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The Effects of Cannabidiol in the Treatment of Epilepsy: a Systematic Review

Os efeitos do canabidiol no tratamento da epilepsia: uma revisão sistemática

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ABSTRACT
Introduction: There are some types of structurally similar cannabinoids, although with different pharmacological actions. Studies demonstrate how cannabidiol has great therapeutic potential against epilepsy. *Objectives:* This review aimed to assess the use of cannabidiol in the treatment of diseases such as epilepsy. *Methods:* The review was conducted and based on the search of scientific articles in the PubMed, Scielo, LILACS and Science Direct electronic databases. Were included articles in English, Portuguese, or Spanish, made available in full and for free within the period from 2009 to 2019, allowing only clinical trials. *Results:* All articles included in the review reported that the experimental groups obtained a favorable result with cannabidiol compared with the placebo during the experimental period. The most common adverse events observed were somnolence, decreased appetite, diarrhea, upper respiratory tract infection and pyrexia. The severe adverse events mentioned were elevated concentrations of aspartate aminotransferase, alanine aminotransferase and gamma-glutamyltransferase. *Conclusion:* The administration of cannabidiol as a complementary anticonvulsant medication is capable to reduce epileptic seizures, especially when epilepsy is resistant to pharmacological treatment. Thus, more effective and safe guide for development of new anticonvulsant drugs, derived from Cannabis Sativa, will improve the quality of life of patients with epilepsy.

DESCRIPTORS
Cannabidiol. Cannabis sativa. Epilepsy. Systematic review.

RESUMO
Introdução: Existem alguns tipos de canabinóides estruturalmente semelhantes, embora com ações farmacológicas diferentes. Estudos demonstram como o canabidiol tem grande potencial terapêutico contra a epilepsia. Objetivos: Esta revisão teve como objetivo avaliar o uso do canabidiol no tratamento de doenças como a epilepsia. Métodos: A revisão foi realizada com base na busca de artigos científicos nas bases de dados eletrônicas PubMed, Scielo, LILACS e Science Direct. Foram incluídos artigos em inglês, português ou espanhol, disponibilizados na íntegra e gratuitamente no período de 2009 a 2019, permitindo apenas ensaios clínicos. Resultados: Todos os artigos incluídos na revisão relataram que os grupos experimentais obtiveram resultado favorável com o canabidiol em comparação com o placebo durante o período experimental. Os eventos adversos mais comuns observados foram sonolência, diminuição do apetite, diarréia, infecção do trato respiratório superior e pirexia. Os eventos adversos graves mencionados foram concentrações elevadas de aspartato aminotransferase, alanina aminotransferase e gama-glutamiltransferase. Conclusão: A administração de canabidiol como medicamento anticonvulsivante complementar é capaz de reduzir as crises epilépticas, principalmente quando a epilepsia é resistente ao tratamento farmacológico. Assim, um guia mais eficaz e seguro para o desenvolvimento de novos medicamentos anticonvulsivantes, derivados da Cannabis Sativa, melhorará a qualidade de vida dos pacientes com epilepsia.

DESCRITORES
Canabidiol. Cannabis sativa. Epilepsia. Revisão sistemática.

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Cannabis sativa is a plant species with approximately 400 chemical substances, 60 of which are called cannabinoids[1]. In the mid-60s, the chemical structure of two substances was determined: tetrahydrocannabinol, responsible for the psychoactive effects of the plant, and cannabidiol, a substance with no psychotropic effect[2]. The term cannabinoid refers to all substances derived from *Cannabis sativa* or substances that act in some way on cannabinoid receptors. There are some types of structurally similar cannabinoids, although with different pharmacological actions, of which cannabidiol is an example[3].

