CNS Drugs - Supplementary Information

Highly purified cannabidiol for epilepsy treatment: a systematic review of epileptic conditions beyond Dravet syndrome and Lennox Gastaut syndrome

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Table e-1. Summary of the included studies

Study	Population	Main Outcomes
GWPCARE6 (NCT02544763)	N=224 patients with TSC; CBD25 (n=75), CBD50 (n=73), placebo (n=76). Mean age 13.7±10.0 years, male sex 58.1%, median ASMs 4, median concomitant ASMs 3, mean monthly TSC-associated seizure frequency 86.7±91.8, mean monthly total seizure frequency 102.4±148.5.	Reduction in TSC-associated seizure frequency: 48.6% (CBD25; p<0.001), 47.5% (CBD50; p=0.002), 26.5% (placebo); responder rate TSC-associated seizure frequency: 36.0% (CBD25; p=0.069), 39.7% (CBD50; p=0.025), 22.4% (placebo); reduction in total seizure frequency: 48% (CBD25; p=0.001), 48% (CBD50; p=0.002), 27% (placebo) during 16-week treatment period. Improvement in overall condition on S/CGIC: 69% (CBD25; p=0.007), 62% (CBD50; p=0.058), 40% (placebo). Treatment withdrawal: 10.3%. AEs: 88.0% (CBD25), 97.3% (CBD50), 89.5% (placebo); diarrhea: 30.7% (CBD25), 54.8% (CBD50), 25.0% (placebo); decreased appetite: 20.0% (CBD25), 23.3% (CBD50), 11.8% (placebo); somnolence: 13.3% (CBD25), 26.0% (CBD50), 9.2% (placebo); vomiting: 16.0% (CBD25), 17.8% (CBD50), 9.2% (placebo); pyrexia: 18.7% (CBD25), 16.4% (CBD50), 7.9% (placebo); increased transaminases: 12.0% (CBD25), 24.7% (CBD50), 0% (placebo). SAEs: 21.3% (CBD25), 13.7% (CBD50), 2.6% (placebo).
GWPCARE7 (NCT02953548)	N=9 patients with infantile spasms. Mean age 12.2±5.6 years, male sex 33.3%. Maximum CBD dose 40 mg/kg/day.	Day 15: freedom of clinical spasms 0/9; resolution of hypsarrhythmia 0/9. Improvement at CGIC 7/9; improvement at PGIC 6/9. Treatment withdrawal: 0%. AEs 5/9 (55.6%). Diarrhea 2/9 (22.2%), upper respiratory tract infection 2/9 (22.2%), somnolence 1/9 (11.1%), constipation 1/9 (11.1%), vomiting 1/9 (11.1%), increased appetite 1/9 (11.1%), irritability 1/9 (11.1%), hematuria 1/9 (11.1%), cough 1/9 (11.1%), application site erosion 1/9 (11.1%). SAEs 1/9 (11.1%) (status epilepticus).
NCT02954887	N=9 patients with infantile spasms (open-label extension phase of GWPCARE7 trial). Mean age 12.2±5.6 years, male sex 33.3%. Maximum CBD dose 40 mg/kg/day.	Freedom of clinical spasms: 1/8 (day 29), 2/6 (day 43), 1/4 (day 127), 1/3 (day 211), 1/2 (day 295), 3/7 (day 379). Resolution of hypsarrhythmia: 1/8 (day 29), 0/6 (day 43), 1/4 (day 127), 0/3 (day 211), 1/2 (day 295), 3/7 (day 379). Freedom of clinical spasms and resolution of hypsarrhythmia: 1/8 (day 29), 0/6 (day 43), 0/4 (day 127), 0/3 (day 211), 1/2 (day 295), 3/7 (day 379). Improvement at CGIC: 7/9 (day 29), 6/9 (day 43), 4/9 (day 127), 3/9 (day 211), 3/9 (day 295), 6/9 (day 379); improvement at PGIC: 4/9 (day 29), 5/9 (day 43), 4/9 (day 127), 1/9 (day 211), 1/9 (day 295), 4/8 (day 379). Treatment withdrawal: 77.8%. AEs (day 417): 7/9 (77.8%). SAEs (day 417): 2/9 (22.2%).
Saade et al., 2015	N=1; 10-month-old boy with malignant migrating partial seizures in infancy, daily seizure frequency 10-20. CBD 25 mg/kg/day.	Reduction in seizure frequency >90% (from 10-20 per day to 5 per week) at M6, with up to 9 days of clinical seizure freedom; improvement in alertness and no AEs.
Geffrey et al., 2015	N=13 patients with refractory epilepsy concomitantly taking CLB and CBD. Age 1-19 years, male sex 53.8%, concomitant ASMs 1-3. CBD 25 mg/kg/day.	Mean change in seizure frequency (week 8): 51%; >50% decrease in seizure frequency (week 8): 9/13 (69.2%). Increased seizure frequency: 2/13 (15.4%). Reduction in CLB dose: 10/13 (76.9%). AEs: 76.9%. Drowsiness 46.2%, ataxia 15.4%, irritability 15.4%, restless sleep 7.7%, urinary retention 7.7%, tremor 7.7%, loss of appetite 7.7%. Treatment withdrawal (week 36): 0%

