THE HIGHS OF CANNABINOID THERAPEUTICS: A REVIEW OF CBD TREATMENT OF PAEDIATRIC EPILEPSY

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ABSTRACT

Epilepsy is a disorder of the central nervous system recognised widely for affecting and debilitating the lives of over 50 million people worldwide (Ali et al., 2018), with a significant proportion of this demographic being children. The symptomatic seizures, acting as a hallmark for diagnosis of the disorder, result from an excess in electrical conductivity and communication between cells in the brain. With drug resistance impeding the treatment of so many paediatric patients, the current initiatives in research seek to find novel therapeutics, including looking to cannabinoids for answers. This article explores the wider literature on the research into cannabinoid (CBD) therapeutics to treat paediatric epilepsy, reviewing the successes, but also evaluating the drawbacks of this arguably controversial use of a drug group renowned for its recreational use. The results discussed in this literature review confirm the potential for CBD to reduce the frequency and severity of paediatric epileptic seizures by the way it interacts with the endocannabinoid system of the central nervous system. Additionally, studies identified in this literature review were evaluated to identify the plethora of adverse effects frequently experienced by participants by illustrating the process of the various clinical trials conducted. This movement finds itself in a position of widespread clinical approval of CBD compounds to treat paediatric epilepsy. This gives leverage for the further investigation into the exact pharmacological pathway of the drug and the potential long-term adverse effects of the CBD administration, suggested by patterns of addiction recognised in its recreational usage.

INTRODUCTION

Frequent seizures manifest as a common symptom of epilepsy and are often first recognised between the ages of three and five years old (Epilepsy Society, 2020). Epilepsy is prevalent in early childhood, with one in 220 children under the age of 18 living with the disorder; early diagnosis is fundamental in control and management of the symptoms (Epilepsy Society, 2020). The most severe category of infancy and childhood onset epilepsies are developmental and epileptic encephalopathies (DEEs), epilepsy secondary to any form of brain insult in the developing brain. The incidence of DEEs is 1 in 2000 births, resulting in severe behavioural and cognitive impairment and a 24% death rate within the first 20 years of diagnosis (Ali et al., 2018). With diagnosis so early in a child's life, patients are often burdened by the disorder and typically experience a lower quality of life due to the common ineffectiveness of treatments. Nearly 1 in 3 epileptic patients suffer drug resistance, defined as a failure to control seizures after prescription of at least two medications (Tzadok et al., 2016), leading to interest in development of new antiepileptic medications to target novel receptors.

Cannabidiol (CBD), derived from marijuana, has been used therapeutically for thousands of years, dating back to as early as 1800 BC when tablets written by the Sumerian people described the treatment of 'nocturnal convulsions' with cannabis (Ali et al., 2018, pg. 13). The prospect of research into the effect of cannabinoids as treatment of epilepsy has long been controversial due to the legal restrictions on marijuana cultivation and the recreational high resulting from the psycho-active Δ9-tetrahydro-cannibinol (THC) component. Of these biologically active cannabinoids derived from cannabis plants (cannabis sativa), THC and CBD are the two most therapeutically researched; with the potential for success in treatments (Ali et al., 2018). Demand for accessibility and legalisation of medical marijuana has been encouraged by public plea and media reports of the efficacy when self-prescribed, contributing to the emergence of clinical research into the therapeutic effects of cannabinoids in paediatric epilepsy. Due to public interest acting as a driving force for study, research on this topic is advancing widely. This paper reviews the current literature, identifying the successes and drawbacks of clinical trials and their administered treatments to encourage further investigation. In doing so, this review aims to contribute to the need to revolutionise the treatment of paediatric epilepsy. The literature will first be contextualised by describing the mechanism of action of epilepsy and how CBD interacts with this pathway, then literature on 2 different types of CBD treatment is evaluated. These two types of epilepsy therapeutics will then be evaluated by acknowledging the drawbacks of the studies, followed by a commentary on how CBD therapeutics interact in the developing brains of paediatric patients.

