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Cannabidiol efficacy and clobazam status.
A systematic review and meta-analysis

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Summary

Objective: To evaluate the potential impact of concomitant clobazam (CLB) use on the efficacy of cannabidiol (CBD) treatment in patients with Dravet syndrome (DS) and Lennox-Gastaut syndrome (LGS) using meta-analytical techniques.

Methods: We searched for randomized, placebo-controlled, single or double-blinded trials. The proportion of patients who achieved ≥50% reduction from baseline in seizure frequency during the treatment period was assessed according to CLB status. Risk ratios (RRs) with 95% confidence intervals (95% CIs) were estimated.

Results: Four trials were included and enrolled 714 participants, 429 for add-on CBD and 285 for add-on placebo groups. Among CBD treated patients, 240 (55.9%) were taking concomitant CLB (CLB-On) and 189 (44.1%) were not taking concomitant CLB (CLB-Off); in placebo treated patients, 158 (55.4%) were CLB-On and 127 (44.6%) CLB-Off. The percentages of patients who had at least 50% reduction in seizure frequency during the treatment period were 29.1% in the CBD arm and 15.7% in the placebo group among CLB-Off patients [RR 1.80 (95% CI 1.12-2.90); p=0.015]. Among CBL-On patients, the ≥50% reduction in seizure frequency was found in 52.9% and 27.8% in the CBD and placebo groups [RR 1.85 (95% CI 1.40-2.44); p<0.001].

Significance: CBD was associated with a higher rate of seizure response in comparison to placebo when added to existing antiepileptic regimen both in patients taking and not taking concomitant CLB. The lack of randomization for CLB status and the limited sample size need to be considered in the interpretation of the findings.

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1. Introduction

Dravet syndrome (DS) and Lennox-Gastaut syndrome (LGS) are among the most severe and difficult to-treat epileptic encephalopathies and there remains the need to identify effective therapeutic options. Recently, randomized, placebo-controlled trials demonstrated the efficacy of a plant-derived pharmaceutical formulation of purified cannabidiol (CBD) in controlling seizures in participants with DS and LGS and led to licensing the drug in patients aged 2 years and older.[1,2]

Drug-drug interactions (DDIs) that can occur between CBD and clobazam (CLB) at pharmacokinetic and pharmacodynamic levels have, however, questioned the intrinsic antiseizure activity of CBD and imposed prescription limits in Europe.[2,3]

To date, open-label uncontrolled studies and clinical trial simulation have not provided consistent findings about the clinical meaning of these interactions. The aim of this study, hence, was to analyze the impact of concomitant use of CLB on the efficacy of CBD treatment in patients with DS and LGS through a meta-analysis of randomized controlled trials (RCTs).

2. Methods

2.1 Search strategy. The report of this systematic review and meta-analysis was made according to the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[4] We systematically searched (March week 1, 2020) MEDLINE (accessed by PubMed), the Cochrane Central Register of Controlled Trials (CENTRAL) and the US National Institutes of Health Clinical Trials Registry (http://www.clinicaltrials.gov) (search strategies are outlined in electronic supplementary material). Additional data were sought in the Drug Approval Package and the Assessment Report of CBD by the U.S. Food & Drug Administration and the European Medicines Agency/Committee for Medicinal Products for Human Use.[1,2] The manufacturer of CBD was contacted for information about any unpublished or ongoing studies. There were no

date limitations or language restrictions. The reference lists of retrieved studies were reviewed to identify additional reports of relevant trials. The protocol was not registered previously.

2.2 Eligibility criteria. Studies were selected when they met the following entry criteria: randomized, double or single blinded, placebo-controlled, parallel group studies with active and control groups receiving CBD and matched placebo, respectively, in addition to existing antiseizure medication (ASM). Participants had to meet the following criteria: any sex, any ethnicity, pediatric and/or adult age, diagnosis of DS or LGS and seizures uncontrolled by concomitant therapeutic regimen.

2.3 Outcome measure. The study outcome was the proportion of patients who achieved ≥50% reduction from baseline in seizure frequency during the treatment period. Convulsive seizures and drop seizures were assessed in DS and LGS trials, respectively. A convulsive seizure was defined as a tonic, clonic, tonic-clonic, or atonic seizure. A drop seizure was defined as an attack or spell (atonic, tonic, or tonic-clonic) involving the entire body, trunk, or head that led or could have led to a fall, injury, slumping in a chair, or hitting the patient's head on a surface.

