [54%] of 41 vs 32 [33%] of 96 patients). In multiple logistic regression analysis, only clobazam use independently predicted a reduction of 50% or more in motor seizures (OR 2.7, 95% CI 1.2–5.8; $p=0.01$).

Discussion

In our open-label study, add-on treatment with pure cannabidiol led to a clinically meaningful reduction in seizure frequency in many patients, and had an adequate safety profile in this patient population with highly treatment-resistant epilepsies. The safety and tolerability of cannabidiol was acceptable, with only five (3%) of 162 patients stopping treatment because of an adverse event. The efficacy of cannabidiol seems promising, with reductions of roughly a third in motor seizures and overall seizures in the efficacy analysis group. However, randomised controlled trials are needed to characterise the safety profile and true efficacy.

The adverse event profile of cannabidiol was favourable, with most patients tolerating the drug well despite its addition to a median of three concomitant antiepileptic drugs. However, the 20% rate of serious adverse events was higher than expected, with half these events deemed possibly related to cannabidiol. The absence of a control group with severe epilepsies, and the high burden of antiepileptic drugs, makes assessment of the rate of cannabidiol-related serious adverse events difficult. Surprisingly, only 3% of patients stopped cannabidiol treatment, even though 12% had a serious adverse event. This result could be because of parental belief in cannabidiol benefits attributable to the social media attention, reduced seizure frequency outweighing the serious adverse event, or occurrence of similar events before cannabidiol treatment (eg, status epilepticus).

Status epilepticus was the most common serious adverse event; this finding was surprising because cannabidiol has been shown not to be proconvulsant in more than 20 animal models of epilepsy.^{5,10} Status epilepticus is common for many of the disorders included in this study—namely, Dravet syndrome and Lennox-Gastaut syndrome—and could either represent background fluctuation in disease severity or could be related to cannabidiol. In patients who had status epilepticus during the study, concomitant antiepileptic drugs had not been reduced before status epilepticus onset. The only other serious adverse events reported in two or more patients were diarrhoea and weight loss, which might have resulted from cannabidiol use or the sesame oil in which cannabidiol is dissolved, or could be unrelated. Because diarrhoea and decreased appetite were both reported in 19% of patients, an association with the sesame-oil vehicle or cannabidiol itself is likely. Paradoxically, cannabidiol is considered a promising

treatment for inflammatory bowel disease on the basis of its anti-inflammatory effects in animals and findings of clinical improvement in human studies.²⁰ Liver function abnormalities and thrombocytopenia were reported in patients who were also taking valproate. Without a control group, we cannot establish whether this effect was related to any interaction between cannabidiol and valproate.

Common adverse events included somnolence, diarrhoea, fatigue, and decreased appetite. Somnolence and fatigue could be partly due to increased concentrations of the clobazam metabolite, N-desmethyl clobazam, via inhibition of CYP2C19 by cannabidiol.^{17,18} This active metabolite has anticonvulsant and toxic effects (somnolence)²¹ and an individual's CYP2C19 genotype has strong effects on the ratio of clobazam to its N-desmethyl metabolite.²² The increased responder rate and somnolence or fatigue in patients taking clobazam might partly reflect increases in the N-desmethyl metabolite. In a study of patients receiving the cannabidiol Epidiolex,¹⁸ N-desmethylclobazam concentrations increased by 60% compared to pre-Epidiolex concentrations, and that increase was associated with side-effects that resolved with clobazam dose reduction. Therefore, assessment of the efficacy of cannabidiol in patients not taking clobazam will be important to investigate in future randomised controlled trials. Notably, in our study, roughly a quarter of patients not taking clobazam also had a reduction in motor seizures of 50% or more, including six of the 14 patients who were free of motor seizures in the last 4 weeks of the observation period, who were not taking clobazam.

Patients included in this study were some of the most treatment-resistant patients at each centre, and had syndromes characterised by poor prognosis, with high rates of status epilepticus, use of rescue medication, and sudden unexpected death in epilepsy. Many of these patients had never achieved complete seizure control despite treatment with antiepileptic drugs, dietary or surgical treatments, or vagus nerve stimulation. The median number of concomitant antiepileptic drugs at the start of the study was three. In this study, the high rates of seizure reduction, and even seizure freedom for a few patients, suggest clinically meaningful efficacy. Additionally, because our observation period included the titration period, many patients did not achieve the target dose of cannabidiol until their 5th or 6th week on the study drug, which might have led to underestimation of the effect of the drug. Conversely, drug–drug interactions, particularly the increase in serum N-desmethylclobazam concentrations, might have played a part in seizure control, leading to an overestimation of cannabidiol efficacy. For many patients who achieved seizure freedom or a reduction in seizures of 90% or more, no previous antiepileptic drug regimen had been as efficacious during the preceding year. However, in view of the variable natural history of seizures in this

cohort, without a control group, the results regarding safety and efficacy must be interpreted cautiously.

