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Epilepsy and cannabidiol - a new perspective for seizures treatment

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Abstract

BACKGROUND: Despite the fact that the number of antiepileptic drugs is constantly increasing, epilepsy can still be a therapeutic challenge. Approximately one-third of patients with epilepsy have persistent seizures refractory to treatment. The limited number of effective alternatives motivates researchers to seek new solutions. There is some hope for cannabidiol (CBD) preparations.

AIM OF THE STUDY: The purpose of this study was to review the most recent available literature on the use of cannabidiol in the treatment of refractory epilepsy in children and adults. For this purpose, the PubMed and Google Scholar databases were reviewed. The phrase "cannabidiol and epilepsy" was used to search the database. After Screening titles and abstracts a total of 19 papers and articles cited in them were received and analyzed in detail.

RESULTS: Nowadays there are many CBD related products available in the market, Cannabis sativa and Cannabis indica are the plants used due to their strong therapeutic effects and also seizure control. Regulations regarding the use of raw marijuana, cannabis extracts, and cannabinoid-based drugs vary from place to place. Many studies have been generated on the efficacy of cannabinoid therapy in the treatment of epilepsy. This therapy in patients with Dravet syndrome and Lennox-Gaust syndrome results in a reduction in the frequency of motor and total seizures. The most commonly reported side effects of CBD are drowsiness, seizures and diarrhea, but the therapy is generally well tolerated.

SUMMARY AND CONCLUSIONS: Many available studies support the efficacy of CBD as a treatment option to reduce seizure frequency in children with drug-resistant epilepsy, particularly in patients with Dravet and Lennox-Gastaut syndrome. However, there is a lack of reports on the use of CBD in the adult population, which may be an area for further research.

Keywords: cannabidiol; epilepsy; children

Introduction

Epilepsy encompasses a wide range of chronic syndromes characterized by recurrent, unprovoked and unpredictable seizures. The disease affects more than 65 million people worldwide, including about 0. 6% of children under 18 and 82% of those under 10 years of age [1,2,3].

The latest research, including the use of novel therapies, is helping to better explain the causes of neurological disorders and improve patient treatment. In particular, the endocannabinoid system (ECS) is crucial for neurological function, and modulation of this system offers therapeutic hope [4]. Cannabidiol is a new compound that exhibits central nervous system effects, but unlike other cannabinoids (such as tetrahydrocannabinol) it does not cause euphoria. This compound has a low affinity for endogenous cannabinoid receptors and may modulate neuronal hyperactivity. Cannabidiol exhibits anticonvulsant and anti-inflammatory effects on the nervous system, it also shows inverse agonism (or antagonism) to cannabinoid receptors, modulation of neuronal channels and enhancement of anandamide actions [5].

In patients with severe refractory epilepsy (TRE), antiepileptic drugs provide only partial seizure relief, often at the expense of severe side effects. The therapeutic potential of cannabidiol (CBD) as an antiepileptic drug is of great interest, especially for severe TREs [6].

Aim of the study

The aim of this study was to review the latest available literature on the use of cannabidiol in the treatment of refractory epilepsy in children and adults. For this purpose, the PubMed and Google Scholar databases were reviewed. The phrase "cannabidiol and epilepsy" was used to search the database. Search criteria were: all open access, 3 years, English. 64 results were obtained. After Screening titles and abstracts a total of 19 papers and articles cited in them were received and analyzed in detail.

Legislation

Regulations on the use of raw marijuana, cannabis extracts and cannabinoid-based drugs in the United States vary from state to state [7]. After the passage of the Marihuana Tax Act of 1937, cannabis use was restricted at the federal level. The Tax Act imposed penalties on physicians prescribing and dispensing drugs in pharmacies, even though the drugs were used for therapeutic purposes prior to the enactment of the Act. In 1970, thanks to the Cannabis Control Act, all uses of marijuana, including medicinal, were officially outlawed with the status of a controlled substance [8].