The first cannabinoid receptor was discovered in 1988, with the description of a receptor that would be associated with a G protein. It was identified as a receptor activated by THC, called cannabinoid-1 or CB1[4]. It was later discovered that this receptor is more expressed in the central nervous system[5]. The second cannabinoid receptor was discovered in 1993, known as cannabinoid-2 or CB2. This receptor is mostly found in the region of peripheral organs and tissues[6]. After the identification of the receptors came the identification of their ligands, such as anandamide, 2-arachidonoylglycerol, virodhamine, N-arachidonoyldopamine, and 2-arachidonoylglyceryl ether. The mechanism of action of cannabidiol is not fully known, but unlike THC, it shows low affinity for the CB1 and CB2 receptors[8]. *Cannabis sativa* has been widely used as a recreational substance, but due to the compounds extracted from it, such as cannabidiol, it has been revealed as very useful to humanity for therapeutic purposes[9]. Cannabidiol shows excellent therapeutic potential for treating diseases such as multiple sclerosis, neuropathic pain, schizophrenia, mood disorders, among others[10,11].

Based on some studies, cannabidiol has revealed its antiepileptic and anxiolytic actions, showing antioxidant and neuroprotective properties[12,13]. Given the unpredictability of seizures, the epileptic individual becomes a self-limited and hesitant person toward life, with a decreased quality of life[14]. Several antiepileptic drugs are used to avoid and control seizures, such as carbamazepine, phenytoin, valproic acid, and lamotrigine. Total control of seizures does not occur in the protocol used for the treatment of epilepsy, and several adverse effects still exist, such as depression, somnolence, tremor, changes in liver function, weight gain, vomiting, nausea, and diplopia, among others, which may lead to poor treatment adherence[15]. Studies show how cannabidiol has great therapeutic potential against epilepsy, especially in refractory epilepsy[16,17]. However, few studies approach this theme. Therefore, this review aims to assess the effect of cannabidiol in the treatment of epilepsy.

METHODS

Data sources, search terms and inclusion criteria

The bibliographic research was elaborated based on a systematic literature review aiming at assessing the effects of cannabidiol in the treatment of epilepsy. The review was conducted and based on the search of scientific articles in the PubMed, Scielo, LILACS, and Science Direct electronic databases. The search strategy included

descriptors such as “cannabidiol”, “cannabis sativa”, and “epilepsy”, which are part of the controlled vocabulary of Health Sciences Descriptors (DeCS) and Medical Subject Headings (MeSH). Boolean connectors were used as appropriate. All articles included in this review addressed the topic of the effects of cannabidiol in the treatment of epilepsy. The review included articles written in English, Portuguese, or Spanish, made available in full and for free within the period from 2009 to 2019, allowing only clinical trials and excluding the articles that did not meet the criteria mentioned above.

Process of analysis

The sorting of articles was made in three stages: title, abstract, and full-text analysis, employing three researchers, two (IV and AH) of which determined the relevance of the topic, while the third was requested upon the occurrence of disagreement (DT). The agreement between the two researchers was calculated according to Cohen’s kappa coefficient. After the initial abstract review, a full-text review was performed, and studies were once again reviewed for final inclusion. The studies that satisfied the inclusion criteria for data extraction were evaluated according to the following variables: the use of cannabidiol in the treatment of epilepsy; the benefit that cannabidiol might bring to patients; the analysis of adverse events during its use; the country where the trial was conducted; the analysis of the sample used in the trial; in addition to the type of publication, language, and year of publication. The study followed the guidelines preconized by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[18] checklist provided as Supporting Information.

RESULTS

CHARACTERISTICS OF THE INCLUDED STUDIES

Using the search descriptors related to epilepsy, the initial search retrieved 304 articles, of which 81 were repeated in more than one database used in the study. The first evaluation was performed by two researchers, who excluded 193 articles that did not satisfy the inclusion criteria. It is worth noting that some titles diverged in the evaluation of the two researchers, being necessary to request the analysis of a third researcher in order for the title to be approved or not. Thus, 30 remaining titles were selected for abstract analysis. Of the 30 abstracts that were read and evaluated, 12 were excluded, with 18 articles remaining to be read and evaluated in full. In this stage, there was also the need for a third researcher to analyze the abstracts that diverged in the evaluation of the first two researchers. Of the 18 articles read, 15 did not satisfy the inclusion criteria of the study, with three articles remaining at the end of the selection process that met all previously established inclusion criteria.

