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CANNABINOIDS IN THE TREATMENT OF EPILEPSY: A REVIEW OF CURRENT EVIDENCE OF EFFICACY AND SAFETY

Stevo Lukić[1,2], Pavle Marković[2], Katarina Marković[3]

Despite the use of appropriate pharmacotherapy, a significant proportion of epilepsy patients still struggle with inadequate seizure control. Consequently, there has been a surge in research exploring alternative therapeutic options. Over the past two decades, there has been a growing focus on investigating the potential of cannabinoids as a treatment for epilepsy. While various cannabis-based preparations are available, their compositions and quality vary widely, posing diverse risks.

Among these cannabinoids, cannabidiol (CBD) stands out as the only one with scientifically supported benefits, balancing both efficacy and safety after a comprehensive assessment of risks. Notably, CBD distinguishes itself by consistently demonstrating efficacy without inducing psychoactive effects. The highly purified form of CBD has obtained approval from both US and EU regulatory agencies for addressing pharmacoresistant seizures linked to rare and severe childhood-onset epileptic syndromes.

Short-term side effects associated with CBD are generally mild to moderate and tend to ameliorate with dose adjustments. However, to gain a deeper understanding of the therapeutic mechanisms, expand the assessment of CBD's effectiveness across various epilepsy types, compare its efficacy with other antiseizure medications, and ensure long-term safety, additional research studies are imperative.

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[1]University of Niš, Faculty of Medicine,Department of Neurology, Niš, Serbia
[2]University Clinical Center Niš, Clinic of Neurology, Niš, Serbia
[3]University Clinical Center Niš, Department of Pediatric Neurology, Niš, Serbia

Contact: Stevo Lukić
81 Dr Zorana Djindjića Blvd., 18000 Niš, Serbia
E-mail: slukic@medfak.ni.ac.rs

Introduction

Epilepsy is a neurological disorder marked by a lasting tendency to experience epileptic seizures, leading to various neurobiological, cognitive, psychological, and social repercussions (1). With a prevalence of approximately 1% across the general population, epilepsy stands as one of the most common chronic neurological conditions affecting individuals of all ages. Despite adequate pharmacotherapy, approximately 30% of epilepsy patients struggle to attain effective seizure control (2). Although newer-generation drugs exhibit improved tolerability and interaction profiles compared to their predecessors, the incidence of pharmacoresistant epilepsy has not shown significant changes over time (3, 4). Consequently, the exploration of novel therapeutic alternatives remains a significant challenge for both healthcare professionals and patients alike.

While cannabis products have been utilized as herbal remedies for managing epileptic seizures since ancient times (5), their potential therapeutic value in this context has garnered significant media attention over the past two decades. Specifically, following the discovery of the endogenous cannabinoid system—an intricate cellular signaling system influenced by cannabis (6)—renewed interest in the clinical application of cannabidiol (CBD)-rich cannabis preparations emerged, driven by the allure of a 'natural' alternative treatment (7). Media coverage highlighting notable cases of efficacy, particularly in children with severe pharmacoresistant epilepsy (8), along with changes in local regulations on cannabis use, such as in Colorado, USA (9), further fueled this interest. Consequently, numerous clinical studies were initiated in the USA to assess the efficacy and safety of a purified form of CBD (Epidiolex; > 99% CBD) in treating pharmacoresistant epilepsy. The outcomes of

these studies prompted approval from the US Food and Drug Administration (FDA) for this purified CBD formulation in the treatment of pharmacoresistant seizures associated with Dravet syndrome (DS), Lennox–Gastaut syndrome (LGS), and tuberous sclerosis complex (TSC) in patients aged two or older. Subsequent approvals were granted by the European Medicines Agency (EMA). Thus, CBD achieved the distinction of being the first non-synthetic preparation derived from the cannabis plant to receive official regulatory approval.

The objective of this paper is to comprehensively review the current scientific evidence regarding the efficacy and safety of CBD in the treatment of epilepsy.

Efficacy

When assessing the efficacy of certain preparations, various types of evidence can be employed. The most robust scientific evidence is derived from well-conducted randomized controlled studies of high quality, involving a thorough comparison between the test substance and an appropriate comparator. Regulatory agencies and professional organizations demand evidence from such research (10, 11), as it alone facilitates a comprehensive evaluation of the balance between benefits and risks, thereby safeguarding the public interest. On the opposite end of the spectrum, we find case reports or anecdotal evidence, which may capture media attention but do not constitute a suitable mechanism for safeguarding public welfare (12).

Diverse forms of cannabinoids are available in the market, exhibiting significant differences in the evidence supporting their usage. Figure 1 presents a general categorization of cannabis and cannabinoid preparations utilized for medicinal purposes. These preparations can be classified into four primary categories based on the available evidence concerning their efficacy and safety, as detailed in Table 1:

1. Regulatory approved cannabis-based medications
2. Non-regulatory approved cannabis-based medications
3. CBD contenting consumer or food products
4. Recreational cannabis

For preparations lacking registration by drug regulatory agencies, there exists considerable variability in quality and safety. Moreover, precise labeling of content is often non-binding, and substance concentrations may not align with stated claims. The commercial oil preparations display vast differences, underscoring the necessity for stringent regulatory oversight and development.

