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Review

Efficacy and adverse event profile of cannabidiol and medicinal cannabis for treatment-resistant epilepsy: Systematic review and meta-analysis

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ABSTRACT

This paper aimed to systematically examine the efficacy and adverse event (AE) profile of cannabidiol and medicinal cannabis by analyzing qualitative and meta-analytic data. We used the terms ("Cannabidiol" OR "Cannabis") AND "Epilepsy" AND ("Treatment" OR "Therapeutics") as keywords to retrieve studies indexed on PubMed, ScienceDirect, and CENTRAL databases. The inclusion criteria were as follows: clinical studies with a longitudinal observational design and intervention using cannabinoid derivatives, especially cannabidiol and medicinal cannabis, whereby some results involved the frequency of epileptic seizures. We used Cochrane Collaboration's Review Manager software (RevMan 5.1.6) for the meta-analysis and dichotomized the articles to a confidence interval of 95%. From 236 articles, we selected 16 for descriptive analysis; we selected only 4 for the meta-analysis. According to the results, a statistically meaningful effect of cannabidiol compared with placebo was observed ($p < 0.00001$). When comparing treatment with cannabidiol or medicinal cannabis, significance was not found for the AE profile ($p = 0.74$). As AEs for cannabidiol were more common under short-term than under long-term treatment ($p < 0.00001$), this approach was favorable in the long term. Furthermore, cannabidiol is more effective than placebo, regardless of the etiology of epileptic syndromes and dosage. Overall, the AE profile did not differ across treatments with cannabidiol or medicinal cannabis, though it did differ favorably for long-term than for short-term treatment.

1. Introduction

Antiepileptic drugs (AEDs) are unable to control seizures in approximately 30% of patients with frequent seizure [1–3]. This group is characterized by a lack of efficacy for two AEDs, resulting in refractory or treatment-resistant epilepsy (TRE) [4]. For these conditions, different treatments, such as ketogenic diets [5] and vagus nerve stimulation [6], have been attempted.

Scientists have also studied treatment with cannabis (CNB) derivative compounds as alternative treatments [7,8]. Cannabis contains two main compounds: Δ9-tetrahydrocanabidiol (THC), which is responsible for the psychotropic effects [9], and cannabidiol (CBD), which has therapeutic effects in epilepsy [10,11]. Both CBD and CNB extracts with THC exhibit therapeutic effects in TRE [12]. However, the CNB extract contains THC, which may cause severe adverse events, mainly with long-term usage [13].

Considering this scenario, the Food and Drug Administration (FDA) has approved Epidiolex®, the first drug derived from cannabis (CNB), which comprises 99% CBD, a major noneuphoric, and less than 0.1% THC. Epidiolex® was first approved for treating refractory epilepsy in patients, who are two years of age and older, with Dravet and Lennox–Gastaut syndromes [14].

Therefore, the main goal of this review was to demonstrate the efficacy of treating TRE with CBD and medicinal CNB. Secondary goals were to reveal adverse events (AEs) in both treatments. For these goals, we developed a systematic review with meta-analysis.

2. Methods

2.1. Research strategy

The databases we used were PubMed, Cochrane Central Register of Controlled Trials (CENTRAL), and ScienceDirect using the tool

Abbreviations: AEDs, antiepileptic drugs; CNB, cannabis; THC, Δ9-tetrahydrocanabidiol; CBD, cannabidiol; FDA, Food and Drug Administration; AEs, adverse events; TRE, treatment-resistant epilepsy.

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"advanced search" in each. We included only original articles with the words ("Cannabidiol" OR "Cannabis") AND "Epilepsy" AND ("Treatment" OR "Therapeutics"), as related to the title, summary, or keywords (feature available on ScienceDirect and CENTRAL). This advanced search strategy helped to decrease false results by, for example, relating journal titles. The searches were performed on two occasions: weeks 1 and 2 of April and September 2019. Eligibility criteria were then applied to select articles for the study.

2.2. Eligibility criteria

2.2.1. Inclusion criteria

The articles chosen should answer the review question 'Do cannabinoid derivatives, especially cannabidiol and medicinal cannabis, have therapeutic effects on epilepsy regardless of age?' For this purpose, we included interventional clinical trials in which the primary outcome was a reduction in epileptic seizure severity or frequency. Interventional studies included crossover, open-label, and randomized blind or double-blind trials. As age does not interfere with the analysis criteria, studies with patients of any age were included. We also included studies in which the dosage was the maximum tolerable, with a defined and detailed daily dosage. The study should also contain a minimum of ten participants in the group treated with CBD or CNB, and it should detail AEs.

