Use of cannabidiol in the treatment of epilepsy: Lennox-Gastaut syndrome, Dravet and Tuberous Sclerosis Complex.

Antônio Silvinato[1,2], Idevaldo Floriano[1], Wanderley Marques Bernardo[2,3]

[1]Medicina Baseada em Evidências, Cooperativa Baixa Mogiana, Mogi-Guaçu (SP) Brasil
[1,2]Medicina Baseada em Evidências, Associação Médica Brasileira, São Paulo (SP) Brasil.
[2,3]Faculdade de Medicina, Universidade de São Paulo, São Paulo (SP) Brasil

Abstract

Purpose: The objective of this systematic review with meta-analysis was to evaluate the efficacy, safety and short- and long-term tolerability of cannabidiol (CBD), as an adjunct treatment, in children and adults with Dravet Syndrome (SD), Lennox-Gataut Syndrome (LGS) or Tuberous Sclerosis Complex (TSC), with inadequate control of seizures.
Methods: This systematic review was conducted through a search for scientific evidence in the Mediline/PubMed, Central Cochrane and ClinicalTrials.gov databases until April 2022. Selected randomized clinical trials (RCTs*)* that presented the outcomes: reduction in the frequency of seizures and total seizures (all types), number of patients with response greater than or equal to 50%, change in Caregiver Global Impression of Charge (CGIC) (improvement ≥1 category in the initial scale), adverse events (AE) and tolerability to treatment. This review followed preferred reporting items for systematic reviews and meta-analyses (PRISMA)
Results: 6 RCTs were included, a total of 1,034 patients with SD, LGS and TSC, of which 3 *Open-Label Extension* (OLE) RCTs. The meta-analysis of the studies showed that the use of CBD as compared with placebo, in patients with convulsive seizures refractory to the use of medications: Reduces the frequency of seizures by 33%; Increases the number of patients with a reduction ≥ 50% in the frequency of seizures by 20%; Increases the number of patients with absence of seizures by 3%; Improvement of the clinical impression evaluated by the caregiver or patient (S/CGIC) in 21%; Increases total AEs by 12%; Increases serious AE by 16%; Increases the risk of treatment abandonment by 12%; Increases the number of patients with transaminase elevation (≥ 3 times the referral) by 15%.
Conclusion: This systematic review, with meta-analysis, supports the use of CBD in the treatment of patients with seizures, originated in DS, LGS and TSC, resistant to the common medications, presenting satisfactory benefits in reducing seizures and tolerable toxicity.

Keywords: Dravet Syndrome (SD); Lennox-Gataut Syndrome (LGS); Tuberous Sclerosis Complex (TSC); cannabidiol (CBD); seizures, seizures refractory.

Introduction

Epilepsy is one of the most common neurological disorders [1]. About one-third of all patients with epilepsy have drug-resistant seizures. The *International League Against Epilepsy* (ILAE) defines drug-resistant epilepsy as the "failure of ≥ 2 appropriate and tolerated antiepileptic drugs (either as monotherapy or in combination) to achieve the sustained freedom of seizures" [2]. Inadequate seizure control significantly affects the quality of life and cognitive function of these patients. Drug-resistant epileptic syndromes (DRES) are associated with significant comorbidity and high rates of cognitive impairment, as well as psychiatric and physical disability. Currently, the cannabidiol is being used for three epileptic syndromes: Lennox-Gastaut syndrome (LGS), Dravet syndrome (DS) and tuberous sclerosis complex (CST). Both LGS and DS are early onset encephalopathic epileptics with poor prognosis and associated with comorbidities.

LGS is a severe epileptic encephalopathy of varying presentation and associated with high rates of seizure-related injury and cognitive impairment [3-5]. LGS has an incidence of approximately 1:4,000 births; estimates of uncertain prevalence, possibly around 15/100,000. LGS is believed to account for 1-4% of all infant epileptics [3-5].

DS is rare, intractable, occurs in early childhood and is characterized by prolonged and recurrent partial crises at onset, with progression to generalized polymorphic seizures resulting in developmental delay, cognitive impairment, and increased mortality. SD has an incidence of approximately 1:20,000 births; estimates of uncertain prevalence, possibly around 3/100,000. SD is believed to account for approximately 7% of all severe epileptics initiated before 3 years of age [6-8].

Cannabidiol was also evaluated under conditions with mainly focal seizures, such as tuberous sclerosis complex (TSC). TSC is a genetic disease that can present in any part of the body. The most common manifestations include benign tumors in the skin, brain, kidneys, lung and heart that cause organic dysfunction [9]. The reported incidence ranges from 1 per 5,800 to 10,000 live births [9] and the prevalence of 1/20,000 people in the UK [9].

Cannabis has been used to treat epilepsy since antiquity, and interest in cannabis-based therapies has increased in the last decade. Cannabidiol, which is one of the main constituents *of the Cannabis sativa* plant, has anticonvulsant properties and does not produce euphoric or intrusive side effects [10]. The lack of regulation and standardization

in the medicinal cannabis industry, however, raises concerns about the composition and consistency of the products that are dispensed [11]. Pharmaceutical grade oral CBD solution is the first product made directly from the cannabis plant, rather than created synthetically, to be authorized by regulatory agencies, and the first of a new class of anticonvulsant drugs.

OBJECTIVE

To assess the efficacy, safety and short- and long-term tolerability of cannabidiol, as adjuvant treatment, in children and adults with inadequately controlled DS, LGS or TSC.

METHOD

This systematic review will be carried out in accordance with *Preferred Reporting Items for Systematic Reviews and Meta-Analyses* (PRISMA) [12].

Clinical doubt - what is the impact of cannabidiol use on outcomes reducing the frequency of seizures and total seizures (all types), number of patients with a response equal to or greater than 50%, impression of clinical improvement by the patient or caregiver, adverse events and tolerability to treatment?