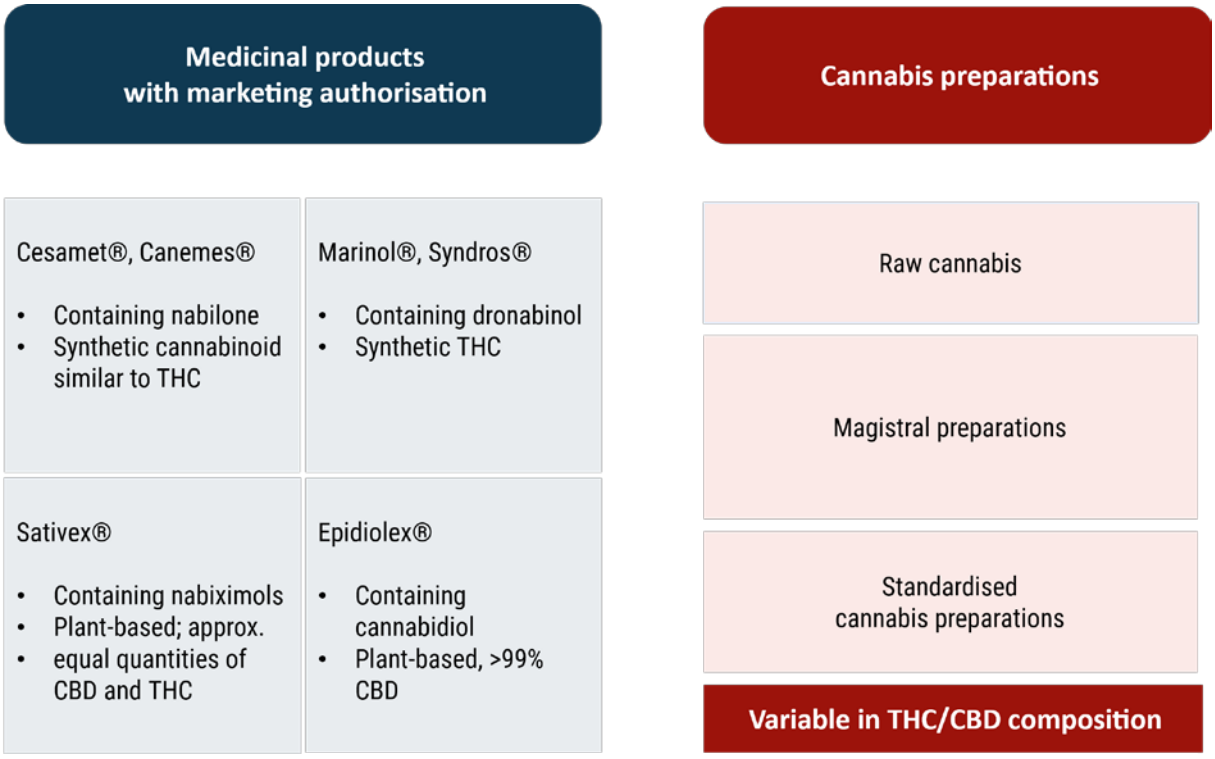

Figure 1. General topology of cannabis preparations and cannabinoids used for medicinal purposes

THC Tetrahydrocannabinol; CBD cannabidiol
(modified and adapted from reference 13)

Table 1. Classification of cannabis-based products based on available scientific evidence of efficacy

	Product class			
	Regulatory approved cannabis-based medications	Non-regulatory approved cannabis-based medications	Consumer or food products containing CBD	Recreational cannabis
Description	Medicines approved by regulatory agencies (e.g. EMA) after assessment of evidence	Medical cannabis available via prescription without the approval of regulatory agencies	Commercially available products containing CBD	Cannabis obtained from non-medical sources, usually by those seeking to achieve feelings of euphoria and relaxation
Evidence to support use	Evidence from RKS proves that the benefits outweigh the potential harms of side effects (13)	Evidence supporting safety and efficacy is lacking. Medication monitoring varies from country to country (13, 14, 15)	Evidence supporting their safety, efficacy, and quality is lacking (16)	Evidence supporting its medicinal use is lacking, but evidence of side effects is increasing (17)

In the 1980s and 1990s, several case reports and studies involving small patient cohorts explored the use of cannabis extracts for epilepsy treatment, yielding conflicting results (18, 19). Subsequent reports remained inconclusive (20), marked by notable methodological flaws or insufficient statistical power. Consequently, systematic reviews conducted by the Cochrane Group and the American Academy of Neurology in 2014 concluded that there was insufficient scientific evidence supporting the use of cannabis for epilepsy treatment (21, 22).