2.4 Study selection, data extraction and assessment of the risk of bias. Two review authors (S.L. and F.B.) independently assessed studies for inclusion and extracted the following trial data: main study author, date of publication, methods of randomization, allocation concealment and blinding, duration of baseline and treatment periods, dose/s of CBD tested, number and demographics of participants, number of participants experiencing the outcome during treatment. Any disagreement was resolved through discussion with a third review author (M.S.). The risk of bias of the included studies was assessed according to the recommendations of the Cochrane Collaboration.[5]

2.5 Statistical analysis. Heterogeneity among the trials was assessed by the Chi squared test and the I^2 statistics for heterogeneity.[6,7] Provided no significant heterogeneity was present ($p>0.05$), re-

sults were synthesized using a fixed effect model. If the probability value was ≤0.05, the heterogeneity was interpreted according to the I^2 statistic and determined the choice of a fixed or random effects model (for I^2 <40% or ≥40%, respectively).[8-12] Risk ratios (RRs) with 95% confidence interval (CIs) were estimated through the inverse variance method. The intention-to-treat (ITT) population data were used. The analysis of the outcome was performed according to CLB status of patients (CLB-On for patients taking and CLB-Off for patients not taking concomitant CLB) and results presented by CBD daily dose. Reported probability values were two-sided, with significance set at <0.05. Data analysis was performed using STATA/IC 13.1 statistical package (StataCorp LP, College Station, TX, USA).

3. Results

3.1 Results of the search. Three hundred and one records were identified by database and trial registers searching. Seven randomized controlled trials (RCTs) were retrieved for detailed assessment; one of them was a dose-ranging pharmacokinetic and safety trial (ClinicalTrials.gov number, NCT02091206) and two were withdrawn by the sponsor before participants were enrolled (NCT02318537, NCT02318563). Accordingly, four studies were eventually included in the meta-analysis (Figure 1): two trials recruited patients with DS[13,14] and two studies enrolled patients with LGS.[15,16]

3.2 Characteristics and risk of bias of included studies. The included studies were multicenter, randomized, double-blind, placebo-controlled, parallel group trials. They enrolled 714 participants according to the ITT, 429 for add-on CBD and 285 for add-on placebo groups. The active treatment was a plant-derived pharmaceutical formulation of purified CBD oral solution (100 mg per milliliter) (Epidiolex®), which was administered as add-on treatment to the preexisting therapeutic regimen. Characteristics of the studies and participants are synthetized in Tables 1 and Table 2. CLB

was the most common concomitant ASM and used by 398 (55.7%) patients across the trials; CLB was prescribed in 204 (64.2%) and 194 (49.0%) patients in DS and LGS cohorts, respectively. Among CBD treated patients, 240 (55.9%) were CLB-On and 189 (44.1%) were CLB-Off; in placebo treated patients, 158 (55.4%) were CLB-On and 127 (44.6%) CLB-Off.

All trials used adequate methods of sequence generation and allocation concealment. We rated the trials at low risk of performance and detection bias as blinding was ensured by matching placebo, and neither the investigators nor the patients knew the identity of the treatment being administered. The risks of attrition and selective reporting bias were judged low, and there was no suspicion of selective outcome reporting. All trials were sponsored by the CBD manufacturer (GW Pharmaceuticals).

3.3 Fifty percent or greater reduction in baseline seizure frequency. Across the trials, the percentages of patients not taking CLB who had at least 50% reduction in seizure frequency during the treatment period were 29.1% in the CBD arm and 15.7% in the placebo group; the corresponding estimated RR was 1.80 [(95% CI 1.12-2.90); p=0.015] (chi squared=3.71, df=3, p=0.294; I^2=19.2%]; among CBL-On patients, the ≥50% reduction in seizure frequency was achieved by 52.9% and 27.8% in the CBD and placebo groups, respectively and the corresponding RR was 1.85 [(95% CI 1.40-2.44); p<0.001] (chi squared=0.75, df=3, p=0.860; I^2=0.0%] (Figure 2A).

The RR to achieve a ≥50% reduction in baseline seizure frequency during the treatment period with CBD at 10 mg/kg/day in comparison with placebo was 3.26 [(95% CI 1.25-8.46); p=0.015] (chi squared=0.30, df=1, p=0.586; I^2=0.0%] in CLB-Off and 1.62 [(95% CI 1.08-2.42); p=0.018] (chi squared=0.22, df=1, p=0.635; I^2=0.0%] in CLB-On patients (Figure 2B). The estimated RR for a 50% or greater reduction in baseline seizure frequency for patients assigned to 20 mg/kg/day in comparison to placebo was 1.78 [(95% CI 1.10-2.88); p=0.019] (chi squared=3.57, df=3, p=0.311;

I^2=16.1%] in CLB-Off and 1.95 [(95% CI 1.47-2.59); p<0.001] (chi squared=0.95, df=3, p=0.813; I^2=0.0%] in CLB-On subgroups (Figure 2C).

