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Trial of Cannabidiol for Drug-Resistant Seizures in the Dravet Syndrome

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ABSTRACT

BACKGROUND

The Dravet syndrome is a complex childhood epilepsy disorder that is associated with drug-resistant seizures and a high mortality rate. We studied cannabidiol for the treatment of drug-resistant seizures in the Dravet syndrome.

METHODS

In this double-blind, placebo-controlled trial, we randomly assigned 120 children and young adults with the Dravet syndrome and drug-resistant seizures to receive either cannabidiol oral solution at a dose of 20 mg per kilogram of body weight per day or placebo, in addition to standard antiepileptic treatment. The primary end point was the change in convulsive-seizure frequency over a 14-week treatment period, as compared with a 4-week baseline period.

RESULTS

The median frequency of convulsive seizures per month decreased from 12.4 to 5.9 with cannabidiol, as compared with a decrease from 14.9 to 14.1 with placebo (adjusted median difference between the cannabidiol group and the placebo group in change in seizure frequency, −22.8 percentage points; 95% confidence interval [CI], −41.1 to −5.4; P=0.01). The percentage of patients who had at least a 50% reduction in convulsive-seizure frequency was 43% with cannabidiol and 27% with placebo (odds ratio, 2.00; 95% CI, 0.93 to 4.30; P=0.08). The patient's overall condition improved by at least one category on the seven-category Caregiver Global Impression of Change scale in 62% of the cannabidiol group as compared with 34% of the placebo group (P=0.02). The frequency of total seizures of all types was significantly reduced with cannabidiol (P=0.03), but there was no significant reduction in nonconvulsive seizures. The percentage of patients who became seizure-free was 5% with cannabidiol and 0% with placebo (P=0.08). Adverse events that occurred more frequently in the cannabidiol group than in the placebo group included diarrhea, vomiting, fatigue, pyrexia, somnolence, and abnormal results on liver-function tests. There were more withdrawals from the trial in the cannabidiol group.

CONCLUSIONS

Among patients with the Dravet syndrome, cannabidiol resulted in a greater reduction in convulsive-seizure frequency than placebo and was associated with higher rates of adverse events. (Funded by GW Pharmaceuticals; ClinicalTrials.gov number, NCT02091375.)

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Seizures are difficult to control in the Dravet syndrome, a rare genetic form of epileptic encephalopathy primarily due to loss-of-function mutations in the *SCN1A* gene. Interest in cannabidiol for the treatment of epilepsy was generated by media reports of efficacy in children with the Dravet syndrome.[1] Four small trials of cannabidiol had yielded mixed results.[2-5] A series of in vitro and in vivo preclinical models of seizure showed that cannabidiol had activity against convulsive seizures.[6] Subsequently, the safety and effectiveness of a standardized oral solution of cannabidiol was tested in an open-label trial involving 214 children and young adults with drug-resistant epilepsy.[7] We conducted a randomized, double-blind, placebo-controlled trial of cannabidiol to treat drug-resistant epilepsy in the Dravet syndrome.

METHODS

TRIAL DESIGN AND OVERSIGHT

This was a multinational, randomized, double-blind trial of adjunctive cannabidiol versus placebo in children and young adults 2 to 18 years of age with the Dravet syndrome whose seizures were not controlled by their current antiepileptic-drug regimen. The trial comprised a 4-week baseline period, a 14-week treatment period (2 weeks of dose escalation and 12 weeks of dose maintenance), a 10-day taper period, and a 4-week safety follow-up period. The trial was approved by the review board or ethics committee at each participating institution and was conducted in accordance with the principles of the Declaration of Helsinki and the International Conference on Harmonisation Good Clinical Practice guidelines. All the patients or their parents or legal representatives provided written informed consent, and children mature enough to understand the trial provided assent. Patients could withdraw at any point without prejudice.

The funding source, GW Pharmaceuticals, was responsible for the trial design (with input from investigators and other experts), trial management, site monitoring, trial pharmacovigilance, data analysis, and statistical analysis. GW Pharmaceuticals prepared and provided the active treatment and placebo. Trial procedures were reviewed at multisite investigator meetings. Services were used for clinical laboratory testing; bioanalytical laboratory testing; design of the case-report form; data management; trial-agent distribution, returns, and destruction; the interactive voice-response system; diagnosis of the Dravet syndrome and seizure classification; and translation of documents. The authors vouch for the accuracy and completeness of the reported data and analyses and for the adherence of the trial to the protocol (available with the full text of this article at NEJM.org). The authors affirm that they approved the final draft of the manuscript.