Devinsky et al., 2016	N=214 patients with severe, intractable, childhood-onset, treatment resistant epilepsy: DS 20%, LGS 19%, unknown 9%, minimal brain dysfunction 8%, generalized epilepsy 6%, CDKL5 mutation 5%, TSC 4%, Aicardi syndrome 4%, epilepsy with myoclonic absences 3%, Doose syndrome 3%, FIRES 2%, dup15q disorders 2%, Ohtahara syndrome 1%, neuronal ceroid lipofuscinosis 1%, Jeavons syndrome 1%, sodium channelopathy (not Dravet) 1%, focal epilepsy of unknown cause 1%, Down syndrome, autoimmune DEPDC5 mutation, stroke, SNAP25 mutation, Rett syndrome (MECP2 mutation), genetic not otherwise specified, myoclonic epilepsy not otherwise specified, MECP2 duplication, epilepsy of infancy with migrating focal seizures (KCNT1 mutation), KCNQ2 encephalopathy, infantile spasms, focal epilepsy due to mesial temporal sclerosis, epileptic encephalopathy due to hypoxic-ischemic encephalopathy, congenital disorder of glycosylation 1P, Angelman-like syndrome (each <1%). Median age 10.5 (IQR 0.9-26.2) years, male sex 49%, median background ASMs 3 (IQR 0-7), median total daily treatments 3 (IQR 1-7), median monthly seizure frequency 60.0 (IQR 22.0-131.8). Mean CBD dose (12 weeks) 22.9 mg/kg/day.	Median reduction in seizure frequency (12 week): 34.6% (all), 55.0% (focal), 54.3% (atonic), 36.5% (tonic), 16% (tonic-clonic); 36.5% (motor). Responder rates (12 week): 37% (all seizures), 39% (motor seizures). Seizure freedom: 4% (motor seizures), 2% (all seizures). AEs: 79.0%. AEs reported in >5% of patients: somnolence 25.3%, decreased appetite 19.1%, diarrhoea 19.1%, fatigue 13.0%, convulsion 11.1%, increased appetite 8.6%, status epilepticus 8.0%, lethargy 7.4%, weight increased 7.4%, weight decreased 6.2%, drug concentration increased 5.6%; elevated liver functions tests 6.8%. SAEs: 12.3%. Diarrhoea or related side-effects (e.g., weight loss) more likely if CBD daily dose >15 mg/kg. Somnolence more common in patients taking CLB. Drug withdrawal due to AEs: 3.1%.
Gofshteyn et al., 2016	N=7 children with FIRES. Male sex 71.4%, median prior ASMs 7 (range 4-9). CBD dose 15-25 mg/kg/day.	Resolution of status epilepticus in 1 out of 2 patients treated in the acute phase. Mean seizure frequency reduction in 5 patients treated in the chronic phase: 90.9% (week 4) and 65.3% (week 48) for all seizure types, 99.6% (week 4) and 62.3% (week 48) for focal motor seizures, 75% (week 4) and 73% (week 48) for generalized tonic-clonic seizures, 99.6% (week 4) and 62.4% (week 48) for focal seizures with impaired consciousness. AEs: dizziness (2/7), decreased appetite and weight loss (1/7), nausea/vomiting (1/7).
Hess et al., 2016	N=18 patients with TSC. Age 2-31 years, male sex 50%, median number of prior ASMs 7 (range 4-11), median number of concomitant ASMs 3 (range 1-7), median weekly seizure frequency 22.0 (IQR 14.8-57.4). CBD dose 15-50 mg/kg/day.	Median seizure frequency reduction (all seizure types): 48.9% (M2), 48.8 (M3), 35.4 (M6), 51.9 (M9), 57.5 (M12). Seizure frequency reduction >50%: 50% (M2), 50% (M3), 38.9% (M6), 50% (M9), and 50% (M12) for all seizure types; 100% (M2), 75% (M3), 100% (M6), 100% (M9), and 100% (M12) for spasms; 75% (M2), 75% (M3), 75% (month 6), 75% (month 9), and 50% (month 12) for atonic seizures; 50% (M2), 66.7% (M3), 50% (M6), 60% (M9), and 100% (M12) for tonic clonic seizures; 38.5% (M2), 53.8% (M3), 30.8% (M6), 53.8% (M9), and 50% (M12) for focal seizures with impairment of consciousness or awareness; 25% (M2), 50% (M3), 50% (M6), 66.7% (M9), and 50%