4. Discussion

Cannabidiol was associated with a higher rate of seizure response in comparison to placebo when added to existing ASMs at the daily dose of both 10 and 20 mg per kilogram in patients with DS and LGS independent of the concomitant use of CLB.

CBD monotherapy has shown antiseizure properties in a variety of experimental settings and therapy-resistant epilepsy models, showing behavioral, EEG, and neuroprotective effects in both acute and chronic protocols.[17] CBD showed anticonvulsant activity in mouse models of DS at 100 mg/kg given intraperitoneally, which approximates doses found efficacious in human trials taking into account interspecies scaling and low oral bioavailability of CBD.[18]

Noteworthy, pharmacokinetic and pharmacodynamic interactions can occur when CBD is administered with other drugs. Remarkably, CBD can inhibit the catalytic activity of the cytochrome P450 (CYP) 2C19 and determine a 2 to 4-fold increase in plasma concentrations of the active metabolite N-desmethylclobazam (N-CLB), which is thought to have one third to one fifth of the antiseizure activity of CLB.[19,20] Conversely, CLB leads to an approximate 1.5-fold increase in 7-hydroxy-CBD, the CBD active metabolite, probably through inhibition of CYP2D6 and glucuronidation.[19,20] CBD is also a positive allosteric modulator of gamma-aminobutyric acid $(GABA)_A$ receptors and a pharmacodynamic interaction occurs, where co-administration of CBD further enhances $GABA_A$-mediated inhibitory activity beyond the actions of CLB and N-CLB alone.[18] In the $Scn1a^{+/-}$ mouse model of DS, combined treatment with CBD and CLB resulted in greater anticonvulsant effect than each

of the ASMs alone against thermally induced seizures when a CBD dose with intrinsic anticonvulsant activity was used. A lower, subthreshold dose of CBD, however, did not promote greater antiseizure effects despite increasing plasma CLB concentrations.[18]

Taken together, these observations have led to speculate that the antiseizure efficacy of CBD can be - partially or totally - explained by DDIs with CLB and concomitant CLB is necessary for the activity of CBD. So far, the clinical relevance of these interactions remains largely unknown.

In one open-label interventional trial of patients with treatment-resistant epilepsy, 51% of participants taking CLB had a greater than 50% reduction in motor seizure frequency at 12 weeks, compared with 27% of those not taking CLB.[21] It is interesting to note that the responder rate was roughly double in the CLB-On than CLB-Off cohort and the proportion of responders among patients not taking CLB approached the rate of participants shown to respond to placebo in DS and LGS studies.[22,23] The study design, however, did not allow to demonstrate whether the efficacy of CBD may be attributable to CLB. Similarly, in a subgroup of patients with tuberous sclerosis complex, the 50% responder rate after 3 months of CBD treatment was 58.3% in the 12 participants taking concurrent CLB compared to 33.3% in the 6 patients not taking CLB.[24]

Findings from other uncontrolled studies suggested that CBD reduces seizure frequency irrespective of concomitant CLB use. Among 132 children and adults with treatment-resistant epilepsy receiving CBD in an open-label Expanded Access Program, there were no significant differences in seizure frequency and severity reduction at 12 weeks between patients taking and not taking concomitant CLB.[25] In a retrospective analysis of data collected from 47 patients with refractory epilepsy and treated with CBD, there was no significant difference in the reduction of mean weekly seizure frequency between those who took concomitant CLB and those who did not, and there was no significant correlation between change in N-CLB or CLB levels and change in seizure frequency.[26]

The open-label, uncontrolled design and naturalistic follow-up of the studies, however, limit the generalizability of results.

In the subset of patients who were taking CLB and stiripentol (STP) at baseline in one pivotal DS trial, a reduction in seizure frequency occurred in 80% and 50% of the cases assigned to CBD and placebo, in absence of any further increase in N-CLB levels.[1] As STP is a strong CYP2C19 inhibitor, it can be assumed that CLB and N-CLB levels were already maximally increased by STP-induced metabolic inhibition and CBD did not determine additional inhibition. Although a pharmacodynamic synergism between CBD and CLB cannot be excluded, these findings suggest that CBD can improve seizure control without a raise in N-CLB exposure.