Patients were eligible if they had an established diagnosis of the Dravet syndrome, were taking one or more antiepileptic drugs, and had had four or more convulsive seizures during the 28-day baseline period. An independent review of the previously documented diagnosis of the Dravet syndrome and the classification of seizure type was conducted for each patient by an independent panel appointed by the Epilepsy Study Consortium, under a standard protocol (see the protocol). All medications or interventions for epilepsy, including a ketogenic diet and vagus-nerve stimulation, were stable for 4 weeks before screening and were to remain unchanged throughout the trial. The dose of cannabidiol used in the trial was recommended by an independent data and safety monitoring committee (see the protocol), whose members reviewed data from a dose-ranging pharmacokinetic and safety evaluation of three doses of cannabidiol (5, 10, and 20 mg per kilogram of body weight per day) and identified the maximum dose that was safe and was not associated with unacceptable side effects.

PROCEDURES

After informed consent was obtained, patients entered a 4-week baseline period. The investigator trained the caregiver to record daily seizure information. Patients who satisfied all eligibility criteria were randomly assigned in a 1:1 ratio to receive cannabidiol or matching placebo, in addition to their stable antiepileptic-drug regimens. Cannabidiol oral solution contained 100 mg of cannabidiol per milliliter. The placebo solution was identical to the cannabidiol solution except for the absence of cannabidiol. The dose was escalated up to 20 mg per kilogram per day (or the equivalent volume of placebo) with the use of a 14-day dosing regimen that was approved by the data and safety monitoring committee.

All doses were administered twice daily. At the end of the treatment period, the cannabidiol and placebo solutions were tapered (10% each day) over a period of 10 days. After trial completion, all patients could enter a long-term open-label study.

Each day, patients or their caregivers recorded the number and type of convulsive seizures (tonic, clonic, tonic–clonic, or atonic) for the primary end-point measure of convulsive-seizure frequency, using an interactive voice-response system. Clinical laboratory assessments were performed at baseline and after 2, 4, 8, and 14 weeks of the trial regimen, as well as at the end of the taper period for those patients who did not enter the open-label extension study or who withdrew early and tapered the trial agent.

END POINTS

The primary end point was the percentage change per 28 days from the 4-week baseline period in convulsive-seizure frequency during the 14-week treatment period among patients who received cannabidiol as compared with placebo. The treatment period extended from randomization to the end of the 14-week trial or the date of the last dose. The maintenance period extended from the end of the 2-week dose-escalation period to the end of the 14-week trial or the date of the last dose. The intention-to-treat analysis set included all patients in the safety analysis set who had postbaseline efficacy data.

The secondary end-point measures were the Caregiver Global Impression of Change (CGIC), assessed on a 7-point Likert-like scale that used 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"; the number of patients with a reduction in convulsive-seizure frequency of at least 25%, at least 50%, at least 75%, and 100%; reduction in total seizure frequency and reduction of seizure subtypes; the duration of seizure subtypes, as assessed by the Caregiver Global Impression of Change in Seizure Duration (CGICSD) on a 3-point scale (decrease, no change, or increase in average duration); sleep disruption, assessed on a numerical rating scale from 0 to 10, with higher scores indicating greater disruption; the change in the score on the Epworth Sleepiness Scale (range, 0 to 24, with higher scores indicating greater daytime sleepiness); the score on the Quality of Life in Childhood Epilepsy questionnaire (range, 0 to 100, with higher scores indicating better function); the age-standardized score on the Vineland Adaptive Behavior Scales, second edition (Vineland-II; range, 20 to 160, with higher scores indicating better behavioral adaptation); the number of hospitalizations due to epilepsy; the number of patients with the emergence of seizure types that had not occurred during the baseline period; and the use of rescue medication.