The use of marijuana for medicinal purposes is currently permitted in many countries, including Argentina, Australia, Canada, Chile, Colombia, Croatia, Ecuador, Cyprus, Germany, Greece, Israel, Italy, Jamaica, Lithuania, Luxembourg, North Macedonia , Norway, the Netherlands, New Zealand, Peru, Poland, Switzerland and Thailand, as well as several states in the United States [9]. In the 33 U. S. states that support the use of marijuana for recreational or medicinal purposes, patients must have a legally validated medical condition to obtain the product for medical reasons. Eligibility conditions, defined by the American College of Physicians in 1996, include HIV/AIDS, cancer, severe muscle spasm, amyotrophic lateral sclerosis, end of life (defined as <1 year of age), Crohn's disease, seizure disorders, glaucoma, and Tourette's syndrome. Despite recent FDA approval, the legality of purified CBD remains controversial [8].

In the European Union (EU) CBD, unlike THC, is not a controlled substance and under EU law CBD products cannot contain more than 0. 2% THC. There are several companies in the EU that produce and distribute CBD-based products derived from the inflorescences of industrial hemp varieties. These products are not subject to any compulsory analytical controls and, in addition, no legal protection or guarantees concerning their composition and quality are required. In addition, mandatory testing and a basic regulatory framework are also not required to define the area of indication, daily dose, route of administration, maximum recommended daily dose, packaging, shelf life and stability. Much of this inaccuracy stems from the fact that it is not legally regulated whether such products should be regulated as food, supplements or drugs [9,10].

Products with CBD

There are many CBD-related products on the market today, with a wide range in purity, effective compound content, and price. The global market for these products is significant and according to the Centre for Medicinal Cannabis (2019) in the UK, at the current rate the market will be worth £1 billion a year by 2025. Importantly, the content of CBD-related products depends on the type of hemp plant, as well as different parts of the plant and growing conditions. Hemp and marijuana can be considered different varieties of the same cannabis plant; while cannabis has a low content of all cannabinoids, including THC (≤0. 3%), marijuana has a higher THC content (> 0. 3%) [9].

Cannabis sativa and Cannabis indica are plants used for their strong therapeutic effects and also for the control of seizures. Of their expressed cannabinoids, Δ9-tetrahydrocannabinol(Δ9-THC) and cannabidiol (CBD) have been characterized as the two main neuroactive components. The former is attributed to psychoactive effects and the latter to anticonvulsant and anti-epileptic effects. Cannabidiol has been shown to both potentiate the therapeutic effects of Δ9-THC and reduce the unwanted effects of THC (anxiety, panic, sedation, dysphoria, tachycardia) This has led to increased research towards developing pure or highly enriched CBD preparations for the treatment of epilepsy and other neurological disorders [3,11,12]. To date, only a small number of cannabis-based medicines in the form of capsules, oromucosal sprays or oily solutions have been authorised or are currently in advanced stages of development [3].

Effectiveness in the treatment of epilepsy in adults

Cannabidiol is a GPR55 antagonist, thereby suppressing neuronal excitability by reducing Glut exocytosis. Action on this signaling pathway may be one of the mechanisms of CBD's anticonvulsant effects and, as a result, a safe therapeutic target for the treatment of epilepsy. An important action of CBD in relation to epilepsy is the regulation of adenosine, a neuromodulator of the central nervous system. It is thought that adenosine plays a role in terminating seizures, by blocking the CBD-mediated equivalent nucleotide transporter (ENT) [13].

The 2019 meta-analysis noted that epilepsy was the most commonly studied medical condition. All 11 studies described beneficial effects of CBD on reducing seizure severity or frequency. Four randomized controlled clinical trials were conducted using an average dose of 15 mg/kg/d. CBD was administered as add-on therapy to regular antiepileptic drugs and significant improvements were observed compared to placebo as add-on therapy. In the other three prospective, open-label studies, CBD was administered at a mean dose of 42 mg/kg/d and significant improvements in quality of life and seizure frequency were observed compared with baseline. In addition, three case series and a single case report described beneficial effects of a mean dose of 21 mg/kg/d CBD on seizure frequency, duration, and severity [14].

Effectiveness in the treatment of epilepsy in children

Studies on CBD-enriched oils show a 50% reduction in seizures in about 30-40% of pediatric patients. However, it should be noted that these are uncontrolled studies with heterogeneous CBD formulations whose CBD content varied from study to study, generally estimated to be <0. 02-50 mg/kg/day. The study by Press and co-authors examined the effects of cannabis extracts in pediatric patients with epilepsy at one tertiary epilepsy center in Colorado, where laws regarding cannabis products are more relaxed. Interestingly, the overall response rate (47%) for patients who moved to Colorado for treatment was greater than (22%) those who already lived in Colorado, indicating a possible positive reporting bias and the need for properly controlled studies [9,15].