A clinical trial simulation with a pharmacokinetic/pharmacodynamic model for the effect of CBD on drop-seizure frequency in patients with LGS has been performed under the assumptions that patients taking 10 or 20 mg CLB would have a 2- to 7-fold increase in N-CLB exposure and CLB-Off patients would have a reduction in drop-seizure frequency and a variability in the percent reduction similar to the placebo group.[27] The results suggested that the effect of 20 mg/kg/day CBD on seizure frequency reduction may be mostly explained by the DDI with CLB. It is however unknown how well mathematical modeling can reflect real-word drug and patients characteristics, including drug compliance and disease evolution. Furthermore, the analyses did not account for CLB dose reduction, which occurred in about one quarter of the patients in the CBD group.[27]

The current meta-analysis of results from patients who participated in high-quality, phase III, prospective, double-blinded RCTs allowed to explore the response to CBD according to concomitant CLB use in a more rigorous fashion than open-label research, and increase the power to identify the presence of a treatment effect in comparison to individual studies. Nonetheless, some shortcomings need to be considered. The main limitation is the lack of randomization for CLB status, which may

have introduced potential confounders, as subgroups consisted of patients allocated to CLB treatment according to decision of treating physician, including individual seizure response and development of side effects. In this regard, however, CLB-Off patients might be considered as a group more difficult to treat as they had failed more ASMs during their lifetime, previously tried CLB and had higher seizure frequency at baseline.[2] Although data of patients with two different epileptic conditions have been pooled, all the RCTs had similar protocols and overlapping designs and our aim was to evaluate the overall response to CBD and impact of CLB use rather than estimate the percentage reduction in specific seizure types. Only four trials with limited sample size and funded by one single pharmaceutical company met the eligibility criteria. Additional analyses were not feasible due to the lack of data on CBD, CLB and N-CLB plasma levels, and further research is warranted to clarify whether and to what extent CLB may enhance CBD response. Finally, potential DDIs with other ASMs and impact of genetic background and polymorphisms in genes coding for CYPs could have not been considered.

5. Conclusion

This analysis suggests cannabidiol to have independent anti-seizure activity and efficacy irrespective of CLB administration and cannot support the current prescription restriction. Interestingly, concomitant CLB has been already shown to affect the safety profile of CBD and increase the incidence of adverse events, mainly somnolence, sedation, and pneumonia.[28,29] DDIs represent a major issue in clinical practice and the knowledge of their potential consequences is critically important for optimization of clinical decisions.

Disclosure of Conflicts of Interest

This study was not funded.

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Ethical Publication Statement

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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Figure and table legends

Table 1: Characteristics of the included studies

Table 2: Characteristics of the study participants

Figure 1: Flow diagram of study selection process

Figure 2: Fifty percent or greater reduction in monthly seizure frequency from baseline during the treatment period according to clobazam status

Supporting information

Supplementary Appendix

PRISMA Statement

Table 1. Characteristics of the included studies

Study [Reference]	Study Design	Main Inclusion Criteria	Treatment Arms
GWPCARE1 Part B [13]	Phase III Multicenter (United States and Europe) Parallel-group, randomized, placebo-controlled trial: ▪ 4-week observational baseline ▪ 14-week double-blind treatment period (2-week titration, 12-week stable dosing maintenance) ▪ ≤10 days tapering-off ▪ 4-week safety follow-up	▪ Aged 2 to 18 years ▪ Documented history of Dravet syndrome not completely controlled by current ASMs ▪ At least four convulsive seizures during the 4-week baseline period ▪ Current treatment with one or more ASMs at a stable dose for at least 4 weeks before screening	▪ Oral placebo, BID ▪ Oral CBD: 20 mg/kg, BID
GWPCARE2 [14]	Phase III Multicenter (United States, Europe, Australia, Israel) Parallel-group, randomized, placebo-controlled trial: ▪ 4-week observational baseline ▪ 14-week double-blind treatment period (2-week titration, 12-week stable dosing maintenance) ▪ ≤10 days tapering-off ▪ 4-week safety follow-up	▪ Aged 2 to 18 years ▪ Documented history of Dravet syndrome not completely controlled by current ASMs ▪ At least four convulsive seizures during the 4-week baseline period ▪ Current treatment with one or more ASMs at a stable dose for at least 4 weeks before screening	▪ Oral placebo, BID ▪ Oral CBD: 10 and 20 mg/kg, BID

