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).

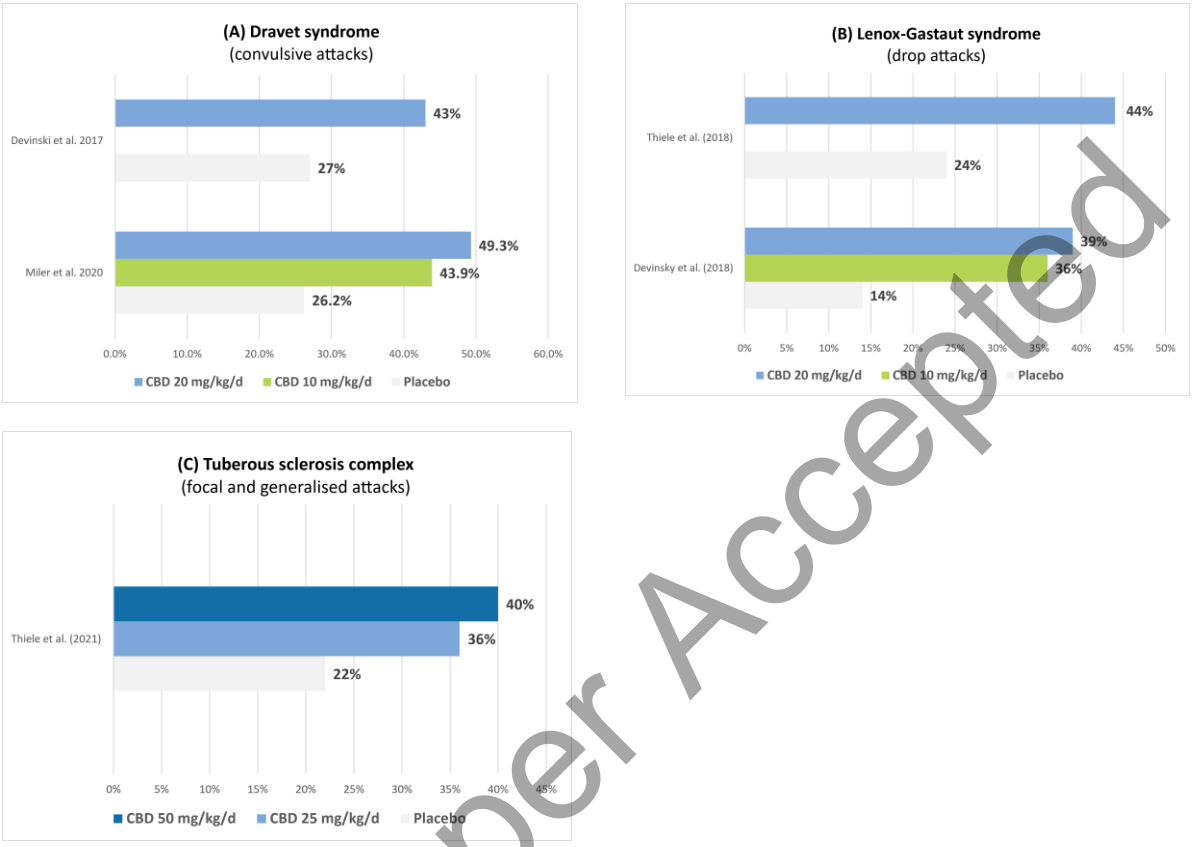

Figure 2 Proportions of patients with a ≥ 50% reduction in seizure frequency compared to baseline in 5 randomized, placebo-controlled trials of cannabidiol (CBD) as adjunctive therapy in (A) convulsive seizures associated with DS (27,28), (B) drop attacks associated with LGS (29,30) and (C) generalized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