		(M12) for focal seizures evolving to bilateral generalized convulsive seizures; 57.1% (M2), 42.9% (M3), 57.1% (M6), 66.7% (M9), and 50% (M12) for tonic seizures. Cognitive gains 12/14 (85.7%), behavioral improvement 6/9 (66.7%). Treatment withdrawal: 16.7%. AEs: 66.7%. Drowsiness 44.4%, ataxia 27.8%, diarrhea 22.2%, agitation 16.7%, poor sleep 11.1%, irritability 11.1%, appetite suppression 5.6%, confusion 5.6%, vomiting 5.6%, increased self-stimulation 5.6%, behavioral difficulties 5.6%. SAEs: 0%
Kaplan et al., 2017	N=5 patients with Sturge-Weber syndrome. Age 2-19 years, male sex 20%, prior ASMs 2-7, concomitant ASMs 1-4, monthly seizure frequency 1-33.5. CBD dose 5-25 mg/kg/day.	Seizure frequency reduction: 10-90% (week 14), 12-100% (at most recent visit – week 6-60). Treatment withdrawal for lack of efficacy: 2/5 (at week 9 and 38). AEs: 5/5; temporary increased seizures (3/5), behavioral issues (2/5), increased transaminases (1/5), tiredness (1/5). All patients reported improvements in quality of life; subjective improvements in motor, speech, and cognitive abilities, level of alertness, vocalization or communication, mood and behavior also reported.
Rosenberg et al., 2017	N=48 patients with childhood onset, treatment resistant epilepsy; DS 16.7%, genetic generalized epilepsy 16.7%, LGS 16.7%, CDKL5 disorder 12.5%, Aicardi syndrome 10.5%, duplication 15q syndromes 10.5%, unknown etiology 6.3%, other 10.5%. Median age 11.7 (range 3.1-27.2) years, male sex 48%, median concomitant ASMs 3 (range 1-5), median monthly motor seizures frequency 27.5 (IQR 12-89). Median maximum CBD dose 28.2 (range 10.2-51) mg/kg/day.	Median reduction in seizure frequency (week 12): 39.4%. Responder rate (week 12): 41.7%. Somnolence, drowsiness, or fatigue: 58.3%. Improvement in patient QOLCE as assessed by caregivers (energy/fatigue, memory, other cognitive functions, control/helplessness, social interactions, behaviour and global quality of life item sub-scores), not related with changes in seizure frequency or adverse events.
Gaston et al., 2017	N=81 patients with treatment-resistant epilepsy. Pediatric arm (n=42): age 10.4±5.3 years, male sex 52.4%, prior ASMs 8.8±3.1, concomitant ASMs 3.0±1.0. Adult arm (n=39): age 29.1±11.3 years, male sex 48.7%, prior ASMs 10.4±3.9, concomitant ASMs 3.2±0.9. CBD maximum dose: 50 mg/kg/day.	Sedation more frequent with higher N-CLB levels in adults and transaminases levels significantly higher in participants taking concomitant VPA. Sedation resulted in CLB dose decrease, but not discontinuation. Increases in topiramate, rufinamide, and N-CLB and decrease in CLB serum levels with increasing CBD dose. Increases in serum levels of zonisamide and eslicarbazepine with increasing CBD dose in adults. Except for CLB and N-CLB, all mean level changes were within the therapeutic ranges.
Warren et al., 2017	N=3 patients with brain tumor related refractory epilepsy. Age 17-38 years, male sex 100%, prior ASMs 4-10, concomitant ASMs 3-4, biweekly seizure frequency 4-11. CBD dose 20-50 mg/kg/day.	Seizure frequency reduction on-study 58-94% (month 2-11) in 2/3. Seizure frequency increase by 21% in 1/3. Improvement in seizure severity as assessed by CSSS (3/3) and TMD score (2/3).
Grayson et al., 2017	N=1 patient with post-stroke epilepsy and warfarin therapy. Age 44 years, male sex, two concomitant ASMs. Maximum CBD dose 40 mg/kg/day.	Non-linear increase in the INR with CBD up-titration. At the most recent study visit (day 518 from starting CBD; CBD dose 35 mg/kg/day), warfarin dose reduced by approximately 30%. No bleeding complications during follow-up.

Szaflarski et al., 2018	N=607 with treatment resistant epilepsy; LGS 16%, DS 9%, TSC 4%, Aicardi syndrome 3%, CDKL5 disorders 3%, Doose/Dup15q/FIRES 4%, other 41%, unknown (20%). Age 13.1 (range 0.4-62.1) years, male sex 52%, concomitant ASMs 3 (range 0-10), median monthly convulsive seizure frequency 72 (IQR 22-196). Median CBD dose between weeks 12 and 96: 25 mg/kg/day.	Median reduction in seizure frequency (week 12-96): 46-53% (total), 44-51% (convulsive). Responder rate (week 12-96): 48-52% (total), 44-52% (convulsive seizures). Seizure freedom rate (week 12-96): 6-8% (total seizures), 9-13% (convulsive). Seizure frequency increase (week 12-96): 19-25% (total), 20-27% (convulsive). Drug withdrawal for lack of efficacy: 14.7%. AEs: 88.3%; diarrhoea 29.2%, somnolence 22.4%, convulsion 16.8%, decreased appetite 12.4%, upper respiratory tract infection 12.4%, vomiting 11.4%, fatigue 10.7%, pyrexia (10.4%), SE 7.4%, pneumonia 6.8%. Increased transaminases: 10% (whose 75% on VPA). Somnolence more common in patients taking (38%) than not taking (14%) CLB. SAEs: 32.8%. Drug withdrawal for AEs: 5.3%.
Devinsky et al. 2018	N=55 patients with severe childhood-onset epilepsy; CDKL5 deficiency disorder 36.4%, Aicardi syndrome 34.6%, Dup15q syndrome 14.5%, Doose syndrome 14.5%. Age 1-30 years, male sex 20%, median monthly convulsive seizure frequency 59.4 (IQR 25-126), median monthly total seizure frequency 77.0 (IQR 31-209). Mean maximum CBD dose: 29.6 mg/kg/day.	Median convulsive seizure frequency reduction 51.4% (week 12), 59.1% (week 48). Convulsive seizures responder: 50% (week 12), 57% (week 48). Withdrawal from extended observation (week 144): for any cause 27%, lack of efficacy 16%, AEs 7%, withdrew consent 2%, lost to follow-up 2%. Diarrhea 27%, somnolence 22%, fatigue 22%, decreased appetite 20%, vomiting 16%, convulsion 9%, respiratory tract infection 9%, weight loss 7%, irritability 7%, pyrexia 7%. SAEs: 30.9%. <u>CDKL5 deficiency disorder</u> Median decrease in convulsive seizure frequency: 40.8% (week 12), 59.7% (week 48). Responder rate (convulsive seizures): 41% (week 12), 53% (week 48). <u>Aicardi syndrome</u> Median decrease in convulsive seizure frequency: 58.3% (week 12), 59.2% (week 48). Responder rate (convulsive seizures): 71% (week 12), 71% (week 48). <u>Dup15q syndrome</u> Median decrease in convulsive seizure frequency: 25.0% (week 12), 38.4% (week 48). Convulsive seizures responder rate: 38% (week 12), 38% (week 48). <u>Doose syndrome</u> Median decrease in convulsive seizure frequency: 58.6% (week 12), 28.8% (week 48). Convulsive seizures responder rate: 43% (week 12), 57% (week 48).
Chen et al., 2018	N=40 patients with drug resistant childhood onset epilepsy; focal/multifocal epilepsy 25%, epileptic encephalopathy (not otherwise specified) 25%, LGS 20%, DS 15%, Doose syndrome 10%, generalized epilepsy 5%. Median age 8.5 years (range 1.6-16.6), male sex 55%, median prior ASMs 9 (range 3-14), median current ASMs 3 (range 1-5). Maximum CBD dose 25 mg/kg/day.	Seizure frequency not reliably recorded because of disease severity. AEs: 62.5%; somnolence 32.5%, diarrhoea 10.0%, anorexia 10.0%, increased seizures 5.0%, vomiting 2.5%, rash 2.5%; increased transaminases 5.0% (all receiving VPA). SAEs: 20.0%. Drug withdrawal for AEs: 5.0%. Improvement at CGIC: 12/40 (30.0%). Improvement at PGIC: 12/40 (30.0%).
Szaflarski et al., 2018	N=132 patients (70 children and 62 adults) with treatment resistant epilepsy.	Seizure frequency reduction: 63.6% (week 12), sustained with no significant differences at week 24 and week 48. Responder rate: 55.4% (week 12), 51.2% (week 24), 63.9% (week 48). Seizure freedom: 6.2% (week 12), 6.8% (week 24), 3.3% (week 48). Significant decrease in AEP at week 12 with stable scores thereafter (week 24 and 48).