Inter-rater agreement of articles’ inclusion was assessed using the kappa coefficient. The kappa coefficient was 0.71, representing substantial agreement for identify studies for titles. Following titles review, the kappa coefficient for abstract review was 0.82, reflecting a good inter-rater agreement. Following abstract review, the kappa coefficient

was 0.81, indicating perfect agreement for full text review article inclusion and following full text review, the kappa coefficient was 1.0, showing excellent agreement for final studies included in the analysis.

Method description

Regarding the place of study, it was observed that all three articles related to epilepsy were multicenter studies and were written in English[19-21]. These articles consisted of trials with patients of two syndromes, two of which addressed patients with Lennox-Gastaut syndrome[19,20] while the other addressed the Dravet syndrome[21]. Patients were mostly younger than 18 years. The sample size varied from 120 to 225 participants. The control group varied from 59 to 85 participants, and the intervention group from 61 to 149 participants[19-21]. For the intervention group, two of the articles used a 20mg/kg daily dose administered in two equally divided doses[20,21], while the third article used two doses, that is, there were two intervention groups, one with 10mg/kg and the other with 20mg/kg per day[19] (Table 1).

Regarding the placebo group, all three articles used pharmaceutical formulations with similar organoleptic properties to the one used in the intervention group, differing only in the absence of cannabidiol. The trials described in the three articles selected went through stages during the experimental period, in which 4 weeks were reserved for screening, followed by 2 weeks of dose escalation, 12 weeks of stable dosing (maintenance period) at 10mg/kg or 20mg/kg, depending on the article, 10 days of tapering, and 4 weeks of a safety follow-up period[19-21]. Two of them used the 2nd, 4th, 8th, and 14th weeks for visits or data collection[19-21] (Table 2 and Table 3), while in the third article, the patients were assessed in the clinic on days 15, 29, 57, and 99, and by telephone on days 43 and 71[21] (Table 3).

Effectiveness of cannabidiol in the treatment of epilepsy and outcomes

All three articles reported that the experimental groups had a favorable result with cannabidiol compared with the placebo group during the treatment period. The outcome was analyzed in two stages: primary and secondary. In the primary stage, all three articles used the same parameter of change from baseline in the frequency of seizures[19-21]. In the secondary stage, one of them used as parameters the percentage of patients who had at least a 50% monthly reduction from baseline in seizure frequency, the percentage change from baseline in the frequency of total seizures, and the Patient or Caregiver Global Impression of Change (GIC)[19]. The second article used as parameters the proportion of patients who achieved a reduction of 50% or more in the monthly frequency of convulsive seizures, change in the monthly frequency of total seizures, frequency of non-drop seizures, and GIC[20]. The third article assessed the percentage of patients who had a reduction of at least 50% in the monthly frequency of convulsive seizures, change in the monthly frequency of total seizures, Caregiver Global Impression of Change (CGIC), sleep disruption (Epworth Sleepiness Scale), and quality of life (Quality of Life in Childhood Epilepsy questionnaire)[21].

Table 1. Description of the PICO strategy in the studies on the use of cannabidiol in the treatment of epilepsy included in the review.