The safety profile of cannabidiol was assessed on the basis of the number, type, and severity of adverse events as well as the Columbia Suicide Severity Rating Scale (for patients ≥6 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 agents was assessed by caregivers on a 5-point scale, ranging from "liked it a lot" to "did not like it at all."

STATISTICAL ANALYSIS

A total of 100 randomly assigned patients were planned. We calculated that this sample size would provide 80% power to detect an absolute difference of 32 percentage points between groups in the primary end point in an intention-to-treat analysis, with a standard deviation of 56% and a two-sided significance level of 5%. Randomization was performed and assigned independently, held centrally, and not divulged to any other person involved in the trial until after database lock.

Analysis of the primary end point was performed with the use of a Wilcoxon rank-sum test. An estimate of the median difference between cannabidiol and placebo, together with the 95% confidence interval, was calculated with the use of the Hodges–Lehmann approach. Sensitivity analyses of this primary end point were prespecified in the trial protocol and statistical analysis plan.

The percentage of patients with a reduction in convulsive-seizure frequency from baseline of at least 25%, at least 50%, at least 75%, or 100% was analyzed with the use of a Cochran–Mantel–Haenszel test and presented with odds ratios. The changes from baseline in the CGIC and the CGICSD were analyzed with the use of an ordinal logistic-regression model. For the secondary

end points, there were no adjustments of P values for multiple comparisons.

RESULTS

TRIAL POPULATION

At 23 centers in the United States and Europe, 177 patients were screened and 120 underwent randomization (Fig. 1). The characteristics of the trial groups were similar (Table 1). The mean age of the patients was 9.8 years (range, 2.3 to 18.4), and 52% were male. The baseline convulsive-seizure frequency was a median of 13.0 seizures per month (range, 3.7 to 1717). A total of 108 patients (90%) completed the treatment period (52 of 61 patients [85%] in the cannabidiol group and 56 of 59 patients [95%] in the placebo group). A total of 12 patients (10%) withdrew from the trial before completion (9 in the cannabidiol group and 3 in the placebo group). Of the 108 patients who completed the trial, 105 entered the open-label extension study.

Patients had previously tried a median of 4.0 antiepileptic drugs (range, 0 to 26) and were taking a median of 3.0 (range, 1 to 5). The most common were clobazam (65%), valproates (all forms, 59%), stiripentol (42%), levetiracetam (28%), and topiramate (26%). The most common type of convulsive seizure was generalized tonic–clonic, in 94 patients (78%), with secondarily generalized tonic–clonic seizures in 25 patients (21%) and other convulsive-seizure types less frequently. Nonconvulsive seizures were reported in 37 patients in the cannabidiol group (61%) and 41 patients in the placebo group (69%). Developmental delay was observed in 114 of the 118 children with available data and was described as severe or profound in 56 (48%) and mild or moderate in 58 (50%).

Adherence to the data acquisition and voice-response system was 97% for the cannabidiol group and 98% for the placebo group during the baseline period and 97% and 96%, respectively, during the treatment period. The mean (±SD) number of days on which a dose was missed was 0.6±2.1 in the cannabidiol group and 0.6±2.9 in the placebo group.

SEIZURE FREQUENCY

In the cannabidiol group, the primary end point of convulsive-seizure frequency decreased from a median of 12.4 seizures per month (range, 3.9 to 1717) at baseline to 5.9 (range, 0.0 to 2159) over the entire treatment period (Table 2), representing a median change of −38.9% (interquartile range, −69.5 to −4.8) from baseline. In the placebo group, the median monthly convulsive-seizure frequency decreased from 14.9 (range, 3.7 to 718) to 14.1 (range, 0.9 to 709), representing a median change of −13.3% (interquartile range, −52.5 to 20.2). The adjusted median difference in convulsive seizures between the cannabidiol group and the placebo group was −22.8 percentage points (95% confidence interval [CI], −41.1 to −5.4; P=0.01). Prespecified sensitivity analyses supported the primary analysis (Fig. S1 in the Supplementary Appendix, available at NEJM.org). The difference in favor of cannabidiol was seen in the first month of the maintenance period, during which the median number of convulsive seizures per month declined from 12.4 to 5.0 in the cannabidiol group and from 14.9 to 13.0 in the placebo group (P=0.002).