	Mean age 19.5±12.9 years, male sex 47%, mean prior ASMs 9.1±3.4, mean concomitant ASMs 2.9±0.9, mean biweekly seizure frequency 144.4±407.9. Mean CBD dose (48 weeks) 27.5 ± 12.4 mg/kg/day.	Retention rate: 77% (week 48). Significant decrease in CSSS scores at 12 weeks and stable thereafter (week 24 and 48).
Sands et al., 2018	N=26 patients with refractory epilepsy; DS 23%, epilepsy with myoclonic absences 19%, CDKL5 epileptic encephalopathy 19%, LGS 15%, other 23%. Mean age 9 (range 1-17) years, male sex 50%, mean prior ASMs 7 (range 4-11), mean concomitant ASMs 2 (range 0-3). Maximum CBD dose 25 mg/kg/day.	Seizure frequency reduction >50%: 38.4% (M3), 56.7% (M6), 42.3% (M9), 38.4% (M12), 42.3% (M18), 34.6% (M24), 26.9% (M36). Seizure freedom: 11.5% AEs: 80.8%. Decreased appetite/food aversion 38.4%, diarrhoea/loose stools 34.6%, weight loss 30.7%, increased seizures 15.4%, increased ASM concentrations 11.5%, elevated transaminases with concurrent VPA 11.5%, nausea/vomiting 7.7%, somnolence/drowsiness 7.7%, agitation 7.7%, insomnia 7.7%, anxiety 3.8%, fatigue/lethargy 3.8%. SAEs 23.1%: hypoalbuminemia 3.8%, status epilepticus 11.5%, catatonia/psychosis 7.7%. Retention rate (48 months): 34.6%. Treatment withdrawal: 57.7% for lack of efficacy, 7.7% for adverse events. <u>CDKL5 deficiency</u> Responder rate 1/5, increased seizure frequency 2/5 (any seizure types; 8-36 months). AEs: 4/5. Drowsiness, weight loss, sleepiness, diarrhea, loose stools, agitation. Treatment withdrawal: 4/5 (at 5-23 months). <u>Epilepsy with myoclonic absences</u> Responder rate 2/5, seizure freedom 2/5, increased seizure frequency 2/5 (any seizure types; 5-53 months). Treatment withdrawal: 3/5 (at 5-6 months). AEs: 5/5; decreased appetite/food aversion, weight loss, elevated transaminases, loose stools, lethargy <u>Epilepsy of infancy with migrating focal seizures</u> CBD discontinued after 6 months for inefficacy. AEs: intermittent vomiting. <u>SCN8A epileptic encephalopathy</u> CBD dose reduced for side effects and discontinued after 25 months for inefficacy. AEs: drowsiness, somnolence. <u>Refractory generalized epilepsy</u> Responder rate (generalized tonic-clonic seizures): 1/1, responder rate (tonic seizures): 1/1 after 43 months of CBD treatment. AEs: decreased appetite, weight loss, diarrhea, elevated transaminases. <u>Refractory focal epilepsy</u> Focal epilepsy (vasculitis): responder rate 1/1 at 40 months; AE: none. Focal epilepsy (unknown etiology): responder rate 0/1; treatment withdrawal 1/1 (at 5 months); AE: diarrhea.
Rajaraman et al. 2018	N=1 patient with super-refractory status epilepticus. Age 12 years, female, history of epilepsy of unknown cause (possible encephalitis). CBD dose 20 mg/kg/day.	Clinical seizure freedom achieved on day 12, clinical and subclinical seizure freedom demonstrated on day 64; sequential discontinuation of phenobarbital, midazolam, perampanel, and dose-reduction of lacosamide. AEs: fatigue, weight gain.