The eligibility elements of the studies are:

1. Patient with patients with Drave Syndromes, Lennox-Gastaut and Complex Tubular Sclerosis;
2. Treatment with cannabidiol plus usual therapy compared to placebo plus usual therapy;
3. Outcomes - reduction in the frequency of seizures and total seizures (all types), number of patients with response greater than or equal to 50%, change in Caregiver Global Impression of Charge (CGIC) (improvement ≥1 category in the initial scale), adverse events and tolerability to treat;
4. Excluding outcomes − intermediaries;
5. Phase III randomized clinical trial (RCT) or observational cohort studies;
6. No period or language limit;

7. Text complete available for access;
8. Follow-up: minimum of 16 weeks.

The search for evidence will be carried out in the Virtual Scientific Information Base Medline using the search strategy - (Cannabis OR Tetrahydrocannabinol OR Cannabinoids OR Cannabinol OR Cannabidiol) AND (Epilepsy OR infantile spasms OR Epilepsies, Myoclonic OR Tuberous Sclerosis OR Lennox Gastaut Syndrome OR Dravet Syndrome OR Sturge-Weber Syndrome OR Drug Resistant Epilepsy) AND Random*; CENTRAL / Cochrane with the search strategy - (Cannabis OR Tetrahydrocannabinol OR Cannabinoids OR Cannabinol OR Cannabidiol) AND (Epilepsy OR infantile spasms OR Epilepsies, Myoclonic OR Tuberous Sclerosis OR Lennox Gastaut Syndrome OR Dravet Syndrome OR Sturge-Weber Syndrome OR Drug Resistant Epilepsy) e ClinicalTrials.gov with the search - (Cannabinol OR Cannabidiol) AND (Tuberous Sclerosis OR Lennox Gastaut Syndrome OR Dravet Syndrome OR Sturge-Weber Syndrome). The search in these databases will be carried out until April 2022.

From the studies will be extracted the following data: author name and year of publication, population studied, methods of intervention and comparison, absolute number of events reductions in the frequency of seizures and total seizures (all types), number of patients with response equal to or greater than 50%, impression of clinical improvement by the patient or caregiver (CGIC), adverse events, in addition to follow-up time. The results of the median percentage change (minimum – maximum) in relation to baseline in the monthly frequency of seizures were also extracted.

The risk of biases scans for randomized clinical trials will be assessed using the rob 2 tool items [13], plus other key elements, and expressed as low, moderate, serious or critical risk of bias, and no information. For cohort studies, the tool currently recommended by the Cochrane Collaboration will be used to assess the risk of bias in estimates of effectiveness and safety in non-randomized Robins-I (Risk of Bias in Non-randomised Studies – of Interventions) intervention studies [14]. ROBINS-I evaluates seven domains of bias, classified by moment of occurrence. The bias risk assessment will be conducted by two independent reviewers (AS and IF), and in case of disagreements, a third reviewer (WB) can deliberate on the evaluation. The quality of evidence will be extrapolated from the risk of bias obtained from the study(s) (if there is no meta-analysis) using the

TERMINOLOGY GRADE [15] in very low, low and high, and through the software GRADE pro [16] (if there is meta-analysis) in very low, low, moderate and high.

The results for categorical outcomes will be expressed by the difference in risk between cannabidiol therapy and placebo treatment. If the difference in risk (DR) between groups is significant (95% confidence) this will be expressed accompanied by the 95% Confidence Interval (95% CI) and a Number Needed to Treat (NNT) or to produce a Harm (NNH). In continuous measures the results are of mean difference (MDs), or median difference with confidence intervals (CI) 95%. Data from observational studies are reported as the percentage of participants who experienced a result.

If there is more than one study included with common outcomes, this will be aggregated through meta-analysis, using RevMan 5.4 software [17], with the overall risk difference with 95% confidence intervals (CI) being the final measure used to support the synthesis of evidence, which will answer the clinical doubt of this assessment. The estimated size of the combined effects was performed by a fixed or random effect model after the evaluation of heterogeneity results. Heterogeneity was also calculated using the value I^2. The results will be evaluated by study design (RCTs and observational cohort) and presented individually.

INCLUDED STUDIES

In the search for evidence, 145 articles were retrieved, and 15 studies evaluating the use of cannabidiol plus usual therapy as compared with placebo, in the treatment of patients with Drave Syndrome, Lennox-Gastaut Syndrome and Tuberous Sclerosis Complex or were observational cohort studies "open-label extension" (OLE). The 15 studies were assessed because they met the eligibility criteria for analysis of the full text. Of these 15 studies, 6 [19-24] ECRs and 3 [25-27] OLE were included to support this evaluation, whose characteristics are described in Table 3 and 4 (Annexes), respectively. The list of the excluded and the reasons are available in the references s and Figure 1.