GWPCARE3 [15]	Phase III Multicenter (United States, Spain, United Kingdom, France) Parallel-group, randomized, placebo-controlled trial: ▪ 4-week observational baseline ▪ 14-week double-blind treatment period (2-week titration, 12-week stable dosing maintenance) ▪ ≤10 days tapering-off ▪ 4-week safety follow-up	▪ Aged 2 to 55 years ▪ Clinical diagnosis of Lennox-Gastaut syndrome (including documented history of slow [<3.0 Hz] spike-and-wave electroencephalographic pattern) and evidence of at least two types of generalized seizures, including drop seizures, for at least 6 months ▪ At least two drop seizures each week during the 4-week baseline period ▪ Current treatment with one or more ASMs at a stable dose for at least 4 weeks before screening ▪ Documented failures on at least two ASMs	▪ Oral placebo, BID ▪ Oral CBD: 10 and 20 mg/kg, BID
GWPCARE4 [16]	Phase III Multicenter (United States, Netherlands, Poland) Parallel-group, randomized, placebo-controlled trial: ▪ 4-week observational baseline ▪ 14-week double-blind treatment period (2-week titration, 12-week stable dosing maintenance) ▪ ≤10 days tapering-off ▪ 4-week safety follow-up	▪ Aged 2 to 55 years ▪ Clinical diagnosis of Lennox-Gastaut syndrome (including documented history of slow [<3.0 Hz] spike-and-wave electroencephalographic pattern) and evidence of at least two types of generalized seizures, including drop seizures, for at least 6 months ▪ At least two drop seizures each week during the 4-week baseline period ▪ Current treatment with one or more ASMs at a stable dose for at least 4 weeks before screening ▪ Documented failures on at least two ASMs	▪ Oral placebo, BID ▪ Oral CBD: 20 mg/kg, BID

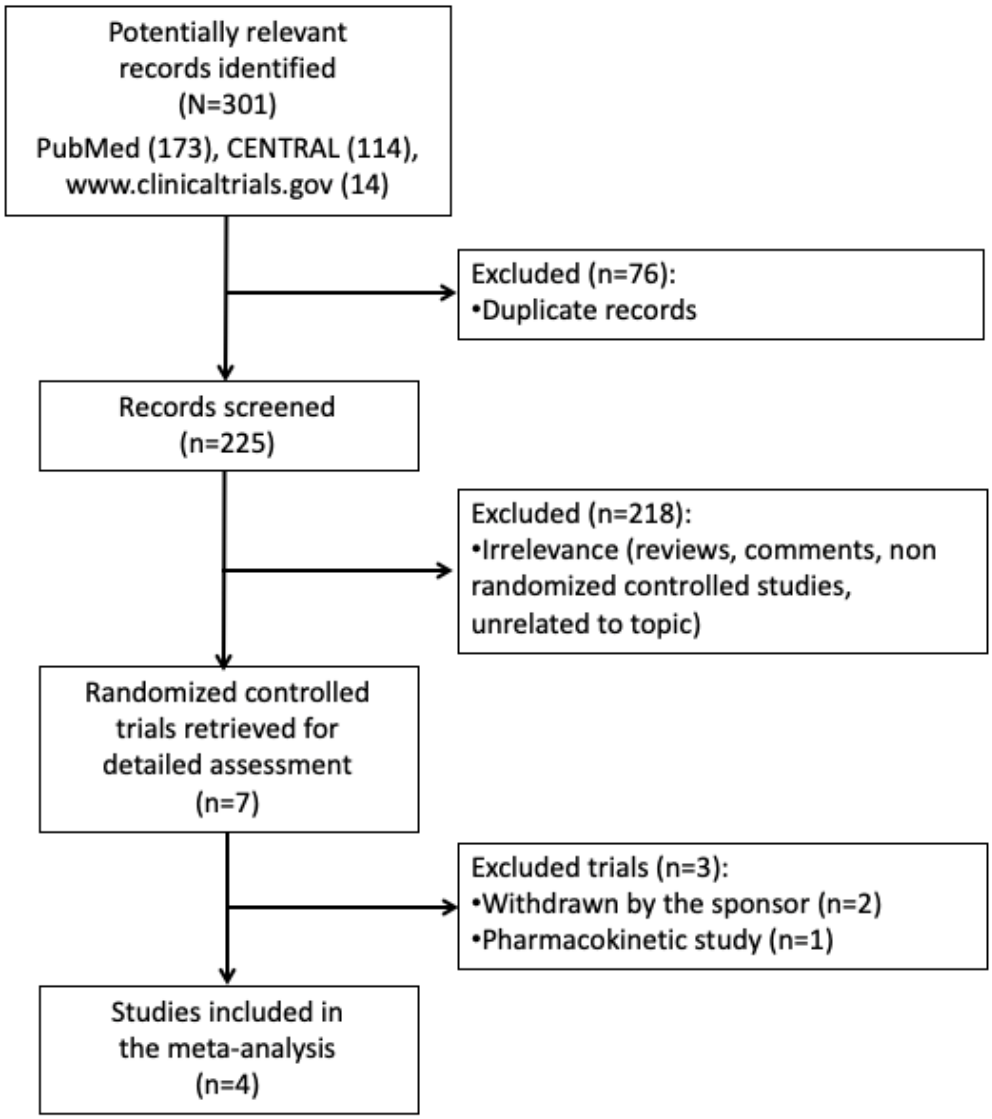
Abbreviations: ASM=antiseizure medication, BID=bis in die, CBD=cannabidiol.

