ORIGINAL ARTICLE

Effect of Cannabidiol on Drop Seizures in the Lennox–Gastaut Syndrome

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ABSTRACT

BACKGROUND

Cannabidiol has been used for treatment-resistant seizures in patients with severe early-onset epilepsy. We investigated the efficacy and safety of cannabidiol added to a regimen of conventional antiepileptic medication to treat drop seizures in patients with the Lennox–Gastaut syndrome, a severe developmental epileptic encephalopathy.

METHODS

In this double-blind, placebo-controlled trial conducted at 30 clinical centers, we randomly assigned patients with the Lennox–Gastaut syndrome (age range, 2 to 55 years) who had had two or more drop seizures per week during a 28-day baseline period to receive cannabidiol oral solution at a dose of either 20 mg per kilogram of body weight (20-mg cannabidiol group) or 10 mg per kilogram (10-mg cannabidiol group) or matching placebo, administered in two equally divided doses daily for 14 weeks. The primary outcome was the percentage change from baseline in the frequency of drop seizures (average per 28 days) during the treatment period.

RESULTS

A total of 225 patients were enrolled; 76 patients were assigned to the 20-mg cannabidiol group, 73 to the 10-mg cannabidiol group, and 76 to the placebo group. During the 28-day baseline period, the median number of drop seizures was 85 in all trial groups combined. The median percent reduction from baseline in drop-seizure frequency during the treatment period was 41.9% in the 20-mg cannabidiol group, 37.2% in the 10-mg cannabidiol group, and 17.2% in the placebo group ($P=0.005$ for the 20-mg cannabidiol group vs. placebo group, and $P=0.002$ for the 10-mg cannabidiol group vs. placebo group). The most common adverse events among the patients in the cannabidiol groups were somnolence, decreased appetite, and diarrhea; these events occurred more frequently in the higher-dose group. Six patients in the 20-mg cannabidiol group and 1 patient in the 10-mg cannabidiol group discontinued the trial medication because of adverse events and were withdrawn from the trial. Fourteen patients who received cannabidiol (9%) had elevated liver aminotransferase concentrations.

CONCLUSIONS

Among children and adults with the Lennox–Gastaut syndrome, the addition of cannabidiol at a dose of 10 mg or 20 mg per kilogram per day to a conventional antiepileptic regimen resulted in greater reductions in the frequency of drop seizures than placebo. Adverse events with cannabidiol included elevated liver aminotransferase concentrations. (Funded by GW Pharmaceuticals; GWPCARE3 ClinicalTrials.gov number, NCT02224560.)

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The Lennox–Gastaut syndrome is a severe developmental epileptic encephalopathy that has multiple causes and an incidence of approximately two cases per 100,000 population.[1] The disorder is characterized by several seizure types, severe cognitive impairment, and an abnormal electroencephalographic pattern of slow spike-and-wave complexes.[2] Seizures usually begin to occur before the age of 8 years and persist into adulthood in more than 90% of patients[3-5] Drop seizures due to an increase in (tonic) or loss of (atonic) motor tone are characteristic of this disorder and often result in serious injury.[6] Six medications are approved to treat seizures in patients with this syndrome. Despite treatment, disabling seizures continue to occur in most patients.[7]

Cannabidiol has been shown to reduce the frequency of seizures in animal models of epilepsy. Open-label data from a trial of a plant-derived pharmaceutical formulation of cannabidiol suggest that this medication may be effective in drug-resistant cases of epilepsy.[8] A randomized, controlled trial showed that cannabidiol significantly reduced the frequency of seizures among children and young adults with the Dravet syndrome, another form of developmental epileptic encephalopathy.[9] We performed a multicenter, randomized, double-blind, placebo-controlled trial to assess the efficacy and safety of two doses of cannabidiol, as compared with placebo, added to a regimen of conventional antiepileptic medication to treat drop seizures in patients with the Lennox–Gastaut syndrome.

Methods

Trial Design and Oversight

We conducted this phase 3, multicenter, randomized, double-blind, placebo-controlled trial at 30 participating centers (20 in the United States, 5 in Spain, 3 in the United Kingdom, and 2 in France). Patients were recruited from June 8 to December 15, 2015. Patients were followed for up to 24 weeks. The trial comprised a 4-week baseline period, a 14-week treatment period (2 weeks of dose escalation, followed by 12 weeks of stable dosing [maintenance phase]), a tapering period of up to 10 days, and a 4-week safety follow-up period after discontinuation of cannabidiol or placebo (Fig. S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org).

The protocol, available at NEJM.org, was approved by the institutional review board or independent ethics committee at each participating center. All the patients or their caregivers provided written informed consent, and children provided assent when possible. A data and safety monitoring committee monitored patient safety, and an adjudication board assessed any signs of potential abuse of the cannabidiol trial medication. The trial was conducted in accordance with the ethical standards in the International Conference on Harmonisation Good Clinical Practice guidelines. All the authors vouch for the accuracy and completeness of the reported outcome data and adverse events and for the fidelity of the trial to the protocol. The cannabidiol and placebo used in the trial were provided by the sponsor (GW Pharmaceuticals). The manuscript was written by the authors, three of whom were employees of GW Pharmaceuticals.

