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Efficacy and safety of cannabidiol for the treatment of pediatric epilepsy

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Abstract

Background: Drug-resistant epilepsy affects one-third of patients, requiring new medications for efficacy. Interest in new antiepileptic properties, targeting novel receptors, is high.

Objectives: Determine which studies have examined the usage of cannabis & products derived from cannabis as a therapy of pediatric epilepsy.

Patients and methods: NRSs and RCTs examining the usage of cannabis as a therapy for any form of epilepsy in kids (eighteen years old or less) have been involved into our analysis. The interventions involved a wide range of cannabis-derived products, such as THC, cannabinol, CBD, or combinations, delivered through various routes (such as inhalation, oral). Pharmacologic (such as analgesics) & nonpharmacologic (such as vagus nerve stimulation, resective brain surgery ,diet therapy) therapies, in addition to placebo, standard care, or no treatment, were eligible comparators.

Results, Conclusion: The administration of CBD resulted in a significant improvement of seizure load. Most kids reported a reduction in the incidence of their seizures. kids with drug-resistant Dravet & Lennox-Gastaut syndromes can benefit from CBD in terms of reduced seizure burden (moderate certainty); nonetheless, few of these children were completely seizure free. Children with other DRE syndromes may also benefit, albeit the evidence is currently limited. It is not appropriate to apply these results to all cannabis-based products, particularly ones whose exact makeup is unknown.

Key words: cannabidiol, pediatric, epilepsy**,** Dravet and Lennox-Gastaut syndromes**.**

Introduction

An approximate one-third of the fifty million people affected by epilepsy worldwide **(1)** have a drug-resistant form **(2)** (antiepileptic drugs [AEDs] have failed two or more adequate studies **(3).** The complications of drug-resistant epilepsy (DRE) during childhood are life-threatening, as recurrent seizures have detrimental effects on cognitive & neurological development, place significant costs on healthcare systems and reduce the quality of life. **(4).(5)** Despite being the cornerstone of treatment, AEDs frequently fail to mitigate seizures and are correlated with a

multitude of adverse events. **(6)** Media coverage of successful cannabis-based interventions for pediatric epilepsy has contributed in part to the increasing interest in the subject **(7). (8)** As prospective antiepileptic agents, cannabidiol (CBD) & nine-delta-tetrahydrocannabinol (THC) have garnered the most interest. Particularly in minors, the psychoactive properties of THC may restrict its applicability as an antiepileptic agent. CBD, on the other hand, exhibits minimal psychoactive properties & protects against multiple forms of seizures in animal models. **(7)**

Nevertheless, clinical research on the safety & efficacy of cannabis-based treatments for epilepsy was limited until recently, &there are significant differences of belief among neurologists and the public regarding the sufficiency of evidence regarding safety & efficacy. **(9)**
Four randomized controlled trials (RCTs) evaluating the use of cannabinoids in adults with epilepsy were included in a 2014 Cochrane review **(10)** which concluded that no reliable conclusions could be derived regarding their safety &efficacy. On the contrary, (RCTs) & nonrandomized studies (NRSs) have indicated that CBD may have a positive impact on the management of pediatric epilepsy **(11-15).** In fact, the initial cannabis-based product (Epidiolex; GW Pharmaceuticals), a pharmaceutical-grade (CBD) extract, was recently accepted by the FDA in the US for treating Dravet syndromes & Lennox-Gastaut (Epidiolex; GW Pharmaceuticals). **(16)**
For the current investigation, a systematic review was conducted to identify research that studied the therapeutic applications of cannabis & cannabis-based products in children with epilepsy.

Methods

RCTs and NRSs analyzing the utilization of cannabis as therapy for any form of epilepsy for kids (eighteen years old or less) were incorporated into our analysis. The interventions encompassed a wide range of cannabis-derived products, such as cannabinol, THC, CBD, or combinations, delivered through various routes (e.g., inhalation, oral). Pharmacologic (e.g., AEDs) & nonpharmacologic (e.g., vagus nerve stimulation, diet therapy, resective brain surgery) therapies, in addition to placebo, standard care, or no treatment, were admissible comparators.
Search strategy, screening, data extraction.