Authors and Year of Publication	Patient (P)	Intervention (I)	Comparison (C)	Outcomes (O)
Thiele et al., 2018	Patients with Lennox-Gastaut syndrome, with evidence of more than one type of generalized seizure, including convulsive seizures, for at least six months. 171 patients were randomly assigned into an intervention group (n = 86), with a mean age of 15.5 (±10.8), and a placebo group (n = 85), with a mean age of 15.3 (±9.8).	Formulation of purified cannabidiol (100 mg/mL) at a daily dose of 20 mg/kg in two administrations + existing medications	Placebo solution + existing medications	Primary: percentage change in the monthly frequency of convulsive seizures from baseline. Secondary: proportion of patients in each treatment group that achieved a reduction of 50% or more in the monthly frequency of convulsive seizures, change in the monthly frequency of total seizures, reduction in the frequency of non-drop seizures, and patient and caregiver global impression of change.
Devinsky et al., 2018	Patients with Lennox-Gastaut syndrome, with at least two types of generalized seizures, including convulsions, for at least six months. 225 patients were randomly assigned into a 20-mg cannabidiol group (n= 76), with a mean age of 16.0 (±10.8), a 10-mg cannabidiol group (n = 73), with a mean age of 15.4 (±9.5), and a placebo group (n = 76), with a mean age of 15.3 (±9.5).	Formulation of purified cannabidiol (100mg/mL) at a dose of either 20 mg/kg or 10 mg/kg administered twice daily + existing medications	Placebo solution + existing medications	Primary: percentage change from baseline in the frequency of convulsive seizures. Secondary: proportion of patients who had a reduction of 50% or more from baseline in the monthly frequency of convulsive seizures, change in the monthly frequency of total seizures, and patient and caregiver global impression of change.
Devinsky et al., 2017	Patients with Dravet syndrome whose syndromes were not controlled by their current antiepileptic drug. 120 patients were randomly assigned into an intervention group (n = 61), with a mean age of 9.7 (± 4.7), and a placebo group (n = 59), with a mean age of 9.8 (± 4.8).	Formulation of purified cannabidiol (100mg/mL) at a dose of 20 mg/kg administered twice daily + existing medications	Placebo solution + existing medications	Primary: percentage change from baseline in the frequency of convulsive seizures. Secondary: proportion of patients with a reduction of 50% or more in the frequency of convulsive seizures, change in the frequency of total seizures, CGIC, sleep disruption (Epworth Sleepiness Scale), and quality of life (Quality of Life in Childhood Epilepsy questionnaire).

PICO, represents an acronym for Patient, Intervention, Comparison and Outcome.

Regarding the primary outcomes, there was a significant reduction in the monthly frequency of convulsive seizures in the intervention group compared with the control group in the three articles included, such as in the study by Thiele *et al.* (2018)[19], in which a reduction of 43.9% occurred in the intervention group versus 21.8% in the control group. In the study by Devinsky *et al.* (2018)[20], the reductions were equivalent to 41.9% (20-mg cannabidiol group) and 37.2% (10-mg cannabidiol group), and 17.2% in the control group. Finally, in the study by Devinsky *et al.* (2017)[21], there was a 38.9% reduction in the intervention group and 13.3% in the control group.

It was observed that, in the secondary outcomes, 44% of the patients in the cannabidiol group had a reduction of 50% or more in the monthly frequency of convulsive seizures compared with 24% of the patients in the control group, with a reduction in the monthly frequency of total seizures corresponding to 41.2% in the intervention group and 13.7% in the control group, and a reduction in the frequency of non-drop seizures of 49.4% in the intervention group and 22.9% in the control group. Another secondary outcome of this trial was related to the patient and caregiver global impression of change, in which 58% of the patients in the intervention group reported improvements in the overall condition versus 34% of the patients in the control group[19] (Table 2).

It was observed that, in the secondary outcomes, there was a reduction of at least 50% in the monthly frequency of convulsive seizures in 39% and 36% of the patients in the 20mg/kg/day and 10mg/kg/day cannabidiol groups, respectively, and in 14% of the patients in the control group. As for the monthly frequency of total seizures, the reductions were equivalent to 38.4% and 36.4% in the 20mg/kg/day and 10mg/kg/day cannabidiol groups, respectively, and 18.5% in the control group. Another secondary outcome of this study was related to the patient and caregiver global impression of change, for which 57% and 66% of the patients in the 20mg/kg/day and 10mg/kg/day cannabidiol groups reported improvements, compared with 44% of the reports in the control group[20] (Table 3).

It was observed that, in the secondary outcomes, there was a reduction of at least 50% in the monthly frequency of convulsive seizures in 43% of the patients in the intervention group and 27% of the patients in the control group, with a reduction in the monthly frequency of total seizures corresponding to 28.6% in the intervention group and 9% in the control group. Another secondary outcome of this trial was related to the caregiver global impression of change, in which 62% of the caregivers in the intervention group reported improvements in the overall condition, compared with 34% of the caregivers in the control group, with no significant difference regarding the remaining outcomes[21] (Table 4).

Adverse events of cannabidiol

In the study by Thiele *et al.* (2018)[19] adverse events of any severity were reported in 86% of the patients in the intervention group (IG) and in 69% of the patients in the control group (CG). In the cannabidiol group, 62% of the patients had treatment-related adverse events compared with 34% in the placebo

Table 2. Method description and effectiveness of cannabidiol in the treatment of epilepsy (Thiele *et al*., 2018).