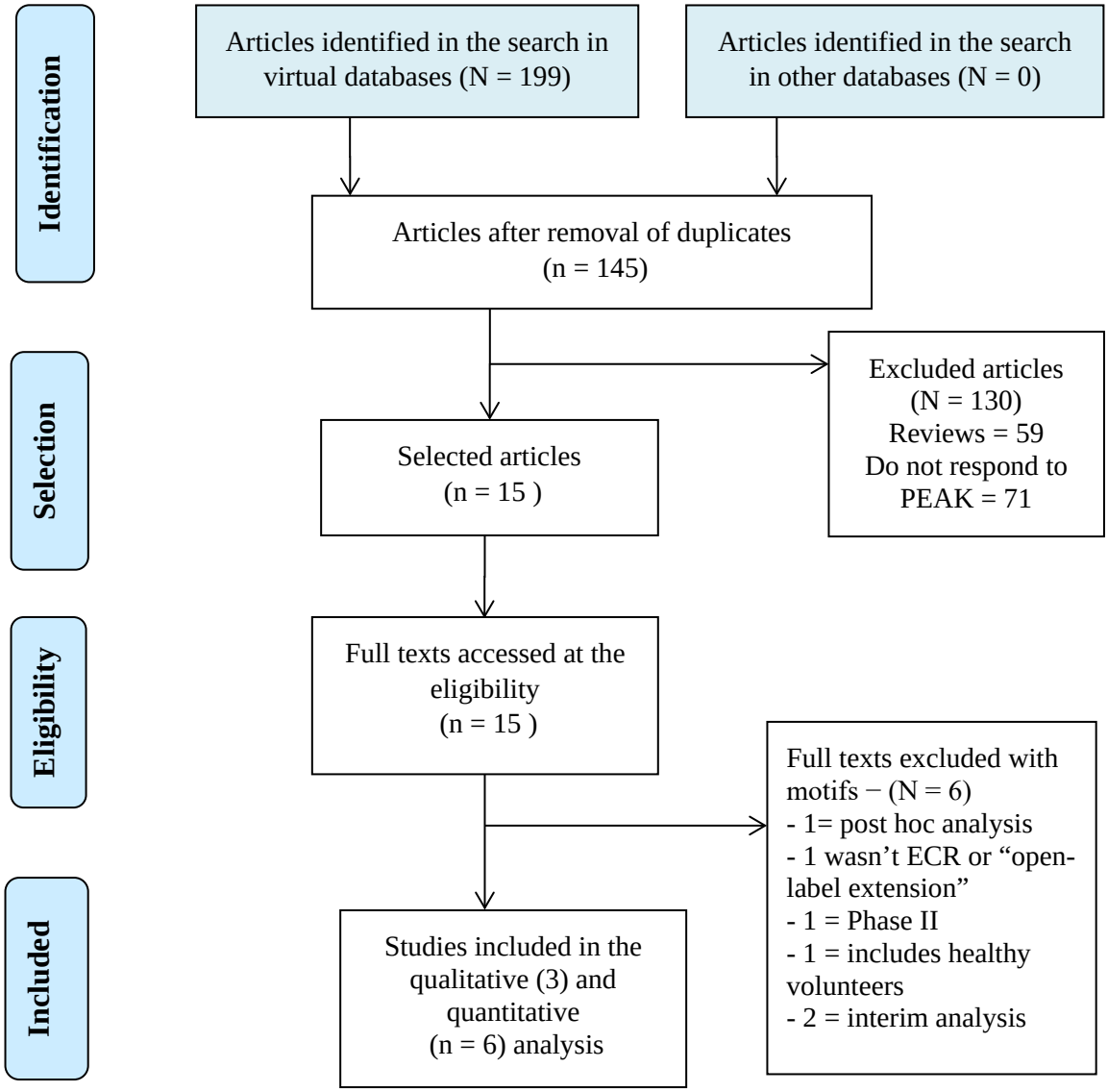

Figure 1. Evidence retrieval and selection diagram

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal. pmed1000097

The 6 RCTs enrolled 1. 034 patients with Drave Syndromes, Lennox-Gastaut and Tuberous Sclerosis Complex, with 485 undergoing treatment with cannabidiol (all dosages) as compared to 325 placebo patients. This population was followed to measure the outcomes reduction in the frequency of seizures and total seizures (all types), number of patients with response greater than or equal to 50%, change in Caregiver Global Impression of Charge, adverse events and tolerability to treatment. The follow-up was 14-16 weeks after the start of treatment (Table 1- Annexes).

These patients who had previously participated in the RCTs were allowed to continue in an open-label extension study (OLE) for each pivotal study (Table 3; Annexes), evaluating the efficacy, safety and tolerability of cannabidiol (CBD) in the long term (median on days ranging from 267 to 1090; N = 880).

Risk of bias in included studies

For this update of the review, a combination of two out of three review authors (from AS, IF, WB) independently re-assessed the risk of bias in each included trial according to pre-defined criteria stated in the methods section (Table 1 and Figure 2).

Regarding the risk of bias of the 6 RCTs included [14-19], none of them were blinded by the evaluator and one did not perform a sample calculation, and the overall risk of the studies may be considered non-severe (Table 1).

Table 1. Risk of bias from RCTs studies included

	RISK OF VIESES IN RANDOMIZED CLINICAL TRIALS									
STUDY	**Random**	**Blind folded allocation**	**Double-blind**	**Blinding of the evaluator**	**Losses < 20%**	**Characteristic prog.**	**Out come**	**ITT**	**Simple size calculation**	**Early interruption**
Devinsky O, 2017 [19]										
Devinsky O, 2018 [20]										
Miller I, 2020 [21]										
Devinsky O, 2018 [22]										
Thiele EA, 2018 [23]										
Thiele EA, 2021 [24]										

Biases of the included ECRs studies (red = absence; green = presence; yellow = risk of unclear bias), ITT = analysis by intention of treatment.

The assessment of the risk of bias in the observational cohort OLE studies was made with the use of the ROBINS-I tool. The 3 studies included [25-27] presented risk of critical bias to the loss domain (Bias due to missing data), all other domains presented low risk of bias. Therefore, the overall risk of bias can be considered moderate (Figure 2).

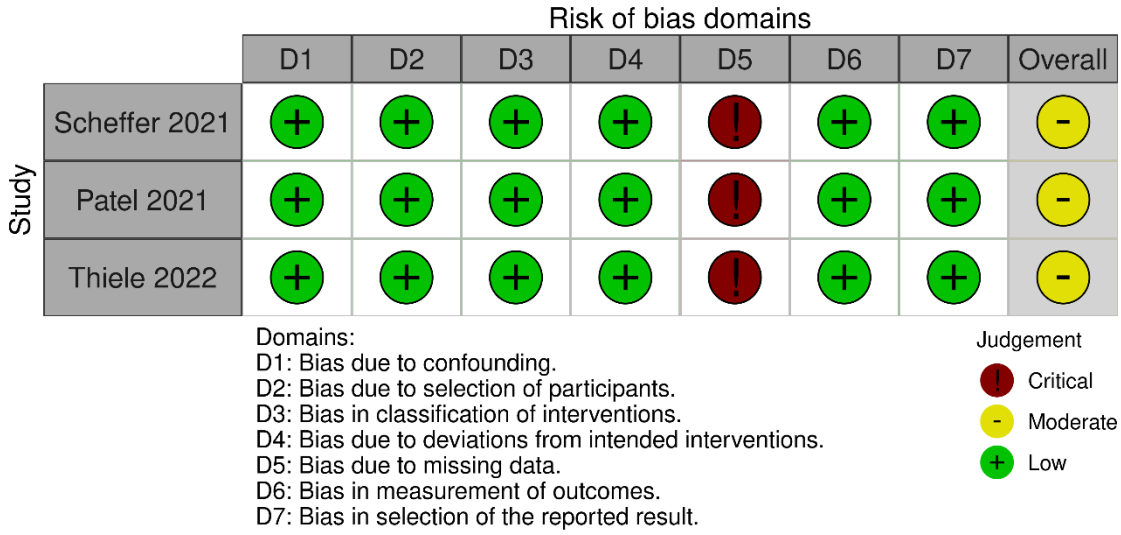

Figure 2: *Risk-of-bias plot* - result of the risk assessment of bias of the observational cohort studies ("open-label extension") included [18].

1. RESULTS OF RANDOMIZED CLINICAL TRIALS

1.1. Five studies [20-24], assessing 726 participants, allowed the evaluation of the outcome "absolute reduction in seizures" treated with CBD as compared to placebo, the follow up time 12 to 16 weeks. In this analysis demonstrated increase in the number of patients who obtained absolute reduction in the frequency of seizures [Risk Difference (RD) = 0.31 (95% CI 0.18 to 0.44; I^2 = 77%)], NNT = 3. Moderate evidence quality (Analysis 1.1; Figure 3 and Table 4).

