

Minerva Access is the Institutional Repository of The University of Melbourne

Author/s:

Ali, S;Scheffer, IE;Sadleir, LG

Title:

Efficacy of cannabinoids in paediatric epilepsy

Date:

2019-01-01

Citation:

Ali, S., Scheffer, I. E. & Sadleir, L. G. (2019). Efficacy of cannabinoids in paediatric epilepsy. *Developmental Medicine and Child Neurology*, 61 (1), pp.13-18. <https://doi.org/10.1111/dmcn.14087>.

Persistent Link:

<https://hdl.handle.net/11343/284748>

MISS SHAYMA ALI (Orcid ID : 0000-0002-9177-4938)

PROFESSOR INGRID EILEEN SCHEFFER (Orcid ID : 0000-0002-2311-2174)

Article type : Invited Review

[Invited Review; 2 figs]

Efficacy of cannabinoids in paediatric epilepsy

SHAYMA ALI¹

INGRID E SCHEFFER^{2,3,4*}

LYNETTE G SADLEIR^{1*}

1 Department of Paediatrics and Child Health, University of Otago, Wellington, New Zealand. **2** Departments of Medicine and Paediatrics, University of Melbourne, Melbourne, Victoria; **3** Austin Health and Royal Children's Hospital, Heidelberg, Victoria; **4** Florey and Murdoch Children's Research Institutes, Melbourne, Victoria, Australia.

Correspondence to Ingrid Scheffer, University of Melbourne, Austin Health, Heidelberg, Victoria, Australia. E-mail: i.scheffer@unimelb.edu.au

***These authors contributed equally to the work.**

PUBICATION DATA

Accepted for publication XX Month 2018.

Published online XX Month 2018.

This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the [Version of Record](#). Please cite this article as [doi: 10.1111/dmcn.14087](https://doi.org/10.1111/dmcn.14087)

ABBREVIATIONS

AED	Antiepileptic drug
CBD	Cannabidiol
DEE	Developmental and epileptic encephalopathy
THC	Δ^9 -tetrahydrocannabinol

There are hundreds of compounds found in the marijuana plant, each contributing differently to the antiepileptic and psychiatric effects. Cannabidiol (CBD) has the most evidence of antiepileptic efficacy and does not have the psychoactive effects of Δ^9 -tetrahydrocannabinol (THC). CBD does not act via cannabinoid receptors and its antiepileptic mechanism of action is unknown. Despite considerable community interest in the use of CBD for epilepsy, there has been little evidence for its use apart from anecdotal reports, until the last year. Three randomized, placebo-controlled, double-blind trials in Dravet syndrome and Lennox–Gastaut syndrome found that CBD produced a 38% to 41% median reduction in all seizures compared to 13% to 19% on placebo. Similarly, CBD resulted in a 39% to 46% responder rate (50% convulsive or drop-seizure reduction) compared to 14% to 27% on placebo. CBD was well tolerated, however sedation, diarrhoea, and decreased appetite were frequent. CBD shows similar efficacy to established antiepileptic drugs.

[Boxed content to appear on page 2]

What this paper adds

- Cannabidiol (CBD) shows similar efficacy in the severe epilepsies to other antiepileptic drugs.
- Careful down-titration of benzodiazepines is essential to minimize sedation with adjunctive CBD.

[First page footer]

© Mac Keith Press 2018

DOI: 10.1111/dmcn.xxxxx

[Left page footer]

[main text]

Therapeutic cannabinoids are primarily derived from the marijuana plant genus *cannabis*. *Cannabis sativa* and *cannabis indica* are the two main species. Cannabis plants contain more than a hundred cannabinoids, but the most biologically active and therapeutically researched are Δ^9 -tetrahydrocannabinol (THC) and cannabidiol (CBD).¹ Each species differs in the proportion of these major components and they can be hybridized to produce strains with different ratios of THC and CBD.

Cannabinoids have been advocated for a range of neurological and psychiatric disorders, including multiple sclerosis, mood disorders, schizophrenia, Parkinson disease, dystonia, neuropathic pain, nausea, anorexia, and epilepsy. There is evidence of efficacy from randomized-controlled trials for neuropathic pain, Tourette syndrome, schizophrenia, Parkinson disease, multiple sclerosis, nausea, and appetite stimulation.² Conversely, no effect has been found for dystonia.³

Epilepsy is the most common serious neurological disorder, affecting over 50 million people worldwide. Thirty per cent of individuals have uncontrolled seizures, which can be associated with poor quality of life and mental illness. The most severe group of childhood epilepsies are the developmental and epileptic encephalopathies (DEEs). The DEEs include a large number of epilepsy syndromes, each relatively rare, but their overall incidence is one in 2000 births.⁴ These devastating disorders are defined by frequent seizures and epileptiform abnormalities that result in severe cognitive and behavioural impairment.⁵ Children with DEEs have a high mortality rate with 24% dying within 20 years of diagnosis.⁶ Historically, the DEEs were thought to be acquired, however, over the last 17 years, increasing numbers of children have been shown to have a genetic basis for the disorder.⁴