2.2.2. Exclusion criteria

Case reports and short communications were excluded because they do not have sufficient clinical data because of low scientific evidence. Original cross-sectional studies that approach "experience reports" and retrospective studies were also excluded because they did not present clinical trials with new treatment protocols for TRE using CBD. We discarded studies with online survey applications because of participation bias, as this category of research allows multiple answers for the same individual and there is lack of equal selectivity of participants, among others [15]. We did not include articles with only a summary, without a published manuscript, letters, editorials, lectures, books, or notes in the final sample.

2.3. Study design

We have adopted a PRISMA flow diagram model. After identification and database search, we applied the inclusion and exclusion criteria based on study type, followed by the application of eligibility (detailed in the previous section) after reading of the full texts. Studies with trials that compare CBD efficacy with placebo and an additional study [16] were used for the meta-analysis.

The data were divided into two parts for descriptive analysis. The first part referred to the study identification data, namely, the size of sample, average age, type of study, etiology, and scales used. The second part referred to evaluation of relevant data, such as associated medication, treatment duration, cannabinoid type and dosage, administered protocol, and seizure outcome(s). Finally, a forest plot was applied to assess AEs and efficacy profiles.

The QUADAS-2 tool was employed because it is a preferred tool for analyzing interventional protocols when reviewing meta-analytic data and measuring the degree to which the individual study criteria matches the review question [17,18]. This classification considers four items: patient selection, index test, reference pattern, and flux and time. Bias and applicability risk are common for the first three, whereas the last one is only associated with bias. Any divergence can be resolved according to the need for diagnostic precision studies [19]. However, the QUADAS-2 results were not an item for article exclusion.

2.4. Outcomes

The primary endpoint was the descriptive analysis approach of the studies in relation to CBD therapeutics, synthesizing study results concerning a ≥50% reduction in seizure frequency in relation to the baseline register of seizure diaries. This same parameter was applied for quantitative approach development. A new filter for the descriptive analysis was developed to perform the meta-analysis, allowing for quantitative comparison of the efficacy of CBD in relation to placebo. The secondary endpoint was related to the descriptive analysis in other studies. Adverse events for CBD in relation to medicinal CNB and to long-term treatment compared with short-term treatment were also part of the secondary endpoint.

2.5. Statistical analysis

To develop the meta-analysis, we used Cochrane Collaboration's Review Manager software (RevMan 5.1.6). Heterogeneity among the trials was assessed by the chi-squared test and I^2 statistics for heterogeneity, the latter of which was categorized as follows: <25% low, 25 to 50% moderate, and >50% high [20]. A dichotomous analysis with a confidence interval of 95% was employed to compare the placebo group (left side) to the group treated with CBD (right side). The Mantel–Haenszel statistical method was used, with fixed effects as an analysis method; odds ratios were calculated. These methods were also used to compare efficacy of (1) CBD × placebo; (2) CBD × medicinal CNB; and (3) short- and long-term treatments. The last two analyses were developed to test the hypothesis of one group presenting more AEs than the other.

3. Results

The PRISMA statement and checklist were adopted (Fig. 1 shows the flow diagram) for this study. Our advanced research using the given keywords indicated above retrieved 236 articles: 183 in PubMed, 25 in ScienceDirect, and 28 in CENTRAL. We also included two papers from outside the database results. A total of sixteen studies were included for the descriptive analysis, with four for the meta-analysis.

The analysis related to the basic identification of the studies is provided in Table 1. Some studies approach a sampling difference between efficacy and AE profiles studies, which occurs because of the removal of some study participants. Data regarding efficacy could not be compiled because the estimated treatment time was not completed, which was different from the findings for AE profile. However, removal of a study was due to many reasons, such as the appearance of serious AEs. Nevertheless, the reduction in sample size was negligible. With regard to the etiology of epileptic syndrome, with Dravet and Lennox–Gastaut syndromes being more common. Of the fourteen studies, thirteen involved child and adolescent patients.

Details about each study are listed in Table 2. For each study, CBD was used alone without other usual AEDs. In seven studies, 50 mg/kg/day was used as the maximum dosage, and three used 20 mg/kg/day, both administered orally. Varying results for seizure frequency reduction were found among the studies, though a more significant reduction was reported in the randomized studies by Devinsky et al. [24], Devinsky et al. [26] and Thiele et al. [32]. In relation to observational studies, the reduction of epileptic seizure frequency compared to the beginning of the treatment was more significant in the studies by Rosenberg et al. [25], Devinsky et al. [27], McCoy et al. [29], and Szaflarski et al. [31].