SECONDARY END POINTS

The results of the secondary end-point measures are shown in Table 3. The end point of a reduction in convulsive-seizure frequency by 50% or more during the treatment period occurred in 43% of the patients in the cannabidiol group and in 27% of the patients in the placebo group (odds ratio, 2.00; 95% CI, 0.93 to 4.30; P=0.08). During the treatment period, 3 patients in the cannabidiol group and no patients in the placebo group were free of seizures (P=0.08). For total seizures (all seizure types), the median frequency of seizures per month decreased from 24.0 to 13.7 in the cannabidiol group (adjusted reduction, 28.6%), versus a decrease from 41.5 to 31.1 in the placebo group (adjusted reduction, 9.0%). The adjusted median difference between groups of −19.2 percentage points was significant (P=0.03). For reduction in nonconvulsive seizures, there was no significant difference between groups (P=0.88). Rescue medication was used by 36 patients (59%) in the cannabidiol group and by 41 patients (69%) in the control group.

On the CGIC scale, 37 of 60 caregivers (62%) judged their child's overall condition improved in the cannabidiol group, as compared with 20 of 58 caregivers (34%) in the placebo group (P=0.02). There was no significant difference between groups in the sleep-disruption score

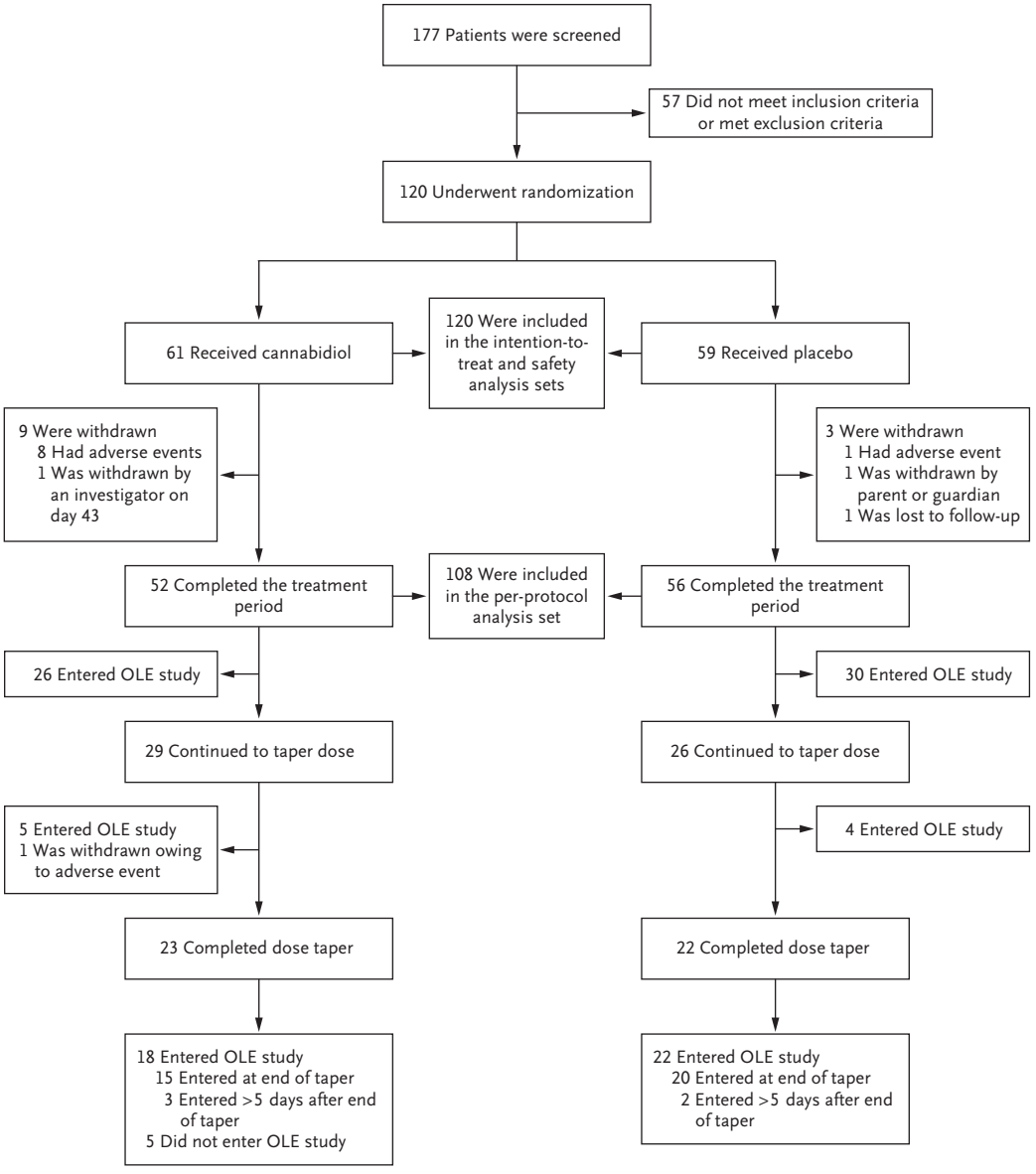

Figure 1. Screening, Randomization, Treatment Period, and Taper Period.

The primary reason that a patient in the cannabidiol group was withdrawn by an investigator on day 43 was nonadherence to trial-agent dosing. However, this patient also had seven serious adverse events that emerged during treatment by day 32, resulting in discontinuation of the trial agent. The 29 patients in the cannabidiol group who continued to taper the dose included 3 patients who were withdrawn during the treatment period and who tapered the trial agent. The 5 patients in the cannabidiol group who completed the dose taper but did not enter the open-label extension (OLE) study included 2 patients who were not eligible to enter the OLE study because they were withdrawn during the treatment period.