MECHANISM OF ACTION OF EPILEPSY AND CBD: PATHOPHYSIOLOGY AND PHARMACOLOGY

Prior to reviewing the literature on CBD therapeutics of epilepsy, it is first necessary to provide background on the underlying neurophysiology of the brain and nervous system and how the pharmacology of CBD interacts with them. The brain is formed from millions of nerve cells called *neurons* which communicate with each other through electrical signals, which are known as *action potentials*. Carrying nerve impulses from the different body parts to the brain and vice versa, these action potentials transmit between the gaps of individual neurones known as *synapses*. A seizure results from paroxysms (outbursts) of abnormal electrical activity within these neurons, propagating high frequency bursts of action potentials. A normal action potential is propagated by the movement of *ions* in and out of the neuron which creates a charge difference to carry the electrical impulse along the cell. In an epileptic seizure, the neuron experiences a prolonged period of positive charge (termed *depolarization*) due to an influx of positive calcium ions. This is followed by a further influx of positive sodium ions to maintain the depolarization of the neuron and prevent the action potential from ceasing in a sequence termed *paroxysmal depolarizing shift* (Bromfield, Cavazos and Sirven, 2015). Due to this increase in neuronal electrical activity, communication between neurons is disturbed, resulting in what

is commonly recognised as a seizure. Seizures are typically either *focal*, originating in neurones on one side of the brain, or *generalised/tonic-clonic*, where neurons of both sides of the brain are affected (International League Against Epilepsy, 2013).

The pharmacological effects of CBD suggest potential for the treatment of epilepsy due to how it interacts with the epilepsy pathophysiology pathway. Despite interest in cannabinoids as epilepsy treatment, the extent of the pharmacological mechanism behind it is not entirely understood, though it is hypothesised that its constituents interact with the *endocannabinoid system* (ECS) (Tzadok et al., 2016). The ECS is a widespread neuromodulatory pathway, modifying neuronal communications through the strength of their connections via neurotransmitter release (Lu and Mackie, 2016). The ECS is largely responsible for regulation of bodily functions in the neuronal control of the central nervous system in response to insults both environmental and endogenous (not attributable to environmental instead originating within the patient) (Lu and Mackie, 2016).

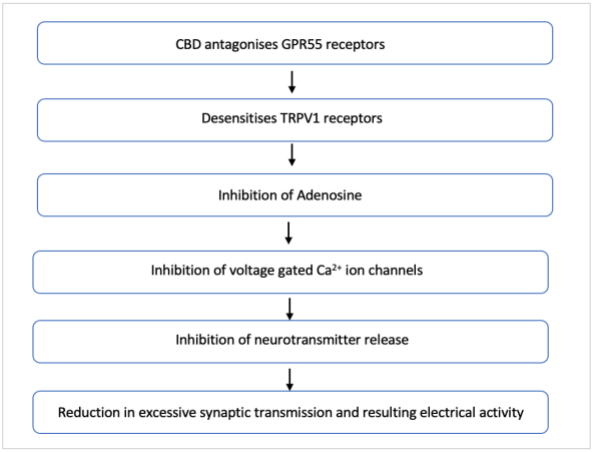

Figure 1: Proposed multimodal mechanism of action of CBD in epilepsy

Neurons express receptor proteins on their cell surface membrane, allowing ions and messenger chemicals called neurotransmitters to bind to and enter the cell. Preclinical evidence suggests CBD functionally antagonises *GPR55 receptors* on neuronal membranes, which in turn desensitises *TRPV1 receptors* (Gray and Whalley, 2020). This acquired desensitivity of the TRPV1 on the neuronal membrane inhibits the action of the neurotransmitter *adenosine* in the modulation of *intercellular neuronal* Ca^{2+} which is typically responsible for the continued *neuronal depolarization* during an epileptic seizure (Gray and Whalley, 2020). This hypothesised CBD inhibition of *voltage-gated* Ca^{2+} *channels* inhibits downstream vesicular neurotransmitter release in the reduction of excessive synaptic transmission by the ECS in the manifestation of epileptic seizures (Blair, Deshpande and DeLorenzo, 2015).

This described neuronal pathway suggests how CBD interacts with the nervous system to prevent the symptoms of epilepsy by reducing the characteristic epileptic seizures commonly recognised in patients in the upcoming reviewed literature.

METHODS

I aimed to explore the successes and drawbacks of current research into the uses of CBD in the treatment of paediatric epilepsy, and the format of a literature review allowed me to explore key themes and methodology of CBD therapeutics in the evaluation of their success. The Medline database was initially searched broadly for the terms relating to 'cannabinoids', 'therapeutics' and 'paediatrics', increasing sensitivity by inclusion of synonyms and spelling variations. Illustrated in Figure 2, Boolean Operators ('AND' and 'OR' used as conjunctions) were subsequently utilised to combine different concepts mentioned in the previous searches; results relating to cannabinoids and therapeutics were combined to a more specific number of results (n= 10844). All results were then collated using AND to a smaller number of papers (n = 61). These 61 papers were then manually filtered against a specific criterion relating to date of publication (2016-2023) and whether they were exclusive to paediatric epilepsy. The final result of this search included systematic reviews which were further refined to primary research studies from reference lists. Supplementary papers were discovered based on ad-hoc searches relating to relevant information mentioned in papers from the prior search. Such information included that of studies whereby paediatric patients made up a smaller subgroup within a larger cohort of epileptic patients, and those categorised by subtype of epilepsy.

