INVITED REVIEW ARTICLE

Neurologia i Neurochirurgia Polska
Polish Journal of Neurology and Neurosurgery
2022, Volume 56, no. 1, pages: 14–20
DOI: 10.5603/PJNNS.a2022.0020

ISSN: 0028-3843, e-ISSN: 1897-4260

LEADING TOPIC

Leading Topic Editor: Natalia Szejko, MD, PhD, Department of Neurology and Bioethics, Medical University of Warsaw, Poland

Use of cannabidiol in the treatment of epilepsy

Maria Mazurkiewicz-Bełdzińska, Marta Zawadzka

Department of Developmental Neurology, Medical University of Gdansk, Poland

ABSTRACT

Introduction. *Cannabis sativa* has been cultivated for human use for about 5,000 years, and has likewise been used in the treatment of epilepsy for thousands of years.

State of the art. Cannabidiol (CBD), which was isolated from *cannabis sativa* in 1940, has an anti-seizure effect and no psychoactive activity. Its effectiveness in reducing various types of seizures has been proven in animal seizure and epilepsy models. Recent randomised, placebo-controlled trials have confirmed its effectiveness in patients with drug-resistant epilepsy.

Clinical implications. The aim of this position paper was to present the specific mechanism of CBD's anti-seizure action and current indications for CBD's use in epilepsy. The only cannabis-derived drug that has successfully passed clinical trials and has obtained United States Food and Drug Administration and European Medicines Agency approval for epilepsy is Epidiolex®. This paper presents the outcomes of the completed clinical trials with the use of this drug.

Future directions. CBD may be an effective drug in drug-resistant epilepsy, particularly in Dravet Syndrome, Lennox-Gastaut Syndrome and seizures associated with tuberous sclerosis complex. Additional randomised, placebo-controlled studies with CBD are needed.

Key words: cannabidiol, drug-resistant epilepsy, Lennox-Gastaut Syndrome, Dravet Syndrome, tuberous sclerosis

(*Neurol Neurochir Pol 2022; 56 (1): 14–20*)

Introduction

Cannabis sativa is a plant which has been cultivated for human use for approximately 5,000 years [1–3]. The cannabis plant contains over 1,000 terpenes and phytocannabinoids including cannabidiol (CBD), 9-delta tetrahydrocannabinol (THC), cannabidivarin (CBDV), 9-delta tetrahydrocannabivarin (THCV), cannabinol (CBN), cannabichromene (CBC), and cannabigerol (CBG) [4]. The ancient Mesopotamians made ointments with cannabis in the treatment of the "Hand of Ghost" (a disease that according to historians is likely to have been epilepsy). Other early reports describe cannabis use for indications such as anxiety, depression and spasticity [1–3].

The history of cannabis use in Poland dates back to early Slavic times. Slavic people squeezed oil from hemp seeds and obtained fibres for fabrics and ropes from its stems. The Slavs also had a spiritual use for cannabis, and described it as "a magical plant" [5]. Despite its suspected beneficial action, the medical application of cannabis was not scientifically studied until the 19th century. In 1851, in the third edition of the United States Pharmacopoeia, cannabis was included as an anti-seizure, analgesic and hypnotic agent. Initially, cannabis was appreciated mainly for its 9-delta-tetrahydrocannabinol content [6]. However, over the past decade there has been growing interest in the use of cannabis to treat drug-resistant seizures [1–3].

Epilepsy is one of the most common neurological disorders [7]. About one-third of all patients with epilepsy experience drug-resistant seizures. The International League Against Epilepsy (ILAE) defines drug-resistant epilepsy as the "failure of adequate trials of two tolerated, appropriately chosen and used anti-epileptic drug schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom" [8]. Inadequate control of seizures significantly affects the quality

Address for correspondence: Marta Zawadzka, Department of Developmental Neurology, Medical University of Gdansk, Dębinki 7 Str., 80–952 Gdansk, Poland; e-mail: marta.zawadzka@gumed.edu.pl

Received: 3.01.2022 Accepted: 11.02.2022 Early publication date: 23.02.2022

of life and cognitive function of these patients. Therefore, anecdotal reports about the effectiveness of cannabis aroused public interest and inspired the families of epilepsy patients to search for cannabis products. The best-known example concerns Charlotte Figi, a five-year-old girl who was diagnosed with Dravet Syndrome in 2013. After administering cannabis extract, the frequency of her seizure episodes was reduced by over 90% [9]. More research into the effectiveness of cannabis was clearly needed.

