PANDA Journal club
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Wits Paeds Neuro

1. Long-term safety and treatment effects of cannabidiol in children and adults with treatment-resistant epilepsies: Expanded access program results.
   Szaflarski JP, Bebin EM, Comi AM, Patel AD, Joshi C, Checketts D, Beal JC, Laux LC, De Boer LM, Wong MH, Lopez M. Epilepsia. 2018 Aug;59(8):1540-8.

   Objective: This study reports interim results on the safety and efficacy of purified cannabidiol (CBD) in the treatment of resistant epilepsy.
   Methods: Patients with treatment resistant epilepsy were enrolled at 25 different epilepsy treatment sites. All patients were on a stable anticonvulsant regimen for at least 4 weeks prior to initiating CBD. The CBD dose of 2-10mg/kg/day was increased to 25-50mg/kg/day over the study period. Countable seizures were diarised and documented at each follow up consultation. Patients were seen 2-4 weekly during the first 16 weeks and 2 to 12-weekly thereafter. The percentage of change in seizure reduction was calculated for each patient and response rates were calculated as the proportion of patients who had 50%, 75%, and 100% reduction in seizure frequency. Doses of 8 commonly used anticonvulsants were documented as well as treatment-emergent adverse events.
   Results: The safety dataset consisted of 607 patients of whom 146 (24%) withdrew from this study: 89/146 (15%) due to lack of efficacy (it made no difference to seizure control) and 32/146(5%) due to adverse events (side effects (32), lost to follow up, consent withdrawn and other). Most frequent reported treatment emergent adverse events were diarrhoea and somnolence. The mean age was 13.1(range 0.4-62.1) years. The listed diagnoses were: Lennox-Gastaut (92), Dravet (55), TSC (26), Aicardi(17), CDKL5(18), Doose(22), other(236) and unknown(114). The median CBD dose was 25mg/kg/day and the median treatment duration was 48 weeks. A 96-week efficacy dataset were available for 138 patients. Seizure reduction of 100%, >75%, and >50% were witnessed in 11%, 31% and 52% of patients

respectively. The seizure response rate was consistent throughout the 96-week period.

Limitations: The study design is limited by the absence of a placebo control group and the fact that neither the participants nor the investigators were blinded. Over-reporting of seizure reduction cannot be excluded. Inclusion protocols were also different at various epilepsy treatment centres.

What this study adds: CBD seems to be a safe add on therapy in patients with treatment resistant epilepsy and leads to a sustained and meaningful reduction of seizure frequency, but further double blinded randomize control trials are needed.

2. Cannabidiol for treating drug-resistant epilepsy in children: The New South Wales experience.

   Chen KA, Farrar M, Cardamone M, Gill D, Smith R, Cowell CT, Truong L, Lawson JA. The Medical Journal of Australia. 2018 Aug 13;209(5):217-21.

   Objective: This study aimed to evaluate the safety of cannabidiol for treating drug resistant epilepsy in children.

   Methods: This was an open label prospective cohort study at three tertiary paediatric neurology service centres in New South Wales. Children with uncountable daily seizures and drug-resistant epilepsy enrolled in the compassionate access scheme were eligible for inclusion. CBD was initiated at 5mg/kg/day and increased weekly to a target dose of 25mg/kg over the 12-week period. Patient demographics, medical history, disabilities as well as previous and current anti-epileptic drugs (AED's) and any admissions were documented. Blood parameters were also assessed. Monitoring was performed at 4, 8 and 12 weeks. Adverse events as well as physician and caregiver Global Impression of Change assessments were recorded.

Results: 39 patients were enrolled. The median age was 8 years. Frequent adverse events were somnolence (15/39) and gastrointestinal disturbances. Increased liver transaminase occurred in 5% of participants. 16 participants reported increased seizure frequency or duration, but reportedly CBD causality was only likely in 2 of these patients. Evaluating efficacy was not the primary objective of this study. A statistically insignificant increase in admissions, status epilepticus and rescue medication were reported while on cannabidiol.

Limitations: The major limitation was the design of this study: Open label, non-placebo-controlled study.

What this study adds: CBD is likely safe. Monitoring of transaminase levels is recommended. Further RCT is recommended.

3. Cannabidiol in patients with seizures associated with Lennox-Gastaut syndrome (GWPCARE4): a randomised, double-blind, placebo-controlled phase 3 trial.
   Thiele EA, Marsh ED, French JA, Mazurkiewicz-Beldzinska M, Benbadis SR, Joshi C, Lyons PD, Taylor A, Roberts C, Sommerville K, Gunning B. The Lancet. 2018 Mar 17;391(10125):1085-96.

   Objective: To evaluate the efficacy of cannabidiol as add on therapy to existing drugs for the treatment of seizures associated with Lennox-Gastaut syndrome.