However, even during that period, cannabidiol (CBD) emerged as a potential candidate for epilepsy treatment, driven by its observed effects in experimental seizure and epilepsy models, as well as early pilot trials in epilepsy patients (18, 23). In comparison to delta-9-THC, CBD exhibited a more consistent anticonvulsant profile in animal models (24) and did not induce the adverse psychoactive effects associated with delta-9-THC (25, 26).

The anticonvulsant properties of CBD have been extensively documented across various experimental models (27, 28). However, the specific molecular mechanisms driving these effects remain unclear. This ambiguity partly stems from the intricate interactions of cannabinoids with numerous receptors and biological systems, many of which influence neuronal excitability (29). Unlike delta-9 THC, CBD exhibits minimal affinity for CB1 and CB2 receptors (30). Recent studies propose the involvement of three key mechanisms: 1) antagonism of G protein-coupled receptor 55 (GPR55), 2) desensitization of transient receptor potential vanilloid type 1 (TRPV1) channels, and 3) enhancement of adenosine-mediated signaling by inhibiting equilibrate nucleoside transporter 1 (ENT-1) (31). These mechanisms are believed to align plausibly with the concentrations of CBD at which the anticonvulsant effects have been demonstrated.

The effectiveness of adjunctive CBD treatment has been demonstrated in five placebo-controlled clinical studies. Two trials focused on patients with DS (32, 33), two on those with LGS (34, 35), and one on epilepsy linked to TSC (36). Table 2 showcases the primary methodological features of these studies.

Across these trials, CBD treatment led to a notable decrease in the frequency of convulsive seizures associated with DS, atonic seizures linked to LGS, and focal or generalized seizures related to TSC (Figure 2). These effects were consistent across all tested daily doses: 10 and 20 mg/kg (in DS and LGS), as well as 25 and 50 mg/kg in TSC. However, the benefit-risk assessment did not favor the utilization of the 50 mg/kg dose. An emerging concern following the publication of these findings was that most CBD-treated patients were also taking clobazam. This has led to investigations to determine whether the observed enhancement in seizure control is directly attributed to CBD or if it results from a

pharmacological interaction with clobazam, potentially resulting in elevated plasma levels of N-desmethylclobazam (37−39).

The impact of an interaction effect with clobazam was explored in three recent studies assessing CBD efficacy in patients with and without clobazam co-medication (28, 40, 41). These studies presented evidence supporting the independent anticonvulsant effects of CBD, albeit with more pronounced effects observed in patients using clobazam. However, methodological limitations such as the absence of randomization for clobazam co-medication, small sample sizes, and the inclusion of patients with different epilepsy syndromes (40, 42) pose challenges in interpreting the data on CBD efficacy, potentially influencing study outcomes. Nevertheless, despite these challenges, the US Food and Drug Administration (FDA) has granted approval for CBD use irrespective of the presence or absence of co-medication (43). In contrast, the European Medicines Agency (EMA) has restricted approval only to the use of CBD in patients concurrently using clobazam (44).

It is crucial to highlight that existing evidence pertains solely to the effectiveness of CBD as an adjunctive therapy in these syndromes when compared to a placebo. To date, there have been no studies directly comparing the efficacy of CBD with other antiseizure medications (ASMs). While preclinical models indicate a potentially broad spectrum of CBD effects, it is imperative to assess its effectiveness under appropriate clinical conditions. For instance, recent pilot studies suggest that CBD may not exhibit efficacy in typical absence seizures (45). Therefore, further research is essential to evaluate the effectiveness of CBD in various types of epilepsy and to directly compare its efficacy with other ASMs.

Table 2. Key methodological characteristics of studies that supported the efficacy of cannabidiol as adjunctive therapy in rare epileptic syndromes

Syndrome	**Dravet syndrome**		**Lenox−Gastaut syndrome**		**Tuberous−sclerotic complex**
Age (years)	2−18		2−55		1−65
Seizure type and number of attacks during the last 4 weeks	Convulsive ≥ 4/week		Drop attacks ≥ 2/week		Focal and generalized ≥ 8
Number of ASM	≥ 1		≥ 1		≥ 1
Name of the study	GWPCARE1 (DS 1332b)	GWPCARE2 (DS 1424)	GWPCARE3 (LGS 1414)	GWPCARE4 (LGS 1423)	GWPCARE6
Sample size	n = 120	n = 199	n = 225	n = 171	n = 225
CBD dose (mg/kg/d)	20	10 & 20	10 & 20	20	25/50
Reference	(32)	(33)	(34)	(35)	(36)

Safety

Cannabidiol

The short-term adverse effects of cannabidiol have been thoroughly identified and documented in the clinical studies that facilitated its registration. Generally, CBD is well tolerated, manifesting as transient, dose-dependent, mild to moderate effects like drowsiness, decreased appetite, or diarrhea. Nevertheless, it is important to note that severe, life-threatening side effects can occur, particularly in association with toxic combinations involving other drugs commonly used in this patient group, such as valproate or clobazam. Comprehensive studies are imperative to evaluate long-term outcomes and ensure the continued assessment of safety.