The cannabinoids with the highest expectations in terms of treating epilepsy have been CBD and THC. The psychoactive effects of THC and its mixed pro- and anti-seizure effects in seizure models were the reasons why little effort was made to evaluate THC's effectiveness in treating epilepsy [10, 11]. CBD is a cannabinoid, first isolated from cannabis in 1940, which has no psychoactive effect. Its effectiveness in reducing various types of seizures has been proven in animal seizure models and epilepsy models [11–13]. These results led to human studies, primarily involving patients with drug-resistant epilepsy. In 2016, the results of phase III, randomised, placebo-controlled trials confirmed the beneficial effects of CBD in the treatment of Lennox-Gastaut Syndrome (LGS) and Dravet Syndrome (DS). CBD was approved by the United States Food and Drug Administration (FDA) in 2018, and by the European Medicines Agency (EMA) in 2019, for the treatment of these two epilepsy syndromes [10]. The indications for CBD use are becoming broader: in 2020, the FDA approved CBD oral solution for the treatment of seizures associated with tuberous sclerosis complex (TSC) in patients aged two years and older [14]. Epidiolex® (GW Pharmaceutical, Cambridge, United Kingdom) is the only pharmaceutical CBD product, although over-the-counter (OTC) CBD products are now in widespread use, a situation which can lead to potential abuse. CBD-containing products are sold OTC as dietary supplements or food additives in a variety of forms: oils, suppositories, nasal sprays and capsules, and all without close pharmaceutical control [6].

Mechanism of action of CBD in epilepsy

CBD's mechanism of action underlying the reduction of seizures in humans is not yet fully elucidated. It is not known why some patients respond to cannabis with spectacular improvement, i.e. the resolution of seizures or least a significant reduction. Differences in responses to CBD treatment may be related to genetic factors [10].

Endocannabinoids (endogenous cannabinoids) have a role in decreasing the release of excitatory neurotransmitters in the central nervous system by acting on G protein-linked endocannabinoid neuroreceptors: cannabinoid type 1 receptor (CB1R) and cannabinoid type 2 receptor (CB2R). This influence is related to their anti-seizure activity. Most phytocannabinoids, including THC, THCV, and CBDV, have also the ability to interact with the CB1 and CB2 receptors. Despite its structural similarity, CBD has low selectivity for both CB1R and CB2R [15]. It seems that CBD carries out its anti-seizure action by interacting with G protein-coupled receptor *55* (GPR-55) and transient receptor potential vanilloid 1 (TRPV-1) channel, by anti-inflammatory effect and influence on the adenosine pathway [15–24].

Influence on G-protein

GPR55 is a G-protein-coupled receptor, highly expressed in the central nervous system (CNS) and is considered to be a novel cannabinoid receptor. CBD interacts with this receptor by inhibiting its action (functional antagonism). More specifically, CBD blocks the excitatory effect of lysophosphatidylinositol (LPI), which is an endogenous agonist of GPR55 lipids [16, 17]. According to Rosenberg et al., (who evaluated the effect of LPI and CBD on post-synaptic currents recorded in acute *ex vivo* hippocampal brain slices obtained from healthy mice), CBD can exert an anti-seizure effect by counteracting the effects of LPI at GPR55 at both inhibitory and excitatory synapses, thereby restoring inhibitory and excitatory coordination. The authors concluded that the LPI-GPR55 axis could be a potential biomarker of prolonged seizure activity and good clinical response to CBD [18].

Influence on TRPV-1 channel

TRPV1 is a vanilloid receptor belonging to the family of transient receptor potential channels. These receptors are expressed widely throughout the brain where they act by modulating the transport of calcium ions across the membrane of neurons. CBD has great affinity for the TRPV1 receptor and causes the desensitisation of it in a concentration-dependent manner. It is also well known that TRPV1 is overexpressed in models of temporal lobe epilepsy and patients with epilepsy, but the exact mechanism of action needs to be clarified [15, 16]. Gray et al. assessed the effect of CBD on the seizure threshold in wild-type and TRPV1 knockout mice using a mouse model of generalised seizure. CBD significantly increased the seizure threshold in the wild-type mice, thus proving that TRPV1 plays an important role in the anti-seizure action of CBD [19].