AUTHOR AND YEAR OF PUBLICATION	METHOD	EFFECTIVENESS
Thiele *et al*., 2018	4-week screening period. Both cannabidiol and placebo were provided in identical 100mL amber glass bottles. Cannabidiol or placebo was administered orally in two equally divided doses (morning and evening) for 14 weeks, including 2 weeks of dose escalation (starting at a daily dose of 2.5 mg per kg, followed by 12 weeks of stable dosing [maintenance]), with a tapering period of 10 days, and a 4-week safety follow-up period. Following randomization (day 1), the patients were assessed in the clinic on days 15, 29, 57, and 99, and by telephone on days 43 and 71. At the beginning of the trial, patients took a median of six antiepileptic drugs, reducing to three concomitant antiepileptic drugs during the trial; the most common were clobazam, valproate, and lamotrigine.	**Monthly frequency of convulsive seizures** In the cannabidiol group, there was a decrease of 43.9% (IQR −69.6 to −1.9), while in the placebo group, the decrease was equivalent to 21.8% (IQR −45.7 to 1.7). The median difference between the groups was −17.21 (95% CI −30.32 to −4.09; p = 0.0135) during the 14 weeks of treatment and −19.45 (95% CI −33·05 to −4·68; p = 0.0096) during the 12 weeks of maintenance. **Reduction of 50% or more in the monthly frequency of convulsive seizures** In the cannabidiol group, 38 patients (44%) had a reduction in drop seizure frequency compared with 20 (24%) patients in the placebo group (OR 2.57, 95% CI 1.33–4.97; p = 0.0043). **Monthly frequency of total seizures** In the cannabidiol group, there was a median reduction of 41.2% (IQR −62.9 to −13.0), while in the placebo group, the median reduction was equivalent to 13.7% (IQR −45.0 to 7.3). The estimated median difference was –21.1 (95% CI −33.3 to −9.4; p = 0.0005) during the 14 weeks of treatment and –23.3 (95% CI –36.3 to –10.5; p = 0.0004) during the 12 weeks of maintenance. **Frequency of non-drop seizures** In the cannabidiol group, the frequency of non-drop seizures was reduced by 49.4% (IQR –81.6 a –25.3), while in the placebo group, the reduction was equivalent to 22.9% (IQR –67.8 to 31.7) during the treatment period, that is, during the 14 weeks. The estimated median difference between the groups was −26.1 (95% CI −46.1 to −8.3; p=0.0044) during the 14 weeks of treatment and −31.0% (95% CI −52.0 to −10.4; p = 0.0008) during the 12 weeks of maintenance. **Patient and caregiver global impression of change** 58% of the patients in the cannabidiol group reported an improvement in their overall condition compared with 34% of the patients in the placebo group (OR 2.54; CI 95% 1.5 – 4.5; p = 0.0012).

CI, confidence interval; IQR, interquartile range; OR, odds ratio.

Table 3. Method description and effectiveness of cannabidiol in the treatment of epilepsy (Devinsky *et al*., 2018).