and Epworth Sleepiness Scale score, suggesting that there was no negative effect of cannabidiol on sleep. The Quality of Life in Childhood Epilepsy and Vineland-II scores showed no significant difference between cannabidiol and placebo. Changes in individual seizure types and the number of patients with the emergence of seizure types that had not occurred during the baseline period are reported in Table S2 in the Supplementary Appendix.

Table 1. Key Baseline Characteristics of the Trial Groups.*

Characteristic	Cannabidiol (N=61)	Placebo (N=59)	Total (N=120)
Age — yr			
Mean	9.7±4.7	9.8±4.8	9.8±4.8
Median (range)	9.1 (2.5–18.0)	9.2 (2.3–18.4)	9.2 (2.3–18.4)
Sex — no. (%)			
Female	26 (43)	32 (54)	58 (48)
Male	35 (57)	27 (46)	62 (52)
Geographic region — no. (%)			
United States	35 (57)	37 (63)	72 (60)
Rest of world	26 (43)	22 (37)	48 (40)
Body-mass index at baseline†	18.3±4.5	19.1±4.7	18.7±4.6
No. of previous antiepileptic drugs‡	4.6±4.3	4.6±3.3	4.6±3.8
No. of concomitant antiepileptic drugs	3.0±1.0	2.9±1.0	2.9±1.0
Antiepileptic drugs — no. (%)			
Clobazam	40 (66)	38 (64)	78 (65)
Valproate, all forms	37 (61)	34 (58)	71 (59)
Stiripentol	30 (49)	21 (36)	51 (42)
Levetiracetam	16 (26)	17 (29)	33 (28)
Topiramate	16 (26)	15 (25)	31 (26)
Other interventions — no. (%)			
Ketogenic diet	6 (10)	4 (7)	10 (8)
Vagus-nerve stimulation	6 (10)	9 (15)	15 (12)

* Plus–minus values are means ±SD.
† The body-mass index is the weight in kilograms divided by the square of the height in meters.
‡ These drugs were no longer being taken.

Table 2. Primary Efficacy End Point of Percentage Change in Convulsive-Seizure Frequency in Each Trial Group.*

Variable	Cannabidiol	Placebo	Adjusted Median Difference (95% CI)	P Value†
			percentage points	
No. of convulsive seizures per mo — median (range)				
Baseline	12.4 (3.9 to 1717)	14.9 (3.7 to 718)		
Treatment period	5.9 (0.0 to 2159)	14.1 (0.9 to 709)		
Percentage change in seizure frequency — median (range)	–38.9 (–100 to 337)	–13.3 (–91.5 to 230)	–22.8 (–41.1 to –5.4)	0.01

* CI denotes confidence interval.
† The P value was calculated with the use of a Wilcoxon rank-sum test with the Hodges–Lehmann approach.