Gaston et al., 2019	N=53 patients with treatment-resistant epilepsy; focal epilepsy 66%, LGS 17%, symptomatic generalized epilepsy 7.5%, idiopathic generalized epilepsy 3.8%, DS 1.9%, TSC 1.9%, electrical status epilepticus during sleep 1.9%. Age 19-62 years, male sex 50.9%, >10 prior ASMs 34.0%, mean concomitant ASMs 3.2 (range 1-5), bi-weekly seizure count 41.5% (<14 seizures), 30.2% (14-50 seizures), 28.3% (>50 seizures). CBD dose at 12 months: 30 mg/kg/day (median), 50 mg/kg/day (maximum).	Seizure count: at enrolment 41.5% (<14 seizures), 30.2% (14-50 seizures), 28.3% (>50 seizures); at 12 months: 62.3% (<14 seizures), 24.5% (14-50 seizures), 13.2% (>50 seizures) ($p<0.001$). Significant improvement in CSSS ($p<0.001$), AEP ($p<0.001$), POMS ($p=0.010$) and QOLIE-89 ($p=0.004$) total scores after 12 months.
Leino et al., 2019	N=1 patient with refractory epilepsy receiving tacrolimus for interstitial nephritis. Age 32 years, female sex. CBD dose 20 mg/kg/day.	Improvement in seizure frequency. Approximately 3-fold increase in dose normalized tacrolimus concentrations while receiving CBD.
Szaflarski et al. 2019	N=100 (44 children, 56 adults) patients with treatment-refractory epilepsy. Mean age 25.5 (±16.1) years, male sex 46%, median concomitant ASMs 3 (range 1-4), mean biweekly seizure frequency 68.9±185.4. Mean CBD dose 24.7±14.6 mg/kg/day.	Median seizure frequency reduction 54%, responder rate 57% (at the time of CBD plasma level testing after stable dosage for at least 14 days). Diarrhoea 30%, sedation 14%, depression and mood issues 7%, nausea/vomiting 3%. Positive linear correlation between CBD dosage (range 5-50 mg/kg/day) and CBD plasma peak level range 7.1-1200 ng/mL). Increased CBD levels related to improvement in seizure frequency after adjusting for age with higher dose/levels associated with a higher response rate.
Allendorfer et al., 2019	N=22 patients with treatment-resistant epilepsy. Median age 30.5 5 years, male sex 36.4%, median monthly seizure frequency 12.5. Median CBD dose 25 mg/kg/day (range 15-25 mg/kg/day).	Improvements in seizure frequency (median reduction: 71.2%, $p=0.0009$), seizure severity (median reduction for CSSS total score: 80.5%, $p<0.0001$), and mood (median reduction for POMS TMD score: 41.3%, $p=0.0026$) after a median time of 10 weeks and achieving a stable CBD dose for at least 2 weeks. CBD reduced right superior frontal gyrus and right insula/ middle frontal gyrus activation related to stimulus conflict resolution and reduced differences in condition-based functional connectivity of the right superior frontal gyrus.
Martin et al., 2019	N=27 patients with treatment resistant epilepsy. Mean age 34±14 years, male sex 48%, mean prior ASMs 10±4, mean concomitant ASMs 3.3±0.9. Mean CBD dose at the time of one-year cognitive testing: 36.5 mg/kg/day.	Mean reduction in seizure severity as assessed by CSSS 63.1±60 ($p<0.0001$) at 12 months. No statistically significant score changes were found across the global composite scales (Fluid and Crystallized) and seven individual tests measuring aspects of working memory, episodic memory, executive function, processing speed, and language of NIH Toolbox Cognition Battery at 12 months. No statistically significant association between changes in cognitive test performance and CBD dose or seizure severity change.
Gaston et al., 2019	N=132 patients with treatment resistant epilepsy. Mean age 19.5±12.9 years, male sex 47%, mean concomitant ASMs 2.8±0.9, mean seizure frequency 144.4±407.9.	Sustained reduction in seizure frequency and severity as assessed by the CSSS at 12, 24, and 48 weeks.