The forest plot in Fig. 2 illustrates the quantitative data based on the meta-analysis in. The odds ratio was calculated to compare (A) efficacy of CBD and placebo and (B) AEs for CBD (short-term) [22–24,26,27,32,36] and medicinal CNB (short-term) [28,29]; and (C) short- [22–24,26,27,32,36] and long-term CBD treatments [31–33,35,37] were examined to determine the AE profile.

Bias risk is depicted in Supplementary Fig. 1. The items "patient selection", "index test", and "flux and time" have potential bias, whereas "reference standard" has low bias risk. All of the studies have high potential for applicability (Supplementary Fig. 2).

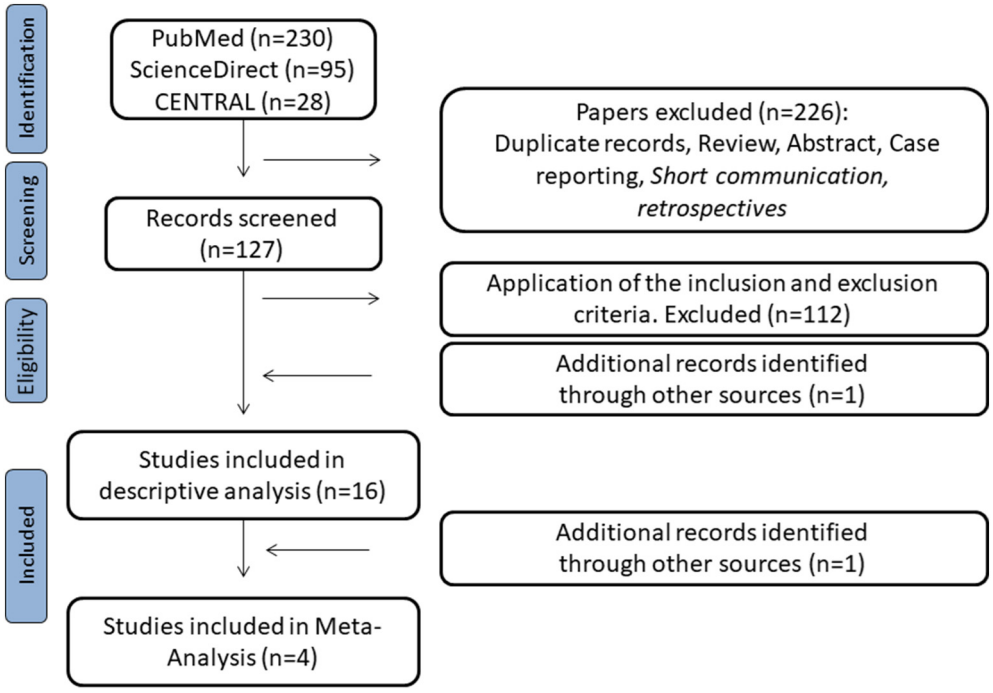

Fig. 1. Flowchart for the selection of studies.
Adapted from the PRISMA statement [21].

As shown in Fig. 2A, CBD treatment was efficacious compared with placebo, and the odds ratio (OR = 3.09, CI 95% = 2.27–4.21; $p < 0.00001$) indicated that this difference was statistically significant. The AE profile is related to tolerable AEs found in studies assessing both CBD and medicinal CNB, revealing in which study AEs are more common. Therefore, Fig. 2B compares AEs in short-term CBD and medicinal CNB treatment, though a significant difference was not found (OR = 0.95, CI 95% = 0.71–1.27; $p = 0.74$). Fig. 2C also compares AEs in short- and long-term CBD treatments, from which a greater tendency of AEs in long-term treatment was observed, and this difference was significant (OR = 0.89, CI 95% = 0.80–0.98; $p < 0.00001$).

At low levels of THC, CNB extract has notable efficacy (Table 2), with minor AEs (Fig. 2B). Indeed, according to the AE profile, the safety of medicinal CNB is similar to that of pure CBD. As indicated in Fig. 2C, the AE profile was more favorable for long-term CBD use ($p < 0.00001$). These data suggest a time-dependent evolution of CBD treatment of epilepsy in terms of the AE profile because AEs are more frequent at the start of treatment.

4. Discussion

The study by Thiele et al. [32] showed the greatest importance (Fig. 2A). With regard to AEs, drowsiness was the most important, followed by seizure worsening and weight loss (Fig. 2B). However, Fig. 2C indicates that diarrhea was the most common AE, followed by drowsiness and appetite loss. Additionally, Allendorfer et al. [38] suggest that CBD modulates attention control processing in patients with TRE.