A prospective, open-label study evaluating a new oral CBD formulation, PTL-01, demonstrated a clear beneficial therapeutic effect of a 12-week treatment period on seizure frequency among patients with TRE. A mean 73. 4% reduction in monthly seizure frequency and a median 81. 9% reduction from baseline were observed. Two patients were completely seizure free within 5 weeks of therapy, with an additional eight patients reporting a 50% reduction in seizure frequency during this time. This translated into a significant improvement in health status, as expressed by caregivers' global impressions of significant overall improvement and marked reduction in seizure severity [3].

After 12 weeks of CBD-added therapy in patients with Dravet syndrome and Lennox-Gaust syndrome, there was a 50% reduction in monthly motor seizure frequency and a 44% reduction in monthly total seizure frequency. These reductions were sustained for up to 96 weeks. After 12 weeks of treatment with CBD, the percentage of LGS/DS patients with seizure reductions of ≥50%, ≥75%, and 100% from baseline were 53%, 23%, and 6% for severe motor seizures and 46%, 26%, and 5% for total seizures. The response rate remained constant between weeks 12 and 96 [6].

a) Lennox-Gastaut syndrome

Lennox-Gastaut syndrome (LGS) is a severe epileptic and developmental encephalopathy. The most common period of its occurrence is at the age of 7. The three main diagnostic criteria for LGS are: multiple types of seizures, mainly generalized, tonic, atonic and atypical seizures, abnormal electroencephalographic (EEG) findings and cognitive impairment or intellectual disability [16].

Randomized trials have also demonstrated the effectiveness of CBD use in this disease entity. The median relative reduction in epileptic seizures was 21. 6% between the 20 mg/kg/day and placebo groups and the median relative reduction of 19. 2% in epileptic seizures between the 10 mg/kg/day and placebo groups. Additionally, a median relative reduction in total seizure frequency of 18. 8% was observed between the 20 mg/kg/day dose and the 2 mg/kg/day and placebo dose, and a median relative reduction in total seizure frequency of 19. 5% was observed between the 10 mg/kg/day and placebo groups [8]. An extended, long-term, open-label study conducted at 53 sites in the United States and Europe found that CBD-enhanced treatment was well tolerated and effective in sustainably reducing the frequency of epileptic seizures and total seizures in people with Lennox-Gaust syndrome. A common symptom of this condition is atonic and tonic seizures, which can cause falls (epileptic seizures). This study showed a reduction in average epileptic seizure frequency after CBD use of up to 46% from baseline and this level of reduction was maintained for 48 weeks [16].

b) Dravet syndrome

Dravet syndrome (DS) is a severe epileptic encephalopathy that begins in the first year of life. It is characterized by the occurrence of recurrent febrile or affective generalized or hemiclonic seizures or status epilepticus against a background of normal development followed by various types of seizures including myoclonic, absence focal seizures impairment of consciousness. This disease is associated with a mutation in the SCN1a gene that encodes sodium channels. Seizures occurring in the course of this syndrome often remain drug-resistant [17,18].

A 2018 paper presented the results of an open-label extension trial. During weeks 1-12 of CBD therapy, the median reduction in monthly seizure frequency from baseline was 37. 5% (from 12. 4 to 7. 5 seizures per month). This reduction persisted in weeks 13-24, 25-36 and 37-48. Five of 104 patients(4. 8%) were seizure-free in the last 12 weeks of treatment. More than 40% of patients had a ≥50% reduction in seizure frequency at each visit window. The median reduction in total seizure frequency from baseline in weeks 1-12 was 39. 5% (reduction from 32. 4 to 14. 5 seizures per month), with reductions in the subsequent 3 treatment windows ranging from 39. 0% to 50. 7%. Three patients were completely seizure-free during the last 12 weeks of treatment. However, there was not a single seizure-free patient for the entire treatment period until the data were cut. During each 12-week follow-up window, 2% to 4% of patients developed status epilepticus with seizures and 3% to 5% developed status epilepticus without seizures, with a baseline incidence of 1% and 5%, respectively. Of the 89 patients/caregivers at each stage of the study, after 48 weeks of treatment, 85% reported an overall improvement in their condition. Similar proportions of patients/caregivers reported improvement at weeks 24 and 38 [17].