	Maximum CBD dose 50 mg/kg/day.	No significant differences in seizure frequency and severity reduction between CLB-On and CLB-Off patients and between patients taking and not taking interacting ASMs (rufinamide, eslicarbazepine, zonisamide, topiramate).
Savage et al., 2020	N=47 (32 CLB-On and 15 CLB-Off) patients with treatment resistant epilepsy; TSC 36.2%, DS 14.9%, other genetic disorders 6.4%, congenital brain malformations 14.9%, generalized epilepsy of unknown aetiology 19.1%, other 8.5%. Age 2.5-51 years, male sex 59.6%, mean weekly seizure frequency 62.3±141.4 (CLB-On) and 45.0±52.3 (CLB-Off) Maximum CBD dose 50 mg/kg/day.	Seizure frequency reduction: 26.8% (CLB-On), 26.2% (CLB-Off) at M2; 58.5% (CLB-On), 49.5% (CLB-Off) at the best point of seizure control within the first year. Responder rate: 50.0% (CLB-On), 26.7% (CLB-Off) at M2; 71.9% (CLB-On), 33.3% (CLB-Off) at the best point of seizure control within the first year. Seizure freedom: 3.1% (CLB-On), 0% (CLB-Off) at M2; 6.3% (CLB-On), 0% (CLB-Off) at the best point of seizure control within the first year. Most common AEs: diarrhoea, somnolence, fatigue; increased serum aminotransferases in patient taking concomitant VPA. Somnolence, ataxia, irritability, and urinary retention were common in the setting of concomitant CLB use and typically resolved after dose adjustments to either CLB or CBD. No significant difference in mean seizure frequency reduction between CLB-On and CLB-Off patients at either time point. There was a significantly greater responder rate for subjects taking CBD and CLB at the point of best seizure control within the first year of treatment. No significant difference in mean CBD doses and no correlation between change in N-CLB or CLB levels and change in seizure frequency.
Ebrahimi-Fakhari et al., 2020	N=25 (13 children 12 adults) patients with TSC treated with a mechanistic target of rapamycin inhibitor (18 everolimus, 7 sirolimus). Median age 17 (range 3-45) years. CBD dose 5-20 mg/kg/day.	Cannabidiol resulted in increased serum levels of mTOR inhibitor levels in 76% patients. Median change from baseline level was 9.8 ng/mL for everolimus and 5.1 ng/mL for sirolimus. AEs: 40%. Diarrhea 12%, lethargy 12%, mouth sores 8%, increased acne, ankle swelling, sinusitis, abdominal pain, mild elevation of transaminases, and increased phenytoin level (each 4.0%). SAE: none.
Poisson et al, 2020	N=2 patients with epilepsy of infancy with migrating focal seizures associated with KCNT1 mutations. Age 21-47 months, male sex 100%, prior ASMs 8-11, concomitant ASMs 1-3, daily seizure frequency 14-100. Maximum CBD dose 25 mg/kg/day.	Patient 1: overall seizure frequency reduction by 12%; three-fold increase in motor arrest seizures with clinically meaningful reduction in seizure intensity, 93% reduction in generalized clonic seizures and 48% reduction in asymmetric tonic seizures during 24-week treatment period. Patient 2: increase seizure frequency by 20% (asymmetric tonic seizures) during 24-week treatment period. AEs: 2/2 (somnolence). SAE: none.
Herlopian et al., 2020	N=9 patients with refractory childhood-onset epileptic spasms; TSC 3/9, Dup15q syndrome 1/9, bilateral cerebral dysgenesis 1/9, lissencephaly 1/9, CASK loss of function mutation 1/9. LGS 3/9. Median age 8 (range 2-16) years, male sex 44.4%, median epileptic spams onset 6 (range 4-21) months, median prior ASMs 8 (range 4-11), median concomitant ASMs 3 (range 2-	Average reduction in epileptic spasm frequency: 67.5% (week 2), 67.2% (M1), 64.1% (M2), 59.0% (M3), 73.7% (M6), 61.5% (M9), 51.4% (M12). Responder rates: 66.7% (week 2), 77.8% (M1), 66.7% (M2), 55.6% (M3), 77.8% (M6), 77.8% (M9), 77.8% (M12). Freedom from epileptic spasms: 22.2% (week 2), 11.1% (M1), 33.3% (M2), 33.3% (M3), 33.3% (M6), 44.4% (M9), 55.6% (M12). Resolution of hypsarrhythmia: 60%. Subjective improvements in cognitive and behavioural domains reported by parents in 44% of patients.

	4), median weekly epileptic spasm frequency 21.8 (range 3.6-51.8). Maximum CBD dose 50 mg/kg/day.	AEs: 88.9%. Drowsiness 77.8%, ataxia 22.2%, appetite loss 22.2%, agitation 22.2%, diarrhea 11.1%, twitchiness 11.1%, irritability 11.1%, elevated liver enzymes 11.1%.
Sharma et al., 2019	N=18 patients with treatment resistant epilepsy; temporal lobe epilepsy 38.9%, frontal lobe epilepsy 16.7%, peritumoral, symptomatic generalized, multifocal, bitemporal epilepsy (each 5.5%), unspecified 22.2%. Mean age 35.6±16.4, male sex 33.3%, mean monthly seizure frequency 29.3±39.4. CBD dose 15-25 mg/kg/day.	Reduction in seizure frequency, CSSS and AEP at ≥10 weeks. Voxel-level paired samples t-tests did not identify significant changes in grey matter volume or cortical thickness.
Ben-Menachem et al., 2020	N=35 patients receiving a stable dose of STP (n=14) or VPA (n=21) randomized 4:1 to CBD or placebo. STP arm: CBD n=12, placebo n=2. VPA arm: CBD n=16, placebo n=4. Mean age 29.5±10.5 years, male sex 65%. CBD dose 20 mg/kg/day.	Coadministration of steady-state CBD led to a small increase in exposure to steady-state STP (17% increase in maximum observed plasma concentration [*C*max]; 30% increase in AUC tau) and little effect on VPA exposure (13% decrease in *C*max; 17% decrease in AUC tau) or its metabolite, 2-propyl-4-pentenoic acid (4-ene-VPA) (23% decrease in *C*max; 30% decrease in AUC tau). STP arm. AEs: 66.7% (CBD), 0% (placebo), diarrhea 41.7% (CBD), 0% (placebo), fatigue 25.0% (CBD), 0% (placebo), nausea 16.7% (CBD), 0% (placebo), decreased appetite 16.7% (CBD), 0% (placebo), increased transaminases 16.7% (CBD), 0% (placebo). AEs leading to discontinuation 8.3% (CBD), 0% (placebo). SAEs: 8.3% (CBD), 0% (placebo). VPA arm. AEs: 87.5% (CBD), 25.0% (placebo), diarrhea 68.8% (CBD), 0% (placebo), nausea 12.5% (CBD), 0% (placebo), nasopharyngitis 12.5% (CBD), 0% (placebo). AEs leading to discontinuation 12.5% (CBD), 0% (placebo). SAEs: 6.3% (CBD), 0% (placebo).
Barnett et al., 2020	N=10 patients with TSC. Age 1-19 years, male sex 30%. Maximum CBD dose 50 mg/kg/day.	Six out of the 7 dominant renal angiomyolipomas and three out of the 3 subependymal giant cell tumors increased in volume during CBD treatment. One angiomyolipomas had a decrease in volume after CBD initiation, which was not considered significant.
Gupta et al., 2020	N=1 patient with early onset epileptic encephalopathy with burst suppression presenting with super refractory status epilepticus. Age 4 months, female. Maximum CBD dose 25 mg/kg/day.	Reduction of frequency in clinical seizures (from 10 to 0-3 episodes per hour) and midazolam drip successfully weaned off.
McNamara et al., 2020	N=87 patients with treatment resistant epilepsy; LGS 82%, DS 7%, others 11%. Age 9.8±5.0 years, male sex 51%, median prior ASMs 4 (IQR=2-6), median concomitant ASMs 3 (IQR 2-4), seizure frequency: less than monthly 6.9%, monthly 3.4%, weekly 27.6%, daily 8%, multiple per day 47 (54%). Highest CBD dose 13.6±5.0 mg/kg/day.	Seizure frequency improvement in 50.7% of patients. Seizure frequency after CBD initiation: less than monthly 8%, monthly 9%, weekly 23%, daily 4%, multiple per day 38%. AEs: sedation 26%, behaviour change 15%, thrombocytopenia 10%, agitation 6%. Thrombocytopenia (platelet nadir range=17000-108000/μL): 9/87 (10%). All cases received CBD and VPA. Most (7/9) of the children had low platelet counts within 3 months of starting CBD, and 4/7 had thrombocytopenia by 2 months. Thrombocytopenia was reversible: 4/9 responded to a reduction of VPA, 3/9 required a reduction of CBD, 1/9 required cessation of CBD, 1/9 recovered spontaneously.
VanLandingham et al., 2020 (NCT02565108)	N=20 (CBD=16, placebo=4) patients with poorly controlled epilepsy already on a stable dose of CLB (≤20 mg/day).	Seizure frequency improved in 56.3% of patients in CBD group and 1/4 (25.0%) patient in placebo group (10-day titration period followed by 21-day maintenance period). AEs: 81.3% (CBD), 50.0% (placebo). Diarrhoea 37.5% (CBD), 25.0% (placebo), nausea 18.8% (CBD), 0% (placebo), vomiting 18.8% (CBD), 0% (placebo), dizziness 12.5% (CBD), 0% (placebo), sedation 12.5% (CBD), 0%