Dravet Syndrome is a prototypic DEE that presents in typically developing children at between 3 months and 15 months of age, with prolonged hemiclonic and/or generalized tonic-clonic seizures, often associated with fever.⁷ Focal, myoclonic, and absence seizures as well as non-convulsive status epilepticus can begin by age 5 years and the child's development typically plateaus or regresses. Seizures are refractory and outcome is poor, with intellectual disability ranging from severe to mild. In 80% of patients, Dravet syndrome

is caused by de novo pathogenic variants in the *SCN1A* gene which encodes the alpha1-subunit of the neuronal voltage-gated sodium channel.⁷

Cannabinoids have been used as therapy for thousands of years. Tablets written by the Sumerian and Akkadian people in 1800BC describe how cannabis was used to treat nocturnal convulsions.⁸ Because of the legal restrictions on marijuana cultivation, research into the therapeutic potential of cannabis has been difficult. However, the push for the accessibility and legislation of medical marijuana, largely fuelled by public demand, has contributed to the current emergence of research into the effect of cannabis in epilepsy.

Widespread community interest in cannabinoid products for epilepsy has grown as a consequence of mainstream and social media reports of successful treatment in individual children. Anecdotal reports in the medical literature have also contributed to the perceived efficacy of cannabinoids.⁹ One notable case, highlighted in a television documentary, is Charlotte Figi, who at 5 years of age was having 50 seizures per day refractory to available therapies. After the administration of an oil with a high CBD/THC ratio derived from cannabis sativa, her seizures decreased significantly and her development improved; the term 'Charlotte's Web'⁹ was later coined for this oil. Media publicity has resulted in high expectations of cannabinoids, particularly from families with children who have intractable epilepsy. This strong belief in efficacy probably contributes to a significant placebo effect. Families who moved to Colorado, one of the first US states where cannabis use was legal, were three times more likely to report improved seizures with cannabis than those who already resided in Colorado.¹⁰ This suggests personal investment in receiving cannabinoid treatment contributes to perceived improvement.

There are several routes of cannabinoid administration. Traditionally, for recreational and medicinal cannabinoid use, the flowers of the cannabis plant are dried, rolled in paper, and smoked. Recent recreational inhalation has been via e-cigarettes using cartridges which burn either marijuana product (dried, oil, or wax) or synthetic cannabinoids at a controlled heat.¹¹ Extracted oils from the cannabis plant can be administered orally. The oils are derived by baking the cannabis flowers, mixing with a lipophilic solution, applying further heat or using solvent extraction, and then straining the ground flowers. This can be administered directly as 'hash oil', in capsules or put into baked food. First pass metabolism, however, significantly reduces the bioavailability of oral cannabis products. To avoid first pass metabolism, pharmaceutical grade products have been delivered effectively via oromucosal spray or transdermal gel.¹² Eye drops, intranasal spray, and rectal suppositories are also being evaluated as delivery methods.¹² Phytocannabinoids refer to all cannabinoids, including CBD

and THC that are found in cannabis plants. These compounds can be purified from plants or made synthetically. Using high performance liquid chromatography, the ratio of CBD to THC in individual plants can be determined. This allows breeding of plants that produce strains high in specific components. Synthetic cannabinoids, made in laboratories, include pure single molecule phytocannabinoids as well as analogue derivatives, not found in plants (non-phytocannabinoids), bearing a similar structure to phytocannabinoids. Synthetic analogues may be more potent than natural phytocannabinoids as they can have a higher affinity to the cannabinoid receptors (CB₁ or CB₂).

Manufacturing quality of cannabinoid products is highly variable, with many compounds not achieving the rigorous standards expected for medicinal use. Oil-based formulations may be home grown or factory-manufactured, and may be non-pharmaceutical grade, mass-produced product marketed as dietary supplements (e.g. Charlotte's Web Hemp Extract CBD Oil, Haleigh's Hope) or pharmaceutical grade products (e.g. Sativex, Epidiolex). To be certified pharmaceutical grade, a product must meet both good manufacturing practice and good distribution practice guidelines, so that the consumer can be confident in the purity of the cannabinoid constituents, the reliability of their ratios in each dose, and the safety of each formulation.

PRECLINICAL ANTIEPILEPTIC TRIALS

Of the more than 100 cannabinoids, THC and CBD have received the most attention because of their neurological and psychiatric effects. CBD has been promoted as the major cannabinoid for epilepsy treatment, while THC is advocated for multiple sclerosis, chemotherapy-induced vomiting, and pain management.