Among children with Dravet syndrome (61) who received CBD in one 14-week randomized trial, 5% avoided seizures, compared with none in the placebo group. Among patients in a nonrandomized trial, 8% avoided seizures after cannabis treatment, where the duration of the trial ranged from 14 days to 53 months with low confidence [19,20]. In the study by Miller and co-authors, the percentage reduction in seizure frequency from baseline during the 14-week treatment period differed between CBD and placebo doses. The greatest reduction in seizures was observed in the 48. 7% CBD10 group and in the 45. 7% CBD20 group and in the 26. 9% placebo group, respectively. Similarly, the percentage reduction in seizure frequency from baseline during the 12-week maintenance period was 49. 2% for the CBD10 group, 48. 6% for the CBD20 group, and 28. 6% for the placebo group. Differences between treatment groups favored cannabidiol over placebo during the first 4 weeks of the maintenance period and these trends continued for the duration of treatment [20].

In a clinical study that investigated the safety and pharmacokinetic parameters of cannabidiol for the treatment of epileptic seizures in children aged 4 to 10 years with Dravet syndrome, an increased incidence of adverse reactions such as fever, somnolence, decreased appetite, vomiting, ataxia, and abnormal behavior was reported in at least three patients at all doses tested [5,22].

Side effects

Previous CBD formulations carried many side effects after repeated use, such as skin lesions, oral ulcers, oral mucosal pain and soreness, dry mouth, and a distinct aftertaste. Moreover, oral CBD oil-based formulations tested in clinical trials were characterized by low bioavailability and also irregular absorption from the gastrointestinal tract. This resulted in variable pharmacokinetics, often leading to high dose administration [3].

In patients with LGS/DA who received ≥1 dose of CBD and ≥1 assessment after baseline, up to 91% experienced treatment-related adverse events and 41% experienced serious adverse events. The most commonly reported AEs from all causes were drowsiness (30%), seizures (24%) and diarrhea (24%) [6]. As for the adverse effects of CBD on the digestive system, an increased incidence of diarrhea has been observed . Single doses of CBD, 1. 5 g and 4. 5 g, were found to induce diarrhea in 10% and 20% of participants in the experimental study, respectively [19,23]. This may illustrate the role of the endocannabinoid system in regulating gastrointestinal motility. CBD treatment was also associated with reduced appetite. The endocannabinoid system contributes to the regulation of food intake and moderates the pleasure derived from food consumption. It has also been observed that CBD found in cannabis can reduce the appetitive effects of food stimuli; however, the molecular mechanism of this action remains unclear [24].

In a study (Laux et al, 2019), the most common serious adverse reactions from all causes in the patients studied were seizures (14%), status epilepticus (9%), pneumonia (5%) and fever (4%). No cases of cannabinoid congestion syndrome have been reported . Abnormal hepatic adverse events (i. e. , alanine aminotransferase/aspartate aminotransferase >3 x upper limit of normal) were reported in 15% (22/152) of patients [6]. In another study, serious adverse events occurred in 40 patients (10 in the placebo group, 13 in the 10g CBD dose group and 17 in the 20g CBD group).

Adverse events resolved by the end of the study in 61 of 118 patients (51. 7%) in both cannabidiol groups and 35 of 58 patients (60. 3%) in the placebo group. No deaths have occurred. An increase in liver transaminase levels more than 3 times the upper limit of the reference range occurred in 16 of 133 patients (12. 0%) of both cannabidiol groups (3 of 44 [6. 8%] in the 10g CBD and 13 of 47 [27. 7%] in the 20g CBD group), all of whom were taking concomitant valproate and no patients in the placebo group [5,21,25].

Drug interactions

CBD interacts with many enzymes, is rapidly removed, and is therefore less susceptible to modulation by drugs that affect metabolizing enzymes. Furthermore, inhibitors and inducers or genetic background do not affect the pharmacokinetic profile of CBD. Bioavailability of oral oil preparations is limited (<6%) due to extensive first-pass metabolism in the liver [9].