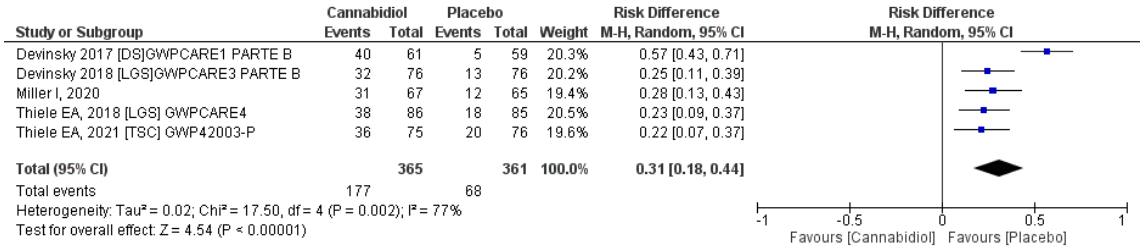

Figure 3 - Meta-analysis of the results of absolute reduction in seizures with CBD

1.2. Meta-analysis of five studies [20-24], assessing 726 participants, found there increased of the "number of patients with ≥ 50% reduction in seizures" for treatment CBD as compared to placebo, the follow up time 12 to 16 weeks [(RD) = 0.20 (95% CI 0.13 to 0.26; I^2 = 0%)], NNT = 5. High evidence quality (Analysis 1.2; Figure 4 and Table 4).

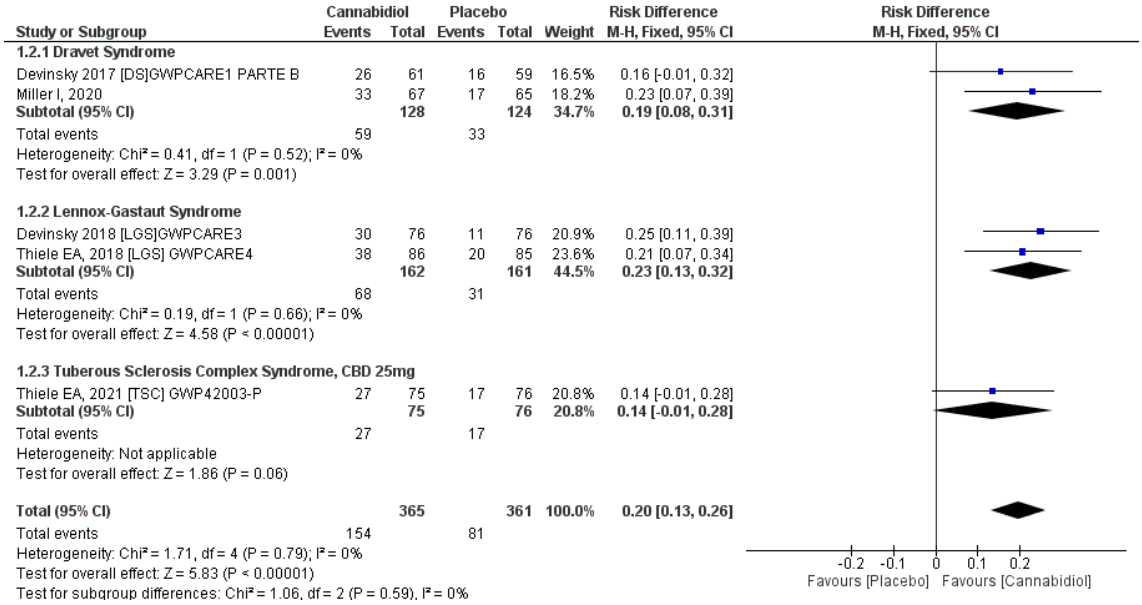

Figure 4 - Meta-analysis of the results of reduction equal to or greater than 50% in seizures.

1.3. Five studies [20-24], assessing 726 participants, have been submitted a meta-analysis, demonstrated a little difference of the outcome "number of patients with absence of seizures" comparing treatment CBD as to placebo, the follow up time 12 to 16 weeks. [(RD) = 0.03 (95% CI 0.01 to 0.03; I^2 = 44%)]. Moderate evidence quality (Analysis 1.3; Figure 5 and Table 4).

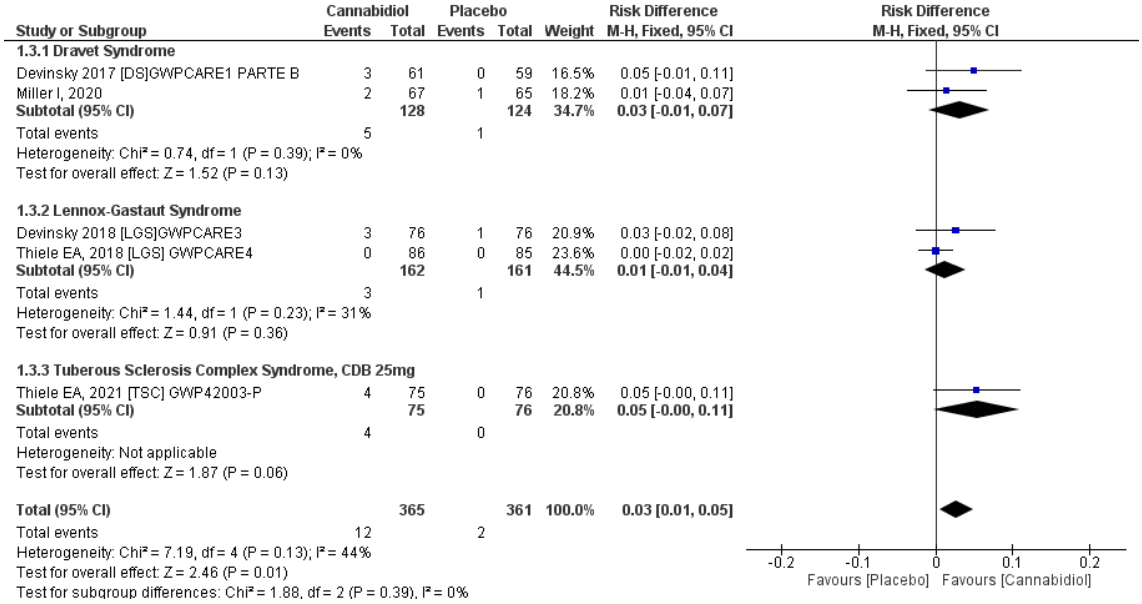

Figure 5 - Meta-analysis of the results of patients with absence of seizures and use of CBD.

1.4. The Caregiver Global Impression of Chan*ge* (7-point Subject/Caregiver Global Impression of Change, S/CGIC), was evaluated through a questionnaire with 7 items [improvement (mild, moderate or intense), worsening (mild, moderate or intense) and without change, was applied to caregivers and patients. Five studies [20-24], assessing 726 participants, the follow up 12 to 16 weeks, demonstrated improved in S/CGIC In the patients who received CBD as compared to placebo [(RD) = 0.21 (95% CI 0.14 to 0.28; I^2 = 0%)], NNT = 5. High evidence quality (Analysis 1.4; Figure 6 and Table 4).