Patients

Patients with the Lennox–Gastaut syndrome were eligible for inclusion in the trial if they were between 2 and 55 years of age; had an electroencephalogram that showed a pattern of slow (<3.0 Hz) spike-and-wave complexes, which is characteristic of the disorder; and had at least two types of generalized seizures, including drop seizures, for at least 6 months. A drop seizure was defined as an epileptic seizure (atonic, tonic, or tonic–clonic) involving the entire body, trunk, or head that leads or could lead to a fall, injury, or slumping in a chair. Eligible patients were taking between one and four antiepileptic drugs and had at least two drop seizures each week during the baseline period. All medication doses and nonpharmacologic interventions for epilepsy (including ketogenic diet and vagus nerve stimulation) had to be stable in the 4 weeks before screening and throughout the trial. Key exclusion criteria were unstable medical conditions during the 4 weeks before screening, a history of alcohol or substance abuse, use of recreational or medicinal cannabis in the previous 3 months, use of corticotropins in the previous 6 months, or current use of felbamate for less than 1 year.

Procedures

Patients began a 4-week baseline period after screening, and those who met the eligibility crite-

ria were randomly assigned to one of three trial groups at a subsequent visit within 28 to 31 days after the screening visit. A computer-generated block randomization schedule, with block sizes of six, was produced by an independent statistician and held at a central location. An interactive voice-response or Web-based response system was used to randomly assign the patients, in a 2:2:1:1 ratio, to receive cannabidiol at a dose of either 20 mg per kilogram of body weight per day (the 20-mg cannabidiol group) or 10 mg per kilogram per day (the 10-mg cannabidiol group) or matching placebo administered at a volume equivalent to that for either the 20-mg cannabidiol dose or the 10-mg dose (the placebo group). The active treatment was a plant-derived pharmaceutical formulation of purified cannabidiol oral solution (100 mg per milliliter). Cannabidiol and the matching placebo solution (excipients alone) were provided in identical 100-ml amber glass bottles.

The cannabidiol or placebo was administered orally twice daily in equally divided doses starting at 2.5 mg per kilogram per day and increasing by 2.5 to 5.0 mg per kilogram every other day until the target dose was reached. Patients or their caregivers were trained to record, using an interactive voice-response system, the number and type of seizures, including drop seizures, that occurred each day. They also recorded in paper diaries cannabidiol or placebo use, use of concomitant medications, and adverse events that occurred during the treatment and follow-up periods. Clinic visits occurred at 2, 4, 8, and 14 weeks after randomization; additional telephone calls to assess the use of concomitant medications and adverse events were made at 6 weeks and 10 weeks, after tapering of the cannabidiol or placebo was completed, and at 4 weeks after the final dose was administered (Fig. S1 in the Supplementary Appendix). Patients who completed the treatment period could enter an open-label extension trial under a separate protocol (ClinicalTrials.gov number, NCT02224573). Information on deviations from the protocol is provided in the Supplementary Appendix.

OUTCOME MEASURES

The primary outcome was the percentage change from baseline in the frequency of drop seizures (average per 28 days) during the treatment period. An independent committee of experts from the Epilepsy Study Consortium (http://epilepsyconsortium.org) reviewed the patients' documented history of seizures and any new seizure types reported during the treatment period.

Key secondary outcomes were the percentage of patients who had at least a 50% reduction from baseline in drop-seizure frequency; the percentage change from baseline in the frequency of all types of seizures (total seizures); and the Patient or Caregiver Global Impression of Change from baseline in overall condition, as assessed on a 7-point scale that included three categories of improvement (slightly improved, much improved, or very much improved), three categories of worsening (slightly worse, much worse, or very much worse), and an option of "no change." These measures were prespecified as key secondary outcomes in the statistical analysis plan (available with the protocol) but not in the protocol. The analysis of the percentage of patients who had at least a 50% reduction from baseline in drop-seizure frequency was included as a key secondary outcome at the request of the European Medicines Agency.

Other secondary outcomes included the percentage of patients who had at least a 25%, at least a 75%, and a 100% reduction from baseline in drop-seizure frequency; the percentage of patients who had worsening or improvement in drop-seizure frequency during the treatment period; the percent reduction from baseline in the frequencies of nondrop seizures (all seizures except drop seizures), convulsive seizures (tonic–clonic, tonic, clonic, or atonic seizures), nonconvulsive seizures (myoclonic seizures, easily identifiable partial seizures because of a motor component, other partial seizures, or absence seizures), and individual seizures according to type; the Patient or Caregiver Global Impression of Change in Seizure Duration from baseline (decreased, stayed the same, or increased); the change from baseline in sleep disruption, as assessed on a scale from 0 (slept extremely well) to 10 (unable to sleep at all); the change from baseline in the score on the Epworth Sleepiness Scale[10] (range, 0 to 24, with higher scores indicating greater daytime sleepiness); the change from baseline in the score on the Quality of Life in Childhood Epilepsy questionnaire[11] (range, 0 to 100, with higher scores indicating better function); the change from baseline in the score on the Vineland Adaptive Behavior Scales, second

edition (Vineland-II; range, 20 to 160, with higher scores indicating better behavioral adaptation); and safety. The severity and causality of adverse events were determined by the investigators and were not independently adjudicated. The statistical analysis plan included additional secondary outcomes that were not analyzed because they had a low frequency of events, had low participation, or were introduced late in the conduct of the trial.