The antiepileptic properties of CBD have been conclusively demonstrated in animal models. In rat hippocampal slices, CBD attenuates epileptiform activity.¹³ In vivo, treating rats with CBD before pentylenetetrazole administration, increases the amount of pentylenetetrazole required to initiate a seizure, reduces the incidence of tonic-clonic seizures, and decreases mortality.^{13,14} In an *SCN1A* knockout mouse model of Dravet syndrome, treatment with CBD decreased the number of spontaneous seizures as well as the duration and severity of thermally-induced seizures. Autistic-like social interaction deficits improved with low dose CBD but, interestingly, not with the higher dose of CBD required for seizure control.¹⁵

Recently, *in vitro* and *in vivo* studies have also demonstrated antiepileptic properties of a natural propyl analogue of CBD, cannabidivarin. Cannabidivarin reduces epileptiform activity in a rat hippocampal slice model¹⁶ and cannabidivarin pretreatment of mice and rats has a positive effect on seizures induced by audiogenic stimulation, electrical stimulation, and pentylenetetrazole.¹⁶

Conversely, THC has demonstrated both anticonvulsive and proconvulsive properties in rodent studies.¹⁷ THC is responsible for the psychiatric effects of marijuana and has a deleterious impact on brain development and cognition in maturing animals and humans.¹⁸

EFFICACY IN HUMANS

Most anecdotal reports, case series, and open label trials suggest CBD has an antiepileptic effect in people with epilepsy, particularly in children with DEEs. This literature undoubtedly shows publication bias, as studies on children who derive no benefit from CBD are far less likely to be published. There are no class I trials of THC for epilepsy in children. The proconvulsive effect of THC in animals and the deleterious effect of THC on the developing human brain means that CBD and THC considerably differ in their risk-benefit ratios.^{17,18} CBD has, therefore, been the focus of epilepsy research.

Two open-label studies of pharmaco-resistant childhood epilepsies reported CBD efficacy.^{19,20} An Israeli retrospective, observational study reported the effect of 3 or more months of enriched cannabis oil (20% CBD, 1% THC; 1–20mg/kg/day CBD) in 74 children. Fifty per cent seizure reduction occurred in 52% of participants, with 18% reporting 75% to 100% seizure reduction.¹⁹ In a study by Devinsky et al.,²⁰ 137 participants, aged up to 30 years, were given up to 50mg/kg/day of 99% CBD pharmaceutical grade oral formulation. Thirty-seven per cent had a greater than 50% seizure reduction.²⁰ Neither study had a placebo arm.

In the last year, there have been three international, randomized, placebo-controlled, double-blind trials of pharmaceutical grade natural CBD in children with DEEs. All trials involved the same compound of 98% CBD (Epidiolex; GW Pharma, Cambridge, UK), and had a similar trial structure. They began with a 4-week baseline period followed by a 2-week escalation phase and a 12-week maintenance period, together termed the 14-week treatment period. CBD was administered at doses of 20mg/kg/day in all three trials, while one trial had an additional arm of 10mg/kg/day.^{21–23}

The first trial enrolled children with Dravet syndrome aged 2 years to 18 years (mean age 9y 9mo). Children had to be on one or more antiepileptic drugs (AEDs) with a minimum of four convulsive seizures per month (median 13 seizures/month). Children were randomized to either CBD ($n=61$) or placebo ($n=59$). Forty-three per cent of patients had greater than 50% convulsive seizure reduction on CBD compared to 27% on placebo. Five per cent of children became seizure free on CBD compared with none on placebo. There was no difference in non-convulsive seizure frequency between groups. Parental impression, based on the Caregiver Global Impression of Change, reported improvement in 62% children compared to 34% children on placebo.²¹

The other trials studied individuals aged 2 years to 55 years who had Lennox–Gastaut syndrome and children were required to have two drop seizures per week in the baseline period ($n=225$ ²² and $n=171$).²³ Drop seizures included tonic, atonic, and tonic–clonic seizures. Individuals taking CBD improved compared to those on placebo: 39% to 46% on 20mg/kg/day, 36% on 10 mg/kg/day, and 14% to 24% on placebo had a 50% or more decrease in frequency of drop seizures. The median per cent reduction in total seizures was 38% to 41% on 20mg/kg/day, 36% on 10mg/kg/day, and 14% to 19% on placebo.^{22,23} Lastly, 57% to 58% of parents in the CBD group reported an improvement in Caregiver Global Impression of Change compared with 38% to 44% of the placebo group.^{22,23}

Another randomized, double-blind, placebo-controlled trial of CBD in epilepsy involved a synthetic transdermal CBD gel. Outcomes have only been reported in poster form at the 2017 American Epilepsy Society and 2018 Meeting of the American Academy of Neurology. This adult trial (participants aged 18–70y) included individuals with pharmacoresistant focal epilepsy ($n=63$ received 195mg CBD, $n=62$ 390mg CBD, and $n=63$ placebo). There was no significant reduction in seizures in the CBD groups compared to the placebo group. This may have been due to the trial doses being too low or the duration of the treatment too short to demonstrate efficacy. It is also possible that focal epilepsy is less responsive to CBD than the DEEs.²⁴