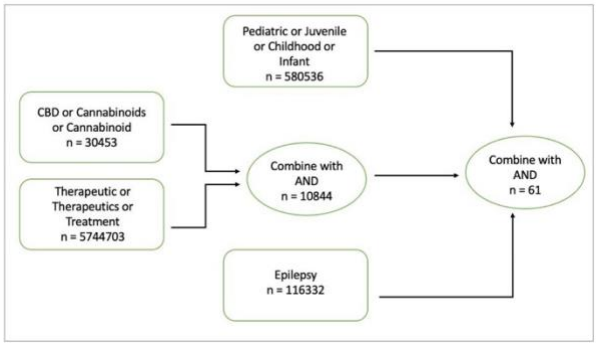

Figure 2: Search terms used for studies,

n = number of results returned at each stage, combination with OR or AND, followed by additional refined search using filters

SELECTED LITERATURE: A TIMELINE OF RESULTS

All drug trials undergo multiple phases of study, and investigation into the efficacy of CBD therapeutics in treatment of paediatric epilepsy is no different. After recruiting participants suffering epilepsy, drug companies investigate varying doses of the CBD drug, studying the efficacy in treatment of epilepsy symptoms whilst noting the adverse effects experienced by the participants. This must be completed before any drug can be approved and rolled out into mainstream treatment. Of these therapeutics, the first treatment type to feature in this review will be the more frequently researched orally administered CBD, followed by transdermal CBD (applied to the skin in gel form), which is limited in quantity due to lack of research on the subtype. Given the limited research into CBD therapeutics for paediatric epilepsy, these two treatment types were most frequently found in my review of the wider literature, making this smaller sample an arguably limiting factor of my review.

Orally administered CBD is the most widely researched type of therapeutic; Devinsky et al. (2016) undertook an open-labelled trial where both investigators and trial participants were aware of the drug dosage given without the use of a placebo. They reported a dose of 2-5mg/kg oral cannabidiol in patients with intractable childhood-onset epilepsy up-titrated (increase of dosage over time) until intolerance (maximum 50mg/kg per day) eliciting a median reduction in total seizures of 34.6%, most favourably in focal seizures. Adverse effects were reported by 79% of patients, the most frequent being

somnolence (drowsiness) (25%), diarrhoea (19%) and convulsions (11%) (Devinsky et al., 2016).

A trial displaying a similar outcome was conducted by Tzadok et al. (2016), retrospectively studying the effects of administering a formula of CBD and THC (ratio 20:1) on childhood-onset epilepsy. The dosage ranged from 1 to 20mg/kg/day between 3-12 months and while 52% of patients reported reduction in seizure frequency greater than 50%, 7% withdrew due to somnolence and aggravation of seizures (Tzadok et al., 2016); this is similar to adverse effects observed by Devinsky et al (2016).

Reporting similar results and adverse effects, a double-blind placebo-controlled trial by Devinsky et al. (2017) investigated CBD treatment. The subgroup studied being the drug-resistant epilepsy (Dravet Syndrome) recognised by the incidence of seizure increasing in line with climbing body temperature and fever. Following a 14-week treatment period of cannabidiol solution at 20mg/kg of body weight, in addition to standard antiepileptic treatment, the median frequency of monthly seizures decreased from baseline by 38.9% (Devinsky et al., 2017). Additionally, the rating instrument 'Caregiver Global Impression of Change Scale' was used to assess condition improvement. Categories include: 1) very much improved; 2) much improved; 3) minimally improved; 4) unchanged; 5) a little worse; 6) much worse; 7) very much worse (Busner and Targum, 2007). The results reported condition improvement by more than 1 category in 62% of children, of which 5% became seizure-free post-treatment (Devinsky et al., 2017). Despite these successes, adverse effects were reported more frequently in the treatment group (93%) than the placebo group (75%), including diarrhoea and somnolence, encouraging 3 participants to withdraw from treatment (Devinsky et al., 2017).