Neuroinflammation

The anti-seizure activity of CBD is also related to its influence on neuroinflammatory processes. Neuroinflammation is recognised as an important factor in the pathophysiology of epilepsy. Cytokine production and the activation of neuroglial cells increase seizure-induced neurotoxicity, which may contribute to epileptogenesis and epilepsy. Microglia are considered to be the macrophages of the brain that act as sentinel immune cells [15]. CBD has been shown to have an anti-inflammatory effect by blocking microglia activation [20]. Juknat et al. identified cannabinoid-regulated microribonucleic acids (miRNAs) in resting and in lipopolysaccharide (LPS)-activated microglia. The CBD inhibited LPS-stimulated expression of proinflammatory miRNAs associated with Toll-like receptor (TLR) and nuclear factor kappa-light-chain-enhancer of

activated B cells (NF-κB) signalling (involving miRNA-146a and miRNA-155) [21]. CBD is also an inhibitor of the adenosine triphosphate (ATP)-induced intracellular calcium increase in cultured microglia [20]. Moreover, CBD may have anti-inflammatory effects by inhibiting the uptake of adenosine in macrophages and microglia. This effect is possible through the interaction with equilibrative nucleoside transporter 1 (ENT-1) and enhancing tumour necrosis factor alpha (TNF-α) suppression [22].

Influence on adenosine pathway

Adenosine is an endogenous anti-seizure agent which acts via adenosine A1 receptor activation and receptor-independent regulation of DNA methylation [23]. The effect of CBD on the concentration of adenosine was first described by Mijangos-Moreno et al., who reported that an injection of CBD into the hypothalamus increased extracellular levels of adenosine in the nucleus accumbens of rats [24]. The effects of CBD on adenosine reuptake in macrophages and microglia, described by Liou et al., were cited above [22]. Gray and Whalley emphasised that CBD's mechanism of seizure control in patients with Lennox-Gastaut and Dravet Syndromes may be the enhancement of adenosine-mediated signalling through the increased availability of extracellular adenosine, necessary for an effective adenosine A1 receptor agonism [16].

Effectiveness of CBD in epilepsy

The effectiveness of CBD in epilepsy has been proven in several double-blind, placebo-controlled randomised clinical trials (RCTs). There are also many other studies on the effectiveness of this treatment in the literature (case series, open-label studies).

Randomised, double-blind, placebo-controlled clinical trials (RCTs)

Randomised, double-blind, placebo-controlled clinical trials were recently carried out with the use of pure CBD, an oral solution containing 100 mg/ml CBD dissolved in sesame oil administered twice a day. The first trials focused on specific epilepsy syndromes in which patients had few therapeutic alternatives [25–30].

Dravet Syndrome

The first published double-blind, placebo-controlled RCT investigated the efficacy of CBD in patients with Dravet Syndrome. 120 patients with drug-resistant convulsive seizures were enrolled in the study. Patients received a placebo or CBD oral solution at a dose of 20 mg/kg for a period of 14 weeks. The study was preceded by a 4-week baseline period. The primary endpoint was the change in convulsive seizure rate over the entire 14-week treatment period compared to the baseline period. Secondary endpoints were a 50% reduction in the mean number of seizures during the month, as well as an improvement in the Caregiver Global Impression of Change (CGIC) score. The mean age of the patients was 9.8 years (range 2.3–18.4). The average baseline was 13 seizures per month, mostly generalised tonic-clonic seizures. 90% of patients (n = 108) completed the study, with the vast majority (n = 105) agreeing to continue treatment in the open-label study. In addition to the study drug, the most common anti-seizure drugs taken by the patients were clobazam, sodium valproate, stiripentol, levetiracetam and topiramate. The study confirmed the effectiveness of CBD treatment in patients with Dravet Syndrome. A 50% clinical response rate (a reduction of convulsive seizures ≥ 50% from baseline) was achieved in 43% of patients taking CBD and 27% in the placebo group. Seizures resolved in 5% of CBD-treated patients and 0% in placebo-treated patients. However, there were no significant differences in the number of seizures other than convulsive seizures between the group treated with CBD and the group treated with the placebo. For the primary endpoint, the median decreased from 12.4 seizure episodes per month to 5.9 per month at the end of treatment. The main adverse events in this study were diarrhoea, vomiting, fatigue, pyrexia, somnolence, and abnormal liver function tests. Eight patients treated with CBD and one patient treated with placebo withdrew from the study due to adverse events. Increased levels of hepatic transaminases (a potential drug-drug interaction) have been reported more frequently in patients treated with sodium valproate. Somnolence was mainly observed in patients taking clobazam concomitantly (higher plasma levels of the parent drug and active metabolite). Adverse events occurred more frequently in CBD-treated patients than in the placebo group, and were usually mild-to-moderate in severity [10, 25].