SAFETY AND TOLERABILITY

There have been more than 650 children and adults with epilepsy who have participated in a trial of some form of CBD. CBD is well tolerated with a similar safety profile to other AEDs. All studies including case reports, observational trials, and randomized-controlled trials report similar adverse effects. Somnolence, diarrhoea, decreased appetite, fatigue, lethargy,

pyrexia and vomiting were commonly reported; elevated hepatic transaminases may also occur.^{21–23}

The three randomized, placebo-controlled, double-blind trials reported more adverse events on 20mg/kg/day CBD (86%–94%) than on placebo (69%–75%).^{21–23} Adverse events generally occurred during the 14-day dose escalation period. Somnolence was the most common adverse event, followed by diarrhoea, and decreased appetite (Fig. 1).^{21–23} Somnolence needs to be carefully managed with reduction of concomitant benzodiazepines; this down-titration can be commenced before or with the introduction of CBD.²⁵ Elevated transaminases (defined as more than three times normal) were seen in patients on valproate. They were more frequent in patients on CBD than placebo when coadministered with valproate (19% vs 5%).²¹ Withdrawal from trials due to adverse events were higher in those taking CBD (7.2%–15%) than placebo (1.2%–1.7%).^{21–23}

Interestingly, an unpublished randomized, placebo-controlled, double-blind trial of transdermal CBD reported no difference in adverse events between placebo (41.3%), 195mg CBD (49.2%), and 39mg CBD (51.6%). Fewer gastrointestinal adverse events were reported in the transdermal trial than the oral trials, probably because of the non-oral route of administration.²⁴

PHARMACOKINETICS AND MECHANISM OF ACTION OF CBD

The pharmacokinetics of CBD are important in understanding the value of different methods of administration and formulations. CBD has low water solubility, with low absorption from the gastrointestinal system, resulting in low bioavailability. CBD is highly lipophilic and, therefore, has a high volume of distribution.¹ In children with Dravet syndrome, peak plasma concentrations of CBD and CBD conjugates occur about 2.5 hours after dosing.²⁶ CBD is predominantly excreted in faeces, and the terminal half-life is 18 hours to 32 hours.¹

Notably, none of the phase II/III trials have assessed the efficacy of CBD without coadministration of other AEDs. It has been mooted that CBD's efficacy is due to its impact on the pharmacokinetics of coadministered AEDs.^{25,26} CBD interacts with the CYP450 pathway and could affect metabolism of other AEDs metabolized through this pathway.

The most important clinical interaction is between CBD and clobazam, as clobazam often needs to be lowered because of excessive sedation. CBD inhibits CYP2C19 and CYP3A4 that catalyse the conversion from clobazam to its active metabolite norclobazam. As a consequence of CBD's inhibition, norclobazam accumulates leading to high plasma concentrations (500%±300% mean increase), compared with lesser increases in clobazam

(60%±80%).²⁵ Interestingly, side effects resolved when clobazam was reduced, despite norclobazam levels remaining high in some individuals. Topiramate, rufinamide, zonisamide, and eslicarbazepine also show increased plasma levels when coadministered with CBD in children and adults.²⁷

The mechanism of action of CBD in epilepsy is not yet understood. A systematic review found that CBD binds to more than 65 molecular targets.²⁸ However, in most of these in vitro experiments the level required for binding would not be achievable in the human brain. Studies show that CBD does not activate cannabinoid receptors. Plausible targets for epilepsy include voltage-dependent anion channel 1, Ca_v3.x, 5-HT_{1A}, glycine receptor, and G protein-coupled receptor 55 and adenosine modulation²⁸ (Fig. 2).

The *SCN1A* mutation in Dravet syndrome causes a loss of function of sodium channels of GABAergic inhibitory interneurons. This interneuronopathy results in decreased cortical inhibition and, therefore, increased excitability. In vitro experiments using *SCN1A* knockout mice found that administration of CBD increased excitability of hippocampal dentate gyrus inhibitory interneurons.¹⁵ Applying a G protein-coupled receptor 55 antagonist mimicked the enhancement of inhibition. When given concurrently with CBD, G protein-coupled receptor 55 occluded the CBD effect. CB₁ is the cannabinoid receptor responsible for the psychoactive effect of THC. Blocking the CB₁ receptor does not change the CBD effect on the interneuron, consistent with previous evidence that CBD does not interact with this receptor.¹⁵

CHALLENGES WITH IMPLEMENTATION OF CBD

While the mechanisms of antiepileptic action of CBD are not fully elucidated, it is clear that administration of CBD as adjunct therapy decreases seizure frequency in patients with Dravet syndrome and Lennox–Gastaut syndrome. Contrary to public expectation of miraculous results, CBD has a similar antiepileptic and side effect profile to other AEDs. Nevertheless, as individual children with these DEEs are often refractory to available AEDs, the addition of another potentially effective therapeutic medicine will be warmly welcomed by families and physicians.