CBD is a potent inhibitor of CYP450, CYP3A4 and CYP2C19 enzymes that metabolize clobazam and sodium valproate. These drugs were prescribed in more than half of the patients in the three major epilepsy studies included in the meta-analysis. Inhibition of CYP2C19 may increase the concentration of the clobazam metabolite (N-desmethylclobazam) by 2-7 fold and this has a significant sedative effect. The exact mechanism of interaction with sodium valproate is not fully understood. Concomitant administration of CBD and valproate does not significantly alter their plasma concentrations or those of their metabolites. However, the metabolite 7-COOH-CBD, valproate and its metabolite 4-en-valproic acid may affect hepatic mitochondrial function [24]. In an efficacy study of cannabidiol in subjects with Lennox-Gaust syndrome, liver enzyme abnormalities were mainly observed in patients who were concurrently receiving valproic acid, which may indicate an interaction with this drug [16]. In patients receiving clobazam with oral cannabidiol solution at 40 mg/kg/day, the mean exposure to cannabidiol increased approximately 2. 5-fold compared to patients not receiving clobazam, possibly indicating the presence of a drug-drug interaction with clobazam. Food has also been shown to increase exposure to cannabidiol [5,16].

In an open study by Gaston and colleagues, CBD may also interact with other antiepileptic drugs such as: a linear increase in serum levels of topiramate and rufinamide (in both adult and pediatric patients) and interactions with eslicarbazepine and zonisamide were documented but only in adult patients [13]. Research suggests that CBD may also interact with benzodiazepines. It has been noted that the active metabolites of benzodiazepines increase significantly with concurrent use of CBD and CBD-rich medical marijuana [26].

Summary and conclusions

In conclusion, newly available studies support the use of CBD as an effective treatment option to reduce seizure frequency in children with drug-resistant epilepsy. Products containing both CBD and THC can be equally effective; however, most of the available evidence relates only to pharmaceutical-grade CBD [19]. In a 2019 study (Laux and co-authors) involving children and adults with TRE, CBD supplementation effectively reduced the median monthly frequency of mainstream seizures and total seizures after 12 weeks of treatment in a subgroup of patients with Dravet and Lennox-Gastaut syndrome. This stabilization lasted for a period of 2 years, without increasing the dose of CBD. On average, nearly half of all patients with Dravet and Lennox-Gastaut syndrome showed a ≥50% reduction in main motor and total seizures after 12 weeks of treatment and at 2-year follow-up [6]. The role of CBD in the treatment of drug-resistant epilepsy is adjuvant and also often overestimated. The majority of patients (91%) experienced side effects but these are usually mild. One of the most common side effects include decreased appetite, diarrhea and fatigue. They occur more frequently in the higher-dose CBD group (e. g. , at doses of 20 mg/kg/d), as do serious side effects that can lead to treatment discontinuation and elevations in liver transaminases of more than three times the reference range. Laboratory monitoring should focus on hepatotoxicity and therapeutic monitoring of other concomitant drugs. The area for further research should include the efficacy and optimal dose of CBD in adult patients with epilepsy, particularly focal epilepsy, long-term psychiatric and cognitive adverse effects associated with CBD, and strategies to reduce costs and improve access to CBD for people with epilepsy. Increasing the availability of CBD as adjunctive medication against severe forms of epilepsy, may in some cases provide significant benefits [6,9,27]. From the available studies in the pediatric population, synthetic cannabidiol oral solution can be considered safe at all doses tested and generally well tolerated in this population [5,10,21].

From the available literature review, there are many studies on the use and efficacy of cannabidiol for the treatment of epileptic seizures in the pediatric population, but there are no reports on the use of CBD in the adult population, which may be an area for further research.

