Review article

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Cannabinoids in the treatment of epilepsy: review of current evidence of efficacy and safety

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Abstract:

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.

Keywords: cannabidiol, epilepsy, safety, efficacy

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—a 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 pertaining to 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.

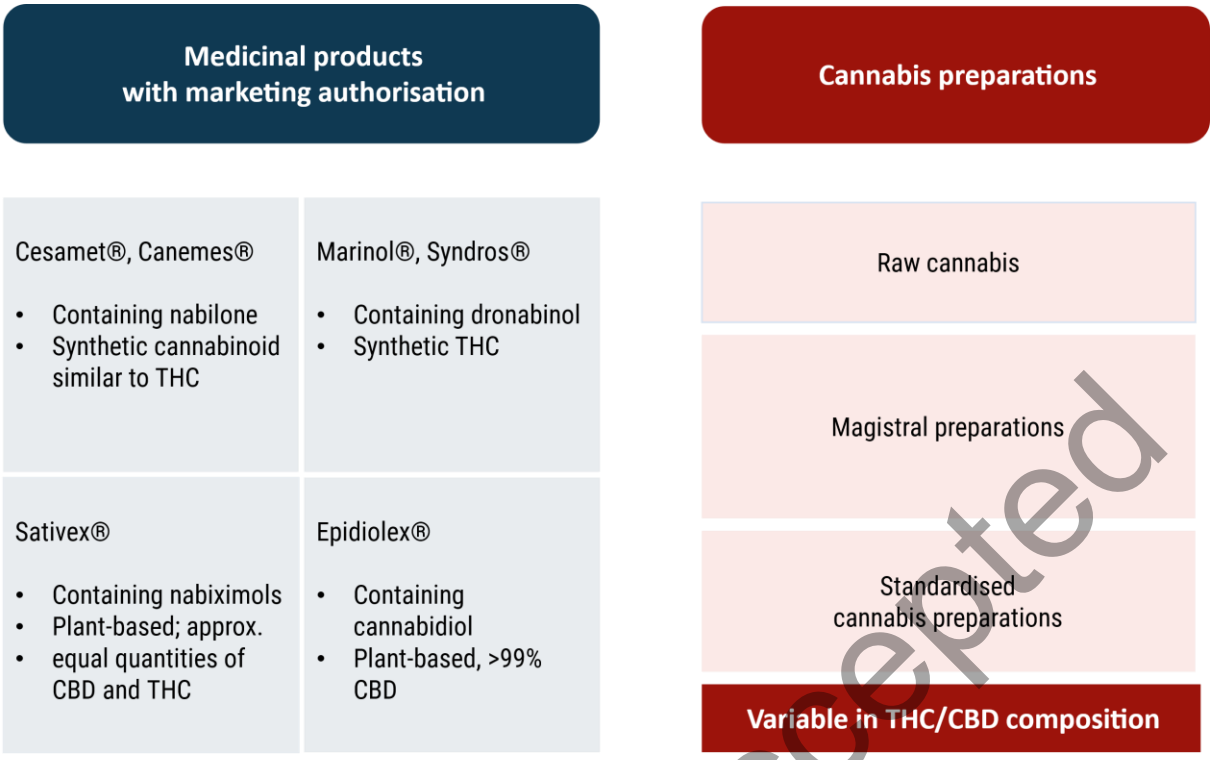

Figure 1 General topology of cannabis preparations and cannabinoids used for medicinal purposes.

THC- Tetrahydrocannabinol; CBD- cannabidiol
Modified and adapted from (59)

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	CBD contenting consumer or food products	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 (59).	Evidence supporting safety and efficacy is lacking. Medication monitoring varies from country to country. (44,45,59)	Evidence supporting their safety, efficacy, and quality is lacking (43).	Evidence supporting its medicinal use is lacking, but evidence of side effects is increasing (56).

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 (13,14). Subsequent reports remained inconclusive (15), 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 (16,17).

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 (13,18). In comparison to delta-9-THC, CBD exhibited a more consistent anticonvulsant profile in animal models (19) and did not induce the adverse psychoactive effects associated with delta-9-THC (20,21).

The anticonvulsant properties of CBD have been extensively documented across various experimental models (22,23). 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 (24). Unlike delta-9 THC, CBD exhibits minimal affinity for CB1 and CB2 receptors (25). 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) (26). 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 Dravet syndrome (DS) (27,28), two on those with Lennox-Gastaut syndrome (LGS) (29,30), and one on epilepsy linked to tuberous sclerosis complex (TSC) (31). Table 2 showcases the primary methodological features of these studies.

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 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	(27)	(28)	(29)	(30)	(31)

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-desmethylclobasam (32-34).