	Mean age 36.8±8.7 years, male sex 50%. CBD dose 20 mg/kg/day.	(placebo), somnolence 12.5% (CBD), 0% (placebo), dermatitis 12.5% (CBD), 0% (placebo) Increased transaminases: 12.5% CBD. SAEs: 6.3% (CBD), 0% (placebo). Treatment withdrawal due to AEs: 12.5% (CBD), 0% (placebo). No evidence of drug-drug interaction between CBD and CLB; significant drug-drug interaction between CBD and N-CLB with 2-to 3-fold increase in N-CLB plasma concentrations.
NCT02564952	N=18 patients with poorly controlled epilepsy already on a stable dose of CLB (≤20 mg/day) (open label extension phase of NCT02565108). Mean age 36.4±9.1 years, male sex 55.6%. Maximum CBD dose 30 mg/kg/day.	AEs: 94.4%. Diarrhea 44.4%, somnolence 38.9%, dizziness 22.2%, headache 22.2%, vomiting 16.7%, fatigue 11.1%, irritability 11.1%, respiratory tract infection 11.1%, seizure 11.1%, hyponatremia 11.1%. SAEs: 11.1%.
Nenert et al., 2020	N=22 patients with treatment resistant epilepsy. Mean age 36.2±15.9 years, male sex 36.4%, monthly seizure frequency 4-1911. CBD dose 15-25 mg/kg/day.	Median seizure frequency decrease 71.2% after receiving a stable dosage of CBD for at least 2 weeks. Improvement in CSSS, AEP, and POMS subscores of confusion, depression, and fatigue. Significant changes in resting state functional connectivity in cerebellum, frontal areas, temporal areas, hippocampus, and amygdala with some of them correlating with improvement in behavioural measures. <u>Focal cortical dysplasia:</u> change in seizure frequency -100% to -70%, seizure freedom 1/2. <u>Tumor related epilepsy:</u> change in seizure frequency -85.7% to -57.1%. <u>Refractory generalized epilepsy:</u> change in seizure frequency: -20.8% to 42.8 %. <u>Refractory focal epilepsy.</u> Focal epilepsy (encephalitis; n=2): change in seizure frequency -53.9% to -42.9%. Multifocal epilepsy (unknown etiology; n=1): change in seizure frequency -100%. Temporal lobe epilepsy (unknown etiology; n=7): change in seizure frequency -100% to 50%, responder rate 5/7, seizure freedom 2/7. Frontal lobe epilepsy (unknown etiology; n=4): change in seizure frequency -100% to 14.3%, responder rate 3/4, seizure freedom 1/4.
Thompson et al., 2020	N=38 patients with treatment resistant epilepsy. Median age 10.0 (IQR 7.0-14.8) years, male sex 42%, median prior ASMs 7.5 (IQR 6.0-9.0), median concomitant ASMs 3 (range 1-5), median seizure frequency 70 (IQR 52-120). Maximum CBD dose 50 mg/kg/day.	Significant improvement in seizure severity at 12 months as assessed by CSSS. No significant change in cognitive performance or functional adaptive status at one year, but there was a trend indicating improved performance in one cognitive subdomain (NIHTB-CB Flanker Inhibitory Control and Attention Test) and one functional adaptive subdomain (ABAS-II Social). For participants unable to complete standardized cognitive testing because of the magnitude of cognitive impairment, their functional adaptive skills were unchanged at one-year.
Gaston et al., 2020	N=20 patients with treatment resistant epilepsy. Mean age: 37.2±16.4 years, male sex 35%, bi-weekly seizure frequency 4-168. CBD dose 15-25 mg/kg/day.	Change in seizure frequency -100% to +50%, responder rate 75%, seizure freedom rate 30% after reaching a stable dosage of CBD for more than 2 weeks and as close to the target dosage of 25 mg/kg/day. No significant changes in modified Sternberg working memory task performance and significant increased activation in inferior frontal gyrus regions n during memory encoding.
D'Onofrio et al., 2020	N=125 patients with treatment resistant epilepsy; LGS 49.6%, DS 38.4%, TSC 4.0%, SYNGAP1-epilepsy 2.4%, epilepsy with migrating focal seizures in infancy 2.4%, other 3.2%.	Seizure frequency reduction: 28.6% (M1), 37.4% (M2), 41.0% (all patients, M6), 42.7% (CLB-On, M6), 38.5% (CLB-Off, M6). Seizure responder (M6): 37.8% (all patients), 43.2% (CLB-On patients), 31% (CLB-Off patients). Seizure frequency reduction ≥70% (M6): 31.1% (all patients), 36.4% (CLB-On patients), 24.1%