In randomized controlled trials conducted in patients with DS and LGS, adverse events were more frequently reported in CBD-treated patients, with an absolute difference in incidence of more than 5% compared to placebo-treated patients. These adverse events included somnolence, decreased appetite, increased transaminases, infections, rash, diarrhea, fatigue, sleep disturbances, irritability/agitation, and lethargy (23). Notably, in these trials, 8.9% of patients receiving CBD discontinued treatment due to side effects, in contrast to 1.8% of those receiving placebo (28).

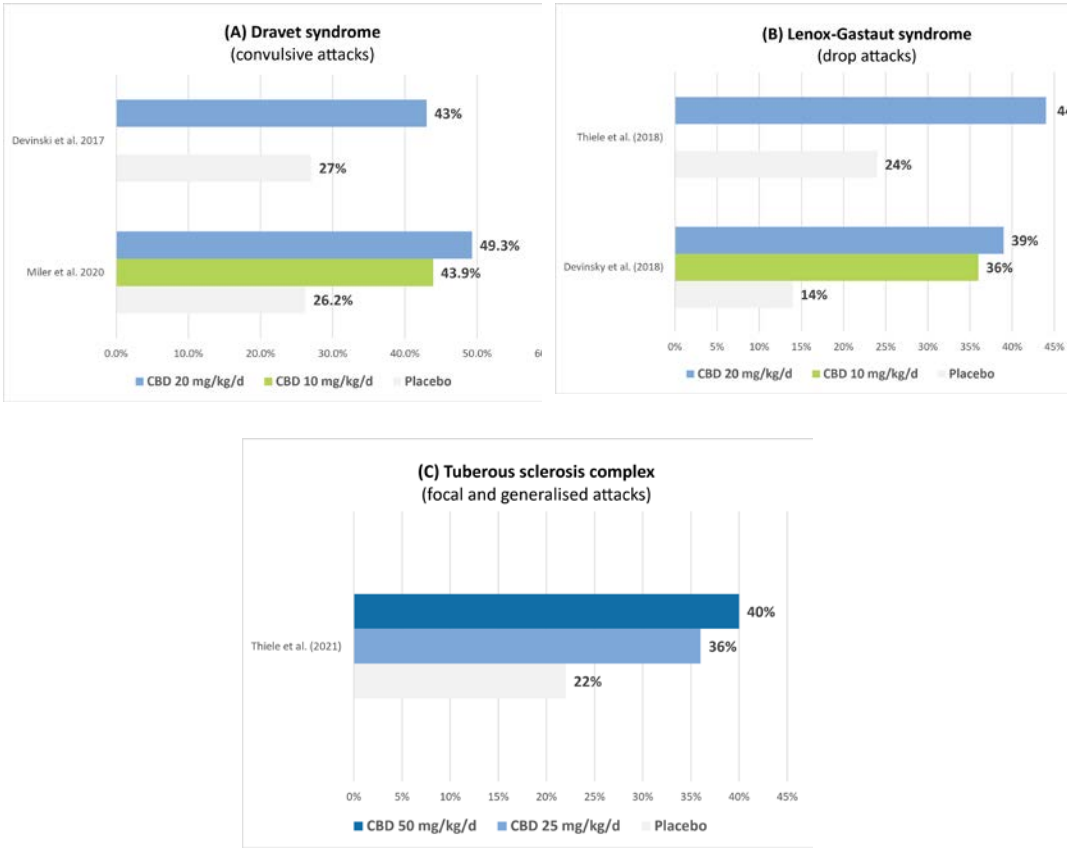

Figure 2. Proportions of patients with a ≥ 50% reduction in seizure frequency compared to baseline in 5 randomized, placebo-controlled trials of cannabidiol (CBD) as adjunctive therapy in (A) convulsive seizures associated with DS (32, 33), (B) drop attacks associated with LGS (34, 35) and (C) generalized and focal attacks associated with TSC (36)

Similarly, in the group receiving 25 mg/kg CBD in patients with TSC, the most reported adverse events were increased transaminases, pyrexia, vomiting, decreased appetite, weight loss, nausea, diarrhea, and anemia. Significantly, 13% of patients receiving CBD discontinued the study due to adverse events, compared to 3% in the placebo group (36).

Serious side effects were observed in approximately 15% of patients undergoing CBD treatment, with the most significant being a clinically substantial elevation (three times the upper limits of reference values) in alanine transaminase (ALT) and aspartate transaminase (AST) levels. This elevation in enzyme levels was more frequent with higher CBD doses and concurrent valproate therapy (46). Rash incidents were infrequent but were typically associated with pyrexia and often led to the discontinuation of treatment (34).

Instances of increased liver enzymes were more prevalent in patients also using valproate, while somnolence, heightened secretion, and pneumonia occurred more frequently in the group concurrently using clobazam (23, 47). Generally, these side effects can be managed by reducing the CBD or clobazam dose.