The reliability of the results presented in Fig. 2A is great because the data are based on randomized and double-blind studies. This favorable result for CBD matches the expectations of Karler and Turkanis [39] regarding its therapeutic use for epilepsy, similar to the reviews of Devinsky et al. [40] and Perucca et al. [41].

Two articles related to CBD treatment standardized the dosage for short-term treatment. In one study, the proportion of CBD:THC was 20:1 [28,42], whereas it was 50:1 in the other study [29]. In general, the quantity of THC was low to reduce the risk of psychosis and brain dysfunction [43–46].

As mentioned above, THC is responsible for the euphoric effects of CNB. In one case study [13], two children were treated with a CNB extract: the first with a THC composition of 4.03% (8.3 mg) and the other with a composition of 3.1% (7.5 mg). Adverse events appeared after the onset of therapeutic benefits and ceased after the treatment was changed to the same dosage of pure CBD (99.6% pure). This percentage is even greater than what is allowed by FDA when they approved Epidiolex®, with 99% purity [47].

The only significant AE was weight loss (Fig. 2B), which showed a statistical significance among the groups analyzed. Regarding long-term CBD administration (Fig. 2C), appetite loss did not significantly follow weight loss. However, Sands et al. [33] reported that weight loss was only observed at 6 months after beginning long-term treatments. This suggests that in the short term, therapeutic usage of CNB may be associated with greater weight loss compared with CBD.

The other significant AEs observed (Fig. 2C) with long-term treatment were diarrhea and pyrexia, though fatigue was the most frequent AE. These AEs are common in patients using antiepileptic drugs. According to Vossler et al. [48], such AEs are common in CBD treatment.

Drowsiness was also among the most prevailing AEs. This finding is consistent with the meta-analysis by Zaccara et al. [49], who verified a significant association between drowsiness and levetiracetam, an AED in some of the studies analyzed. Adverse events observed with concomitant use of CBD and clobazam have been described as caused by the combination and not the use of CBD [24]. Cannabidiol inhibits the CYP2C19 enzyme, which is responsible for metabolizing *N*-desmethylclobazam, an active metabolite of clobazam [50], whereas CBD is metabolized by cytochrome P450 [51]. As shown in Table 2, all the studies involved concomitant administration of CBD and other AEDs.

Cannabidiol combined with clobazam reduced the number of drop and nondrop seizures when compared with usual care in patients with Dravet and Lennox–Gastaut syndromes [52]. However, Gaston et al. [53] suggest the possible lack of a differential effect of

Table 1
Basic data identification of the interventional studies.