The second study was a randomised, double-blind, 14-week comparison of two doses of CBD (10 mg/kg/day and 20 mg/kg/day) versus a placebo in 198 patients with Dravet Syndrome aged 2 to 18 years. 190 patients completed the study. The primary endpoint was the change from baseline in seizure frequency during the treatment period. Secondary outcomes included change in all seizure frequency and change in Caregiver Global Impression of Change. Treatment with CBD at doses of 10 or 20 mg/kg/day resulted in a similar, clinically significant, reduction in the frequency of seizures. Better safety and tolerability profiles were noted in patients treated with lower doses, and therefore the authors argued that increasing the dose of CBD to > 10 mg/kg/day should be tailored to individual efficacy and safety [26].

Lennox-Gastaut Syndrome

Patients with Lennox-Gastaut Syndrome are another group in which double-blind, placebo-controlled randomised clinical trials using CBD have been conducted [27, 28]. The first study with patients with Lennox-Gastaut Syndrome looked at the effectiveness of CBD treatment at two different doses of 10 mg/kg or 20 mg/kg compared to a placebo. 225 patients with drop seizures (atonic, tonic or tonic-clonic seizures) aged

Table 1. Results of completed randomised clinical trials with CBD in epilepsy [25–30]

Condition	ClinicalTrials.gov identifiers	Type of study	Type of seizures evaluated in study (primary outcome)	Age of patients (in years)	Study size (N - number of patients)	Dosage	Patients with 50% clinical response rate (%)
Dravet Syndrome [25]	NCT02091206	Randomised, double-blind, placebo-controlled study of GWP42003-P in children and young adults with Dravet Syndrome	Convulsive seizures	2–18	N -108	20 mg/kg/day	43% (reduction of convulsive seizures)
Dravet Syndrome [26]	NCT02224703	Randomised, double-blind, comparison of two dose levels (10 and 20 mg/kg/day) of GWP42003-P versus placebo	Convulsive seizures	2–18	N -190	10 mg/kg/day and 20 mg/kg/day	48.7% and 45.7% (reduction of convulsive seizures)
Lennox-Gastaut Syndrome [27]	NCT02224560	Randomised, double-blind, comparison of two dose levels (10 and 20 mg/kg/day) of GWP42003-P versus placebo	Drop seizures	2–55	N - 218	10 mg/kg/day and 20 mg/kg/day	37.2% and 41.9% (reduction of drop seizures)
Lennox-Gastaut Syndrome [28]	NCT02224690	Randomised, double-blind, placebo-controlled study to investigate efficacy and safety of cannabidiol (GWP42003-P; CBD) as adjunctive treatment for seizures associated with Lennox-Gastaut Syndrome in children and adults	Drop seizures	2–55	N - 156	20 mg/kg/day	43.9% (reduction of drop seizures)
Lennox-Gastaut Syndrome and Dravet Syndrome [29]	NCT02224573	Open label extension study of cannabidiol (GWP42003-P) in children and young adults with Dravet or Lennox-Gastaut Syndromes	Drop seizures and total seizures		N - 681	Up to 30 mg/kg/day	In Lennox-Gastaut Syndrome group: 48–71% for drop seizures and 48–68% for total seizures
Tuberous sclerosis complex and epilepsy [30]	NCT02544763	Double-blind, randomised, placebo-controlled study to investigate efficacy and safety of cannabidiol (GWP42003-P, CBD) as add-on therapy in patients with tuberous sclerosis complex who experience inadequately-controlled seizures	TSC-associated seizures	1-65	N - 204	25 mg/kg/day and 50 mg/kg/day	48.6% and 47.5%

2 to 55 years were randomised into the study, 76 patients in the CBD 20 mg/kg group, 73 in the CBD 10 mg/kg group, and 76 in the placebo group. Both doses (10 and 20 mg/kg) of CBD resulted in a greater reduction in the number of drop seizures compared to the placebo. As in the two previous studies, there were more adverse events in the CBD groups than in the placebo group. The most common adverse events were somnolence, decreased appetite, and diarrhoea. Patients taking CBD at 20 mg/kg reported more of these events than did patients in the 10 mg/kg group [10, 27].

In the second study, a placebo was compared to an oral CBD solution of 20 mg/kg. 171 patients aged 2 to 55 years were enrolled in the study. The primary endpoint was a change in the monthly frequency of drop seizures during the 14-week treatment period. 171 patients were randomly assigned, and the target dose of CBD of 20 mg/kg was administered twice daily. 86 patients (including 30 patients > 18 years of age) were qualified to the group treated with CBD, with the other 85 patients (including 28 patients > 18 years) qualified to the group treated with a placebo. Fourteen patients randomised to the CBD treatment group and one randomised to the placebo treatment group withdrew from the study. During the treatment period, the median decrease in the number of drop seizures was 43.9% in the CBD group and 21.8% in the placebo group. Three patients in the CBD treatment group, but none of the patients taking the placebo, were seizure-free during the treatment maintenance period. As in the previous studies, the most common adverse reactions, reported by >10% of patients, were diarrhoea, somnolence, pyrexia, decreased appetite, and vomiting. Most symptoms resolved spontaneously or with dose reduction. Adverse events were considered to be mild or moderate. Thiele et al. proved that adjuvant therapy with CBD is efficacious for the treatment of patients with drop seizures associated with Lennox-Gastaut Syndrome and is generally well-tolerated [10, 28].