STATISTICAL ANALYSIS

On the basis of previously reported placebo effects on seizure rates in other trials involving patients with the Lennox–Gastaut syndrome[12,13] and allowing for a slightly greater placebo effect because of a higher expectation of effect with cannabidiol than with other agents, we assumed that the patients assigned to receive placebo would have a mean 18% reduction from baseline in drop-seizure frequency and that patients assigned to receive cannabidiol would have a mean 50% reduction. We calculated that 50 patients per trial group would provide 80% power to detect a 32 percentage-point difference between the cannabidiol group and the placebo group at a two-tailed significance level of 5%. Because of the rapid recruitment after notification of pending closure of recruitment, more patients underwent randomization than originally planned.

The primary outcome was analyzed with the use of a Wilcoxon rank-sum test, and the estimated median difference (with 95% confidence intervals) between the trial groups was calculated with the use of the Hodges–Lehmann approach. Hypotheses were tested in the following order: the 20-mg cannabidiol group, followed by the 10-mg cannabidiol group, was compared with the placebo group with respect to the primary outcome; the 20-mg cannabidiol group was then compared with the placebo group with respect to each key secondary outcome in the order listed above, and then the 10-mg cannabidiol group was compared with the placebo group with respect to each key secondary outcome in the same order. For the primary and key secondary outcomes only, the type I error was controlled by a hierarchical gate-keeping procedure, wherein each successive outcome was tested only if the preceding comparison was significant at a two-sided P value of 0.05.

The percentage of patients who had a response (≥50%, ≥75%, and 100% reductions in seizure frequency) was analyzed with the use of a Cochran–Mantel–Haenszel test that was stratified according to age group. An odds ratio (when applicable) with 95% confidence intervals is also presented. The median percentage change in the frequency of seizures (total, nondrop, convulsive, nonconvulsive, and individual seizures by type) was analyzed with the same methods as those used in the primary outcome analysis. Patient or Caregiver Global Impression of Change (overall condition and seizure duration) was analyzed with the use of ordinal logistic regression that included trial group (for analysis of overall condition and seizure duration) and age group (for analysis of seizure duration only) as factors. The secondary outcomes of sleep disruption, Epworth Sleepiness Scale, and Quality of Life in Childhood Epilepsy were assessed with the use of an analysis of covariance that included baseline scores and age group as covariates and trial group assignment as a fixed factor.

For patients who withdrew from the trial, data up to the time of withdrawal were included in the outcome analyses, and no imputation for missing data was performed. The monthly frequency of seizures during the treatment period was calculated with the use of available data from day 1 through day 99 or of available data at the time of the last dose of cannabidiol or placebo if the patient was withdrawn from the trial. Monthly frequency of seizures was calculated according to the following formula: ([number of seizures in the period] ÷ [number of days reported in the interactive response system in the period]) × 28. Sensitivity analyses were performed for the primary and key secondary outcomes, including one in which missing data from the days that were not reported in the interactive response system were imputed as the highest number of seizures for each patient according to the last observation carried forward, the next observation carried backward, and the mean number of daily seizures during the treatment period (calculated from nonmissing data) (Figs. S2 to S4 in the Supplementary Appendix). For the secondary outcomes other than the key secondary outcomes, the type 1 error was not controlled, and thus only descriptive statistics and 95% confidence intervals are reported. Analyses were performed with SAS software, version 9.3 (SAS Institute).