The major limitations of this study were that it was open label and uncontrolled. The issue of the placebo response is especially relevant in paediatric trials of cannabis-derived treatments. Among findings from 32 randomised controlled trials of add-on treatment in patients with epilepsy, children had a significantly higher response to placebo (19%) than adults (9.9–15.2%),²³ whereas responder rates to the trial intervention were similar. Across five studies in patients with Lennox-Gastaut syndrome, the placebo response rate for reduction in median seizure frequency was about 10%, whereas the placebo response for a greater than 50% reduction in seizure frequency was about 19%.²⁴ A placebo effect is more concerning with cannabis-based preparations than with other antiepileptic drugs because of the intense media and family interest in the compound. In children in Colorado who received non-purified cannabis preparations, parents who had relocated were more than twice as likely to report a 50% reduction in seizures than were those who were long-time residents (47% vs 22%).²⁵ This finding strongly suggests a placebo response, because the relocated residents had such belief of efficacy that they moved to another state. Although diagnoses and preparations did not clearly differ between these groups, no analysis of the composition of the products was reported.

A 2015 FDA analysis showed that six (33%) of 18 over-the-counter cannabidiol preparations contained no cannabinoid.²⁶ Because our study assessed the effects of a 99% pure cannabidiol product with minimum amounts of other cannabinoids, our results cannot be extrapolated to non-purified forms of medical marijuana, including tetrahydrocannabinol and other cannabinoid and non-cannabinoid compounds. The possibility of a so-called entourage effect, whereby natural mixtures of multiple compounds produced by cannabis plants are more effective than isolated compounds, remains unproven in animals or humans. However, even if there was synergy between the cannabinoids, the issue remains that chronic use of recreational cannabis, which has a relatively high tetrahydrocannabinol content, is associated with addiction and chronic cognitive and behavioural disorders.⁶ Irrespective of whether with purified cannabidiol or cannabidiol in association with other cannabinoids, both safety and efficacy need to be assessed through blinded, randomised controlled studies using consistent study medication of known composition. Such studies are now underway for cannabidiol use in patients with Dravet syndrome or Lennox-Gastaut syndrome (ClinicalTrials.gov, numbers NCT02224703, NCT02224690, NCT02224560), and the results will be the start of any future research into use of cannabinoids in patients with epilepsy. Finally, another limitation of our study was that nocturnal seizures were not systematically ascertained, which is something that will need to be addressed in future studies.

Contributors

OD, EM, DF, and MRC planned the study, collected and analysed the data, and wrote and edited the manuscript. ET and LL planned the study, collected the data, and edited the manuscript. JS, IM, RF, AW, FF, and MW collected the data and edited the manuscript. NT, PB, JH, RK, JM, SN, NSS, and CAW collected the data and reviewed the manuscript. JB and AP collected the data and edited the manuscript. Each author was responsible for the integrity of their site's data.

Declaration of interests

OD has received funding support from the National Institute of Neurological Disorders and Stroke (NINDS) and the Centers for Disease Control and Prevention (CDC). EM has received personal fees from Stanley Brothers Social Enterprise, and grants from NINDS and the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), outside the submitted work. ET received support from GW Pharmaceuticals during the conduct of the study. LL has received supported, in part, from the National Institutes of Health (NIH) National Center for Advancing Translational Sciences (grant number 8UL1TR000150). The content presented here is solely the responsibility of the authors and does not necessarily represent the official views of the NIH. JS has received personal fees from Epilepsy Study Consortium, outside the submitted work. MW received support from GW Pharmaceuticals during the conduct of the study. PB received research funding from GW Pharmaceuticals for the neuropsychological testing component of this trial. JM has received personal fees from Cyberonics, outside the submitted work. SN has received grants from GW Research, outside the submitted work. AP reports grants from Pediatric Epilepsy Research Foundation, grants and personal fees from Cyberonics, grants from GW Pharmaceuticals, personal fees from GW Pharmaceuticals, personal fees from Health Logix, outside the submitted work. DF received non-financial support from GW Pharmaceuticals during the conduct of the study, and salary support to New York University from the Epilepsy Study Consortium, personal fees from Cyberonics, grants from UCB Pharmaceuticals, the Epilepsy Foundation, NINDS, and the CDC, and personal fees from Oxford University Press, outside the submitted work. MRC received a grant from the Epilepsy Therapy Project of the Epilepsy Foundation, and administrative support from GW Pharmaceuticals, during the conduct of the study. IM, RF, AW, FF, NT, JB, JH, RK, NSS, CAW declare no competing interests.

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