Following the success of trials in 2016 and 2017, Devinsky and colleagues (Devinsky et al., 2018) investigated the effect of increasing dosage of CBD on seizure incidence. Following twice daily treatment for 14 weeks, the median percent reduction from baseline in drop seizure frequency was 37.2% in patients receiving 10mg/kg body weight and 41.9% in patients receiving 20mg/kg body weight (Devinsky et al., 2018). However, with increased dosage came increased adverse effect incidence; this was reported by 84% of patients in the 10mg/kg group and 94% of patients in the 20mg/kg group (Devinsky et al., 2018).

An additional randomised, double-blind, placebo-controlled trail was conducted by Thiele et al. (2018), investigating the efficacy of cannabidiol as an add-on therapeutic for drop-seizures. The chosen cohort studied were patients suffering an early onset subtype of severe epilepsy (Lennox-Gastaut syndrome) characterised by repeated seizures. 20 mg/kg of purified CBD oral solution was administered once daily, resulting in a median drop seizure incidence decrease from baseline in 43.9% of patients in the cannabidiol group (Thiele et al., 2018). Despite this, reports of diarrhoea, somnolence and pyrexia (fever) led to the withdrawal of 14% of patients (Thiele et al., 2018).

Further to orally administered CBD, transdermal CBD is studied as an epilepsy therapeutic: the application of the CBD gel to the skin allows the active agents to permeate the porous skin barrier to interact with cannabinoid receptors. Scheffer and colleagues trialled 48 children with a transdermal CBD gel targeting DEEs in a non-randomised controlled study (Scheffer et al., 2021). Following the 6.5-month treatment period of twice daily 4.2% topical CBD transdermal gel application, median seizure reduction from baseline was 12.3% (Scheffer et al. 2021). Focal impaired awareness seizures and tonic-clonic seizures elicited the most favourable response rate despite reports of application site dryness in 8% of participants (Scheffer et al., 2021).

DRAWBACKS AND LIMITATIONS OF REVIEWED LITERATURE

In addition to the reported adverse effects, results must be interpreted sensitively due to cofounding variables of each study. In order to meet ethical protocol, no participant of the studies was made to cease treatment with other antiepileptic medication during the trial. Thus, CBD therapeutic results must be interpreted as adjuvant treatment of epilepsy, whereby CBD therapeutics are given in addition to each patient's usual, prescribed treatment. However, since the studies fail to report the types/doses of additional therapeutics participants were already prescribed, it's impossible to accurately replicate the results unless all participants were taking the same known combination of therapeutics in addition to CBD. Not all studies provided a placebo, instead calculating a baseline frequency of seizure influence as a comparison value in retrospective studies like Tzadok et al. (2016). This may be seen as a more objective design whereby participants were in both the CBD and control groups, accounting for difference in cofounding variables such as additional medication and medical history. In trials using a placebo, groups should have been matched on characteristics where possible, including vagus nerve stimulation and ketogenic diet, which are known for their relationship with seizure incidence (Epilepsy Society, 2023). In all reported studies, an attempt at standardization of results was made by objectively reporting the dependent variable as number of seizures. However, this disregards the characteristic of 'severity', risking the possibility of seizures being less frequent but more severe than baseline. All drug trials undergo multiple phases of study, and investigation into the efficacy of CBD therapeutics in treatment of paediatric epilepsy is no different. After recruiting participants suffering epilepsy, drug companies investigate varying doses of the CBD drug, studying the efficacy in treatment of epilepsy symptoms whilst noting the adverse effects experienced by the participants. This must be completed before any drug can be approved and rolled out into mainstream treatment. Of these therapeutics, the first treatment type to feature in this review will be the more frequently researched orally administered CBD, followed by transdermal CBD (applied to the skin in gel form), which is limited in quantity due to lack of research on the subtype. Given the limited research into CBD therapeutics for paediatric epilepsy, these two treatment types were most frequently found in my review of the wider literature, making this smaller sample an arguably limiting factor of my review.