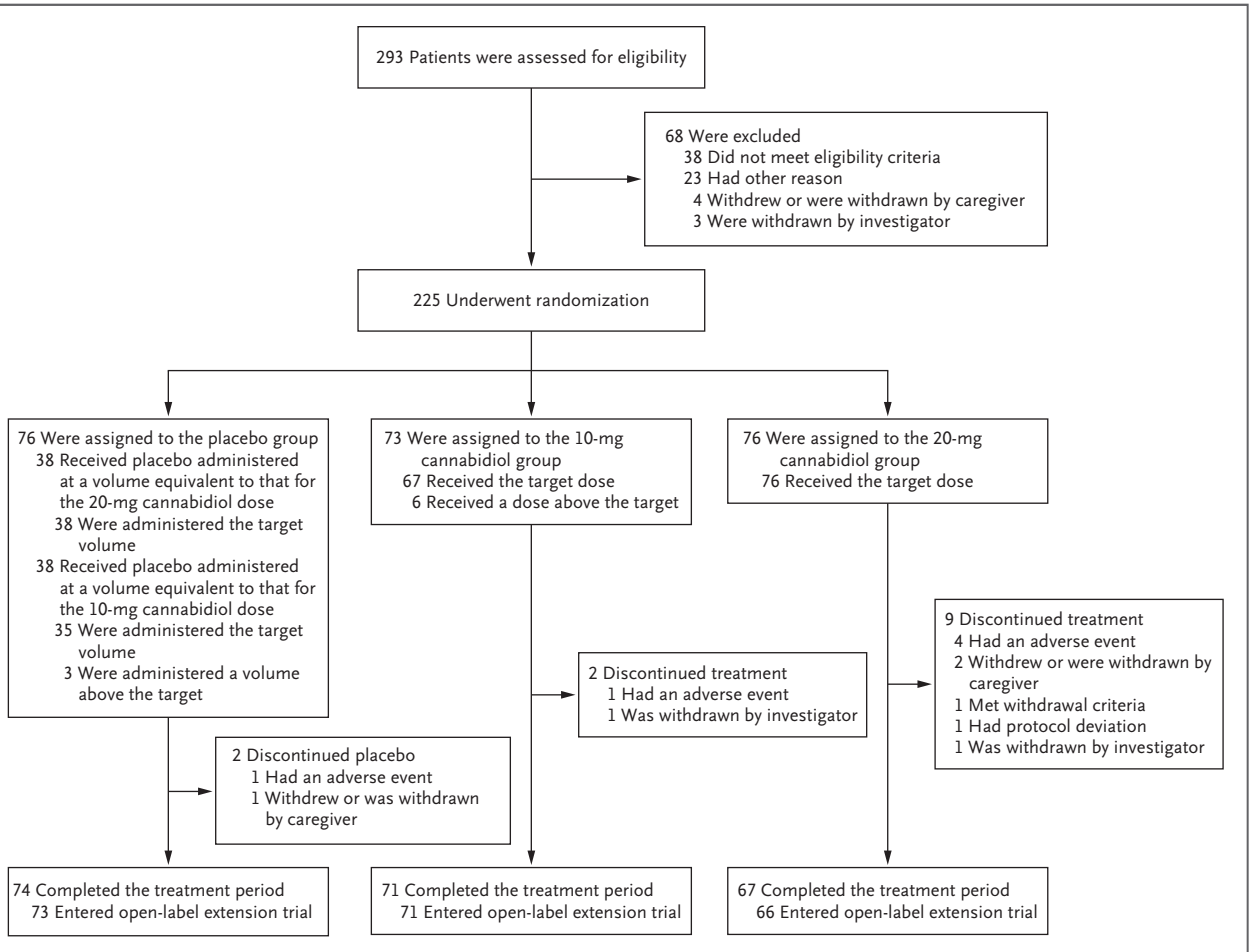

Figure 1. Screening, Randomization, and Treatment Period.

Patients were randomly assigned to receive cannabidiol at a dose of 20 mg per kilogram of body weight per day, cannabidiol at a dose of 10 mg per kilogram per day, or placebo. Among the 23 patients who had some "other reason" for exclusion, 12 had a change of investigator, 5 did not adhere to the use of the interactive voice-response system, 4 did not meet inclusion criteria or met exclusion criteria, 1 had a change in a concomitant antiepileptic drug, and 1 did not meet the randomization window. Six patients in the 10-mg cannabidiol group temporarily received a dose that was above the target and were therefore included in the 20-mg cannabidiol group for the safety analysis. Among the 9 patients who discontinued treatment in the 20-mg cannabidiol group, the one patient who met withdrawal criteria and the one patient who had a protocol deviation also had adverse events leading to discontinuation. Withdrawals are shown according to the primary reason reported for each patient.

RESULTS

PATIENTS

A total of 293 patients were assessed for eligibility at 30 clinical centers; 68 were excluded (Fig. 1). The remaining 225 patients underwent randomization, of whom 76 were assigned to the 20-mg cannabidiol group, 73 to the 10-mg cannabidiol group, and 76 to the placebo group; all patients received at least one dose of cannabidiol or placebo. A total of 13 patients (6%) discontinued either cannabidiol (11 patients) or placebo (2 patients); in 7 of the 11 patients who discontinued cannabidiol, the treatment was discontinued because of adverse events. Baseline characteristics were similar in the trial groups (Table 1); the majority of patients were white and were from the United States, and 30% were older than 18 years of age (Table S1 in the Supplementary Appendix). Patients in each group had previously received a median of 6 antiepileptic drugs (range, 0 to 22), but the drugs had failed to control the seizures; the patients were receiving a median of 3 antiepileptic drugs concomitantly at

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Variable	Placebo (N=76)	10-mg Cannabidiol (N=73)	20-mg Cannabidiol (N=76)
Age — yr			
Mean	15.3±9.3	15.4±9.5	16.0±10.8
Range	2.6–43.4	2.6–42.6	2.6–48.0
Male sex — no. (%)	44 (58)	40 (55)	45 (59)
Median no. of previous antiepileptic drugs (range)	6 (1–22)	6 (0–21)	6 (1–18)
Median no. of concomitant antiepileptic drugs (range)	3 (1–5)	3 (1–5)	3 (0–5)
Concomitant antiepileptic drugs — no. of patients (%)			
Clobazam	37 (49)	37 (51)	36 (47)
Valproate (all forms)	30 (39)	27 (37)	28 (37)
Levetiracetam	23 (30)	22 (30)	24 (32)
Lamotrigine	25 (33)	22 (30)	20 (26)
Rufinamide	20 (26)	19 (26)	26 (34)
Other concomitant interventions — no. of patients (%)			
Vagus nerve stimulation	21 (28)	15 (21)	17 (22)
Ketogenic diet	6 (8)	6 (8)	6 (8)
Median no. of seizures during the 28-day baseline period (interquartile range)			
Drop seizures	80.3 (47.8–148.0)	86.9 (40.6–190.0)	85.5 (38.3–161.5)
Total seizures: all types combined	180.6 (90.4–431.3)	165.0 (81.3–359.0)	174.3 (82.7–392.4)
Nondrop seizures†	78.0 (22.0–216.0)	95.7 (14.0–280.0)	93.7 (22.2–278.4)