Patients with Dravet Syndrome or Lennox-Gastaut Syndrome who had previously participated in double-blind, placebo-controlled clinical trials were allowed to continue in an open-label extension study. In the Lennox-Gastaut Syndrome group, the reduction in seizures was sustained over the next 156 weeks. Moreover, the prolonged, add-on CBD treatment had a similar safety profile as in the randomised controlled trial. It is also worth emphasising that at least 87% of patients/caregivers reported an improvement on the Subject/Caregiver Global Impression of Change Scale [29].

Tuberous sclerosis and epilepsy

In another double-blind, placebo-controlled randomised clinical trial, 224 patients with tuberous sclerosis complex (TSC) and epilepsy were randomised (mean age 11.4 years, range 1.1–56.8). The study assessed the effectiveness of CBD treatment at a dose of 25 mg/kg/day (the 'CBD25' group) or 50 mg/kg/day (the 'CBD50' group) compared to a placebo. The patients who received the greatest benefit from treatment were treated with CBD. A 50% reduction in seizures was achieved in 48.6% of patients in the CBD25 group and 47.5% in the CBD50 group, compared to 26.5% in the placebo group. The most common adverse events were diarrhoea and somnolence. Eight patients in the CBD25 group, 10 in the CBD50 group, and two in the placebo group discontinued treatment due to adverse events. CBD significantly reduced TSC-related seizures compared to the placebo. The 25 mg/kg/day dose had a better safety profile than the 50 mg/kg/day dose [30].

Other clinical studies

The main double-blind, placebo-controlled RCTs were conducted in patients with severe epilepsy syndrome. Evidence regarding the use of CBD in focal and generalised epilepsy is scarce. The effectiveness of CBD in other types of epilepsy has been confirmed in open-label studies. A pre-clinical study has shown that CBD is a seizure reduction drug in patients with drug-resistant seizures associated with CDKL5 deficiency disorder, Dup15q, Aicardi and Doose Syndromes (class III evidence for long-term efficacy and safety) [31]. An additional recent study concerning the long term efficacy of CBD shows that it is effective in reducing seizures over a treatment period of up to 60 months. The study group consisted of patients with drug-resistant epilepsy of various aetiologies enrolled in the Massachusetts General Hospital's Open Label Expanded Access Programme. Despite the broad dose range (up to 50 mg/kg/day), CBD was well-tolerated and safe. The greatest therapeutic benefits were experienced by patients with TSC and patients with absence seizures and epileptic spasms [32]. Park et al. reached similar conclusions proving the long-term efficacy and safety of CBD in children with treatment-resistant epilepsy who were ineligible to participate in randomised controlled trials [33]. Interesting conclusions came from the study by Gaston et al. comparing a group of adults and children treated with CBD. The authors noted a significant difference in seizure severity reduction, with adults reporting a greater reduction in seizure severity [34].

In addition to the anti-seizure action of CBD, reports on its effects on sleep architecture are particularly interesting. Recent studies have investigated the effects of CBD on interictal epileptiform discharges (IED) and sleep architecture in children with drug-resistant epilepsy. They suggest the utility of CBD in reducing IEDs and improving sleep microstructure. Further studies are needed; however, the improvement of behaviour associated with CBD treatment may be due to the reduction in IEDs [35]. This has further implications for studying CBD's effects on cognition. It is very important to underline that CBD has a neutral, or mildly beneficial, effect on cognition. There are no studies which have indicated negative effects of CBD on cognition [36].

Cannabidiol pharmacokinetics and drug-drug interactions

CBD's pharmacokinetics is complex and its bioavailability is variable, which makes it difficult to develop an appropriate form for oral administration [37]. Interaction with other medications is

another complication in its daily use. CBD and its main active metabolite 7-hydroxy CBD affect many cytochrome (CYP)450 isoforms (including 1A2, 3A4, 2B6, 2C8, 2C9, 2C19, and 2E1) which are involved in the metabolism of many therapeutic agents. CBD also has an inhibitory effect on uridine 5′-diphospho-glucoronosyltransferase (UGT1A9 and UGT2B7) [38]. CBD may inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9 (i.e. phenytoin), CYP2C19 (i.e. clobazam), and UGT1A9 and UGT2B7 (i.e. lorazepam, lamotrigine), and induce CYP1A2 and CYP2B6, causing interactions with many anti-seizure drugs [39].