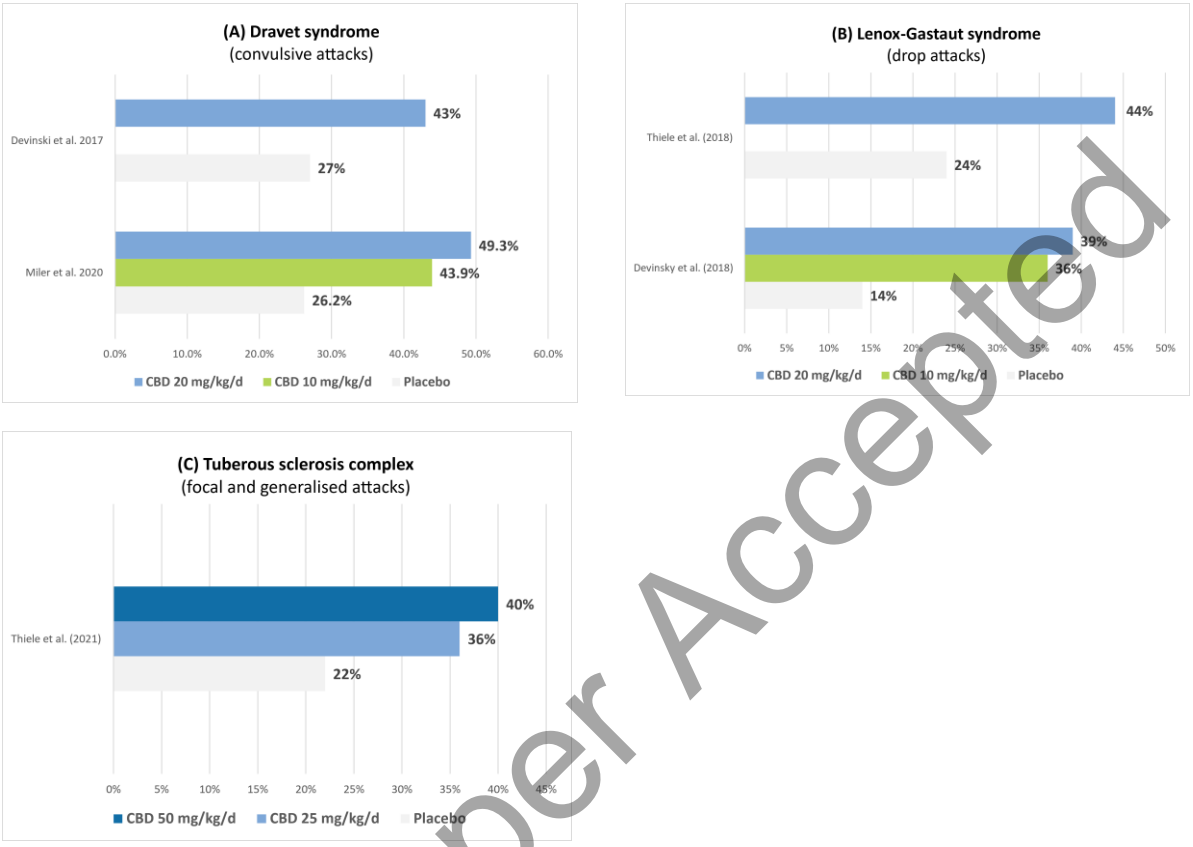

Figure 2 Proportions of patients with a ≥ 50% reduction in seizure frequency compared to baseline in 5 randomized, placebo-controlled trials of cannabidiol (CBD) as adjunctive therapy in (A) convulsive seizures associated with DS (27,28), (B) drop attacks associated with LGS (29,30) and (C) generalized and focal attacks associated with TSC (31).

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 (23,35,36). These studies presented evidence supporting 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 (35,37) 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 (38). In contrast, the European Medicines Agency (EMA) has restricted approval only to the use of CBD in patients concurrently using clobazam (39).

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 (40). 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.

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 Dravet syndrome (DS) and Lennox-Gastaut syndrome (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 (18). 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 (23).

Similarly, in the group receiving 25 mg/kg CBD in patients with tuberous sclerosis complex (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 (31).

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 (41). Rash incidents were infrequent but were typically associated with pyrexia and often led to the discontinuation of treatment (29).

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 (18) (42). 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 (43). 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 (44-46).

CBD contenting consumer or food products

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 (43,47-50).

c) The actual CBD content may differ from what is stated on the packaging (43, 47-49).

d) There is a risk of contamination with pesticides, heavy metals, or other phytocannabinoids, including THC (46,49,51-53).

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 (54). The utilization of such products is associated with significant acute and long-term side effects. Acute effects encompass anxiety and memory impairment (55,56), while long-term side effects may involve mental disorders, cardiovascular issues, and respiratory diseases (56,57). Additionally, recreational cannabis carries the risk of addiction (58). 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.

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PRIMENA KANABINIODA ZA LEČENJE EPILEPSIJA: AKTUELNI DOKAZI O EFIKSNOSTI I BEZBEDNOSTI

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Sažetak:

Jedna trećina pacijenata sa epilepsijom nema adekvatnu kontrolu napada i pored primene adekvatne farmakoterapije. Ovo je motivisalo istraživanja novih terapijskih opcija. U poslednje dve dekade evidentiran je povećani interes za proučavanje terapijskih potencijala kanabinoida za lečenje epilepsije. Na tržištu su dostupni različiti preparati bazirani na kanabisu ali oni značajno variraju po sastavu i kvalitetu i njihova primena je udružena sa različitim rizicima. Jedini kanabinoid za koji aktuelno postoje naučni dokazi o prednostima upotrebe, nakon procene benefita i rizika je kanabidiol (CBD). Kanabidiol se razlikuje od drugih kanabinoida po dokazima o konstantnoj efikasnosti i odsustvu psihoaktivnih efekata. Visoko prečišćeni oblik CBD je prva supstancija dobijena od biljke kanabisa, koja je dobila odobrenje regulatornih agencija SAD i EU, za lečenje farmakorezistentnih napada udruženih sa retkim i teškim epileptičkim sindromima sa početkom u

detinjstvu. Kratkoročni neželjeni efekti su blagog i umerenog stepena i popravljaju se nakon prilagođavanja doze. Dalje studije su neophodne radi otkrivanja preciznih mehanizama terapijskih efekata, procene efikasnosti CBD i u drugim vrstama epilepsije, direktnog poređenje sa drugim antiepileptičkim lekovima i procenu dugotrajne bezbednosti.

Ključne reči: kanabidiol, epilepsija, efikasnost, bezbednost