Study ID no.	Size of sample	Average age (SD/CI)	Type of study	Etiology	Scales	Authors
1	162 — security 137 — efficiency	10.5 (0.9–26.2) 10.5 (1–22.2)	Open interventional of expanded access	Various etiology, especially Dravet, Lennox–Gastaut syndromes	Liverpool Adverse Events Profile (LAEP) and Pediatric Epilepsy Side Effects Questionnaire	Devinsky et al. [22]
2	18	14	Expanded access	Tuberous sclerosis complex	Not applied	Hess et al. [23]
3	CBD: 61 PCB: 59	9.7 ± 4.7 9.8 ± 4.8	Intervention, randomized, placebo controlled and double blind	Dravet syndrome	Caregiver Global Impression of Change (CGIC), Caregiver Global Impression of Change in Seizure Duration (CGICSD), QOLCE, and Columbia Suicide Severity Rating Scale	Devinsky et al. [24]
4	48	11.7 (3.1–27.2)	Prospective, open and expanded access to phase II	Dravet, Lennox–Gastaut, Aicardi syndromes; genetic disorders, generalized genetic epilepsy, and unknown causes	Quality of Life in Childhood Epilepsy (QOLCE)	Rosenberg et al. [25]
5	PCB: 76 CBD 10: 73 CBD 20: 76	15.3 ± 9.3 15.4 ± 9.5 16 ± 10.8	Phase III, multicenter, randomized, double-blind, controlled placebo	Lennox–Gastaut syndrome	Epworth Sleepiness Scale, QOLCE, and Vineland Adaptive Behavior Scales	Devinsky et al. [26]
6	46	1–30	Prospect interventional, compassionate, and open	Deficiency disorder CDKL5 and Doose, Dup15q, Aicardi syndromes	LOCF	Devinsky et al. [27]
7	S: 57 E: 46	9.6 ± 4.9	Open and prospective	Various etiology	Not applied	Hausman-Kedem et al. [28]
8	20	10.15 (2.1–17.8)	Interventional, open, and prospective	Dravet syndrome	QOLCE, Vineland Adaptive Behavior Scales, and Pediatric Epilepsy Side Effect Questionnaire (PESQ)	McCoy et al. [29]
9	132	19.5 (±12.9)	Wide, prospective, single-center, and open	Various etiologies (Except Lennox–Gastaut and Dravet syndromes)	Chalfont Seizure Severity Scale (CSSS)	Szaflarski et al. [30]
10	S: 607 E: 580	13.2 (0.4–62.1) 13.1 (0.4–62.1)	Open extensive and multicenter	Dravet and Lennox–Gastaut syndrome, febrile infection, Doose and Aicardi, Tuberous sclerosis, mutations, and unknown causes	Medical Dictionary for Regulatory Activities (MedDRA) and Last-Observation-Carried-Forward (LOCF)	Szaflarski et al. [31]
11	366	15.9 (9.5)	Interventional open extensive study	Lennox–Gastaut syndrome	S/CGIC to LOCF	Thiele et al. [32]
12	26	9 (1–17)	Prospective open of expanded access	Various etiologies, especially Dravet and Lennox–Gastaut syndromes	Not related	Sands et al. [33]
13	CBD: 86 PCB: 85	15.5 (8.7) 15.3 (9.8)	Randomized study, controlled placebo, double-blind, and phase III	Lennox–Gastaut syndrome	Columbia Suicide Severity Rating Scale (C-SSRS), CGIC,	Thiele et al. [34]
14	264	9.8 (±4.4)	Extensive open study with continuity of patients who previously completed randomized studies	Dravet syndrome	Subject/Caregiver Global Impression of Change (S/CGIC)	Devinsky et al. [35]
15	16	9.1 (±3.4)	Phase II, prospective study, and open-label	Not informed. Only patients diagnosed as having TRE.	Caregiver Global Impression of improvement (CGI-I) and Caregiver Global Impression of Seizures Severity (CGI-S)	Mitelpunkt et al. [36]
16	LGS: 152 Others TREs: 455	12.8 (1.7–51) 13.3 (0.4–62.1)	Ongoing and open-label study	Various etiologies (except Lennox–Gastaut and Dravet syndromes)	Not related	Laux et al. [37]

CBD: cannabidiol, PCB: placebo, S: safety, E: efficacy, SD: standard deviation, CI: confidence interval, TRE: treatment-resistant epilepsy, LGS: Lennox–Gastaut syndrome, DS: Dravet syndrome.

various combinations (clobazam, topiramate, rufinamide, zonisamide, and eslicarbazepine) on reducing seizure frequency or severity with CBD.

Among related enzymes, CYP2C19 is inhibited by topiramate, another drug used concomitantly [54]. This interaction also occurs with CNB extract [55]. Gaston et al. [56] believe that sesame oil (vehicle of Epidiolex®) can promote drug interaction and increase serum levels of topiramate, rufinamide, zonisamide, and eslicarbazepine.

In addition, topiramate induces weight loss [57]. This may explain the occurrence of weight loss in some studies as a confounding bias, especially for studies in which it was used concomitantly. Topiramate has also been correlated with appetite loss [58], another reported AE.

It should be noted that this is not the only systematic review and meta-analysis on this topic. Lattanzi et al. [59] performed a meta-analysis on the efficacy and safety of CBD for Lennox–Gastaut syndrome and also reported the efficacy and safety of CBD as treatment of epilepsy originating from Dravet and Lennox–Gastaut syndromes using a standardized dosage [60].

Our study covers samples with other etiologies and studies with a standardized dosage or the maximum tolerated by each patient [22,23,25,28,30,31]. In addition, we assessed studies involving the maximum tolerated dosage or up to 50 mg/kg/day. The unpublished data in our study relate to the meta-analysis comparing AEs with the therapeutic use of CBD with medicinal CNB and CBD in the short and long term.

This review has limitations in terms of a low number of studies for the meta-analysis. In addition, the four papers used in the meta-analysis are from the same research groups. It is not clear whether the different articles were derived from overlapping samples. In addition,

Table 2
Details and endpoints of studies.