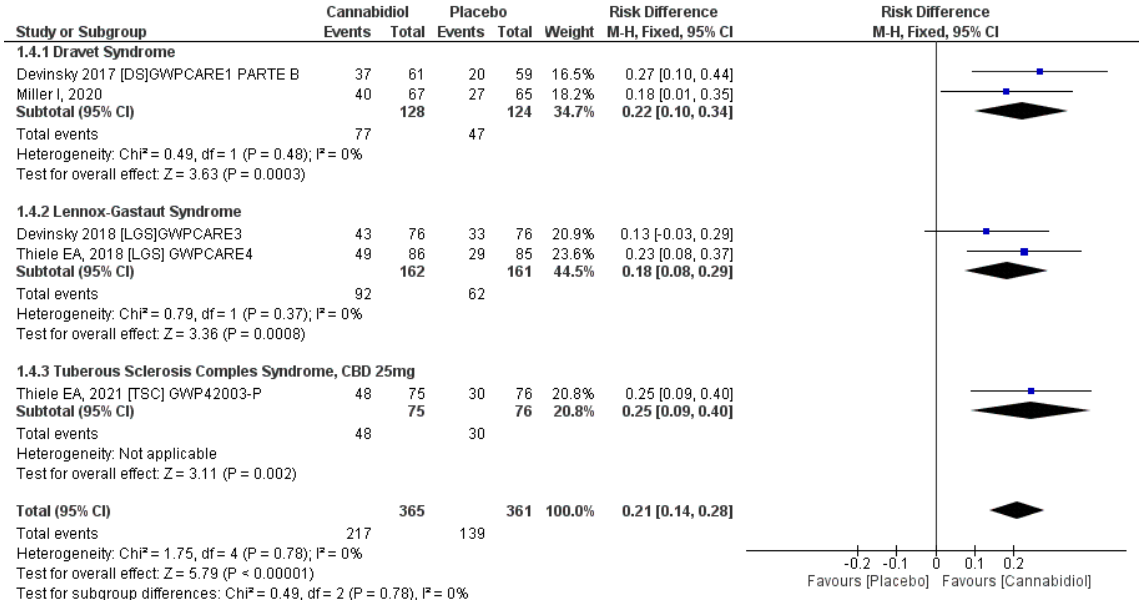

Figure 6 - Meta-analysis of the results of Caregiver Global Impression of Chan*ge*

1.5 Adverse events (AEs), six studies [19-24], assessing 733 participants, evaluated "frequency of total adverse events" (any), the follow up time 4 to 16 weeks, comparing use of CBD to placebo. This analysis demonstrated increase in the risk of AEs with the use of CBD in the treatment of DS, LGS e TSC [(RD) = 0.21 (95% CI 0.14 to 0.28; I^2 = 83%)], NNT = 8. Very low evidence quality (Analysis 1.5; Figure 7 and Table 4).

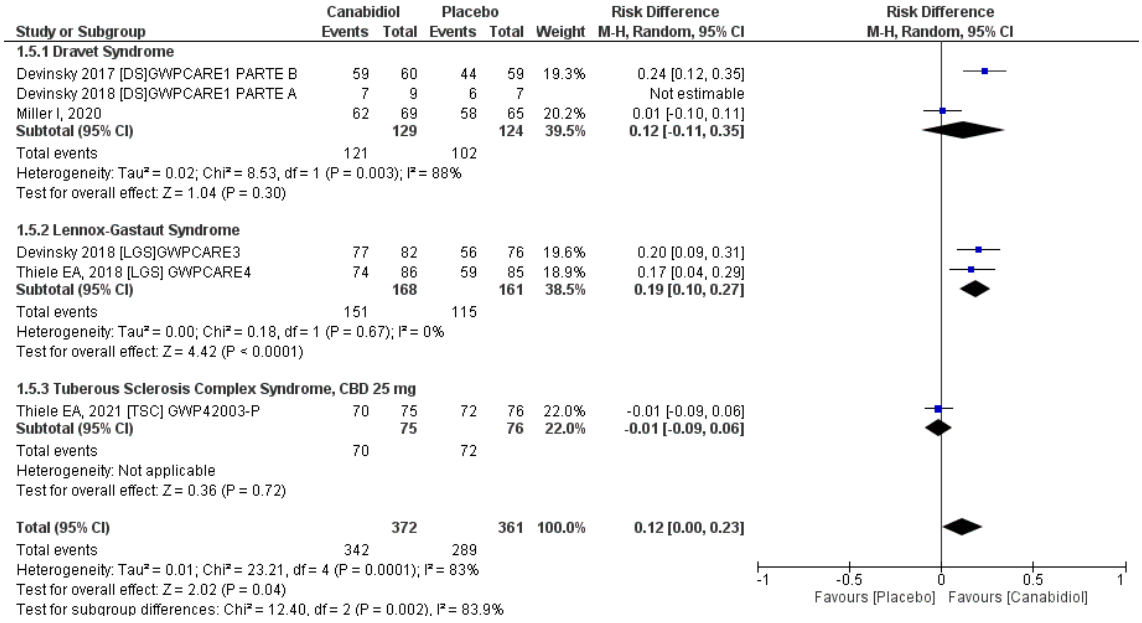

Figure 7 - Meta-analysis of the results of total adverse events.

1.6. The frequency of "severe adverse events" was evaluated in five studies [20-24], assessing 727 participants, the follow-up time was 12 to 16 weeks. This analysis demonstrated increased risk of serious adverse events with the use of CBD when compared to placebo [(RD) = 0.16 (95% CI 0.07 to 0.26; I^2 = 72%)], NNT = 6. Moderate evidence quality. (Analysis 1.6; Figure 8 and Table 4).