* Plus–minus values are means ±SD. Patients were randomly assigned to receive cannabidiol at a dose of 20 mg per kilogram of body weight per day, cannabidiol at a dose of 10 mg per kilogram per day, or placebo.
† Nondrop seizures were defined as all seizures except drop seizures and were assessed among 70 patients in the placebo group, 55 patients in the 10-mg cannabidiol group, and 64 patients in the 20-mg cannabidiol group.

the time of trial entry. The most common antiepileptic drug was clobazam (49% of all patients). The median number of drop seizures during the 28-day baseline period was 85 across all groups. Of the 212 patients who completed the treatment period, 210 (99%) entered the open-label extension trial.

PRIMARY OUTCOME

The median percent reduction from baseline in the frequency of drop seizures per 28 days during the treatment period was 41.9% in the 20-mg cannabidiol group, 37.2% in the 10-mg cannabidiol group, and 17.2% in the placebo group. The estimated median difference in reduction between the 20-mg cannabidiol group and the placebo group was 21.6 percentage points (95% confidence interval [CI], 6.7 to 34.8; P=0.005), and the estimated median difference in reduction between the 10-mg cannabidiol group and the placebo group was 19.2 percentage points (95% CI, 7.7 to 31.2; P=0.002) (Fig. 2).

The results of the sensitivity analyses, including those performed to account for missing data, were consistent with the results of the primary analysis (Fig. S2 in the Supplementary Appendix). The differences between trial groups favored cannabidiol over placebo during the first 4 weeks of the maintenance phase and persisted throughout the treatment period.

KEY SECONDARY OUTCOMES

During the treatment period, a total of 30 patients (39%) in the 20-mg cannabidiol group, 26 patients (36%) in the 10-mg cannabidiol group, and 11 patients (14%) in the placebo group had at least a 50% reduction from their baseline in drop-seizure frequency (odds ratio for the 20-mg cannabidiol group vs. the placebo group, 3.85; 95% CI, 1.75 to 8.47; P<0.001; and odds ratio for

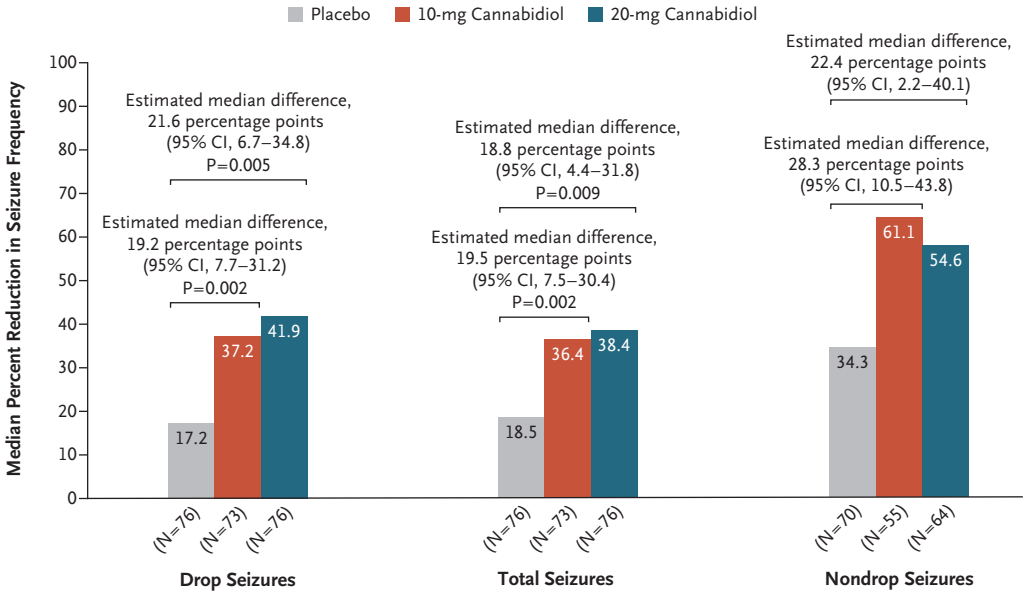

Figure 2. Median Percent Reductions in Monthly Seizure Frequency during the Treatment Period.