   Methods: A randomised, double-blind, placebo-controlled phase 3 trial at 24 sites. Patients aged 2 to 55 years with refractory epilepsy, meeting criteria for Lennox-Gastaut syndrome and at least two drop seizures per week during a 4-week baseline assessment, were eligible for inclusion. Patients were randomised to receive either 20mg/kg of purified cannabidiol or placebo for 12 weeks and were stratified according to age. The primary outcome was percentage change from baseline. Secondary outcomes included a responder analysis in which the proportion of patients with a >50%, >75%, and 100 % reduction of frequency of drop attacks were calculated. Other secondary outcomes included specific safety endpoints.

Results: 171 patients were included in the analysis. Of 86 patients assigned to the cannabidiol group 74 reported adverse events and 14 discontinued treatment: 8 had adverse events, 4 met withdrawal criteria and 2 were not specified. Three of the patients that met withdrawal criteria had raised transaminase levels. The placebo group consisted of 85 patients of which 59 reported adverse events. Diarrhoea, somnolence, pyrexia, decreased appetite and vomiting were the most common adverse events. The percentage reduction in the frequency of drop attacks were 43.9% in the cannabidiol group vs 21.8% in the placebo group (p=0.0135). A significantly higher proportion of patients in the cannabidiol group reported perceived improvement on the Global Impression of Change questionnaire.

Limitations: Drug-drug interactions could have impacted safety and efficacy data as cannabidiol was an add-on to existing treatment regimens. Patients were stratified according to age, but age groups were not compared against each other (or at least not mentioned in this publication)

What this study adds: This is the only randomised, double-blind, controlled study evaluating the use of cannabidiol in Lennox-Gastaut syndrome. Cannabidiol seems effective and tolerable as add-on treatment in this group of patients.

4. Libzon S, Schleider LB, Saban N, Levit L, , Tamari Y, Linder I, Lerman-Sagie T, Blumkin L. Medical Cannabis for Pediatric Moderate to Severe Complex Motor Disorders. Journal of Child Neurology 2018, Vol. 33(9) 565-571

Why is the topic important? Cannabis has been studied as treatment for certain neurological disorders like drug resistant epilepsy, autism and complex movement disorders but the results remain controversial.

Objectives: To look at the efficacy, safety, and tolerability of medical cannabis in children with **complex motor disorder (CMD).**

Study design: Experimental randomised controlled trial.

Population: Children between ages 1-18years with a diagnosis of complex movement disorders (dystonia, spasticity or both). They only included patients with a normal ECG and stable cardiorespiratory function. They excluded patients who had medical or surgical interventions (such as orthopedic surgery or botulinum toxin injections.) in the past 6 months or those who would require it during the study period. Children with a psychiatric illness or in their first degree family members were also excluded.

Twenty five patients were recruited. They were randomly selected into one arm of the study and observed for 2 months before starting treatment in case the disease evolved. One patient had CMD secondary to traumatic brain injury, 5 from neurogenetic syndromes and 19 from cerebral palsy. Out of 25 patients, 20 completed the study. Five were withdrawn for different reasons and they were analysed as intention to treat.

Intervention/exposure: Participants were exposed to cannabidiol enriched 5% oil formulations with different tetrahydrocannabinol **(**THC) strengths. They were started on 3 drops three times a day (**cannabidiol 6 mg and THC 0.99 mg for the 6:1 group and cannabidiol 6 mg and THC 0.3 mg daily for the 20:1 group)** either orally or via nasogastric tube. The dose was titrated until the patient developed intolerance, serious side effects, reached maximum THC of 15mg or until the end of the study. They continued with their other medications but benzodiazepine doses were decreased in five patients.

Table 3. Outcome Measures Scores.[a]