References

1. Russ SA, Larson K, Halfon N. A national profile of childhood epilepsy and seizure disorder. *Pediatrics*. 2012;129(2):256-264. doi:10.1542/peds.2010-137.
2. Kramer U, Nevo Y, Neufeld MY, Fatal A, Leitner Y, Harel S. Epidemiology of epilepsy in childhood: a cohort of 440 consecutive patients. *Pediatr Neurol*. 1998;18(1):46-50. doi:10.1016/s0887-8994(97)00154-9.
3. Mitelpunkt A, Kramer U, Hausman Kedem M, et al. The safety, tolerability, and effectiveness of PTL-101, an oral cannabidiol formulation, in pediatric intractable epilepsy: A phase II, open-label, single-center study. *Epilepsy Behav*. 2019;98(Pt A):233-237. doi:10.1016/j.yebeh.2019.07.007.
4. Cheung KAK, Peiris H, Wallace G, Holland OJ, Mitchell MD. The Interplay between the Endocannabinoid System, Epilepsy and Cannabinoids. Int J Mol Sci. 2019 Dec 2;20(23):6079. doi: 10.3390/ijms20236079.
5. Wheless JW, Dlugos D, Miller I, Oh DA, Parikh N, Phillips S, Renfroe JB, Roberts CM, Saeed I, Sparagana SP, Yu J, Cilio MR; INS011-14-029 Study Investigators.

Pharmacokinetics and Tolerability of Multiple Doses of Pharmaceutical-Grade Synthetic Cannabidiol in Pediatric Patients with Treatment-Resistant Epilepsy. CNS Drugs. 2019 Jun;33(6):593-604. doi: 10.1007/s40263-019-00624-4.

6. Laux LC, Bebin EM, Checketts D, Chez M, Flamini R, Marsh ED, Miller I, Nichol K, Park Y, Segal E, Seltzer L, Szaflarski JP, Thiele EA, Weinstock A; CBD EAP study group. Long-term safety and efficacy of cannabidiol in children and adults with treatment resistant Lennox-Gastaut syndrome or Dravet syndrome: Expanded access program results. Epilepsy Res. 2019 Aug;154:13-20. doi: 10.1016/j.eplepsyres.2019.03.015.
7. Abuhasira R, Shbiro L, Landschaft Y. Medical use of cannabis and cannabinoids containing products - Regulations in Europe and North America. Eur J Intern Med. 2018 Mar;49:2-6. doi: 10.1016/j.ejim.2018.01.001.
8. Abu-Sawwa R, Scutt B, Park Y. Emerging Use of Epidiolex (Cannabidiol) in Epilepsy. J Pediatr Pharmacol Ther. 2020;25(6):485-499. doi: 10.5863/1551-6776-25.6.485.
9. Arzimanoglou A, Brandl U, Cross JH, Gil-Nagel A, Lagae L, Landmark CJ, Specchio N, Nabbout R, Thiele EA, Gubbay O, The Cannabinoids International Experts Panel; Collaborators. Epilepsy and cannabidiol: a guide to treatment. Epileptic Disord. 2020 Feb 1;22(1):1-14. doi: 10.1684/epd.2020.1141.
10. Raucci U, Pietrafusa N, Paolino MC, Di Nardo G, Villa MP, Pavone P, Terrin G, Specchio N, Striano P, Parisi P. Cannabidiol Treatment for Refractory Epilepsies in Pediatrics. Front Pharmacol. 2020 Sep 29;11:586110. doi: 10.3389/fphar.2020.586110.
11. Dalton WS, Martz R, Lemberger L, Rodda BE, Forney RB. Influence of cannabidiol on delta-9-tetrahydrocannabinol effects. Clin Pharmacol Ther. 1976 Mar;19(3):300-9. doi: 10.1002/cpt1976193300.
12. Karniol IG, Shirakawa I, Kasinski N, Pfeferman A, Carlini EA. Cannabidiol interferes with the effects of delta 9 - tetrahydrocannabinol in man. Eur J Pharmacol. 1974 Sep;28(1):172-7. doi: 10.1016/0014-2999(74)90129-0.
13. Morano A, Fanella M, Albini M, Cifelli P, Palma E, Giallonardo AT, Di Bonaventura C. Cannabinoids in the Treatment of Epilepsy: Current Status and Future Prospects. Neuropsychiatr Dis Treat. 2020 Feb 7;16:381-396. doi: 10.2147/NDT.S203782.
14. Millar SA, Stone NL, Bellman ZD, Yates AS, England TJ, O'Sullivan SE. A systematic review of cannabidiol dosing in clinical populations. Br J Clin Pharmacol. 2019 Sep;85(9):1888-1900. doi: 10.1111/bcp.14038.
15. Press CA, Knupp KG, Chapman KE. Parental reporting of response to oral cannabis extracts for treatment of refractory epilepsy. Epilepsy Behav. 2015 Apr;45:49-52. doi: 10.1016/j.yebeh.2015.02.043.
16. Dravet C, Oguni H. Dravet syndrome (severe myoclonic epilepsy in infancy). Handb Clin Neurol. 2013;111:627-33. doi: 10.1016/B978-0-444-52891-9.00065-8.
17. Devinsky O, Nabbout R, Miller I, Laux L, Zolnowska M, Wright S, Roberts C. Long-term cannabidiol treatment in patients with Dravet syndrome: An open-label extension trial. Epilepsia. 2019 Feb;60(2):294-302. doi: 10.1111/epi.14628.