Identification authors	Concomitant related AEDs	Treatment duration	Cannabinoid type and dose	Administration protocol	Seizure outcome(s)
Devinsky et al. [22]	Not informed. However, CBD was concomitantly used to an average of three other AEDs.	12 weeks	Oral solution of pure CBD (100 mg/mL)	Initial dose from 2 to 5 mg/kg/day, given twice a day in the first week. Followed by a progressive increase from 2 to 5 mg/kg/day each week, until the maximum dose of 25 mg/kg/day was reached. If necessary, it was increased until 50 mg/kg/day.	Fifty-four experienced seizure reduction of 50% or more. Among them, 12 experienced seizure frequency reduction of >90%.
Hess et al. [23]	Lacosamide, clobazam, levetiracetam, lamotrigine, valproic acid, and vigabatrin	12 months	Oral solution of pure CBD (100 mg/mL)	Initial dose from 5 mg/kg/day was administered twice a day in the first week. Increased 5 mg/kg/day all weeks until maximum dose of 25 mg/kg/day. In case of no effect, this dose was increased 5 mg/kg/day until maximum tolerated dose or 50 mg/kg/day	Eight patients got to the end of the study. Among them, four experienced seizure frequency reduction of >50% (answerers). Percentage seizure reduction of >80% in five patients and > 90% in two patients was also observed.
Devinsky et al. [24]	Clobazam, valproate, stiripentol, levetiracetam, and topiramate	14 weeks	Oral solution of pure CBD (100 mg/mL)	Dose was established at 20 mg/kg/day in test and placebo group (which contained formulation without CBD). The dose was administered twice a day.	The group which used CBD had reduced seizure frequency, in average from 12.9 seizure frequency/month to 5.9 during the treatment. During this same period, seizure frequency in placebo group was reduced from 14.9 to 14.1
Rosenberg et al. [25]	Not informed. However, CBD was concomitantly to three other AEDs.	12 weeks	Oral solution of pure CBD (100 mg/mL)	Dose from 2 to 5 mg/kg/day given twice a day, administrated during first week, adding 2 to 5 mg/kg/day until maximum tolerated dose of 50 mg/kg/day	The average of seizure frequency was reduced from 27.5 to 13.9. Among them, twenty participants had seizure frequency reduction of >50%.
Devinsky et al. [26]	Clobazam, valproate, levetiracetam, lamotrigine, and rufinamide	14 weeks	Oral solution of pure CBD (100 mg/mL)	Started with 2.5 mg/kg/day and gradual increase, from 2.5 to 5 mg/kg/day until the target dose (10 or 20 mg/kg/day or corresponding placebo). Administered 2× a day.	Seizure reduction of 50% in relation to pretreatment period was observed in 30 (39%) patients in CBD 20 mg group, 26 (36%) patients in CBD 10 mg group, and 11 (14%) patients in placebo group. Respectively, 5, 3, and 1 patients were seizure-free at the end of the study
Devinsky et al. [27]	Clobazam, lamotrigine, topiramate, rufinamide, valproic acid, levetiracetam, and felbamate	48 weeks	Oral solution of pure CBD (25 or 100 mg/mL)	Started with administration of 5 mg/kg/day and increased from 2 to 10 mg/kg/day until intolerance or maximum dose of 25 mg/kg/day	During the study period, twenty-three (50%) patients experienced reduction of >50% on 12th week and twenty-six (57%) experienced reduced seizure frequency of more than 50% on 48th week.
Hausman-Kedem et al. [28]	Mainly levetiracetam, clobazam, valproic acid, phenobarbital, topiramate, and lamotrigine	12 weeks	Oral solution 20:1 of CBD/THC	Initial daily dose from 2 to 5 mg/kg/day administrated 3× a day. Additional dose was increased until maximum tolerable limit or 50 mg/kg/day.	The reduction of >50% of seizure frequency was observed in 26 patients. Fourteen patients experienced reduction between 50 and 75%. And both were seizure-free.
McCoy et al. [29]	Clobazam, valproate, stiripentol, levetiracetam, topiramate, phenobarbital, lacosamide, and phenytoin	20 weeks	Oral solution 50:1 of CBD/THC (100 mg/mL)	Initial dose from 2 mg/kg/day were weekly increased until maximum dose of 16 mg/kg/day. Administered 2× a day.	There was seizure reduction of 70.6%. During preintervention period, the average was 17 seizures, and this was reduced to five on last week. Twelve patients had seizure frequency reduced of >50%; among them, three experienced reduction of >90%.
Szaflarski et al. [30]	Not informed. However, it was an average of 2.9 ± 0.9	48 weeks	Oral solution of pure CBD (100 mg/mL)	The first week dose was 5 mg/kg/day and gradually increased until the tolerable limit of 50 mg/kg/day was reached. This dose could be reduced in case of intolerability.	On 12th week, 54 (49.2%) of the patients experienced minimum seizure reduction of 50%. On 48th week, the last week of study, this index increased to 85 (64.7%). Additionally, 8 (5.9%) patients were seizure-free at the end of the study.
Szaflarski et al. [31]	Clobazam, lamotrigine, topiramate, rufinamide, valproic acid, levetiracetam, stiripentol, and felbamate	96 weeks	Oral solution of pure CBD (100 mg/mL)	Initial dose from 2 to 10 mg/kg/day until maximum dose of 25 to 50 mg/kg/day was reached	Reducing ≥50% of seizure frequency in 285 (47%) patients, the study also showed 100% of efficiency on seizure frequency reduction in 30 (5%) patients.
Thiele et al. [32]	Clobazam, valproic acid, lamotrigine, levetiracetam, and rufinamide	48 weeks	Oral solution of pure CBD (100 mg/mL)	Dose administered was 20 mg/kg/day. If necessary, the dose could be reduced or increased to 30 mg/kg/day, in case it is tolerable.	The average on total seizure frequency reduction was 57% at the end of the study; 216 (59%) patients experienced ≥50% of seizure reduction.
Sands et al. [33]	Mainly topiramate, clobazam, clonazepam, levetiracetam, and oxicarbamazepine	42 months	Oral solution of pure CBD (100 mg/mL)	Treatment started with dose of 5 mg/kg/day, and continued with 5 mg/kg/day for one week until reaching the dose of 25 mg/kg/day.	From the 26 initial participants, only 6 responded until the last month of study. All experienced seizure frequency reduction >75%. On 4th month, only 10 experienced seizure reduction of >50
Thiele et al. [34]	Clobazam, valproate, lamotrigine, levetiracetam, and rufinamide	14 weeks	Oral solution of pure CBD (100 mg/mL)	Initial dose from 2 to 5 mg/kg/day until the dose of 20 mg/kg/day. Administered 3× a day	The study pointed that 40 (46%) patients experienced 50% seizure reduction compared with 20 (24%) patients in placebo group. Among them, 5 (6%) patients were seizure-free in treatment group, and none in placebo group.
Devinsky et al. [35]	Clobazam, valproic acid, stiripentol, levetiracetam, and topiramate	48 weeks	Oral solution of pure CBD (100 mg/mL)	Dose from 2.5 mg/kg/day until the desired dose of 20 mg/kg/day. If tolerable, it can reach 30 mg/kg/day.	Study showed efficiency in a total of 129 (51%) patients with ≥50% of seizure reduction. Additionally, thirteen of these participants experienced total seizure frequency reduction at the end of the study.