The advent of CBD use in epilepsy has been associated with unprecedented challenges and opportunities. The strongly held convictions of the community, before the availability of robust evidence, that medical marijuana is highly effective for seizures, has pushed the transition of this alternative therapy into mainstream medical management at a

blinding pace.^{29,30} As there is presently limited clinical availability outside of research trials of pharmaceutical grade CBD, families are giving non-pharmaceutical grade CBD or inappropriate products with THC in addition to CBD to their sick children. This raises concerns about the use of products with THC on the developing brain. Paediatricians and paediatric neurologists can be placed in the invidious situation of being asked to prescribe unsuitable formulations and in settings deemed clinically inappropriate. Moreover, families are self-medicating their children with natural products accessed via the Internet or products they have sourced locally.

The legal status of cannabis has added to both the hype surrounding CBD and to the complications associated with bringing pharmaceutical grade CBD to the clinic. Epidiolex is the only pharmaceutical grade form approved by the Food and Drug Administration for epilepsy. As pure CBD does not have psychoactive properties nor potential for abuse, regulations regarding medicinal use have recently been reduced to that of a regular prescription in some countries. While cannabis is available in some states in the USA, cannabis remains on schedule I of the Controlled Substances Act, which includes drugs with no currently accepted medical use, high potential for abuse, and lack of accepted safety, and highlights the disparity between federal and state laws in the USA.

The data showing efficacy of CBD in specific syndromes may not reveal the full clinical picture. For example, the majority of children with Dravet syndrome do not have four convulsive seizures per month as required for the trials reported above. CBD may well be effective in protecting children with Dravet syndrome who have less frequent seizures from life-threatening monthly (or less frequent) episodes of convulsive status epilepticus. Trial design is based on pharmaco-economic outcomes and, thus, does not necessarily focus on all the critical issues for patients with refractory epilepsy.

FUTURE DIRECTIONS

Future research needs to focus on defining the breadth of epilepsy syndromes for which CBD is effective, including the wider group of DEEs. Alternative methods of administration of CBD to avoid the first pass effect in the gut deserve consideration, particularly for the DEE population, as administration of oral medication can be challenging. There is community pressure to trial THC in combination with CBD for children with epilepsy. Unfortunately, there is little evidence to support a beneficial role for this combination, as chronic administration of THC is proconvulsant in animal models.¹⁷ Further, there are concerns about

the effect of THC on the developing brain with well documented earlier onset of psychosis in patients who take recreational THC.¹⁸ There are a large number of other cannabinoids with fewer side effects as suggested by animal models, some of which are under investigation and may hold promise for treatment of epilepsy in the future. Community debate about the use of CBD and access to this antiepileptic therapy has been heated. With further trials and greater understanding of its role, the place of CBD in our antiepileptic armamentarium and its impact on comorbidities will become clearer.