SAFETY

Adverse events that emerged during the treatment period were reported in 93% of the patients in the cannabidiol group and 75% of the patients in the placebo group. Among patients with adverse events, 89% had events that were mild or moderate in severity (84% in the cannabidiol group and 95% in the placebo group). In the cannabidiol group, 75% of the patients with adverse events had events that were deemed

Table 3. Summary of Secondary End-Point Results during the Treatment Period (Intention-to-Treat Analysis Set).*

End Point	Cannabidiol vs. Placebo		P Value†
	Difference (95% CI)	Odds Ratio (95% CI)‡	
Change from baseline in CGIC score	−1.0 (−1.0 to 0.0)§		0.02
Reduction in convulsive seizures from baseline¶			
≥25% reduction		2.10 (1.01 to 4.35)	0.05
≥50% reduction: key secondary end point		2.00 (0.93 to 4.30)	0.08
≥75% reduction		2.21 (0.82 to 5.95)	0.11
100% reduction	4.9 (−0.5 to 10.3)‖		0.08
Percentage change from baseline in seizure frequency**			
Total seizures	−19.20 (−39.25 to −1.17)§		0.03
Total nonconvulsive seizures	0.00 (−21.36 to 31.59)§		0.88
Reduction from baseline in duration of seizure subtypes††			
Tonic–clonic seizures		2.48 (0.94 to 6.51)	0.07
Tonic seizures		3.40 (0.52 to 22.23)	0.20
Clonic seizures		1.25 (0.15 to 10.57)	0.84
Atonic seizures		7.44 (0.27 to 204.96)	0.24
Myoclonic seizures		2.89 (0.58 to 14.47)	0.20
Countable partial seizures		6.01 (0.83 to 43.21)	0.08
Other partial seizures		1.00 (<0.01 to >999.99)	1.00
Absence seizures		0.61 (0.14 to 2.62)	0.50
Change from baseline in other variables‡‡			
Sleep-disruption score	−0.4 (−1.5 to 0.7)		0.45
Epworth Sleepiness Scale score	1.5 (−0.2 to 3.2)		0.08
Quality of Life in Childhood Epilepsy score	1.5 (−3.8 to 6.8)		0.58
Vineland-II score	−2.6 (−6.8 to 1.6)		0.21
Inpatient hospitalizations due to epilepsy	0.0 (0.0 to 0.1)		0.54

* Scores on the Caregiver Global Impression of Change (CGIC) scale range from 1 (very much improved) to 7 (very much worse). Scores on the numerical rating scale for sleep disruption range from 0 to 10, with higher scores indicating greater disruption. Scores on the Epworth Sleepiness Scale range from 0 to 24, with higher scores indicating greater daytime sleepiness. Scores on the Quality of Life in Childhood Epilepsy questionnaire range from 0 to 100, with higher scores indicating better function. Age-standardized scores on the Vineland Adaptive Behavior Scales, second edition (Vineland-II), range from 20 to 160, with higher scores indicating better behavioral adaptation.

† P values of less than 0.05 were considered to indicate statistical significance. P values for change in CGIC score and percentage change from baseline in seizure frequency were calculated with the use of a Wilcoxon rank-sum test. P values for reduction in convulsive seizures for baseline were calculated with the use of a Cochran–Mantel–Haenszel test. P values for reduction from baseline in duration of seizure subtypes were calculated with the use of ordinal logistic regression. P values for change from baseline in other variables were calculated with the use of an analysis of covariance. P values were not adjusted for multiple comparisons.

‡ Odds ratios for reduction in convulsive seizures from baseline were calculated with the use of a Cochran–Mantel–Haenszel test. Odds ratios for reduction from baseline in duration of seizure subtypes were calculated with the use of ordinal logistic regression. Values greater than 1 are in favor of cannabidiol, and values less than 1 are in favor of placebo.

§ Shown is the estimated median difference (Hodges–Lehmann estimate). Negative values are numerically in favor of cannabidiol, and positive values are numerically in favor of placebo.