EFFECT ON THE DEVELOPING BRAIN

In addition to the adverse effects of orally administered and transdermal CBD treatment of paediatric epilepsy, there is concern regarding the effects of CBD on the developing brains of children. Though many studies investigate isolated CBD, Tzadok et al. (2016) worked with a ratio of CBD to THC, the psychoactive component relating to incidences of psychosis and addiction when taken recreationally. Studies of long-term THC users revealed a 9% incidence of addiction in addition to risk of cognitive impairment, decreased motivation and psychiatric disorders (Friedman and Devinsky, 2015). The ECS undergoes extensive development in childhood, raising the concern that juvenile exposure and long-term usage of CBD may result in cognitive and behavioural changes. Brain imaging studies in long term users reveal impaired connectivity of the precuneus, involved most notably in memory formation and recollection, and prefrontal cortices, noted for cognitive function relating to impulse control and comprehension in response to actions and emotions (Friedman and Devinsky, 2015). Despite this

concerning evidence, it cannot be confirmed whether these adverse effects are mediated solely by THC or whether paediatric exposure to CBD produces the same detrimental outcome.

CONCLUSION: NEXT STEPS FOR CANNABOID THERAPEUTICS

The aim of this literature review was to identify and evaluate the successes and drawbacks of the use of CBD therapeutics for paediatric epilepsy in clinical trials conducted in the movement towards approval and legislation of its clinical use. The intention behind this was to highlight the adverse effects experienced alongside a reduction in epilepsy symptoms following administration of CBD drugs, and to provide further insight into the rigorous procedure of drug testing. Consequently, the conclusion based on these clinical findings is that CBD therapeutics (despite reported adverse effects) have demonstrated a reduction in symptoms of paediatric epilepsy; more often so when administered in addition to existing prescribed epilepsy therapeutics.

The approach taken to review literature on the topic of CBD paediatric epilepsy therapeutics may be perceived as a limitation. All studies reviewed demonstrated a correlation between administration of CBD therapeutics and a reduction in symptoms, without reporting the findings of studies that failed to produce this corelation. Future literature reviews on this topic may benefit from reviewing literature that failed to report reductions on paediatric epilepsy symptoms. Nonetheless, the approach I took was intentional, as the initial aim of this review was to identify the success of CBD therapeutics of paediatric epilepsy and subsequently scrutinise any drawbacks in the methodology or reported adverse effects of treatment.

The reported research into paediatric cannabinoid therapeutics has led to the success and approval of CBD treatments clinically. Currently in the UK, Epidyolex (an orally administered CBD liquid) can be prescribed for children and adults suffering Lennox Gastaut syndrome and Dravet syndrome (NHS, 2019). Unsurprisingly, within paediatric epilepsy no two cases are the same and, like many prescription medicines, adverse effects will appear differently. This hence offers the suggestion that a more personalised treatment approach may be encouraged to investigate the patient's genetics and family history of prescription and recreational drug usage in prediction of CBD efficacy. However, with further research must come destigmatisation of CBD therapeutics. The removal of the psychoactive element THC and formulation of accessible prescription CBD would reduce the concern of non-prescription CBD being sourced by patients and risking addiction and brain development issues. Ultimately, the aforementioned neurodevelopmental risks associated with CBD must be weighed against the benefits of seizure control, as further research into this postulation is encouraged to better the future of the effective treatment of paediatric epilepsy.

REFERENCES

Ali, S., Scheffer, I. E. and Sadleir, L. G., 2018. Efficacy of cannabinoids in paediatric epilepsy. *Developmental Medicine & Child Neurology*, 61(1), pp.13–18. doi:https://doi.org/10.1111/dmcn.14087.

Blair, R. E., Deshpande, L. S. and DeLorenzo, R. J., 2015. Cannabinoids: is there a potential treatment role in epilepsy? *Expert Opinion on Pharmacotherapy*, 16(13), pp.1911–1914. doi:https://doi.org/10.1517/14656566.2015.1074181.

Busner, J. and Targum, S. D., 2007. The clinical global impressions scale: applying a research tool in clinical practice. *Psychiatry (Edgmont)*, 4(7), pp.28–37. Available at: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2880930/> [Accessed 13 Aug. 2023].

Bromfield, E. B., Cavazos, J. E. and Sirven, J. I., 2015. *An introduction to epilepsy*. [e-book] University of California: Davis School of Medicine. Available at: <https://www.ncbi.nlm.nih.gov/books/NBK2510/> [Accessed 2 Feb. 2023].

Devinsky, O., Cross, J. H., Laux, L., Marsh, E., Miller, I., Nabbout, R., Scheffer, I. E., Thiele, E. A. and Wright, S., 2017. Trial of cannabidiol for drug-resistant seizures in the Dravet Syndrome. *The New England Journal of Medicine*, 376(21), pp.2011–2020. doi:https://doi.org/10.1056/NEJMoa1611618.