It is well-known that CBD inhibits the metabolism of clobazam and its active metabolite N-desmethylclobazam, thereby increasing its sedative properties [40]. CBD also inhibits the metabolism of topiramate, zonisamide and eslicarbazepine acetate [41].

Due to a similar metabolism as many other drugs, the potential-risk of drug-drug interaction with CBD is also high. Warfarin, a commonly used oral anti-coagulant, is metabolised via the same CYP450 hepatic enzyme complex as is CBD. By enzyme competition, the degradation of warfarin can be impaired, which can lead to pathological bleeding. Moreover, due to the reported effects on UGT1A9 and UGT2B7, product labelling recommends avoiding co-administration and reducing substrate doses of such agents as acetaminophen, haloperidol, ibuprofen and propofol [38].

Not all of the possible interactions have been clinically proven yet. Nevertheless, adverse pharmacokinetic properties complicate the therapeutic use of CBD and demonstrate the need for further research with newer substances such as its propyl analogue, CBDV [10, 39].

Conclusion

Cannabidiol has brought a novel approach to the clinical management of patients with epilepsy. However, given its widespread availability and popularity, its unique mechanism of action and emerging drug-drug interactions make CBD an important drug to understand. It might be an effective alternative to the currently available anti-seizure treatment for Dravet and Lennox-Gastaut Syndromes or in TSC-related seizures in both adult and paediatric patients. More randomised, placebo-controlled studies with the use of CBD in other types of epilepsy are needed.

Conflict of interest: *None.*

References

1. Friedman D, Sirven JI. Historical perspective on the medical use of cannabis for epilepsy: Ancient times to the 1980s. Epilepsy Behav. 2017; 70(Pt B): 298–301, doi: 10.1016/j.yebeh.2016.11.033, indexed in Pubmed: 28089286.
2. Russo EB. Cannabis and epilepsy: An ancient treatment returns to the fore. Epilepsy Behav. 2017; 70(Pt B): 292–297, doi: 10.1016/j.yebeh.2016.09.040, indexed in Pubmed: 27989385.
3. Fasinu PS, Phillips S, ElSohly MA, et al. Current Status and Prospects for Cannabidiol Preparations as New Therapeutic Agents. Pharmacotherapy. 2016; 36(7): 781–796, doi: 10.1002/phar.1780, indexed in Pubmed: 27285147.
4. Arabas I. Z historii stosowania konopi w Polsce. Kwartalnik Historii Nauki i Techniki. 1990; 35(2/3): 329–336.
5. Pertwee RG. Cannabinoid pharmacology: the first 66 years. Br J Pharmacol. 2006; 147 Suppl 1: S163–S171, doi: 10.1038/sj.bjp.0706406, indexed in Pubmed: 16402100.
6. Stasiłowicz A, Tomala A, Podolak I, et al. L. as a Natural Drug Meeting the Criteria of a Multitarget Approach to Treatment. Int J Mol Sci. 2021; 22(2), doi: 10.3390/ijms22020778, indexed in Pubmed: 33466734.
7. Wężyk K, Słowik A, Bosak M. Predictors of remission in patients with epilepsy. Neurol Neurochir Pol. 2020; 54(5): 434–439, doi: 10.5603/PJNNS.a2020.0059, indexed in Pubmed: 32757204.
8. Kwan P, Arzimanoglou A, Berg AT, et al. Definition of drug resistant epilepsy: consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies. Epilepsia. 2010; 51(6): 1069–1077, doi: 10.1111/j.1528-1167.2009.02397.x, indexed in Pubmed: 19889013.
9. Maa E, Figi P. The case for medical marijuana in epilepsy. Epilepsia. 2014; 55(6): 783–786, doi: 10.1111/epi.12610, indexed in Pubmed: 24854149.
10. Brodie MJ, Ben-Menachem E. Cannabinoids for epilepsy: What do we know and where do we go? Epilepsia. 2018; 59(2): 291–296, doi: 10.1111/epi.13973, indexed in Pubmed: 29214639.
11. Benson MJ, Anderson LL, Low IK, et al. Evaluation of the Possible Anticonvulsant Effect of Δ-Tetrahydrocannabinolic Acid in Murine Seizure Models. Cannabis Cannabinoid Res. 2022; 7(1): 46–57, doi: 10.1089/can.2020.0073, indexed in Pubmed: 33998858.
12. Patra PH, Barker-Haliski M, White HS, et al. Cannabidiol reduces seizures and associated behavioral comorbidities in a range of animal seizure and epilepsy models. Epilepsia. 2019; 60(2): 303–314, doi: 10.1111/epi.14629, indexed in Pubmed: 30588604.
13. Crocq MA. History of cannabis and the endocannabinoid system . Dialogues Clin Neurosci. 2020; 22(3): 223–228, doi: 10.31887/DCNS.2020.22.3/mcrocq, indexed in Pubmed: 33162765.
14. https://www.fda.gov/news-events/press-announcements/fda-approves-new-indication-drug-containing-active-ingredient-derived-cannabis-treat-seizures-care. (3.01.2022).
15. Boleti AP, Frihling BE, E Silva PS, et al. Biochemical aspects and therapeutic mechanisms of cannabidiol in epilepsy. Neurosci Biobehav Rev. 2022; 132: 1214–1228, doi: 10.1016/j.neubiorev.2020.09.027, indexed in Pubmed: 33031814.
16. Gray RA, Whalley BJ. The proposed mechanisms of action of CBD in epilepsy. Epileptic Disord. 2020; 22(S1): 10–15, doi: 10.1684/epd.2020.1135, indexed in Pubmed: 32053110.
17. Sharir H, Abood ME. Pharmacological characterization of GPR55, a putative cannabinoid receptor. Pharmacol Ther. 2010; 126(3): 301–313, doi: 10.1016/j.pharmthera.2010.02.004, indexed in Pubmed: 20298715.
18. Rosenberg E, Bazelot M, Chamberland S, et al. Cannabidiol(CBD) exerts anti-epileptic actions by targeting the LPI-GPR55signaling system potentiated by seizures. Abstr. 3.052. American Epilepsy Society; 2018.
19. Gray RA, Stott CG, Jones NA, et al. Anticonvulsive Properties of Cannabidiol in a Model of Generalized Seizure Are Transient Receptor Potential Vanilloid 1 Dependent. Cannabis Cannabinoid Res. 2020;

