Thiele 2018

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Bibliographic Reference	Thiele, Elizabeth A.; Marsh, Eric D.; French, Jacqueline A.; Mazurkiewicz-Beldzinska, Maria; Benbadis, Selim R.; Joshi, Charuta; Lyons, Paul D.; Taylor, Adam; Roberts, Claire; Sommerville, Kenneth; Group, Gwpcare Study; Cannabidiol in patients with seizures associated with Lennox-Gastaut syndrome (GWPCARE4): a randomised, double-blind, placebo-controlled phase 3 trial; Lancet (London, England); 2018; vol. 391 (no. 10125); 1085-1096

Study details

Study type	Randomised controlled trial (RCT)
Study location	USA, Netherlands, Poland
Study setting	Clinical sites
Study dates	April 2015 - October 2015
Duration of follow-up	14 weeks
Sources of funding	GW Pharmaceuticals
Inclusion criteria	Age 2 - 55 years Diagnosis of Lennox-Gastaut syndrome including documented history of slow [<3·0 Hz] spike-and-wave electroencephalograms, and evidence of more than one type of generalised seizure, including drop seizures, for at least 6 months Current therapy failed to provide adequate relief inadequately managed on at least two antiepileptic drugs, inclusive of previous and current treatments), were taking one to four antiepileptic drugs, and had at least two drop seizures per week during the 4-week baseline period Stable treatment including ketogenic diet and vagus nerve stimulation for 4 weeks before screening
Exclusion criteria	Clinically significant unstable illness other than epilepsy in 4 weeks before screening Known history of alcohol or substance abuse Prior cannabinoid use taken corticotrophins in the previous 6 months Taking felbamate for less than 1 year before screening Positive urine tetrahydrocannabinol screen

	Pregnant or lactating or planning pregnancy during or within 3 months of the end of the trial
Sample size	171
Outcome measures	% change in monthly seizures drop seizures (attack or spell (atonic, tonic, or tonic-clonic) involving the entire body, trunk, or head that led or could have led to a fall, injury, slumping in a chair, or hitting the patient's head on a surface) Seizure responders (>50% reduction from baseline) >50% reduction in monthly drop seizures % change total seizure frequency All seizure subtypes reported Global Impression of Change Patient and caregiver for seizure duration, and change in sleep disruption and daytime sleepiness, quality of life, and adaptive behaviours Responders (% reduction in drop seizures) 25%, 50%, 75%, 100% % reduction in seizures non-drop, convulsive (tonic-clonic, tonic, clonic, or atonic seizures), non-convulsive (myoclonic, countable focal, other focal, or absence seizures), and individual seizure types Hospital admissions for epilepsy

Study arms

Cannabidiol (N = 86)	
Loss to follow-up	14
% Female	48%
Mean age (SD)	15.5 (8.7)
Formulation	Cannabidiol oral solution 20 mg/kg/day in two doses
How dose was titrated up	2 week titration period Initial dose 2.5 mg/kg/day
What the maintenance dose was	20 mg/kg/day in two doses
How long the maintenance dose was sustained for	12 weeks followed by tapering period of up to 10 days

Monitoring/reviewing procedure	Assessed in clinic on days 15, 29, 57 and 99
Stopping criteria	Adverse events

Placebo (N = 85)

Split between study groups	Cannabidiol: 86
Loss to follow-up	1
% Female	49%
Mean age (SD)	15.3 (9.8)
Formulation	Identical oral placebo 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

Some concerns

(Insufficient data collected for some outcomes (Cannabis Withdrawal Scale, number of hospital admissions, and cognitive function))

Overall bias and Directness

Risk of bias judgement

Low

Overall Directness

Partially applicable

(Patients with Lennox-Gastaut syndrome)