	Visit 1	Visit 2	Visit 4	Visit 7	*P* value
All patients					
BADS	15.68 ± 6.23	15.52 ± 5.92	14.90 ± 5.66	12.69 ± 4.62	.009
NRS for dystonia	7.36 ± 2.63	8.32 ± 1.35	6.83 ± 2.40	6.40 ± 2.68	.002
NRS for spasticity	8.29 ± 1.16	8.08 ± 1.55	6.83 ± 2.35	6.60 ± 2.43	.002
GMFM total	11.49 ± 16.20	12.16 ± 15.39	11.16 ± 10.23	14.71 ± 15.06	.001
GMFM lay	34.82 ± 3.42	36.63 ± 29.63	38.40 ± 28.44	44.39 ± 29.88	.001
GMFM sit	13.13 ± 21.44	15.60 ± 22.21	14.10 ± 17.32	19.72 ± 23.27	.009
QOL	40 (0-80)	40 (0-80)	60 (20-80)	60 (20-80)	.036
VAS	5.68 ± 3.14	5.98 ± 2.88	4.70 ± 3.09	4.27 ± 2.65	.022
Mood	4.56 ± 1.64	4.68 ± 1.65	4.96 ± 1.57	5.32 ± 1.35	.018
Appetite	5.00 ± 1.67	4.68 ± 2.00	5.00 ± 1.91	5.32 ± 1.80	.027
Stool	4.44 ± 2.02	4.60 ± 1.98	5.04 ± 2.01	5.74 ± 1.69	.021
Sleep	3.48 ± 2.00	3.80 ± 1.80	4.54 ± 1.56	5.08 ± 1.19	.002
6:1 group					
BADS	14.64 ± 7.58	14.93 ± 6.56	13.97 ± 6.89	11.97 ± 5.39	.951
Dystonia NRS	6.64 ± 3.18	7.86 ± 1.23	6.33 ± 2.64	6.57 ± 2.17	.087
NRS spasticity	8.21 ± 1.18	7.86 ± 1.56	6.62 ± 2.06	6.93 ± 1.86	.011
GMFM total	12.57 ± 20.38	12.91 ± 19.21	10.16 ± 10.08	15.33 ± 17.69	.284
GMFM lay	32.92 ± 21.8	34.18 ± 31.5	34.54 ± 27.67	41.87 ± 31.50	.047
GMFM sit	14.88 ± 26.05	16.67 ± 26.47	12.18 ± 15.59	22.42 ± 27.07	.695
QOL	46.67 ± 21.46	43.08 ± 21.36	60.00 ± 19.07	55.38 ± 20.56	.011
VAS	6.22 ± 2.87	6.24 ± 3.18	4.78 ± 3.36	4.74 ± 2.63	.426
Mood	4.43 ± 1.60	4.36 ± 1.44	4.92 ± 1.61	5.29 ± 1.50	.057
Appetite	4.82 ± 1.83	4.72 ± 1.85	5.30 ± 1.57	5.36 ± 1.57	.098
Stool	5.42 ± 1.87	5.14 ± 1.79	5.38 ± 2.02	5.69 ± 1.80	.751
Sleep	3.43 ± 1.87	3.71 ± 1.73	5.08 ± 0.95	5.36 ± 0.63	.011
20:1 group					
BADS	17.00 ± 3.87	16.27 ± 5.13	16.00 ± 3.80	13.55 ± 3.56	.021
Dystonia NRS	8.27 ± 1.35	8.91 ± 1.30	7.36 ± 2.11	6.18 ± 3.31	.036
NRS spasticity	8.40 ± 1.17	8.36 ± 1.57	7.09 ± 2.74	6.18 ± 2.06	.048
GMFM total	10.12 ± 9.28	11.21 ± 9.29	12.33 ± 10.76	13.93 ± 11.69	.054
GMFM lay	37.25 ± 29.91	39.75 ± 28.25	42.96 ± 29.99	47.59 ± 28.85	.079
GMFM sit	11.36 ± 14.60	14.24 ± 16.44	16.36 ± 19.69	16.51 ± 18.60	.277
QOL	30.91 ± 20.71	34.55 ± 28.41	49.09 ± 16.40	57.78 ± 12.02	.023
VAS	4.91 ± 3.49	5.61 ± 2.52	4.58 ± 2.89	3.62 ± 2.67	1
Mood	4.73 ± 1.74	5.09 ± 1.87	5.00 ± 1.61	5.36 ± 1.21	.185
Appetite	5.25 ± 1.49	4.63 ± 2.33	4.63 ± 2.33	5.25 ± 2.19	.891
Stool	3.18 ± 1.47	3.91 ± 2.07	4.64 ± 2.01	5.80 ± 1.62	.011
Sleep	3.55 ± 2.25	2.91 ± 1.92	3.91 ± 1.92	4.73 ± 1.62	.107

Abbreviations: BADS, Barry Albright Dystonia Scale; GMFM, Gross Motor Function Measure; NRS, numeric rating scale; QOL, quality of life; VAS, visual analog scale.
[a]Results for all measurements are presented as mean ± SD.

Method used to measure the effect (table 3): Researchers used Berry Albright Dystonia scale (BAD); Gross Motor Function Measure (GMFM); Cerebral Palsy Child questionnaire for quality of life (QOL); numeric rating scale for spasticity, mood, appetite, stool function, and sleep; and visual analog scale scores by visit.

Outcome: There was no difference between both formulations in reducing the severity of dystonia and spasticity, and improving motor function ability and quality of life. All participants demonstrated mood and appetite improvement. Patients in the 20:1 group

demonstrated improvement of constipation, whereas those in the 6:1 group showed sleep improvement.

Time: Duration of the study was 7 months per patient (2 months observation period and 5 months observation while on CBD oil).

Critical appraisal of the study

This study is not a true representation of our general population. The study sample was very small with a short duration of observation. It is not clear what happened to the participants after 5 months. The participants were randomly allocated to two groups to avoid bias. It is unclear whether there was blinding or not.