REFERENCES

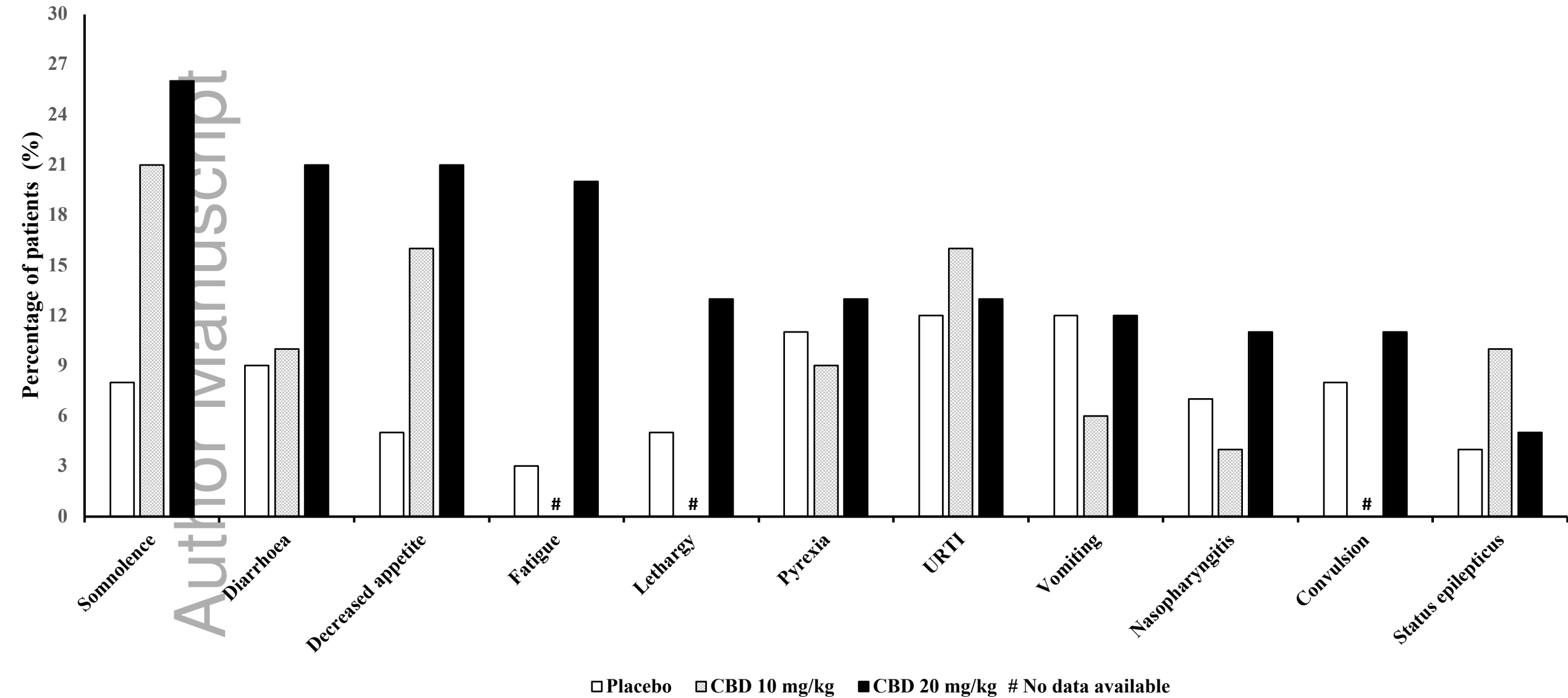
1. Devinsky O, Cilio MR, Cross H, et al. Cannabidiol: pharmacology and potential therapeutic role in epilepsy and other neuropsychiatric disorders. *Epilepsia* 2014; **55**: 791–802.
2. Whiting PF, Wolff RF, Deshpande S, et al. Cannabinoids for medical use: a systematic review and meta-analysis. *JAMA* 2015; **313**: 2456–73.
3. Fox SH, Kellett M, Moore AP, Crossman AR, Brotchie JM. Randomised, double-blind, placebo-controlled trial to assess the potential of cannabinoid receptor stimulation in the treatment of dystonia. *Mov Disord* 2002; **17**: 145–9.
4. Howell KB, Eggers S, Dalziel K, et al. A population-based cost-effectiveness study of early genetic testing in severe epilepsies of infancy. *Epilepsia* 2018; **59**: 1177–87.
5. Scheffer IE, Berkovic S, Capovilla G, et al. ILAE classification of the epilepsies: Position paper of the ILAE Commission for Classification and Terminology. *Epilepsia* 2017; **58**: 512–21.
6. Camfield P, Camfield C. Long-term prognosis for symptomatic (secondarily) generalized epilepsies: a population-based study. *Epilepsia* 2007; **48**: 1128–32.
7. Brunklaus A, Zuberi SM. Dravet syndrome--from epileptic encephalopathy to channelopathy. *Epilepsia* 2014; **55**: 979–84.
8. Russo EB. Cannabis and epilepsy: An ancient treatment returns to the fore. *Epilepsy Behav.* 2017; **70**(Pt B): 292–7.
9. Maa E, Figi P. The case for medical marijuana in epilepsy. *Epilepsia* 2014; **55**: 783–6.
10. Press CA, Knupp KG, Chapman KE. Parental reporting of response to oral cannabis extracts for treatment of refractory epilepsy. *Epilepsy Behav* 2015; **45**: 49–52.
11. Morean ME, Kong G, Camenga DR, Cavallo DA, Krishnan-Sarin S. High school students' use of electronic cigarettes to vaporize cannabis. *Pediatrics* 2015; **136**: 611–6.