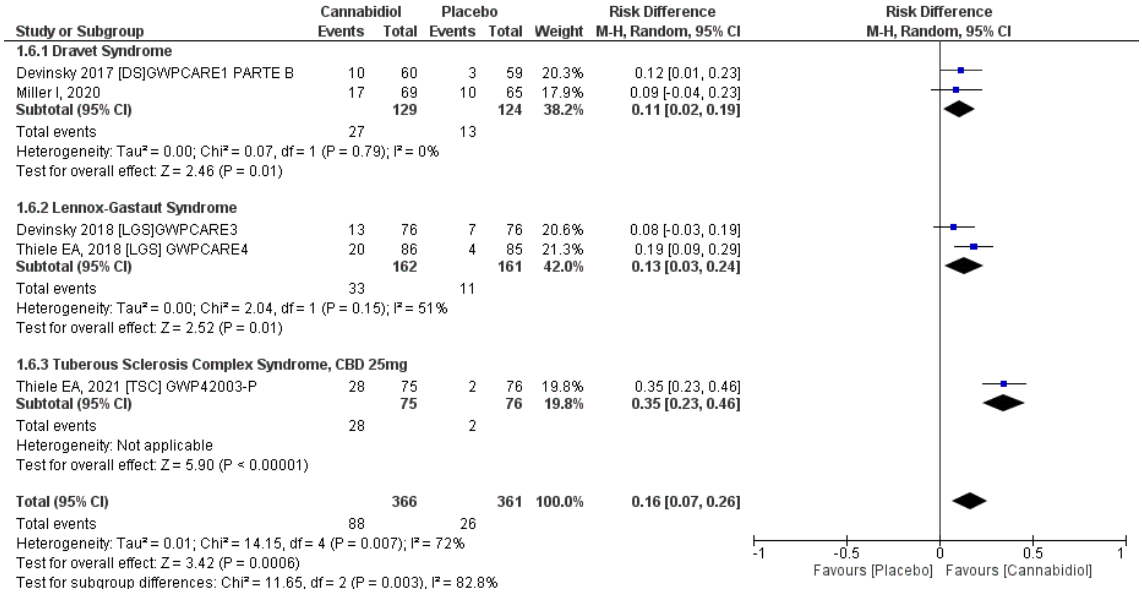

Figure 8 - Meta-analysis of the results of severe adverse events with CBD

1.7. The "*risk of treatment abando*nment" was evaluated in six studies [19-24], assessing 741 participants, the follow-up time was 4 to 16 weeks. CBD increased the risk of

treatment abandonment in the patients who received CBD as compared to placebo [(RD) = 0.12 (95% CI 0.06 to 0.17; I^2 = 50%)], NNH = 8. High evidence quality (Analysis 1.7; Figure 9 and Table 4).

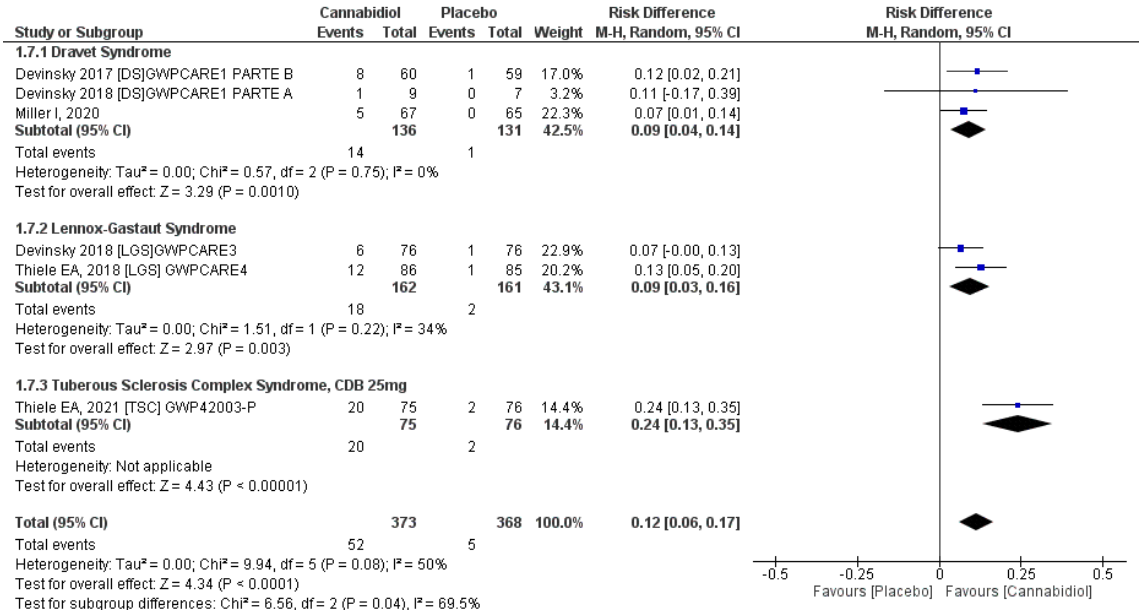

Figure 9 - Meta-analysis of the results of the risk of abandonment to CBD treatment.

1.8. Meta-analysis of studies [19-24], assessing 721 participants, the follow up time 4 to 16 weeks, evaluated the number of patients with "transaminase elevation (≥ 3 times the reference)" comparing the use of CBD to placebo. This analysis demonstrated increased risk of transaminase elevation ≥ 3 times the reference value in patients who received CBD, as compared to placebo 0.15 (95% CI 0.05 to 0.24; I^2 = 85%)], NNH = 6. Low evidence quality (Analysis 1.8; Figure 10 and Table 4).

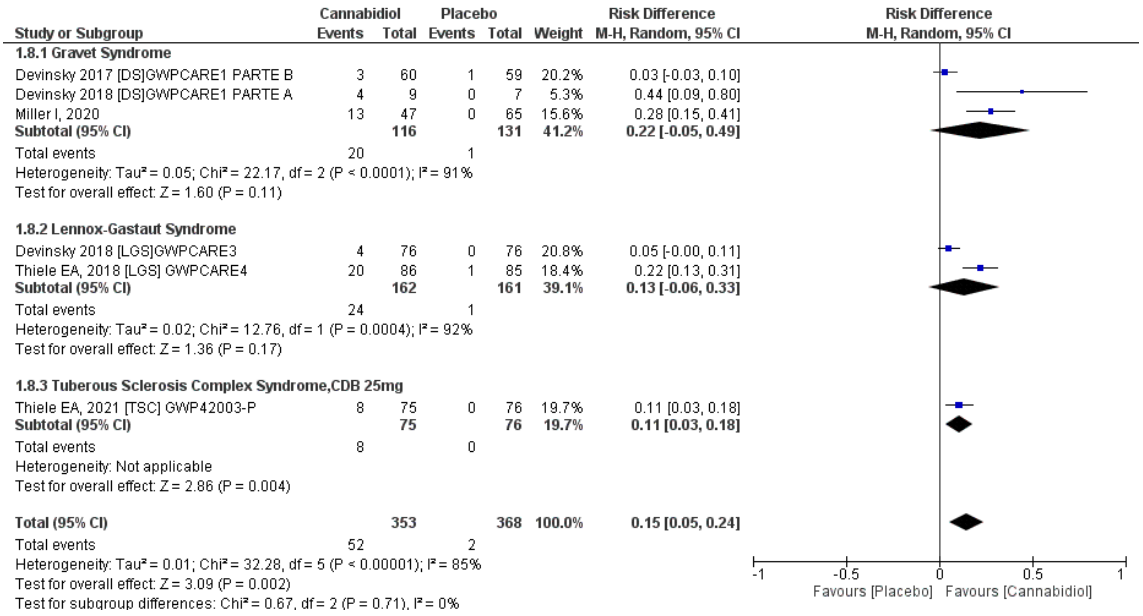

Figure 10 - Meta-analysis of the results of the elevation of transaminases ≥ 3 times the reference.