(continued on next page)

Table 2 (*continued*)

Identification authors	Concomitant related AEDs	Treatment duration	Cannabinoid type and dose	Administration protocol	Seizure outcome(s)
Mitelpunkt et al. [36]	Not informed. However, CBD was concomitantly to 1–4 other AEDs	Tree groups: 1–4 weeks; 5–8 weeks; 9–12 weeks	CBD capsules (50 mg)	Initial dose of 50 mg was administered. Dose elevations (at increment of 50 mg) were implemented in the evenings. The maximum dose allowed was 25 mg/kg/day or 450 mg/day, the lower of two.	Two patients were already fully seizure-free within 5 weeks of treatment, while an additional eight patients reported a >50% reduction in seizure frequency in study.
Laux et al. [37]	Clobazam, felbamate, lamotrigine, levetiracetam, rufinamide, stiripentol, topiramate, and valproic acid	96 weeks	Oral solution of pure CBD (100 mg/mL)	Initial dose from 2 to 5 mg/kg/day until tolerability limit or a maximum dose of 25–50 mg/kg/day	After 96 weeks of CBD add-on therapy, the percentage of patients with LGS/DS who had ≥50%, ≥75%, and 100% seizure reductions compared with baseline were 49%, 21%, and 5% for total seizures. The percentage of other patients with TREs who had ≥50%, ≥75%, and 100% seizure reductions compared with baseline were 49%, 37%, and 7% for total seizures.

CBD: cannabidiol, AED: antiepileptic drug, S: scale, D: descriptive, TRE: treatment-resistant epilepsy.

it was not possible to perform a meta-analysis regarding the efficacy of medicinal CNB because of the lack of comparative studies. Some articles reported a minimum percentage of AEs. Finally, limitations in relation to the descriptive analysis pertain to the eleven open studies, which likely involve bias in the results.