5(2): 145–149, doi: 10.1089/can.2019.0028, indexed in Pubmed: 32656346.
20. Ożarowski M, Karpiński TM, Zielińska A, et al. Cannabidiol in Neurological and Neoplastic Diseases: Latest Developments on the Molecular Mechanism of Action. Int J Mol Sci. 2021; 22(9), doi: 10.3390/ijms22094294, indexed in Pubmed: 33919010.
21. Juknat A, Gao F, Coppola G, et al. miRNA expression profiles and molecular networks in resting and LPS-activated BV-2 microglia-Effect of cannabinoids. PLoS One. 2019; 14(2): e0212039, doi: 10.1371/journal.pone.0212039, indexed in Pubmed: 30742662.
22. Liou GI, Auchampach JA, Hillard CJ, et al. Mediation of cannabidiol anti-inflammation in the retina by equilibrative nucleoside transporter and A2A adenosine receptor. Invest Ophthalmol Vis Sci. 2008; 49(12): 5526–5531, doi: 10.1167/iovs.08-2196, indexed in Pubmed: 18641283.
23. Weltha L, Reemmer J, Boison D. The role of adenosine in epilepsy. Brain Res Bull. 2019; 151: 46–54, doi: 10.1016/j.brainresbull.2018.11.008, indexed in Pubmed: 30468847.
24. Mijangos-Moreno S, Poot-Aké A, Arankowsky-Sandoval G, et al. Intrahypothalamic injection of cannabidiol increases the extracellular levels of adenosine in nucleus accumbens in rats. Neurosci Res. 2014; 84: 60–63, doi: 10.1016/j.neures.2014.04.006, indexed in Pubmed: 24800644.
25. Devinsky O, Cross JH, Laux L, et al. Cannabidiol in Dravet Syndrome Study Group. Trial of Cannabidiol for Drug-Resistant Seizures in the Dravet Syndrome. N Engl J Med. 2017; 376(21): 2011–2020, doi: 10.1056/NEJMoa1611618, indexed in Pubmed: 28538134.
26. Miller I, Scheffer IE, Gunning B, et al. 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; 77(5): 613–621, doi: 10.1001/jamaneurol.2020.0073, indexed in Pubmed: 32119035.
27. Devinsky O, Patel AD, Cross JH, et al. GWPCARE3 Study Group. Effect of Cannabidiol on Drop Seizures in the Lennox-Gastaut Syndrome. N Engl J Med. 2018; 378(20): 1888–1897, doi: 10.1056/NEJMoa1714631, indexed in Pubmed: 29768152.
28. Thiele EA, Marsh ED, French JA, et al. GWPCARE4 Study Group. Cannabidiol in patients with seizures associated with Lennox-Gastaut syndrome (GWPCARE4): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet. 2018; 391(10125): 1085–1096, doi: 10.1016/S0140-6736(18)30136-3, indexed in Pubmed: 29395273.
29. Patel AD, Mazurkiewicz-Bełdzińska M, Chin RF, et al. Long-term safety and efficacy of add-on cannabidiol in patients with Lennox-Gastaut syndrome: Results of a long-term open-label extension trial. Epilepsia. 2021; 62(9): 2228–2239, doi: 10.1111/epi.17000, indexed in Pubmed: 34287833.
30. Thiele EA, Bebin EM, Bhathal H, et al. GWPCARE6 Study Group. Add-on Cannabidiol Treatment for Drug-Resistant Seizures in Tuberous Sclerosis Complex: A Placebo-Controlled Randomized Clinical Trial. JAMA Neurol. 2021; 78(3): 285–292, doi: 10.1001/jamaneurol.2020.4607, indexed in Pubmed: 33346789.