In a recent study, the side effects of CBD were assessed based on the findings from double-blind randomized placebo-controlled studies across various health conditions (48). A meta-analysis was conducted on data from 12 trials involving 803 participants. The results indicated that compared to the placebo, CBD was more likely to be discontinued due to side effects. This trend was observed for both serious adverse events (such as abnormal liver function tests and pneumonia) and milder adverse events (including reduced appetite, diarrhea, drowsiness, and sedation).

Associations with abnormal liver function tests, somnolence, sedation, and pneumonia were specifically identified in studies involving pediatric patients. However, upon excluding these studies, the only adverse event consistently associated with CBD was diarrhea. The authors suggested that interactions with other drugs, particularly valproate and clobazam, contribute to apparent differences in treatment outcomes between patients with epilepsy and those with other conditions.

Non-regulatory approved cannabis-based medications

In certain countries, these preparations are accessible with a doctor's prescription. The primary challenge lies in the absence of evidence substantiating their safety and efficacy. Medication monitoring practices differ from one country to another (14–16).

Consumer or food products containing CBD

Commercially available products such as CBD oils are commonly accessible, and there exists a misconception that their use is risk-free. However, several crucial considerations should be noted:

a) They are marketed without substantiated proof of efficacy and safety.

b) Quality is not consistently assured, potentially impacting their safety (16, 49–52).

c) The actual CBD content may differ from what is stated on the packaging (16, 49–51).

d) There is a risk of contamination with pesticides, heavy metals, or other phytocannabinoids, including THC (48, 51, 53–55).

Recreational cannabis

There are notable risks linked to the usage of this kind of preparation. In Europe, there has been an observed increase in THC levels in recreational cannabis preparations in recent years (56). The utilization of such products is associated with significant acute and long-term side effects. Acute effects encompass anxiety and memory impairment (17, 57), while long-term side effects may involve mental disorders, cardiovascular issues, and respiratory diseases (17,58). Additionally, recreational cannabis carries the risk of addiction (59). Despite the growing understanding of the side effects associated with this type of preparation, routine monitoring of these effects, like other drugs, is not commonly implemented.

Conclusion

Various cannabis-based preparations exhibit considerable differences in their composition and quality, leading to varying associated risks.

Among these preparations, the sole one currently supported by scientific evidence, following a comprehensive assessment of its benefits and risks, is the purified form of cannabidiol (CBD). This form has shown benefits as an adjunct therapy for patients with pharmacoresistant seizures associated with Dravet syndrome (DS), Lennox–Gastaut syndrome (LGS), and tuberous sclerosis (TS).

CBD is generally well tolerated, with most short-term side effects being mild to moderate and often improving with dosage adjustments.

However, further studies are imperative to assess CBD's efficacy through direct comparisons with other antiseizure medications (ASMs) and to ensure a thorough evaluation of its long-term safety.