They had a standardized way of measuring the outcome and there was a doctor always available so that adverse effects are not missed and treated as they presented.

Recommendations: A bigger study is required with different patients from different regions with a control group. This will help with the generalization of the results. It will also make it easier to confirm or reject the hypothesis.

5. Gu B. Cannabidiol provides viable treatment opportunity for multiple neurological pathologies of autism spectrum disorder. Glob Drugs Therap, 2017. Volume 2(6): 1-4.

Why is the topic important? Autism spectrum disorder (ASD) is a neurodevelopmental disorder affecting over 1% of the general population of all ages worldwide. There is no single cause for ASD and it is well known that ASD comes from a combination of genetic and environmental factors, making curative therapy very difficult to establish. ASD is often accompanied by other comorbidities including anxiety, mood disorders, sleep disturbances and seizures. There is currently no single drug that can provide symptomatic relief of ASD and these disorders.

Objectives: To review studies done on cannabidiol (CBD) as treatment for ASD, epilepsy, anxiety and psychosis.

Cannabis: It is a naturally grown plant which contains over 80 different biochemical compounds called cannabinoids. Cannabinoids have three sub-groups namely phyto**cannabinoids,** endo**cannabinoids** and synthetic **cannabinoids**. Phytocannabinoids are found naturally in the cannabis plant, of which **cannabidiol (CBD)** is the second most naturally abundant in the plant. CBD has been gaining increasing worldwide attention because of its broad therapeutic potential in treating certain neurological disorders like drug resistant epilepsy, autism and complex movement disorders.

Mechanism of action of CBD: it remains unknown however some evidence demonstrates that dysregulated cannabinoid signalling could play a critical role in the pathophysiology of social functioning deficits in ASD.

Figure 1 shows ASD associated comorbidities that have been shown to respond to cannabis both in animal and human studies.

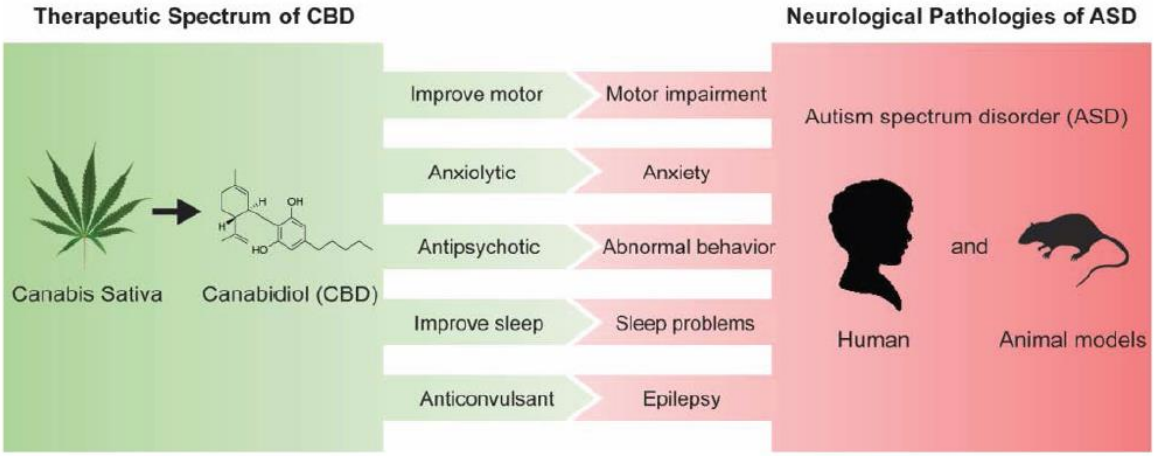

Figure 1. The beneficial spectrum of CBD provides a strategy for treating ASD pathologies.

Anticonvulsant effect of CBD: Between 20-30% of patients with ASD have epilepsy. CBD has been shown to reduce the frequency of seizures of all types including drug resistant epilepsy. The mechanism of action remains unknown.

Anxiolytic effect of CBD: About 40% of children with ASD have an anxiety disorder which may worsen the symptoms of ASD. CBD has been shown to be effective in patients with anxiety disorders i.e. social anxiety disorder, anxiety induced by public speaking and anxiety that is related to sleep problems. One case study showed decreased anxiety and improved quality of sleep in a patient who was given CBD for post-traumatic stress disorder (PTSD).

Wide-spectrum behavioural benefits of CBD: Only animal studies have shown success in treating behavioural disorders with CDB.

Conclusion: CBD seems to be a promising and a broad spectrum drug that can be used to treat ASD and its comorbidities. There is still a need to explore its safety, tolerability, efficacy and the cost of this drug compared to our standard drugs that are currently being used to alleviate these symptoms.