Table 2. Characteristics of the study participants

Study / Baseline characteristics of participants	GWPCARE1 Part B [13]		GWPCARE2 [14]			GWPCARE3 [15]			GWPCARE4 [16]	
Treatment arm	**CBD 20 mg/kg** (n=61)	**PBO** (n=59)	**CBD 10 mg/kg** (n=66)	**CBD 20 mg/kg** (n=67)	**PBO** (n=65)	**CBD 10 mg/kg** (n=73)	**CBD 20 mg/kg** (n=76)	**PBO** (n=76)	**CBD 20 mg/kg** (n=86)	**PBO** (n=85)
Male sex, %	57.4	45.8	40.9	53.7	47.7	54.8	59.2	57.9	52.3	50.6
Age, mean (SD) [years]	9.7 (4.7)	9.8 (4.8)	9.2 (4.3)	9.3 (4.3)	9.6 (4.6)	15.4 (9.5)	16.0 (10.8)	15.3 (9.3)	15.5 (8.7)	15.3 (9.8)
Number of prior ASMs, median (range)	4 (0-26)	4 (0-14)	4 (0-19)	4 (0-11)	4 (0-11)	6 (0-21)	6 (1-18)	6 (1-22)	6 (1-18)	6 (0-28)
Number of concomitant ASMs, median (range)	3 (1-5)	3 (1-5)	3 (1-5)	3 (1-4)	3 (1-5)	3 (1-5)	3 (0-5)	3 (1-5)	3 (1-5)	3 (1-4)
Concomitant ASMs, %										
Clobazam	65.6	64.4	68.2	59.7	63.1	50.7	47.4	48.7	47.7	50.6
Valproate	60.7	57.6	66.7	70.1	73.8	37.0	36.8	39.5	41.9	38.8
Levetiracetam	26.2	28.8	28.8	31.3	21.5	30.1	31.6	30.3	27.9	40.0
Stiripentol	49.2	35.6	37.9	32.8	36.9	-	-	-	-	-
Topiramate	26.2	25.4	16.7	26.9	26.2	-	-	-	-	-
Lamotrigine	-	-	-	-	-	30.1	26.3	32.3	38.4	36.5
Rufinamide	-	-	-	-	-	26.0	34.2	26.3	27.9	25.9

Abbreviations: ASM=antiseizure medication, CBD=cannabidiol, PBO=placebo, SD=standard deviation.

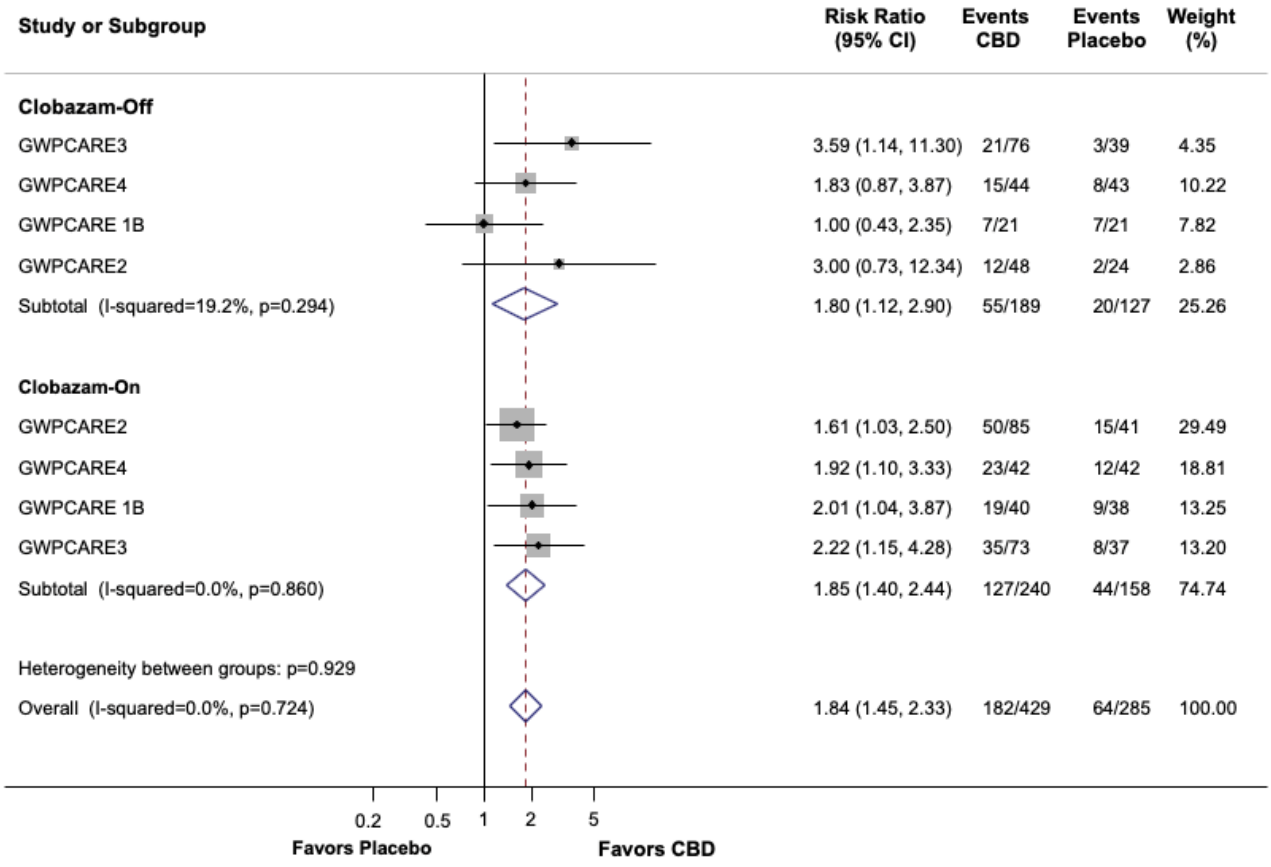
Figure 1. Flow diagram of study selection process