References

1. Fisher RS, Van Emde Boas W, Blume W, Elger C, Genton P, Lee P, et al. Epileptic seizures and epilepsy: definitions proposed by the International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE). Epilepsia 2005;46(4):470-472. [CrossRef][PubMed]
2. Perucca E, Perucca P, White HS, Wirrell EC. Drug resistance in epilepsy. Lancet Neurol 2023;22(8):723-734. [CrossRef][PubMed]
3. Chen Z, Brodie MJ, Liew D, Kwan P. Treatment outcomes in patients with newly diagnosed epilepsy treated with established and new antiepileptic drugs a 30-year longitudinal cohort study. JAMA Neurol 2018;75(3):279-286. [CrossRef][PubMed]
4. Hauser AW. Questioning the effectiveness of newer antiseizure medications. JAMA Neurol 2018;75(3):273–274. [CrossRef][PubMed]
5. Friedman D, Sirven JI. Historical perspective on the medical use of cannabis. Epilepsy Behav 2017;70(PtB):298-301. [CrossRef][PubMed]
6. Devane WA, Hanuš L, Breuer A, Pertwee RG, Stevenson LA, Griffin G, et al. Isolation and structure of a brain constituent that binds to the cannabinoid receptor. Science 1992;258(5090):1946-1949. [CrossRef][PubMed]
7. Friedman D, Devinsky O. Cannabinoids in the treatment of epilepsy. N Engl J Med 2015;373(11):1048-1058. [CrossRef][PubMed]
8. Maa E, Figi P. The case for medical marijuana in epilepsy. Epilepsia 2014;55(6):783-786. [CrossRef][PubMed]
9. Porter BE, Jacobson C. Report of a parent survey of cannabidiol-enriched cannabis use in pediatric treatment-resistant epilepsy. Epilepsy Behav 2013;29(3):574-577. [CrossRef][PubMed]
10. European Medical Agency. From laboratory to patient: the journey of a centrally authorised medicine [Internet]. London: EMA; 2019 [cited 2023 Dec 15]. Available from: https://www.ema.europa.eu/en/documents/other/laboratory-patient-journey-centrally-authorised-medicine_en.pdf.
11. American Academy of Neurology. Position statement: Use of medical cannabis for neurologic disorders [Internet]. Minneapolis (MN): American Academy of Neurology; 2018 [cited 2023 Dec 15]. Available from: https://www.aan.com/siteassets/home-page/policy-and-guidelines/policy/position-statements/cannabis-position-statement.pdf.
12. Irwig L, Irwig J, Trevena L, Sweet M, editors. Smart health choices: Making sense of health advice London: Hammersmith Press; 2008.
13. European Monitoring Centre for Drugs and Drug Addiction. Medical use of cannabis and cannabinoids: questions and answers for policymaking [Internet]. Luxembourg: Publications Office of the European Union; 2018 [cited 2023 Dec]. Available from: https://www.euda.europa.eu/system/files/publications/10171/20185584_TD0618186ENN_PDF.pdf.
14. Pratt M, Stevens A, Thuku M, Butler C, Skidmore B, Wieland LS, et al. Benefits and harms of medical cannabis: a scoping review of systematic reviews. Syst Rev 2019;8(1):320. [CrossRef][PubMed]
15. Schlag A. An evaluation of regulatory regimes of medical cannabis: what lessons can be learned for the UK?. Med Cannabis Cannabinoids 2020;3(1):76-83. [CrossRef][PubMed]
16. Chesney E, Oliver D, Green A, Sovi S, Wilson J, Englund A, et al. Adverse effects of cannabidiol: a systematic review and meta-analysis of randomized clinical trials. Neuropsychopharmacology 2020;45(11):1799-1806. [CrossRef][PubMed]
17. World Health Organization. The health and social effects of nonmedical cannabis use [Internet]. Geneva: World Health Organization; 2016 [cited 2023 Dec 15]. Available from: https://iris.who.int/handle/10665/251056.
18. Cunha JM, Carlini EA, Pereira AE, Ramos OL, Pimentel C, Gagliardi R, et al. Chronic administration of cannabidiol to healthy volunteers and epileptic patients. Pharmacology 1980;21(3):175-185. [CrossRef][PubMed]
19. Ames FR, Cridland S. Anticonvulsant effect of cannabidiol. Afr Med J 1986;69(1):14. [PubMed]
20. Gross DW, Hamm J, Ashworth NL, Quigley D. Marijuana use and epilepsy: prevalence in patients of a tertiary care epilepsy center. Neurology 2004;62(11):2095-2097. [CrossRef][PubMed]
21. Gloss D, Vickrey B. Cannabinoids for epilepsy. The Cochrane database of systematic reviews 2014;2014(3):CD009270. [CrossRef][PubMed]
22. Koppel BS, Brust JCM, Fife T, Bronstein J, Youssof S, Gronseth G, et al. Systematic review: efficacy and safety of medical marijuana in selected neurologic disorders: report of the Guideline Development Subcommittee of the American Academy of Neurology. Neurology 2014;82(17):1556-1563. [CrossRef][PubMed]
23. Franco V, Perucca E. Pharmacological and therapeutic properties of cannabidiol for epilepsy. Drugs 2019;79(13):1435-1454. [CrossRef][PubMed]
24. Devinsky O, Cilio MR, Cross H, Fernandez-Ruiz J, French J, Hill C, et al. Cannabidiol: pharmacology and potential therapeutic role in epilepsy and other neuropsychiatric disorders. Epilepsia 2014;55(6):791-802. [CrossRef][PubMed]
25. Assareh N, Gururajan A, Zhou C, Luo JL, Kevin RC, Arnold JC. Cannabidiol disrupts conditioned fear expression and cannabidiolic acid reduces trauma-induced anxiety-related behaviour in mice. Behavioural pharmacology 2020;31(6):591-596. [CrossRef][PubMed]
26. Mechoulam R, Shani A, Edery H, Grunfeld Y. Chemical basis of hashish activity. Science 1970;169(3945):611-612. [CrossRef][PubMed]
27. Klein BD, Jacobson CA, Metcalf CS, Smith MD, Wilcox KS, Hampson AJ, et al. Evaluation of cannabidiol in animal seizure models by the epilepsy therapy screening program (ETSP). Neurochem Res 2017;42(7):1939-1948. [CrossRef][PubMed]