¶ The number of patients in each category was as follows: reduction of 25% or more, 38 patients in the cannabidiol group and 26 patients in the placebo group; reduction of 50% or more, 26 and 16, respectively; reduction of 75% or more, 14 and 7; and 100% reduction, 3 and 0. Because there were no patients in the placebo group with a 100% reduction, an odds ratio could not be calculated.

‖ Shown is the difference in percentage points, calculated with the use of a Cochran–Mantel–Haenszel test. Positive values indicate a difference in favor of cannabidiol, and negative values indicates a difference in favor of placebo.

** The number of patients analyzed was as follows: total seizures, 61 patients in the cannabidiol group and 59 patients in the placebo group; and total nonconvulsive seizures, 37 and 41, respectively.

†† This end point was assessed by means of the Caregiver Global Impression of Change in Seizure Duration (responses included decrease, no change, or increase in average duration). The number of patients analyzed was as follows: tonic–clonic seizures, 49 patients in the cannabidiol group and 41 patients in the placebo group; tonic seizures, 12 and 15, respectively; clonic seizures, 11 and 7; atonic seizures, 3 and 7; myoclonic seizures, 14 and 18; countable partial seizures, 12 and 13; other partial seizures, 3 and 5; and absence seizures, 16 and 19.

‡‡ Shown is the adjusted mean difference, calculated with the use of an analysis of covariance. For the sleep-disruption score, Epworth Sleepiness Scale score, and Vineland-II score, negative values are numerically in favor of cannabidiol, and positive values are numerically in favor of placebo. For the Quality of Life in Childhood Epilepsy score, positive values indicate a difference in favor of cannabidiol, and negative values indicate a difference in favor of placebo.

to be related to the trial agent, as compared with 36% in the placebo group. In both groups, the first occurrence of an adverse event was most commonly reported during the 14 days of dose escalation. Common adverse events (>10% frequency) in the cannabidiol group were vomiting, fatigue, pyrexia, upper respiratory tract infection, decreased appetite, convulsion, lethargy, somnolence, and diarrhea (Table 4). In the cannabidiol group, 8 patients withdrew from the trial owing to adverse events, as compared with 1 in the placebo group. The most common adverse event was somnolence, reported in 22 patients (36%) in the cannabidiol group and 6 patients (10%) in the placebo group. Of the 22 patients in the cannabidiol group in whom somnolence was reported, 18 were taking clobazam, as compared with 5 of 6 patients in the placebo group. Adverse events led to a dose reduction in 10 patients in the cannabidiol group. After dose reduction, the adverse events resolved completely in 8 patients and partially in 1 patient; in the remaining patient, the adverse event (loss of appetite) was ongoing. There were few dose adjustments of concomitant antiepileptic drugs during the trial.

Table 4. Adverse Events Occurring with a Frequency of Greater Than 10% in Either Trial Group, According to System Organ Class and Preferred Term.*

System Organ Class and Preferred Term	Cannabidiol (N=61)	Placebo (N=59)
	no. of patients (%)	
Gastrointestinal		
Diarrhea	19 (31)	6 (10)
Vomiting	9 (15)	3 (5)
General		
Fatigue	12 (20)	2 (3)
Pyrexia	9 (15)	5 (8)
Infections: upper respiratory tract infection	7 (11)	5 (8)
Metabolism: decreased appetite	17 (28)	3 (5)
Nervous system		
Convulsion	7 (11)	3 (5)
Lethargy	8 (13)	3 (5)
Somnolence	22 (36)	6 (10)

* Events were classified according to the *Medical Dictionary for Regulatory Activities*, version 17.0.

