Devinsky 2018

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Bibliographic Reference	Devinsky, Orrin; Patel, Anup D.; Thiele, Elizabeth A.; Wong, Matthew H.; Appleton, Richard; Harden, Cynthia L.; Greenwood, Sam; Morrison, Gilmour; Sommerville, Kenneth; Group, Gwpcare Part A Study; Randomized, dose-ranging safety trial of cannabidiol in Dravet syndrome; Neurology; 2018; vol. 90 (no. 14); e1204-e1211

Study details

Study type	Randomised controlled trial (RCT)
Study location	USA & UK
Study setting	11 sites
Study dates	October 2014 - March 2015
Duration of follow-up	3 weeks
Sources of funding	GW Research Ltd
Inclusion criteria	Age 4-10 years Diagnosis of Dravet syndrome Taking 1 or more antiepileptic drugs Less than 4 convulsive seizures during 4 week baseline Stable treatment Including ketogenic diet and vagus nerve stimulation, stable for 4 weeks
Exclusion criteria	Not stated
Sample size	34
Outcome measures	Incidences of adverse events Seizure frequency

Study arms

	Cannabidiol 5 mg (N = 10)	
	Split between study groups	10

% Female	50%
Mean age (SD)	7.2 (1.9)
Formulation	Cannabidiol oral solution with 25 or 100 mg cannabidiol per ml
How dose was titrated up	Initial dose 2.5 mg/kg/day Increased by 2.5 - 5.0 mg/kg every other day until 5 mg/kg/day reached (3 day titration phase). Dose reductions allowed in the case of adverse events
What the maintenance dose was	5 mg/kg/day
How long the maintenance dose was sustained for	3 weeks
Monitoring/reviewing procedure	No information on timing of clinic visits Monitoring included review of haematology, biochemistry and urinalysis, physical examinations, monitoring of vital signs and ECGs and assessments for adverse events, seizure frequency and suicidality
Stopping criteria	Stopping criteria not reported. 10 day taper period

Cannabidiol 10 mg (N = 8)

Split between study groups	CBD (10 mg): 8 CBD (20 mg): 20 Placebo: 7
% Female	63%
Mean age (SD)	7.4 (2.1)
Formulation	Cannabidiol oral solution with 25 or 100 mg cannabidiol per ml
How dose was titrated up	Initial dose 2.5 mg/kg/day Increased by 2.5 - 5.0 mg/kg every other day until 10 mg/kg/day reached (7 day titration phase). Dose reductions allowed in the case of adverse events

What the maintenance dose was	10 mg/kg/day
How long the maintenance dose was sustained for	3 weeks
Monitoring/reviewing procedure	No information on timing of clinic visits Monitoring included review of haematology, biochemistry and urinalysis, physical examinations, monitoring of vital signs and ECGs and assessments for adverse events, seizure frequency and suicidality
Stopping criteria	Stopping criteria not reported. 10 day taper period

Cannabidiol 20 mg (N = 20)

Split between study groups	CBD (20 mg): 20 Placebo: 7
% Female	67%
Mean age (SD)	CBD (20 mg): 8.7 (1.8) Placebo: 7.0 (0.9)
Formulation	Cannabidiol oral solution with 25 or 100 mg cannabidiol per ml
How dose was titrated up	Initial dose 2.5 mg/kg/day Increased by 2.5 - 5.0 mg/kg every other day until 20 mg/kg/day reached (11 day titration phase). Dose reductions allowed in the case of adverse events
What the maintenance dose was	20 mg/kg/day
How long the maintenance dose was sustained for	3 weeks
Monitoring/reviewing procedure	No information on timing of clinic visits Monitoring included review of haematology, biochemistry and urinalysis, physical examinations, monitoring of vital signs and ECGs and assessments for adverse events, seizure frequency and suicidality

Stopping criteria	Stopping criteria not reported. 10 day taper period

Placebo (N = 7)

Split between study groups	CBD (20 mg): 20 Placebo: 7
% Female	Placebo: 29%
Mean age (SD)	Placebo: 7.0 (0.9)
Formulation	Identical placebo oral solution

- Risk of bias

Domain 1: Bias arising from the randomization process

Risk of bias judgement for this domain

Some concerns

(No information for allocation concealment and some differences in baseline characteristics (e.g. gender and ethnicity %, but this may be because of low number of participants))

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

(Adverse events)

Domain 4. Bias in measurement of the outcome

Risk-of-bias judgement for this domain

Some concerns

(No information on whether outcome assessors were aware of the intervention)

Domain 5. Bias in selection of the reported result

Risk-of-bias judgement domain

Low

Overall bias and Directness

Risk of bias judgement

Some concerns

(No information for allocation concealment, some differences in baseline characteristics (e.g. gender and ethnicity %, but this may be because of low number of participants), and no information on whether outcome assessors were aware of the intervention)

Overall Directness

Partially applicable

(Patients with Dravet syndrome)