31. Devinsky O, Verducci C, Thiele EA, et al. Open-label use of highly purified CBD (Epidiolex®) in patients with CDKL5 deficiency disorder and Aicardi, Dup15q, and Doose syndromes. Epilepsy Behav. 2018; 86: 131–137, doi: 10.1016/j.yebeh.2018.05.013, indexed in Pubmed: 30006259.
32. Patel S, Grinspoon R, Fleming B, et al. The long-term efficacy of cannabidiol in the treatment of refractory epilepsy. Epilepsia. 2021; 62(7): 1594–1603, doi: 10.1111/epi.16936, indexed in Pubmed: 34050682.
33. Park YD, Linder DF, Pope J, et al. Long-term efficacy and safety of cannabidiol (CBD) in children with treatment-resistant epilepsy: Results from a state-based expanded access program. Epilepsy Behav. 2020; 112: 107474, doi: 10.1016/j.yebeh.2020.107474, indexed in Pubmed: 33181893.
34. Gaston TE, Ampah SB, Martina Bebin E, et al. UAB CBD Program. Long-term safety and efficacy of highly purified cannabidiol for treatment refractory epilepsy. Epilepsy Behav. 2021; 117: 107862, doi: 10.1016/j.yebeh.2021.107862, indexed in Pubmed: 33667843.
35. Klotz KA, Grob D, Schönberger J, et al. Effect of Cannabidiol on Interictal Epileptiform Activity and Sleep Architecture in Children with Intractable Epilepsy: A Prospective Open-Label Study. CNS Drugs. 2021; 35(11): 1207–1215, doi: 10.1007/s40263-021-00867-0, indexed in Pubmed: 34687005.
36. Gaston TE, Martin RC, Szaflarski JP. Cannabidiol (CBD) and cognition in epilepsy. Epilepsy Behav. 2021 [Epub ahead of print]; 124: 108316, doi: 10.1016/j.yebeh.2021.108316, indexed in Pubmed: 34563808.
37. Iannotti FA, Hill CL, Leo A, et al. Nonpsychotropic plant cannabinoids, cannabidivarin (CBDV) and cannabidiol (CBD), activate and desensitize transient receptor potential vanilloid 1 (TRPV1) channels in vitro: potential for the treatment of neuronal hyperexcitability. ACS Chem Neurosci. 2014; 5(11): 1131–1141, doi: 10.1021/cn5000524, indexed in Pubmed: 25029033.
38. Brown JD, Winterstein AG. Potential Adverse Drug Events and Drug-Drug Interactions with Medical and Consumer Cannabidiol (CBD) Use. J Clin Med. 2019; 8(7), doi: 10.3390/jcm8070989, indexed in Pubmed: 31288397.
39. 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, indexed in Pubmed: 32839652.
40. Geffrey AL, Pollack SF, Bruno PL, et al. Drug-drug interaction between clobazam and cannabidiol in children with refractory epilepsy. Epilepsia. 2015; 56(8): 1246–1251, doi: 10.1111/epi.13060, indexed in Pubmed: 26114620.
41. Gaston TE, Bebin EM, Cutter GR, et al. Szaflarki JP for the UAB CBD programme. In-teractions between cannabidiol and commonly used antiepileptic drugs. Epilepsia. 2017; 70: 313–8.