2. RESULTS OF THE "*OPEN-LABEL EXTENSION*"

2.1. SAFETY AND TOLERABILITY

Three *"Open-Label Extension*" (OLE) studies [25-27] allow the evaluation of treatment-emergent adverse events (TEAEs) in the use of cannabidiol, in the different types of primary seizure, in the long term (median treatment time between 267 to 1. 090 days). Adverse events for the grouped LGS, DS and CTS populations are summarized by pathology in Table 2.

The majority (95.8%) of all patients had at least one TEAE during follow-up; there was no significant difference between disease groups (97% in DS, 96.4% in LGS and 92% in TSC).

The incidence of severe AEs was much lower in the TSC group (29 [15%]) compared to groups DS (132 [42%]) and LGS (155 [42.3%]); similar result occurred with the elevation of transaminases (>70% had associated valproic acid). However, we should consider that the follow-up time for CST [median of 267 (range =18 to 910) days] was shorter compared to DS [444 (18 to 1,535)] and LGS [1,090 (3 to 1,421)].

The most commonly reported TEAEs were pyrexia, and other related to the gastrointestinal tract, including diarrhea, vomiting and reduced appetite, but also neurological including drowsiness.

Overall, the reported TEAEs, including the observed frequencies and severity, are comparable with previous observations of pivotal assays.

The percentage of patients who permanently discontinued treatment with cannabidiol was 9.4% (n = 83). The most common reasons were seizures and increased liver enzymes. Both are events known to cause discontinuation of CBD treatment.

Table 2. Summary of adverse events emerging from cannabidiol treatment for grouped (OLE) LGS, DS and TSC, median the follow up time 267 to 1,090 days.

Emerging Adverse Events of Treatment during OLE				
Type of Adverse Event	**Dravet syndrome (N = 315) n (%)**	**Lennox-Gastaut syndrome (N = 366) n (%)**	**Tuberous Sclerosis Complex (N = 199) n (%)**	**Total (N = 880) n (%)**
All TEAEs	306 (97)	353 (96.4)	184 (92)	843 (95.8)
Graves TEAEs	132 (42)	155 (42.3)	29 (15)	316 (36)
Abandonment due to adverse events	28 (9)	43 (11.7)	12 (6)	83 (9.4%)
Elevated hepatic transaminases* (ALT or AST) >3 × higher	69 (22%); 58 of which (84%) had concomitant use of valproic acid.	55 (15%); 40 of which (73%) with concomitant use of valproic acid.	17 (9%); 12 of which (71 %) with concomitant use of valproic acid	141 (16)

TAEAs, *treatment-emergent adverse event*; * Elevations of liver enzymes include only those reported as adverse events.

SUMMARY OF EVIDENCE

1. Randomized clinical trials

The use of cannabidiol in patients with Dravet Syndromes, Lennox-Gastaut and Tuberous Sclerosis Complex as comparison to placebo, follow-up time 12 to 16 weeks:

- Shows an absolute reduction in the frequency of seizures of 33%; 3 patients for 1 benefit (NNT = 3) are needed. Moderate evidence quality.
- Increases the number of patients with a 50% ≥ reduction in the frequency of seizures by 20%; NNT = 5. High evidence quality.
- Increases the number of patients with absence of seizures by 3%; NNT = 33. Moderate evidence quality.

- Improvement of the change in Caregiver/patient Global Impression of Charge (S/CGIC) in 21%; NNT = 5. High evidence quality.
- Increases all adverse events by 12%, and it is necessary to treat 8 patients to obtain damage (NNH = 8). Very low evidence quality.
- Increases serious adverse events by 16%; NNH= 6. Quality of evidence was moderate.
- Increases the risk of treatment abandonment by 12%; NNH=8. High evidence quality.
- Increases the number of patients with transaminase elevation (≥ 3 times the reference) by 15%; NNH=6. Low evidence quality.

2. Observational studies' cohort "open-label extension"

In treatment with cannabidiol of different types of primary seizure, in the long term (follow-up median 1 to 3 years):

- 95.8% of all patients have at least one emerging adverse treatment event (TEAE) with cannabidiol;
- The rate of severe TEAEs can be up to 36%;
- Transaminase levels (ALT, AST) ≥ 3 times the reference, may occur in 16% of patients;
- The most commonly reported TEAEs are pyrexia, diarrhea, vomiting, reduced appetite, and drowsiness;
- The percentage of patients who can permanently discontinue treatment with cannabidiol is 9.4%. The most common reasons are seizures and increased liver enzymes.

These results have very low evidence quality.

Conclusion

This systematic review, with meta-analysis, supports the use of cannabidiol in the treatment of patients with seizures, originating in Dravet syndromes, Lennox-Gastaut and

Tuberous Sclerosis Complex, resistant to the common medications, satisfactory benefits in reducing seizures and tolerable toxicity.

Author's contributions

Silvinato, Idevaldo and Bernardo designed the study, developed and executed the search strategy, selected studies for inclusion and extracted data, analyzed the data and wrote the first draft of the manuscript, which was critically revised for intellectual content by all authors. All authors approved the final version submitted for publication.

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None conflict of interest

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ANNEXES

Table 3. Characteristics of clinical studies evaluating the use of cannabidiol in patients with Dravet Syndromes, Lennox-Gastaut and Tuberous Sclerosis Complex