Devinsky, O., Marsh, E., Friedman, D., Thiele, E., Laux, L., Sullivan, J., Miller, I., Flamini, R., Wilfong, A., Filloux, F., Wong, M., Tilton, N., Bruno, P., Bluvstein, J., Hedlund, J., Kamens, R., Maclean, J., Nangia, S., Singhal, N.S. and Wilson, C.A., 2016. Cannabidiol in patients with treatment-resistant epilepsy: an open-label interventional trial. *The Lancet Neurology*, 15(3), pp.270–278. doi:https://doi.org/10.1016/s1474-4422(15)00379-8.

Devinsky, O., Patel, A. D., Cross, J. H., Villanueva, V., Wirrell, E. C., Privitera, M., Greenwood, S. M., Roberts, C., Checketts, D., VanLandingham, K. E. and Zuberi, S. M., 2018. Effect of cannabidiol on drop seizures in the Lennox–Gastaut syndrome. *New England Journal of Medicine*, 378(20), pp.1888–1897. doi:https://doi.org/10.1056/nejmoa1714631.

Eiben, I., Eiben, P. and Watson, K., 2018. *Crash course general medicine*. 5th ed. [e-book] Elsevier: ClinicalKey. Available at: <https://www.clinicalkey.com/student/content/book/3-s2.0B9780702073724000320#hl0000462> [Accessed 2 Feb. 2023].

Epilepsy Society. 2020. *Epilepsy in childhood | Epilepsy Society*. [online] Available at: <https://epilepsysociety.org.uk/about-epilepsy/information-parents/epilepsy-childhood?gclid=CjwKCAjwscGjBhAXEiwAswQqNLP0j07UURUAJXCEMTamMt_AA3-6VUYoCUpPkP-OlPO_Vvu8kWmLBxoCbI4QAvD_BwE> [Accessed 26 May 2023].

Epilepsy Society. 2020. *Ketogenic diet | Epilepsy Society*. [online] Available at: <https://epilepsysociety.org.uk/about-epilepsy/treatment/ketogenic-diet> [Accessed 17 July 2023].

Friedman, D. and Devinsky, O., 2015. Cannabinoids in the treatment of Epilepsy. *New England Journal of Medicine*, 373(11), pp.1048–1058. doi:https://doi.org/10.1056/nejmra1407304.

Gray, R. and Whalley, B., 2020. The proposed mechanisms of action of CBD in epilepsy. *Epileptic Disord*, 22, pp.10–15. doi:https://doi.org/10.1684/epd.2020.1135.

International League Against Epilepsy. 2013. *Definition & Classification // International League Against Epilepsy*. [online] Available at: <https://www.ilae.org/guidelines/definition-and-classification> [Accessed 26 May 2023]

Lu, H. C. and Mackie, K., 2016. An introduction to the endogenous cannabinoid system. *Biological Psychiatry*, 79(7), pp.516–525. doi:https://doi.org/10.1016/j.biopsych.2015.07.028.

NHS. 2019. *Medical cannabis (and cannabis oils).* [online] Available at: <https://www.nhs.uk/conditions/medical-cannabis/> [Accessed 9 Feb. 2023].

Scheffer, I. E., Hulihan, J., Messenheimer, J., Ali, S., Keenan, N., Griesser, J., Gutterman, D. L., Sebree, T. and Sadleir, L.G., 2021. Safety and tolerability of transdermal cannabidiol gel in children with developmental and epileptic encephalopathies: a nonrandomized controlled trial. *JAMA Network Open*, 4(9), pp.e2123930–e2123930. doi:https://doi.org/10.1001/jamanetworkopen.2021.23930.

Thiele, E. A., Marsh, E. D., French, J. A., Mazurkiewicz-Beldzinska, M., Benbadis, S. R., Joshi, C., Lyons, P. D., Taylor, A., Roberts, C., Sommerville, K. and GWPCARE4 Study Group., 2018. Cannabidiol in patients with seizures associated with Lennox-Gastaut syndrome (GWPCARE4): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet (London, England),* 391(10125), pp.1085–1096. doi:https://doi.org/10.1016/S01406736(18)30136-3.

Tzadok, M., Uliel-Siboni, S., Linder, I., Kramer, U., Epstein, O., Menascu, S., Nissenkorn, A., Yosef, O. B., Hyman, E., Granot, D., Dor, M., Lerman-Sagie, T. and Ben-Zeev, B., 2016. CBD enriched medical cannabis for intractable pediatric epilepsy. *Seizure*, 35, pp.41–44. doi:https://doi.org/10.1016/j.seizure.2016.01.004.