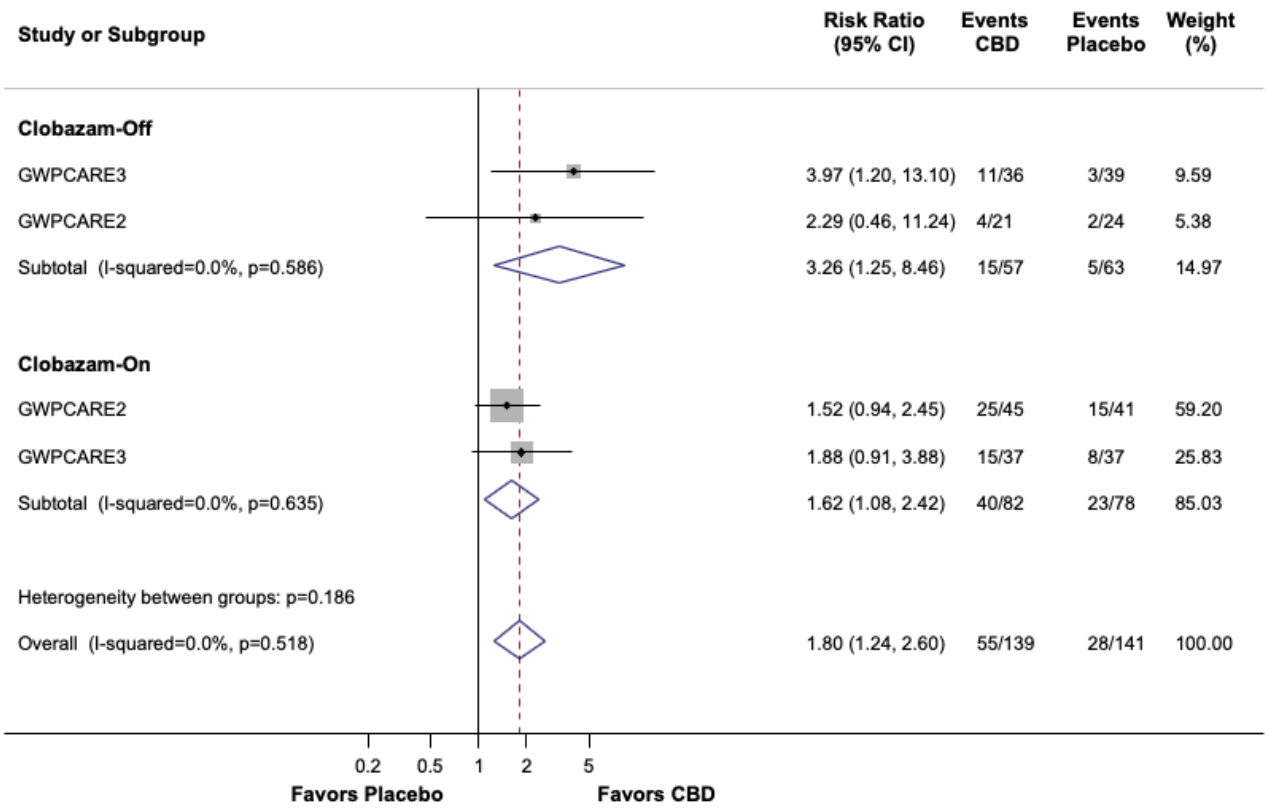
Abbreviation: CENTRAL=Cochrane Central Register of Controlled Trials.