The estimated median differences are for the comparisons between each cannabidiol group and the placebo group and were calculated with the use of the Hodges–Lehmann approach. The P values were calculated with the use of a Wilcoxon rank-sum test. Drop seizures are defined as epileptic seizures (atonic, tonic, or tonic–clonic) involving the entire body, trunk, or head that lead or could lead to a fall, injury, or slumping in a chair; total seizures were defined as all types of seizures combined, and nondrop seizures as all seizures except drop seizures. P values for nondrop seizures are not shown because this was not a key secondary outcome, and type 1 error was not controlled.

the 10-mg cannabidiol group vs. the placebo group, 3.27; 95% CI, 1.47 to 7.26; P=0.003) (Fig. 3). The direction of these findings was consistent in the sensitivity analyses (Figs. S3 and S4 in the Supplementary Appendix). The percentage of patients who had at least a 75% reduction from baseline in drop-seizure frequency was higher in the 20-mg cannabidiol group (25%) and the 10-mg cannabidiol group (11%) than in the placebo group (3%) (Fig. 3). No patients were free from drop seizures during the entire treatment period (day 1 onward); however, 5 patients (7%) in the 20-mg cannabidiol group, 3 patients (4%) in the 10-mg cannabidiol group, and 1 patient in the placebo group (1%) were free from drop seizures during the entire maintenance phase (day 15 onward).

The median percent reduction from baseline in the frequency of all seizures per 28 days during the treatment period was 38.4% in the 20-mg cannabidiol group, 36.4% in the 10-mg cannabidiol group, and 18.5% in the placebo group. The estimated median difference in reduction between the 20-mg cannabidiol group and the placebo group was 18.8 percentage points (95% CI, 4.4 to 31.8; P=0.009), and the estimated median difference in reduction between the 10-mg cannabidiol group and the placebo group was 19.5 percentage points (95% CI, 7.5 to 30.4; P=0.002) (Fig. 2). The direction of these findings was consistent in the sensitivity analyses (Fig. S4 in the Supplementary Appendix).

An improvement from baseline in overall condition (slightly improved, much improved, or very much improved) according to the Patient or Caregiver Global Impression of Change at the last visit was reported in 43 of 75 patients (57%) in the 20-mg cannabidiol group, in 48 of 73 patients (66%) in the 10-mg cannabidiol group, and in 33 of 75 patients (44%) in the placebo group (odds ratio for the 20-mg cannabidiol group vs. the placebo group, 1.83; 95% CI, 1.02 to 3.30; P=0.04; and odds ratio for the 10-mg cannabidiol group vs. the placebo group, 2.57; 95% CI, 1.41 to 4.66; P=0.002) (Fig. S5 in the Supplementary Appendix).

OTHER SECONDARY OUTCOMES

The type 1 error was not controlled in the analysis of the other secondary outcomes. Therefore, only descriptive statistics and 95% confidence are presented in Table S3 in the Supplementary Appendix.

ADVERSE EVENTS

Six patients in the 10-mg cannabidiol group temporarily received a dose that was above the target and were therefore included in the 20-mg cannabidiol group for the safety analysis. Adverse events were reported in 77 of 82 patients (94%) in the 20-mg cannabidiol group, in 56 of 67 patients (84%) in the 10-mg cannabidiol group, and in 55 of 76 patients (72%) in the placebo group. Reductions in the dose of cannabidiol or placebo were permitted if unacceptable adverse events occurred, and changes in the doses of concomitant antiepileptic drugs (Table S4 in the Supplementary Appendix) were permitted on clinical grounds (e.g., on the basis of adverse events, laboratory findings, or plasma levels of concomitant medications). Of the adverse events that occurred among the patients, 89% were judged by the investigators (without independent adjudication) to be of mild or moderate severity. Common adverse events included somnolence, decreased appetite, diarrhea, upper respiratory tract infection, pyrexia, and vomiting (Table 2). A total of 8 patients discontinued cannabidiol or placebo because of adverse events and were withdrawn from the trial (6 in the 20-mg cannabidiol group, 1 in the 10-mg cannabidiol group, and 1 in the placebo group); elevation of serum aminotransferase concentrations was the most common adverse event among these patients, occurring in 4 of the 6 patients in the 20-mg cannabidiol group and in the patient in the 10-mg cannabidiol group, with maximum elevations in aspartate aminotransferase or alanine aminotransferase concentrations that were 3.2 to 12.2 times the upper limit of the normal range. Serious adverse events were reported in 33 patients (13 in each cannabidiol group and 7 in the placebo group). Among the 26 patients in the cannabidiol groups who had serious adverse events, the events were considered by the investigator to be related to the cannabidiol treatment in 7 patients (1 patient had multiple events); these events included elevated aspartate aminotransferase concentration (2 patients), elevated alanine aminotransferase concentration (1 patient), elevated γ-glutamyltransferase concentration (1 patient), somnolence (1 patient), increased seizures during weaning (1 patient), nonconvulsive status epilepticus (1 patient), lethargy (1 patient), constipation (1 patient), and worsening chronic cholecystitis (1 patient). Increases in serum aminotransferase concentrations greater than 3 times the upper limit of the normal range occurred in 14 of the 149 patients (9%) who received cannabidiol (11 patients in the 20-mg group and 3 in the 10-mg group [no patient in the placebo group had such an event]). Of these 14 patients, 11 (79%; 9 patients in the 20-mg group and 2 in the 10-mg group) were receiving valproic acid concomitantly. No patient met the criteria for severe drug-induced liver injury, and all cases of elevated aminotransferase concentrations greater than 3 times the upper limit of the normal range resolved either spontaneously during the treatment period (3 patients), after entry into the open-label extension trial (2 patients), or after the dose of