	Median age 9 (IQR 6-14) years, male sex 47.2%, median concomitant ASMs 3 (IQR 3-4), median monthly seizure frequency 30.5 (IQR 5-122). Mean CBD dose 13.5±4.2 mg/kg/day	(CLB-Off patients). Seizure frequency reduction ≥90% (M6): 8.1% (all patients), 11.4% (CLB-On patients), 3.4% (CLB-Off patients). AEs: 48.8%. Somnolence 20.8%, fatigue 16.0%, behavior disorders 12.8%, decreased appetite 9.6%, sleep disturbance 5.6%, diarrhea 4.8%, convulsion 0.8%. Increased transaminases: 9.6% (all patients receiving both CLB and VPA and CLB). Treatment withdrawal for any cause 20.8%, lack of efficacy 15.2%, AEs 1.6%, both reasons 3.2%, sudden unexpected death in epilepsy 0.8%. AE and efficacy did not differ between CLB-On and CLB-Off patients. Improvement at CGIC. No statistical difference in C/PCGI scores between CLB-On and CLB-Off patients. Forty-seven (37.6%) patients reduced or suspended comedications, mainly CLB, VPA, and topiramate. Fifteen (12.0%) patients increased or introduced new ASMs; CBD was maintained in some of these cases for a benefit beyond seizure decrease as on behavior or interaction.
Kuchenbuch et al., 2020	N=3 patients with SYNGAP1 developmental and epileptic encephalopathy Age 3.5-7.5 years, male sex 66.6%, prior ASMs 4-7, concomitant ASMs 1-3, daily seizure frequency 20-100. Maximum CBD dose 10-23 mg/kg/day.	Seizure frequency reduction: 0-85% (M2), 80-95% (M9). Responder rate: 2/3 (M2), 3/3 (M9). AEs: 1/3 (sleep disorder). Slight (x 1.5) increase in transaminases (1/3). EEG improvement in background activity and interictal anomalies. Caregiver evaluated as much improved the status of their children.
Cortopassi et al., 2020	N=1 patient with drug resistant epilepsy and taking warfarin. Age 46 years, male sex, monthly seizure frequency 2. CBD dose 20 mg/kg/day.	Seizure frequency reduction 50% (M6). Increase in INR during CBD titration, which required a nearly 20% warfarin dose reduction.

Abbreviations: ABAS-II= Adaptive Behavior Assessment System – Second Edition, AE=adverse event, AEP=Adverse Event Profile, ASM=antiseizure medications, AUC TAU area under the concentration–time curve, CBD=cannabidiol, CBD25=CBD 25 mg/kg/day, CBD50=CBD 50 mg/kg/day, CGIC=Caregiver Clinical Global Impression of Change, CLB=clobazam, CSSS=Chalfont Seizure Severity Scale, FIRES=Febrile Infection-Related Epilepsy Syndrome, IQR=interquartile range, M1=month 1, M2=month 2, M6=month 6, M9=month 9, M12=month 12, INR=international normalized ratio, N-CLB=N-desmethylclobazam, NIHTB-CB=NIH Toolbox Cognition Battery, PGIC=Physician Global Impression of Change, POMS=Profile of Moods States, QOLCE=Quality of Life in Childhood Epilepsy, QOLIE-89=Quality of Life in Epilepsy-89, SAE=serious adverse events, TMD=Total Mood Disturbance, TSC=Tuberous sclerosis complex, VPA=valproic acid.

e-Appendix I

PubMed search strategy
[("cannabidiol"[MeSH Terms] OR "cannabidiol"[All Fields] OR "cannabidiolic"[All Fields]) AND ("seizural"[All Fields] OR "seizure's"[All Fields] OR "seizured"[All Fields] OR "seizures"[MeSH Terms] OR "seizures"[All Fields] OR "seizure"[All Fields] OR "seizuring"[All Fields] OR "epilep*"[All Fields])]

ClinicalTrials.gov search strategy
(cannabidiol OR GWP42003P) AND (epilepsy OR seizure) | Studies With Results