Serious adverse events were reported in 10 patients in the cannabidiol group and 3 in the placebo group. Status epilepticus was reported in 3 patients in the cannabidiol group and 3 in the placebo group; none of these events led to withdrawal from the trial, and none were deemed to be related to the trial agent. Elevated levels of liver aminotransferase enzymes (alanine aminotransferase or aspartate aminotransferase level >3 times the upper limit of the normal range) led to withdrawal from the trial of 3 patients in the cannabidiol group and 1 in the placebo group. Overall, elevated aminotransferase levels occurred in 12 patients in the cannabidiol group and 1 in the placebo group. All these patients were taking a form of valproate. Shift tables (in which baseline clinical laboratory values were categorized as "low," "normal," or "high" and any shift between categories was noted for post-baseline visits) confirmed that raised aminotransferase levels were more frequent in the cannabidiol group than in the placebo group. In the 9 cases of raised aminotransferase levels in which the patient continued in the trial, the enzyme levels returned to normal while the patient was receiving cannabidiol. There were no other clinically significant changes in clinical laboratory safety measures and no instances of suicidal ideation on the Columbia Suicide Severity Rating Scale in the 77 patients who completed the questionnaire. There were no deaths.

DISCUSSION

The Dravet syndrome is a catastrophic early-onset encephalopathic epilepsy, with a high mortality rate,[8] for which no antiepileptic drug has been approved in the United States. Convulsive seizures are associated with the risk of sudden unexpected death in epilepsy.[9] This randomized, controlled trial showed that cannabidiol resulted in a greater reduction in convulsive-seizure frequency than placebo among children and young adults with drug-resistant Dravet syndrome.

The screening criteria ensured that patients in the trial had severe epilepsy and met the International League against Epilepsy definition of drug-resistant epilepsy.[10] In this context, complete freedom from seizures was attained in three patients in the cannabidiol group and no patients in the placebo group during the entire treatment

period. An additional four patients were seizure-free in the maintenance period, but three of them withdrew early from the trial.

The global impression of change is an end point used in epilepsy studies to indicate the clinical relevance of a reduction in seizure frequency,[11] and the findings in this trial suggest that the reduction in convulsive-seizure frequency was meaningful as assessed by caregivers. The lack of a significant reduction in nonconvulsive-seizure frequency suggests that the antiseizure effect of cannabidiol may be specific to convulsive seizures in the Dravet syndrome or that the frequency of nonconvulsive seizures (e.g., brief staring spells) cannot be reliably counted by parents in developmentally delayed children. Nonconvulsive-seizure frequency was a secondary end point but not part of the primary efficacy assessment in this trial.

The adverse-event profile of cannabidiol in this trial was similar to that in the previous open-label trial.[7] Serious adverse events were more common in the cannabidiol group than in the placebo group (16% vs. 5%), and adverse events led to the withdrawal of eight patients in the cannabidiol group as compared with one in the placebo group. Some effects of cannabidiol may relate to interactions with other antiepileptic drugs.[12] Notable among these are somnolence (36% in the cannabidiol group vs. 10% in the placebo group), loss of appetite (28% vs. 5%), and diarrhea (31% vs. 10%). Abnormalities of hepatic aminotransferase levels occurred only in patients taking valproate, suggesting an interaction in which cannabidiol may potentiate a valproic acid–induced change in hepatic aminotransferase levels. The observation that the increases in hepatic aminotransferase levels mostly resolved while the patients continued taking the drug suggests that a transient metabolic stress on the liver may be responsible.

The trial design used here and the primary end point are common to other trials of recently approved antiepileptic drugs. A potential limitation to this partially subjective end point of convulsive-seizure frequency reported by caregivers is that the side effects of the drug being tested might unblind patients or caregivers to the trial-group assignments. However, a post hoc analysis of the reduction in seizure frequency showed that there was no relationship between the most common side effect (somnolence) and the treatment effect (see the Supplementary Appendix). Caregiver assessment showed differences in unpalatability between the active treatment and placebo (Table S1 in the Supplementary Appendix), which could have affected blinding in a small number of patients.

Cannabidiol lacks appreciable affinity or activity at the cannabinoid receptors and lacks the psychoactivity of the archetypal cannabinoid, tetrahydrocannabinol (THC). Cannabidiol did not provoke suicidality according to the approved assessment instrument, the Columbia Suicide Severity Rating Scale,[13,14] although its applicability to the population with the Dravet syndrome is unclear, because most patients have cognitive impairment.

This trial showed that cannabidiol reduced the frequency of convulsive seizures among children and young adults with the Dravet syndrome over a 14-week period but was associated with adverse events including somnolence and elevation of liver-enzyme levels. Additional data are needed to determine the long-term efficacy and safety of cannabidiol for the Dravet syndrome.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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