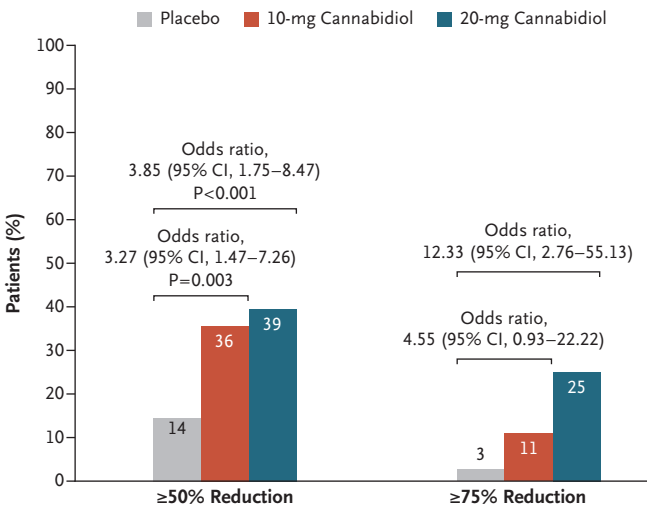

Figure 3. Reductions of at Least 50% and 75% from Baseline in Drop-Seizure Frequency during the Treatment Period.

The odds ratios are for the comparisons between each cannabidiol group and the placebo group. The P values were calculated with the use of a Cochran–Mantel–Haenszel test, with stratification according to age group (2 to 5 years, 6 to 11 years, 12 to 17 years, and 18 to 55 years). P values for reductions of at least 75% from baseline in drop-seizure frequency are not shown because this was not a key secondary outcome, and type 1 error was not controlled.

Table 2. Common Adverse Events Among Patients in the Safety-Analysis Set.*

Adverse Event	Placebo (N=76)	10-mg Cannabidiol (N=67)	20-mg Cannabidiol (N=82)
	number of patients (percent)		
Somnolence†	4 (5)	14 (21)	25 (30)
Mild	3 (4)	9 (13)	18 (22)
Moderate	1 (1)	4 (6)	6 (7)
Severe	0	1 (1)	1 (1)
Decreased appetite	6 (8)	11 (16)	21 (26)
Mild	5 (7)	8 (12)	15 (18)
Moderate	1 (1)	3 (4)	5 (6)
Severe	0	0	1 (1)
Diarrhea	6 (8)	7 (10)	12 (15)
Mild	6 (8)	6 (9)	10 (12)
Moderate	0	1 (1)	2 (2)
Upper respiratory tract infection	11 (14)	11 (16)	11 (13)
Mild	11 (14)	10 (15)	8 (10)
Moderate	0	1 (1)	3 (4)
Pyrexia	12 (16)	6 (9)	10 (12)
Mild	11 (14)	5 (7)	10 (12)
Moderate	1 (1)	1 (1)	0
Vomiting	9 (12)	4 (6)	10 (12)
Mild	9 (12)	2 (3)	10 (12)
Moderate	0	2 (3)	0
Mild nasopharyngitis	5 (7)	3 (4)	9 (11)
Status epilepticus	3 (4)	7 (10)	4 (5)
Mild	2 (3)	1 (1)	1 (1)
Moderate	1 (1)	4 (6)	3 (4)
Severe	0	2 (3)	0

* The table shows the adverse events that occurred in more than 10% of patients in any trial group. The severity of adverse events was determined by the investigators and was not independently adjudicated. Of the 73 patients who had been randomly assigned to the 10-mg cannabidiol group, 6 received a dose that was above the target (among whom 3 had somnolence, 3 had decreased appetite, and 1 had nasopharyngitis [patients could have >1 adverse event]); therefore, these patients were included in the 20-mg cannabidiol group in the safety analysis. Of the 3 patients with somnolence in the 10-mg cannabidiol group, 1 was taking clobazam concomitantly.

† Among the patients with somnolence, 15 of 25 patients (60%) in the 20-mg cannabidiol group, 11 of 14 patients (79%) in the 10-mg cannabidiol group, and 1 of 4 patients (25%) in the placebo group were taking clobazam concomitantly.

cannabidiol was tapered, cannabidiol was discontinued, or the dose of another antiepileptic drug was reduced (9 patients).

DISCUSSION

This trial involving children and adults with the Lennox–Gastaut syndrome showed that a pharmaceutical formulation of purified cannabidiol, administered at a dose of either 10 mg or 20 mg per kilogram per day, resulted in a significantly greater reduction in the frequency of drop seizures than placebo. Significant results in favor of cannabidiol were also seen in secondary outcome measures of at least a 50% reduction in the frequency of drop seizures, the reduction in the frequency of all seizures, and improvement in overall condition. Eight patients (5%) who received cannabidiol were free from drop seizures during the entire maintenance phase, as compared with one patient in the placebo group. These results are similar to those from trials of cannabidiol at a dose of 20 mg per kilogram per day in patients with the Lennox–Gastaut syndrome[14] and those with the Dravet syndrome.[9]

A prospective, open-label study of cannabidiol in patients with childhood epilepsy of various causes showed improvements in several components of quality of life.[15] However, an overall quality-of-life assessment in our trial showed no significant difference between cannabidiol and placebo.