Figure 2. Fifty percent or greater reduction in monthly seizure frequency from baseline during the treatment period according to clobazam status

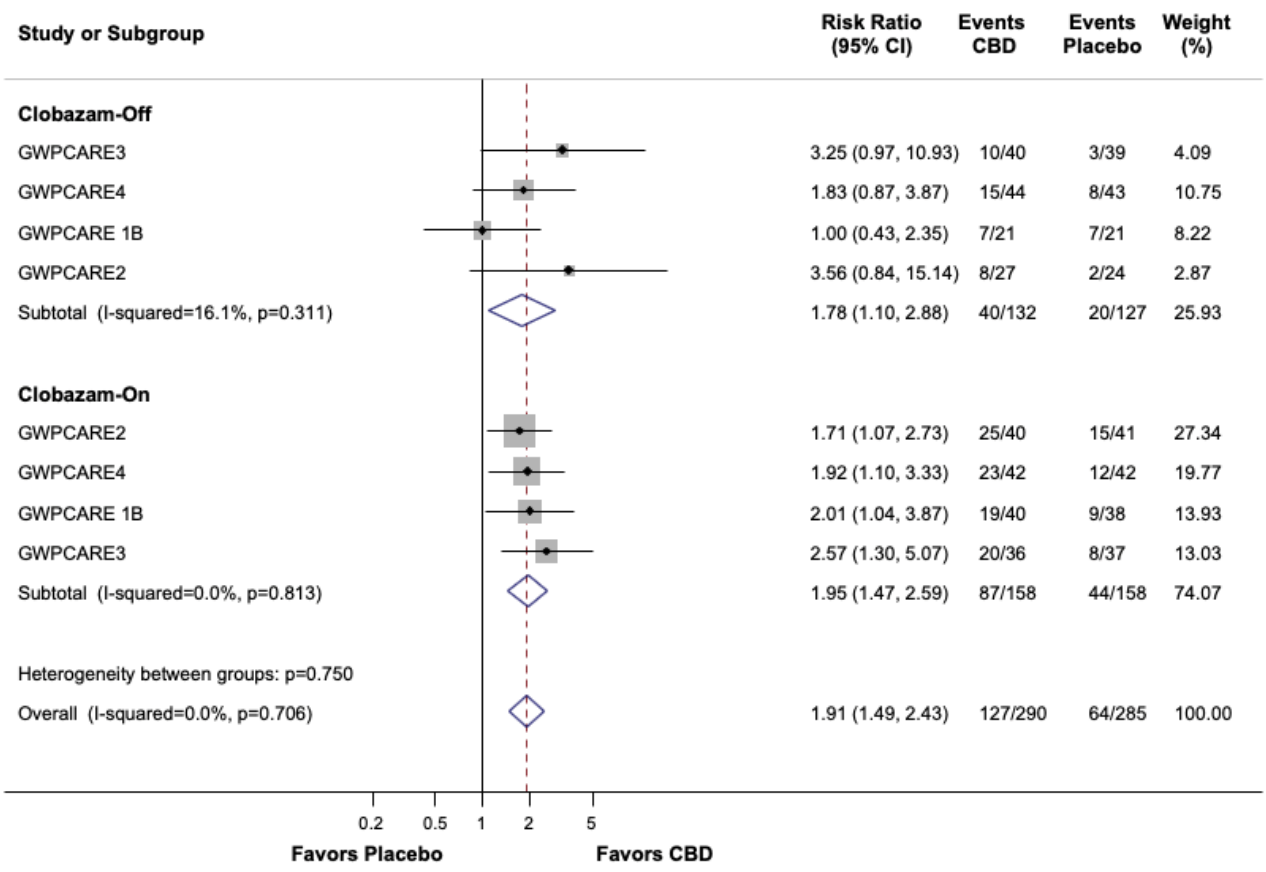
A. Cannabidiol any dose



B. Cannabidiol 10 mg/kg/die



C. Cannabidiol 20 mg/kg/die



Abbreviations: CBD=cannabidiol, CI=confidence interval.