28. Lattanzi S, Brigo F, Trinka E, Zaccara G, Cagnetti C, Del Giovane C, et al. Efficacy and safety of cannabidiol in epilepsy: A systematic review and meta-analysis. Drugs 2018;78(17):1791-1804. [CrossRef][PubMed]
29. Senn L, Cannazza G, Biagini G. Receptors and channels possibly mediating the effects of phytocannabinoids on seizures and epilepsy. Pharmaceuticals (Basel) 2020;13(8):174. [CrossRef][PubMed]
30. Pertwee RG. The diverse CB1 and CB2 receptor pharmacology of three plant cannabinoids: delta9-tetrahydrocannabinol, cannabidiol and delta9-tetrahydrocannabivarin. Br J Pharmacol 2008;153(2):199-215. [CrossRef][PubMed]
31. Gray RA, Whalley BJ. The proposed mechanisms of action of CBD in epilepsy. Epileptic Disord 2020;22(S1):10-15. [CrossRef][PubMed]
32. Devinsky O, Cross JH, Laux L, Marsh E, Miller I, Nabbout R, et al. Trial of cannabidiol for drug-resistant seizures in the Dravet syndrome. N Engl J Med 2017;376(21):2011-2020. [CrossRef][PubMed]
33. Miller I, Scheffer IE, Gunning B, Sanchez-Carpintero R, Gil-Nagel A, Perry MS, et al. Dose-ranging effect of adjunctive oral cannabidiol vs placebo on convulsive seizure frequency in Dravet syndrome. JAMA Neurology 2020;77(5):613-621. [CrossRef][PubMed]
34. Devinsky O, Patel AD, Cross JH, Villanueva V, Wirrell EC, Privitera M, et al. Effect of cannabidiol on drop seizures in the Lennox-Gastaut syndrome. N Engl J Med 2018;378(20):1888-1897. [CrossRef][PubMed]
35. Thiele EA, Marsh ED, French JA, Mazurkiewicz-Beldzinska M, Benbadis SR, Joshi C, et al. Cannabidiol in patients with seizures associated with Lennox-Gastaut syndrome (GWPCARE4): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet 2018;391(10125):1085-1096. [CrossRef][PubMed]
36. Thiele EA, Bebin EM, Bhathal H, Jansen FE, Kotulska K, Lawson JA, et al. Add-on cannabidiol treatment for drug-resistant seizures in tuberous sclerosis complex. JAMA Neurol 2021;78(3):285-292. [CrossRef][PubMed]
37. Bergmann KR, Broekhuizen K, Groeneveld GJ. Clinical trial simulations of the interaction between cannabidiol and clobazam and effect on drop-seizure frequency. Br J Clin Pharmacol 2020;86(2):380-385. [CrossRef][PubMed]
38. Groeneveld GJ, Martin JH. Parasitic pharmacology: A plausible mechanism of action for cannabidiol. Br J Clin Pharmacol 2020;86(2):189-191. [CrossRef][PubMed]
39. Martin JH, Schneider J, Lucas CJ, Galettis P. Exogenous cannabinoid efficacy: Merely a pharmacokinetic interaction?. Clin Pharmacokinet 2018;57(5):539-545. [CrossRef][PubMed]
40. Bialer M, Perucca E. Does cannabidiol have antiseizure activity independent of its interactions with clobazam? An appraisal of the evidence from randomized controlled trials. Epilepsia 2020;61(6):1082-1089. [CrossRef][PubMed]
41. Devinsky O, Thiele EA, Wright S, Checketts D, Morrison G, Dunayevich E, et al. Cannabidiol efficacy independent of clobazam: Meta-analysis of four randomized controlled trials. Acta Neurol Scand 2020;142(6):531-540. [CrossRef][PubMed]
42. Lattanzi S, Trinka E, Striano P, Zaccara G, Del Giovane C, Nardone R, et al. Cannabidiol efficacy and clobazam status: A systematic review and meta-analysis. Epilepsia 2020;61(6):1090-1098. [CrossRef][PubMed]
43. U.S. Food and Drug Administration. FDA approves first drug comprised of an active ingredient derived from marijuana to treat rare, severe forms of epilepsy [Internet]. Silver Spring (MD): FDA; 2018 [cited 2023 Dec 15]. Available from: https://www.fda.gov/news-events/press-announcements/fda-approves-first-drug-comprised-active-ingredient-derived-marijuana-treat-rare-severe-forms.
44. European Medicines Agency. Epidyolex: EPAR – Product information [Internet]. London: EMA; 2019 [cited 2023 Dec 15]. Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/epidyolex.
45. Azevedo M, Benbadis SR. Efficacy of highly purified cannabidiol (CBD) in typical absence seizures: A pilot study. Epilepsy & Behavior 2023;149:109512. [CrossRef][PubMed]
46. Devinsky O, Nabbout R, Miller I, Laux L, Zolnowska M, Wright S, et al. Long-term cannabidiol treatment in patients with Dravet syndrome: an open-label extension trial. Epilepsia 2019;60(2):294-302. [CrossRef][PubMed]
47. Cross JH, Cock H. A perspective on cannabinoids for treating epilepsy: Do they really change the landscape?. Neuropharmacology 2020;170:107861. [CrossRef][PubMed]
48. Chesney E, Oliver D, Green A, Sovi S, Wilson J, Englund A, et al. Adverse effects of cannabidiol: a systematic review and meta-analysis of randomized clinical trials. Neuropsychopharmacology 2020;45(11):1799-1806. [CrossRef][PubMed]
49. Hazekamp A. The trouble with CBD Oil. Med Cannabis Cannabinoids 2018;1(1):65-72. [CrossRef][PubMed]
50. Bonn-Miller MO, Loflin MJ, Thomas BF, Marcu JP, Marcu JP, Hyke T, et al. Labeling accuracy of cannabidiol extracts sold online. JAMA 2017;318(17):1708-1709. [CrossRef][PubMed]
51. Liebling JP, Clarkson NJ, Gibbs BW, Yates AS, O'Sullivan SE. An analysis of over-the-counter cannabidiol products in the United Kingdom. Cannabis Cannabinoid Res 2020;7(2):207-213. [CrossRef][PubMed]
52. U.S. Food and Drug Administration. What you need to know (and what we're working to find out) about products containing cannabis or cannabis-derived compounds [Internet]. Silver Spring (MD): FDA; 2019 [cited 2023 Dec 15]. Available from: https://www.fda.gov/consumers/consumer-updates/what-you-need-know-and-what-were-working-find-out-about-products-containing-cannabis-or-cannabis.
53. Morales P, Hurst DP, Reggio PH. Molecular targets of the phytocannabinoids: A complex picture. Prog Chem Org Nat Prod 2017;103:103-131. [CrossRef][PubMed]
54. Potter DJ. A review of the cultivation and processing of cannabis (Cannabis sativa L.) for production of prescription medicines in the UK. Drug Test Anal 2014;6(1-2):31-38. [CrossRef][PubMed]
55. Dryburgh LM, Bolan NS, Grof C, Galettis P, Schneider J, Lucas C, et al. Cannabis contaminants: sources, distribution, human toxicity and pharmacologic effects. Br J Clin Pharmacol 2018;84(11):2468-2476. [CrossRef][PubMed]