12. Grotenhermen F. Pharmacokinetics and pharmacodynamics of cannabinoids. *Clin Pharmacokinet* 2003; **42**: 327-60.
13. Jones NA, Hill AJ, Smith I, et al. Cannabidiol displays antiepileptiform and antiseizure properties in vitro and in vivo. *J Pharmacol Exp Ther* 2010; **332**: 569–77.
14. Shirazi-zand Z, Ahmad-Molaei L, Motamedi F, Naderi N. The role of potassium BK channels in anticonvulsant effect of cannabidiol in pentylenetetrazole and maximal electroshock models of seizure in mice. *Epilepsy Behav* 2013; **28**: 1–7.
15. Kaplan JS, Stella N, Catterall WA, Westenbroek RE. Cannabidiol attenuates seizures and social deficits in a mouse model of Dravet syndrome. *Proc Natl Acad Sci U S A* 2017; **114**: 11229–34.
16. Hill AJ, Mercier MS, Hill TD, Glyn SE, et al. Cannabidivarin is anticonvulsant in mouse and rat. *Br J Pharmacol* 2012; **167**: 1629–42.
17. Whalley B. Cannabis in the management and treatment of seizures and epilepsy: A scientific review. Scotts Valley, CA: American Herbal Pharmacopoeia, 2014.
18. Lubman DI, Cheetham A, Yücel M. Cannabis and adolescent brain development. *Pharmacol Ther* 2015; **148**: 1–16.
19. Tzadok M, Uliel-Siboni S, Linder I, et al. CBD-enriched medical cannabis for intractable pediatric epilepsy: The current Israeli experience. *Seizure* 2016; **35**: 41–4.
20. Devinsky O, Marsh E, Friedman D, T, et al. Cannabidiol in patients with treatment-resistant epilepsy: an open-label interventional trial. *Lancet Neurol* 2016; **15**: 270–8.
21. Devinsky O, Cross JH, Laux L, et al. Trial of cannabidiol for drug-resistant seizures in the Dravet syndrome. *N Engl J Med* 2017; **376**: 2011–20.
22. Devinsky O, Patel AD, Cross JH, et al. Effect of cannabidiol on drop seizures in the Lennox-Gastaut syndrome. *N Engl J Med* 2018; **378**: 1888–97.
23. Thiele EA, Marsh ED, French JA, et al. Cannabidiol in patients with seizures associated with Lennox-Gastaut syndrome (GWPCARE4): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet* 2018; **391**: 1085–96.
24. Messenheimer J OBT, Berkovic S, French J, Bonn-Miller MO, Gutterman D. Transdermal cannabidiol (CBD) gel for the treatment of focal epilepsy in adults. Annual Meeting of the American Academy of Neurology; April 21–27 2018, Los Angeles, CA.
25. Geffrey AL, Pollack SF, Bruno PL, Thiele EA. Drug-drug interaction between clobazam and cannabidiol in children with refractory epilepsy. *Epilepsia* 2015; **56**: 1246–51.
26. Devinsky O, Patel AD, Thiele EA, et al. Randomized, dose-ranging safety trial of cannabidiol in Dravet syndrome. *Neurology* 2018; **90**: e1204–11.

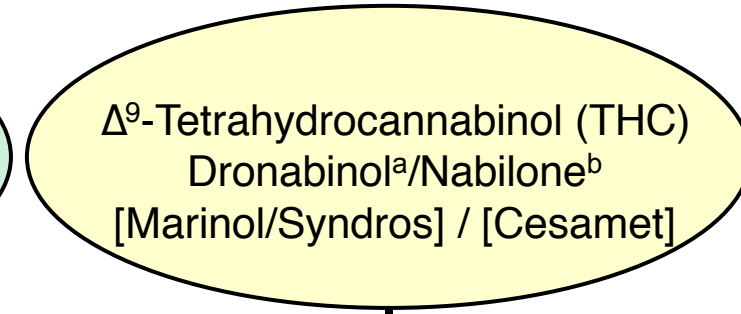
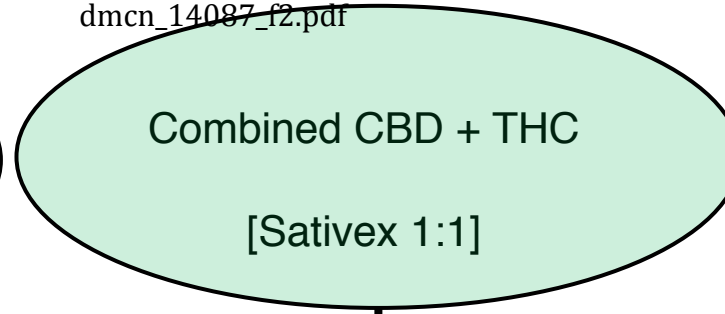
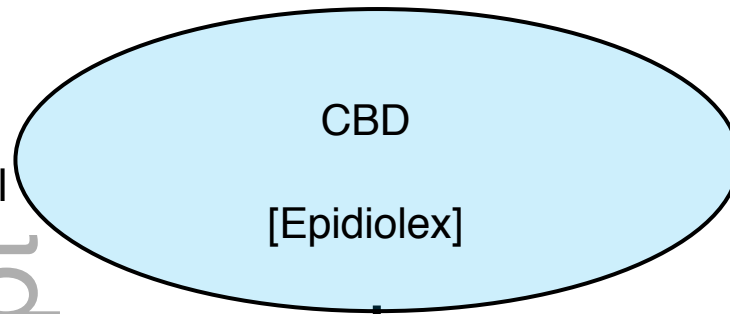
27. Gaston TE, Bebin EM, Cutter GR, Liu Y, Szaflarski JP; UAB CBD Program. Interactions between cannabidiol and commonly used antiepileptic drugs. *Epilepsia* 2017; **58**: 1586–92.
28. Ibeas Bih C, Chen T, Nunn AV, Bazetot M, Dallas M, Whalley BJ. Molecular targets of cannabidiol in neurological disorders. *Neurotherapeutics* 2015; **12**: 699–730.
29. Hussain SA, Zhou R, Jacobson C, et al. Perceived efficacy of cannabidiol-enriched cannabis extracts for treatment of pediatric epilepsy: A potential role for infantile spasms and Lennox-Gastaut syndrome. *Epilepsy Behav* 2015; **47**: 138–41.
30. Dan B. Cannabinoids in paediatric neurology. *Dev Med Child Neurol*. 2015; **57**: 984.