5. Conclusions

This study indicated that CBD treatment for epilepsy is effective in reducing the frequency of seizures. Therefore, more evidence that CBD is effective and safe is needed. We present the AE profile based on a

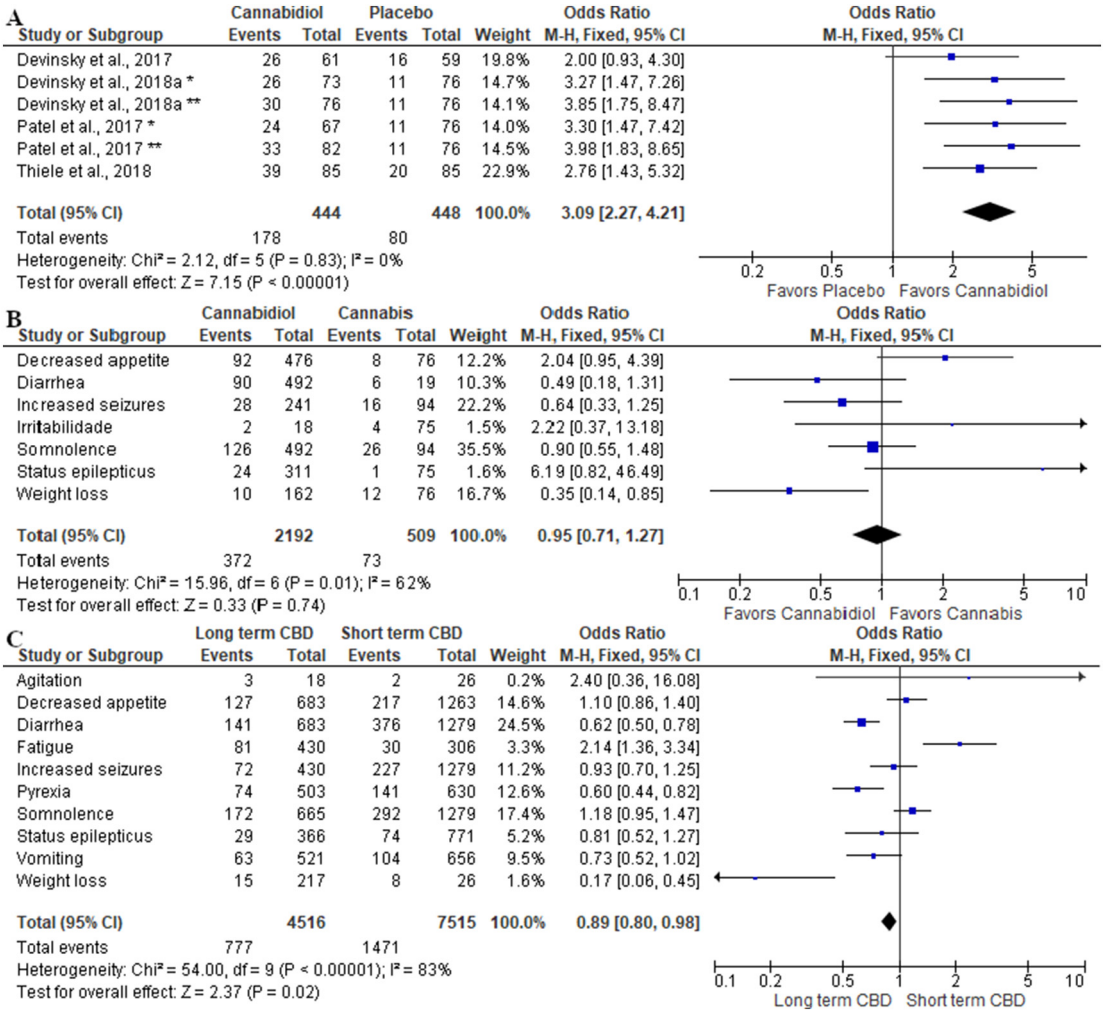

Fig. 2. A — Efficacy of CBD. B — Comparative of the adverse events profile of the CBD and medicinal CNB. C — Comparison of the short-term and long-term adverse events profile of CBD treatment. *Treatment with 10 mg/kg/day; **Treatment with 20 mg/kg/day.

meta-analysis after determining that CBD is safe, as revealed by the articles explored. Medicinal CNB is as safe as CBD, though only at low THC levels. Adverse events were more prevalent under short-term compared with long-term CBD treatment, suggesting lower AE profiles during long-term treatment.

Long-term studies using medicinal CNB are necessary to verify AE profiles for extended treatment durations, and there is also a need for studies about formulations with low amounts of THC to allow for comparing weight loss with other AEs related to CBD or CNB. In addition, a new meta-analysis with CNB should be conducted.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.yebeh.2019.106635.

Disclosures

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Declaration of competing interest

The authors declare no conflict of interest.

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