Devinsky 2018

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Bibliographic Reference	Devinsky, Orrin; Patel, Anup D.; Cross, J. Helen; Villanueva, Vicente; Wirrell, Elaine C.; Privitera, Michael; Greenwood, Sam M.; Roberts, Claire; Checketts, Daniel; VanLandingham, Kevan E.; Zuberi, Sameer M.; Group, Gwpcare Study; Effect of Cannabidiol on Drop Seizures in the Lennox-Gastaut Syndrome; The New England journal of medicine; 2018; vol. 378 (no. 20); 1888-1897

Study details

Study type	Randomised controlled trial (RCT)
Study location	USA, Spain, UK, France
Study setting	30 centres
Study dates	June 2015 - December 2015
Duration of follow-up	24 weeks
Sources of funding	GW Pharmaceuticals

Inclusion criteria	Diagnosis of Lennox-Gastaut syndrome with an electroencephalogram that showed a pattern of slow (<3.0 Hz) spike-and-wave complexes Age 2-55 years At least 2 types of generalised seizures, including drop seizures, for at least 6 months Taking 1-4 antiepileptic drugs At least 2 drop seizures during baseline period At least 2 each week . Baseline = 4 weeks Stable treatment For 4 weeks before screening, including ketogenic diet and vagus nerve stimulation
Exclusion criteria	Unstable medical conditions during 4 weeks before screening Known history of alcohol or substance abuse Prior cannabinoid use Recreational or medicinal in 3 months before screening Taking felbamate for less than 1 year before screening taken corticotrophins in the previous 6 months
Sample size	255
Outcome measures	% change in monthly seizures Monthly drop seizures Seizure responders (>50% reduction from baseline) Drop seizures % change total seizure frequency Global Impression of Change Responders (% reduction in drop seizures) % of patients with at least 25%, 50%, 75% and 100% reduction in drop seizure frequency % patients with worsening or improvements in drop seizure frequency % reduction from baseline in the frequencies of nondrop seizures Patient or Caregiver Global Impression of Change in Seizure Duration Change from baseline in sleep disruption Change from baseline in the score on the Epworth Sleepiness Scale Change from baseline in the score on the Quality of Life in Childhood Epilepsy questionnaire Change from baseline in the score on the Vineland Adaptive Behavior Scales Incidences of adverse events

Study arms

Cannabidiol 10 mg (N = 73)

Split between study groups	10 mg: 73
Loss to follow-up	10 mg: 4
% Female	10 mg: 45%
Mean age (SD)	10 mg: 15.4 (9.5)
Outcome measures	Global Impression of Change % reduction from baseline in the frequencies of nondrop seizures
Formulation	Cannabidiol oral solution with 100 mg/ml
How dose was titrated up	4 week baseline period Initial dose 2.5 mg/kg/day. Increased by 2.5 - 5.0 mg/kg every other day until 10 mg/kg/day reached
What the maintenance dose was	10 mg/kg/day
How long the maintenance dose was sustained for	12 weeks
Monitoring/reviewing procedure	Clinic visits at 2, 4, 8 and 14 weeks Phone calls to assess use of concomitant medication and adverse events at 6 and 10 weeks, after tapering period and 4 weeks after final dose Patients or caregivers trained to record number and type of seizures per day using interactive voice-response system. Used diaries to record use of CBD or placebo, use of concomitant medications and adverse events
Stopping criteria	Stopping criteria not reported 10 day tapering period

Cannabidiol 20 mg (N = 76)

Split between study groups	20 mg: 76

Loss to follow-up	20 mg: 18
% Female	20 mg: 41%
Mean age (SD)	20 mg: 16.0 (10.8)
Outcome measures	Patient or Caregiver Global Impression of Change in Seizure Duration
Formulation	Cannabidiol oral solution with 100 mg cannabidiol per ml
How dose was titrated up	4 week baseline period Initial dose 2.5 mg/kg/day. Increased by 2.5 - 5.0 mg/kg/day until reached 20 mg/kg/day
What the maintenance dose was	20 mg/kg/day
How long the maintenance dose was sustained for	12 weeks
Monitoring/reviewing procedure	Clinic visits at 2, 4, 8 and 14 weeks Phone calls to assess use of concomitant medication and adverse events at 6 and 10 weeks, after tapering period and 4 weeks after final dose Patients or caregivers trained to record number and type of seizures per day using interactive voice-response system. Used diaries to record use of CBD or placebo, use of concomitant medications and adverse events
Stopping criteria	Stopping criteria not reported 10 day tapering period

Placebo (N = 76)

Split between study groups	Placebo: 76
Loss to follow-up	Placebo: 4
% Female	Placebo: 42%

Mean age (SD)	Placebo: 15.3 (9.3)
Outcome measures	% change total seizure frequency
Formulation	Identical placebo oral solution

- Risk of bias

Domain 1: Bias arising from the randomization process

Risk of bias judgement for this domain

Low

Domain 2: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)

Risk of bias for this domain

Low

Domain 3. Bias due to missing outcome data

Risk-of-bias judgement for this domain

Low

Domain 4. Bias in measurement of the outcome

Risk-of-bias judgement for this domain

Low

Domain 5. Bias in selection of the reported result

Risk-of-bias judgement domain

Low

Overall bias and Directness

Risk of bias judgement

Low

Overall Directness

Partially applicable

(Patients with Lennox-Gastuat syndrome)