18. Elliott J, DeJean D, Clifford T, Coyle D, Potter BK, Skidmore B, Alexander C, Repetski AE, Shukla V, McCoy B, Wells GA. Cannabis-based products for pediatric epilepsy: A systematic review. Epilepsia. 2019 Jan;60(1):6-19. doi: 10.1111/epi.14608.
19. Devinsky O, Cross JH, Laux L, Marsh E, Miller I, Nabbout R, Scheffer IE, Thiele EA, Wright S; Cannabidiol in Dravet Syndrome Study Group. Trial of Cannabidiol for Drug-Resistant Seizures in the Dravet Syndrome. N Engl J Med. 2017 May 25;376(21):2011-2020. doi: 10.1056/NEJMoa1611618.
20. Miller I, Scheffer IE, Gunning B, Sanchez-Carpintero R, Gil-Nagel A, Perry MS, Saneto RP, Checketts D, Dunayevich E, Knappertz V; GWPCARE2 Study Group. Dose-Ranging Effect of Adjunctive Oral Cannabidiol vs Placebo on Convulsive Seizure Frequency in Dravet Syndrome: A Randomized Clinical Trial. JAMA Neurol. 2020 May 1;77(5):613-621. doi: 10.1001/jamaneurol.2020.0073.
21. Devinsky O, Patel AD, Thiele EA, Wong MH, Appleton R, Harden CL, Greenwood S, Morrison G, Sommerville K; GWPCARE1 Part A Study Group. Randomized, dose-ranging safety trial of cannabidiol in Dravet syndrome. Neurology. 2018 Apr 3;90(14):e1204-e1211. doi: 10.1212/WNL.0000000000005254.
22. Elliott J, DeJean D, Clifford T, Coyle D, Potter BK, Skidmore B, Alexander C, Repetski AE, Shukla V, McCoy B, Wells GA. Cannabis-based products for pediatric epilepsy: A systematic review. Epilepsia. 2019 Jan;60(1):6-19. doi: 10.1111/epi.14608.
23. Schoedel KA, Szeto I, Setnik B, Sellers EM, Levy-Cooperman N, Mills C, Etges T, Sommerville K. Abuse potential assessment of cannabidiol (CBD) in recreational polydrug users: A randomized, double-blind, controlled trial. Epilepsy Behav. 2018 Nov;88:162-171. doi: 10.1016/j.yebeh.2018.07.027.
24. Chesney E, Oliver D, Green A, Sovi S, Wilson J, Englund A, Freeman TP, McGuire P. Adverse effects of cannabidiol: a systematic review and meta-analysis of randomized clinical trials. Neuropsychopharmacology. 2020 Oct;45(11):1799-1806. doi: 10.1038/s41386-020-0667-2.
25. Silvestro S, Mammana S, Cavalli E, Bramanti P, Mazzon E. Use of Cannabidiol in the Treatment of Epilepsy: Efficacy and Security in Clinical Trials. Molecules. 2019 Apr 12;24(8):1459. doi: 10.3390/molecules24081459.
26. Aran A, Cayam-Rand D. Medical Cannabis in Children. Rambam Maimonides Med J. 2020 Jan 30;11(1):e0003. doi: 10.5041/RMMJ.10386.
27. Silva GD, Del Guerra FB, de Oliveira Lelis M, Pinto LF. Cannabidiol in the Treatment of Epilepsy: A Focused Review of Evidence and Gaps. Front Neurol. 2020 Oct 19;11:531939. doi: 10.3389/fneur.2020.531939.