STUDY	DRAWING	POPULATION	INTERVENTION	COMPARISON	DENOUEMENT	FOLLOW-UP TIME
Devinsky 2017 [DS]GWPCARE1 PART B	ECR	Pivotal phase 3 study; patients (N =120) diagnosed with Dravet Syndrome; 2 to 18 years; with uncontrolled epileptic seizures, using more than one anticonvulsant drug, for more than 4 weeks. Multicenter (USA, UK, Poland)	Staggered dose 5.10 to 20mg/kg/day divided into 2 times a day. Maintenance doses for 12 weeks: 20mg/kg/d.	Placebo	Primary: reduction in the median monthly frequency of convulsions. Secondary: Change in the overall impression of caregivers and patients (S/CGIC); reduction in percentage of the number of seizures (25,50,75 and 100%); adverse events (number, type and severity).	14 weeks
Miller 2020 [DS]GWPCARE2	ECR	Pivotal phase 3 study; patients (N =199) diagnosed with Dravet Syndrome; 2 to 18 years; more than 1 anticonvulsant drug for more than 4 weeks. Multicenter (USA, Spain, Poland, Netherlands, Australia and Israel)	Staggered dose 5.10 to 20mg/kg/day, divided into 2 times a day. Maintenance doses for 12 weeks: 10 or 20mg/kg/d	Placebo	Primary: reduction in the frequency of the number of convulsions. Secondary: Change in the overall impression of caregivers and patients (S/CGIC); reduction in percentage of the number of seizures (25, 50, 75 and 100%); adverse events (number, type and severity).	14 weeks
Devinsky 2018 [DS]GWPCARE1 AGWPCARE PART3	ECR	Patients (N = 34); age between 4 and 10 years; with Dravet syndrome. Evaluation of pharmacokinetics and safety of cannabidiol.	Staggered dose 5.10 or 20mg/kg/day divided into 2 times a day; treatment maintained for 3 weeks.	Placebo	Dose titration and adverse events	4 weeks
Devinsky 2018 [LGS]GWPCARE3 PART B	ECR	Pivotal phase 3 study; patients (N=225) with Lennox-Gastaut syndrome; age 2 to 55 years; diagnosed by electroencephalographic alterations; anticonvulsants drugs for more than 4 weeks, without seizure control.	Staggered dose 5.10 to 20mg/kg/day divided into 2 times a day. Maintenance doses for 12 weeks: 10 or 20mg/kg/d	Placebo	Primary: median reduction in the number of drop seizures and total monthly seizures. Secondary: Change in overall impression by caregivers and patients (S/CGIC); reduction in percentage of the number of seizures (25,50,75 and 100%); adverse events (number, type and severity).	14 weeks
Thiele EA, 2018 [LGS] GWPCARE4	ECR	Pivotal phase 3 study; patients (N=171) with Lennox-Gastaut Syndrome; age 2 to 55 years; clinically diagnosed by electroencephalogram (including documented history of slow electroencephalograms [<3·0 Hz]), associated with more than one type of generalized seizure, including falls, for at least 6 previous months; on use of anticonvulsant drugs for more than 4 weeks.	Staggered dose 5.10 to 20mg/kg/day divided into 2 times a day. Maintenance doses for 12 weeks: 20mg/kg/d.	Placebo	Primary: median reduction in the number of drop seizures and total monthly seizures. Secondary: Change in the overall impression of caregivers ant patients (S/CGIC); reduction in percentage of the number of seizures (25, 50, 75 and 100%); adverse events (number, type and severity).	14 weeks

Thiele EA, 2021 [TSC] GWP42003-P	ECR	Pivotal Phase 3 Study; patients (N =255) with diagnostic tuberous sclerosis complex; age between 1 and 65 years; using more than 1 anticonvulsant drug, for more than 4 weeks. (Poland, Australia, Spain, Netherlands, United Kingdom and United States).	Staggered dose, with an increase of 5mg, up to 25 or 50mg/kg/day, divided into 2 doses per day. Maintenance doses for 12 weeks: 25 or 50mg/kg/d	Placebo	Primary: reduction in the number of seizures. Secondary: proportion of patients with a 50% reduction in the number of seizures, Change in the overall impression of patients and caregivers (S/CGIC) and adverse events.	14 weeks

Table 4. Quality of evidence (GRADE)

Cannabidiol compared to placebo for seizures

Patient or population: Lennox-Gastaut Syndrome, Dravet and Tuberous Sclerosis Complex
Context: Efficacy, safety and tolerability
Intervention: cannabidiol
Comparison: placebo

Outcomes	In the number of participants (studies)Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Potential absolute effects	
				Risk with placebo	Risk difference with cannabidiol
Absolute reduction in seizures follow: range 12 weeks to 16 weeks	726(5 ECRs)	⊕⊕⊕◯ Moderate[a]	not priceless	188 per 1000	**188 less per 1000** (188 less for 188 less)
Number of patients with a reduction equal to or greater than 50% in seizures following: range 12 weeks to 16 weeks	726(5 ECRs)	⊕⊕⊕⊕ High	**RR 1.88** (1.50 para 2.35)	224 per 1000	**197 more per 1000** (112 more to 303 more)
Number of patients without seizures follow: range 12 weeks to 16 weeks	726(5 ECRs)	⊕⊕⊕◯ Moderate[b]	**RR 4.29** (1.24 para 14.87)	6 per 1000	**18 more per 1000** (1 more to 77 more)
Improvement of clinical impression evaluated by patient or caregiver (S/CGIC) follow-up: range from 12 weeks to 16 weeks	726(5 ECRs)	⊕⊕⊕⊕ High	**RR 1.54** (1.32 para 1.80)	385 per 1000	**208 more per 1000** (123 more to 308 more)
Total adverse events follow-up: range 4 weeks to 16 weeks	733(5 ECRs)	⊕'very low[b,c]	**RR 1.15** (1.00 para 1.32)	801 per 1000	**120 more per 1000** (0 less for 256 more)
Severe adverse events follow: range 12 weeks to 16 weeks	727(5 ECRs)	⊕⊕⊕◯ Moderada[d]	**RR 3.25** (1.56 para 6.74)	72 per 1000	**162 more per 1000** (40 more to 413 more)
Risk of treatment abandonment follow-up: range 4 weeks to 16 weeks	741(6 ECRs)	⊕⊕⊕⊕ High	**RR 8.70** (3.80 para 19.89)	14 per 1000	**105 more per 1000** (38 more to 257 more)
Number of patients with transaminase elevation equal to or greater 3 times the follow-up reference: range 4 weeks to 16 weeks	721(6 ECRs)	⊕⊕' low and	**RR 11.20** (4.03 para 31.16)	5 per 1000	**55 more per 1000** (16 more to 164 more)

* **The risk in the intervention group** (and its 95% confidence interval) is based on the risk assumed from the comparator group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; RR: Risk ratio

Cannabidiol compared to placebo for seizures

Patient or population: Lennox-Gastaut Syndrome, Dravet and Tuberous Sclerosis Complex
Context: Efficacy, safety and tolerability
Intervention: cannabidiol
Comparison: placebo

Outcomes	In the number of participants (studies)Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Potential absolute effects	
				Risk with placebo	Risk difference with cannabidiol

GRADE Working Group grades of evidence High certainty:
we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations

a. Heterogeneity equal to 77%

b. Wide confidence interval

c. Heterogeneity equal to 83%

d. Heterogeneity equal to 72%

e. Heterogeneity equal to 85%