56. Freeman TP, Groshkova T, Cunningham A, Sedefov R, Griffiths P, Lynskey MT. Increasing potency and price of cannabis in Europe, 2006-16. Addiction 2019;114(6):1015-1023. [CrossRef][PubMed]
57. Hindley G, Beck K, Borgan F. Psychiatric symptoms caused by cannabis constituents: a systematic review and meta-analysis. Lancet Psychiatry 2020;7(4):344-353. [CrossRef][PubMed]
58. Bonomo Y, Souza J, Jackson A, Crippa J, Solowij N. Clinical issues in cannabis use. Br J Clin Pharmacol 2018;84(11):2495-2498. [CrossRef][PubMed]
59. Volkow ND, Baler RD, Compton WM, Weiss SR. Adverse health effects of marijuana use. N Engl J Med 2014;370(23):2219-2227. [CrossRef][PubMed]

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PRIMENA KANABINOIDA U LEČENJU EPILEPSIJE: AKTUELNI DOKAZI O EFIKASNOSTI I BEZBEDNOSTI

Stevo Lukić[1,2], Pavle Marković[2], Katarina Marković[3]

[1]Univerzitet u Nišu, Medicinski fakultet, Katedra za neurologiju, Niš, Srbija
[2]Univerzitetski klinički centar Niš, Klinika za neurologiju, Niš, Srbija
[3]Univerzitetski klinički centar Niš, Klinika za pedijatriju, Odeljenje za dečiju neurologiju, Niš, Srbija

Kontakt: Stevo Lukić
Bulevar dr Zorana Đinđića 81, 18000 Niš, Srbija
E-mail: slukic@medfak.ni.ac.rs

Činjenica da kod jedne trećine osoba sa epilepsijom ne postoji adekvatna kontrola napada uprkos primeni odgovarajuće farmakoterapije motivisala je istraživanja novih terapijskih opcija. U poslednje dve decenije zabeleženo je povećanje interesovanja za proučavanje terapijskih potencijala kanabinoida za lečenje epilepsije. Na tržištu su dostupni razni preparati bazirani na kanabisu; oni znatno variraju po sastavu i kvalitetu, a njihova primena udružena je sa različitim rizicima. Jedini kanabinoid o čijim prednostima upotrebe trenutno postoje naučni dokazi, dobijeni nakon procene benefita i rizika, jeste kanabidiol (engl. *Cannabidiol* – CBD). Kanabidiol se razlikuje od drugih kanabinoida po tome što postoje dokazi o njegovoj konstantnoj efikasnosti i o odsustvu psihoaktivnih efekata. Visoko prečišćeni oblik CBD-a prva je supstanca dobijena od biljke kanabisa koja je dobila odobrenje regulatornih agencija Sjedinjenih Američkih Država i Evropske unije za lečenje napada rezistentnih na farmakoterapiju koji su udruženi sa retkim i teškim epileptičkim sindromima koji su se pojavili u detinjstvu. Kratkoročni neželjeni efekti blagog su i umerenog stepena i popravljaju se nakon prilagođavanja doze. Da bi se otkrili precizni mehanizmi terapijskih efekata, procenila efikasnost CBD-a i u drugim vrstama epilepsije, izvršilo direktno poređenje sa drugim antiepileptičkim lekovima i procenila dugotrajna bezbednost njegove upotrebe, neophodno je sprovesti dalja istraživanja.

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***Ključne reči**: kanabidiol, epilepsija, efikasnost, bezbednost*