The most common adverse events with cannabidiol were somnolence, decreased appetite, and diarrhea, particularly in the 20-mg cannabidiol group.[12,16] Serious adverse events and trial withdrawal were more common in the cannabidiol groups than in the placebo group.[5,17] Elevations in liver aminotransferase concentrations greater than three times the upper limit of the normal range occurred more frequently among the patients who received cannabidiol; most occurred in the 20-mg cannabidiol group and among patients receiving valproate concomitantly. A dose-ranging safety study of cannabidiol in the treatment of the Dravet syndrome showed that cannabidiol had no effect on systemic levels of valproate,[18] which suggests that any drug–drug interaction between valproate and cannabidiol is pharmacodynamic rather than pharmacokinetic. Cannabidiol inhibits the catalytic activity of cytochrome P450 2C19 and increases levels of the N-desmethyl metabolite of clobazam, which has biologic activity and may have contributed to the efficacy of the active drug in this trial.[19] Approximately half the pa-

tients in the cannabidiol and placebo groups were receiving clobazam concomitantly, and decreases in the dose of clobazam occurred more frequently among the patients in the cannabidiol groups than among those in the placebo group. A trial examining the effect of cannabidiol on serum concentrations of clobazam is under way (NCT02565108).

In the current trial comparing two different doses of cannabidiol with placebo in patients with the Lennox–Gastaut syndrome, cannabidiol was associated with greater reductions in the frequencies of drop seizures and all seizures than placebo. More adverse events were observed in each cannabidiol group than in the placebo group; the 10-mg cannabidiol group had a lower incidence of adverse events than the 20-mg group. Elevations in liver aminotransferase concentrations occurred in 9% of the patients who received cannabidiol.

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REFERENCES

1. Heiskala H. Community-based study of Lennox-Gastaut syndrome. Epilepsia 1997;38:526-31.

2. Arzimanoglou A, French J, Blume WT, et al. Lennox-Gastaut syndrome: a consensus approach on diagnosis, assessment, management, and trial methodology. Lancet Neurol 2009;8:82-93.

3. Kim HJ, Kim HD, Lee JS, Heo K, Kim DS, Kang HC. Long-term prognosis of patients with Lennox-Gastaut syndrome in recent decades. Epilepsy Res 2015;110:10-9.

4. Panayiotopoulos C. Epileptic encephalopathies in infancy and early childhood in which the epileptiform abnormalities may contribute to progressive dysfunction. In: Panayiotopoulos C, ed. The epilepsies: seizures, syndromes and management. Oxfordshire, United Kingdom: Bladon Medical Publishing, 2005:137-206.

5. Commission on Classification and Terminology of the International League Against Epilepsy. Proposal for revised classification of epilepsies and epileptic syndromes. Epilepsia 1989;30:389-99.

6. Camfield PR. Definition and natural history of Lennox-Gastaut syndrome. Epilepsia 2011;52:Suppl 5:3-9.

7. Douglass LM. Conclusions: long-term management of Lennox-Gastaut syndrome: future directions. Epilepsia 2011;52:Suppl 5:28.

8. Devinsky O, Marsh E, Friedman D, et al. Cannabidiol in patients with treatment-resistant epilepsy: an open-label interventional trial. Lancet Neurol 2016;15:270-8.

9. Devinsky O, Cross JH, Laux L, et al. Trial of cannabidiol for drug-resistant seizures in the Dravet syndrome. N Engl J Med 2017;376:2011-20.

10. Johns MW. A new method for measuring daytime sleepiness: the Epworth Sleepiness Scale. Sleep 1991;14:540-5.

11. Sabaz M, Cairns DR, Lawson JA, Nheu N, Bleasel AF, Bye AM. Validation of a new quality of life measure for children with epilepsy. Epilepsia 2000;41:765-74.

12. Ng YT, Conry JA, Drummond R, Stolle J, Weinberg MA. Randomized, phase III study results of clobazam in Lennox-Gastaut syndrome. Neurology 2011;77:1473-81.

13. Purcarin G, Ng YT. Experience in the use of clobazam in the treatment of Lennox-Gastaut syndrome. Ther Adv Neurol Disord 2014;7:169-76.

14. Thiele EA, Marsh ED, French JA, et al. Cannabidiol in patients with seizures associated with Lennox-Gastaut syndrome (GWPCARE4): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet 2018;391:1085-96.

15. Rosenberg EC, Louik J, Conway E, Devinsky O, Friedman D. Quality of Life in Childhood Epilepsy in pediatric patients enrolled in a prospective, open-label clinical study with cannabidiol. Epilepsia 2017;58(8):e96-e100.

16. 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.

17. Ng YT, Conry J, Paolicchi J, et al. Long-term safety and efficacy of clobazam for Lennox-Gastaut syndrome: interim results of an open-label extension study. Epilepsy Behav 2012;25:687-94.

18. Devinsky O, Patel AD, Thiele EA, et al. Randomized, dose-ranging safety trial of cannabidiol in Dravet syndrome. Neurology 2018 March 14 (Epub ahead of print).

19. 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.