Figure 1: Reported adverse events in randomized, placebo-controlled, double-blind trials of cannabidiol (CBD) (10mg and 20mg/kg/day) in developmental and epileptic encephalopathies. URTI, upper respiratory tract infection.

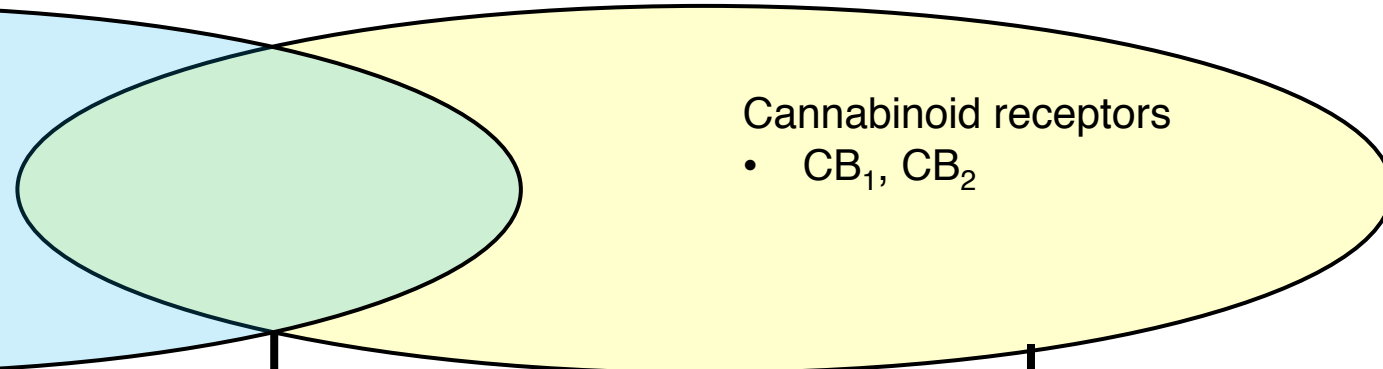
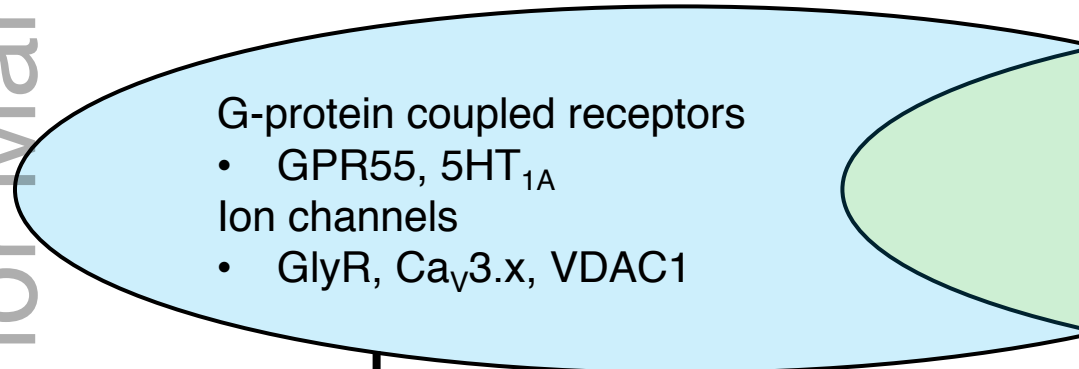
Figure 2: Indications and postulated mechanisms of action for pharmaceutical grade cannabinoids. ^aDronabinol is the International Nonproprietary Name for the pure isomer of Δ^9 -tetrahydrocannabinol (THC). ^bNabilone is a synthetic analogue of THC. GPR55, G-protein coupled receptor 55; 5HT_{1A}, serotonin 1A receptor; GlyR, glycine receptor; Ca_v3.x, voltage-gated calcium channel type 3; VDAC1, voltage-dependent anion channel 1; CB_{1/2}, cannabinoid receptor type 1/2.



Cannabinoid
components
[Pharmaceutical
grade
formulation]



Postulated
mechanisms
of action



Disease