Without regard to language or date restrictions, we conducted a search of the Cochrane Library on Wiley, Ovid MEDLINE, PsycINFO & Embase on Ovid (Appendix S2). The CADTH's Grey Matters Light, ICTRP Search Portal, ClinicalTrials & Google Scholar. gov were utilized to locate gray literature. Two independent reviewers (J.E. and D.D.) assessed the titles & abstracts of any record. In addition, all texts of any records considered potentially relevant were included. One reviewer collected data from primary reports and supplementary reports , while another verified the data for accuracy and completeness. The resolution of disagreements occurred through discussion.

Results

Table (1) Characters of the studied groups:

Authors	Year	Country	Type of study	Age
Devinsky et al. (17)	2018	USA, and AK	Parallel-group, randomized, placebo-controlled trial	4-10 years
Devinsky et al. (18) (GWPCARE1 Part B)	2017	(USA, Europe)	Parallel-group, randomized, placebo-controlled trial	2–18 years
Devinsky et al. (19), 2018 (GWPCARE3)	2018	(USA, Spain, UK, France)	Parallel-group, randomized, placebo-controlled trial	Aged 2–55 years
Thiele et al.(20), 2018 (GWPCARE4)	2018	(USA, Netherlands, Poland)	Parallel-group, randomized, placebo-controlled trial	Aged 2–55 years

Table (2) characters of the studied groups:

Authors	population	Treatment arms	Duration
Devinsky et al. (17), 2018	Dravet syndrome	Oral placebo bid	Three weeks of treatment, ten days of tapering, and four weeks of follow-up

Devinsky et al. (18), 2017 (GWPCARE1 Part B)	Dravet syndrome	Oral placebo bid Oral CBD: 20 mg/kg bid	fourteen weeks of treatment (two weeks of escalation and twelve weeks of maintenance), followed by a four-week follow-up after a ten day taper.
Devinsky et al. (19), 2018 (GWPCARE3)	Lennox-Gastaut syndrome	Oral placebo bid Oral CBD: 10 & 20 mg/kg bid	fourteen weeks (four weeks follow-up, two-week escalation, twelve weeks of treatment)
Thiele et al. (20), 2018 (GWPCARE4)	Lennox-Gastaut syndrome	Oral placebo bid Oral CBD: 20 mg/kg bid	fourteen weeks (two weeks of escalation, twelve weeks of treatment), tapering period, and four weeks of follow-up.

Discussion

Epilepsy is among the most prevalent chronic neurological disorders. It has a point prevalence of four to ten cases per thousand individuals &an annual incidence is around eighty cases per one hundred thousand individuals **(21)**. It impacts approximately 65 million people globally. Although sustained remission is achievable in most cases with epilepsy, around one-third persist in suffering seizures despite receiving adequate therapy **(22, 23)**. Despite significant advancements in treatment options such as neuromodulatory, dietary interventions, pharmacological & surgical ,the prevalence of treatment-resistant epilepsy has exhibited a relatively consistent pattern throughout the years **(24)**. This shows the ongoing necessity of investigating new therapeutic alternatives.

In the past decade, the antiepileptic properties of cannabinoids have garnered considerable interest. (CBD) is a significant chemical constituent present in the resin of Cannabis sativa, more widely recognized under the term marijuana. CBD is mostly devoid of abuse liability, and, in contrast tetrahydrocannabinol, it doesn't cause euphoric or intrusive side effects **(25)** & lacks psychoactive properties. The anticonvulsant effects of CBD are mediated by multiple mechanisms, including antagonist & agonist effects on neurotransmitter transporters, multiple 7-transmembrane receptors &ionic channels, **(26)**. These effects aren't directly associated with cannabinoid receptors.

The US FDA approved CBD in June 2018 as an adjunctive anti-epileptic drug (AED) for cases with Dravet syndrome & Lennox–Gastaut syndrome , formerly defined as severe myoclonic epilepsy of infancy, who are at least two years old. At present, the pharmaceutical drugs are under regulatory evaluation by the European Medicines Agency; an outcome is anticipated during the initial quarter of 2019 **(27, 28).**

In a prior systematic review that examined both pediatric and adult patients with epilepsy, CBD was shown to be more effective than placebo at increasing treatment response and decreasing the regularity of seizures. stockings & Colleagues, in contrast to our findings, reported that CBD enhanced quality of life and seizure freedom. These apparent inconsistencies are most likely

attributable to variations in methodology. stockings & Colleagues incorporated estimates of freedom from convulsive or drop seizures with freedom from all seizures in their analysis of seizure freedom. In contrast, our evaluation exclusively included studies that reported freedom from all seizures. While no statistically significant distinction among groups was observed, it is important to note that this conclusion was derived from a single RCT. Further studies that evaluate the absence of seizures in their entirety will provide further clarity regarding the potential beneficial effects of CBD **(29)**. The Caregiver Global Impression of Change score was used by Stockings and colleagues to evaluate quality of life. This score quantifies whether the caregiver observes an overall improvement in the child's condition. **(29)**
Parents of kids diagnosed with DRE claim, "unacceptable AED side effects" & the perceived superiority of cannabis-based products as "more natural" & efficacious reasons for their inclination to involve their child in a cannabinoid study for epilepsy. **(30)** In contrast, a prior analysis documented a heightened likelihood of adverse reactions, including severe adverse reactions, in both adults and children administered CBD in comparison to those receiving a placebo. Our own investigation revealed a particularly pronounced risk of diarrhea among the children who were administered CBD. Therefore, it is imperative that the administration of CBD or other products derived from cannabis be determined through an interactive method involving health care providers and parents, considering the potential advantages and disadvantages **(29)**.

The first was a retrospective study that described a telephone/Internet survey of nineteen kids' parents received CBD-enriched medical marijuana for various childhood epileptic encephalopathies: sixteen (eighty-four percent) noticed a decrease in seizure regularity & two became seizure-free. **(31)**

A retrospective chart review was conducted at a tertiary epilepsy center, encompassing adolescents & seventy five children who were administered medical cannabis for a variety of epileptic encephalopathies **(32)**. fifty-seven percent of respondents indicated an enhancement in seizure control, whereas thirty three percent documented a decrease in seizures of at least fifty percent. The response rate varied by syndrome: 23% for Dravet syndrome, zero percent for Doose syndrome, & 88.9 percent for Lennox–Gastaut syndrome. An absence of benefit was observed in the EEGs that were accessible. An online parental survey concerning the tolerability, dosage, and perceived efficacy of CBD-enriched cannabis preparations for children with infantile spasms, Lennox–Gastaut syndrome, & other intractable epilepsies comprised the third report. 117 parents in total participated in the survey. Perceived efficacy & tolerability exhibited comparable levels among etiologic subgroups; fourteen percent of respondents reported complete independence from seizures, while eighty-five percent documented a decrease in seizure frequency. The period of CBD exposure & the median dosage were, respectively, 4.3 mg/kg/day and 6.8 months. An increase in seizure frequency, somnolence/fatigue, & a greater appetite were among the few adverse effects documented in these three studies **(31, 32)**. Developmental regression, status epilepticus necessitating intubation, abnormal movements, & mortality were uncommon adverse events. Parents reported improved sleep quality, heightened alertness, & enhanced mood as additional positive effects of CBD therapy, in addition to seizure control, across all three studies. A ten percent proportion of patients exhibited language and motor skill improvements, according to a study by **Hussain et al. (32).**

Conclusion

kids with drug-resistant Dravet & Lennox-Gastaut syndromes can benefit from CBD in terms of reduced seizure burden (moderate certainty); nonetheless, few of these children were completely seizure free. Children with other DRE syndromes may also benefit, albeit the evidence is currently limited. It is not appropriate to apply these results to all cannabis-based products, particularly ones whose exact makeup is unknown.

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