Devinsky *et al*., 2018	4-week screening period. Both cannabidiol and placebo were provided in identical 100mL amber glass bottles. The cannabidiol or placebo was administered orally twice daily, for 14 weeks, in equally divided doses starting at 2.5 mg per kg per day and increasing by 2.5 to 5.0 mg per kilogram every other day for 2 weeks, which was called dose escalation, until the target dose was reached, followed by 12 weeks of stable dosing [maintenance], then by a tapering period of up to 10 days, and finally by a 4-week safety follow-up period. Patients or their caregivers were instructed to record everything that occurred during treatment. Clinic visits occurred in the 2nd, 4th, 8th, and 14th weeks.	**Monthly frequency of convulsive seizures** Reduction of 41.9% in the 20-mg cannabidiol group, 37.2% in the 10-mg cannabidiol group, and 17.2% in the placebo group. The estimated median difference between the 20-mg cannabidiol group and the placebo group was 21.6 percentage points (95% CI, 6.7 to 34.8; p = 0.005). The estimated median difference in reduction between the 10-mg cannabidiol group and the placebo group was 19.2 percentage points (95% CI, 7.7 to 31.2; p = 0.002). **Reduction of 50% or more in the monthly frequency of convulsive seizures** During the treatment period, a total of 30 patients (39%) in the 20-mg cannabidiol group, 26 patients (36%) in the 10-mg cannabidiol group, and 11 patients (14%) in the placebo group had a reduction of at least 50% in the frequency of seizures (OR 3.85 for the 20-mg cannabidiol group versus placebo group, 95% CI, 1.75 to 8.47, p<0.001; OR 3.27 for the 10-mg cannabidiol group x placebo group, 95% CI, 1.47 to 7.26; p = 0.003). **Monthly frequency of total seizures** Reduction of 38.4% in the 20-mg cannabidiol group, 36.4% in the 10-mg cannabidiol group, and 18.5% in the placebo group. The estimated median difference in reduction between the 20-mg cannabidiol group and the placebo group was 18.8 percentage points (95% CI 4.4 to 31.8; p = 0.009). The estimated median difference in reduction between the 10-mg cannabidiol group and the placebo group was 19.5 percentage points (95% CI 7.5 to 30.4; p = 0.002). **Patient and caregiver global impression of change** 57% of the patients in the 20-mg cannabidiol group and 66% of the patients in the 10-mg cannabidiol group reported an improvement in overall condition compared with 44% in the placebo group (OR 1.83 for the 20-mg cannabidiol group x placebo group, 95% CI, 1.02 to 3.30, p = 0.04; OR 2.57 for the 10-mg cannabidiol group x placebo group, 95% CI, 1.41 to 4.66; p = 0.002).

CI, confidence interval; IQR, interquartile range; OR, odds ratio.

Table 4. Method description and effectiveness of cannabidiol in the treatment of epilepsy (Devinsky *et al*., 2017).

AUTHOR AND YEAR OF PUBLICATION	METHOD	EFFECTIVENESS
Devinsky *et al*., 2017	The trial comprised a 4-week screening period, a 14-week treatment period (2 weeks of dose escalation and 12 weeks of dose maintenance), a 10-day taper period, and a 4-week safety follow-up period. Both cannabidiol and placebo were provided in identical 100mL amber glass bottles. The dose was escalated up to 20 mg per kilogram per day using a 14-day dosing regimen approved by the data and safety monitoring committee. All doses were administered twice daily. Patients or their caregivers were instructed to record everything that occurred during treatment. Clinical laboratory assessments were performed at baseline and after 2, 4, 8, and 14 weeks of the trial regimen.	**Monthly frequency of convulsive seizures** Reduction in the frequency of convulsive seizures in the cannabidiol group, with a median of 12.4 seizures per month (range, 3.9 to 1717) at baseline to 5.9 (range, 0.0 to 2159) during the entire treatment period, representing a median change of 38.9% (IQR, -69.5 to -4.8) from baseline. In the placebo group, the median monthly frequency of convulsive seizures decreased from 14.9 (range, 3.7 to 718) to 14.1 (range, 0.9 to 709), representing a median change of -13.3% (IQR, -52.5 to 20.2). The adjusted median difference between the groups was −22.8 percentage points (95% CI, −41.1 to −5.4; p = 0.01). **Reduction of 50% or more in the monthly frequency of convulsive seizures** Reduction in 43% of the patients in the cannabidiol group and in 27% of the patients in the placebo group (OR, 2.00; CI 95%, 0.93 to 4.30; p = 0.08). **Monthly frequency of total seizures** Median reduction from 24.0 to 13.7 in the cannabidiol group (adjusted reduction, 28.6%), versus a decrease from 41.5 to 31.1 in the placebo group (adjusted reduction, 9.0%). Adjusted median frequency of -19.2 percentage points (p = 0.03). **Caregiver global impression of change** 62% of the caregivers judged their child's overall condition improved in the cannabidiol group, compared with 34% in the placebo group (p = 0.02). **There was no significant difference in the other outcomes**

CI, confidence interval; IQR, interquartile range; OR, odds ratio.

group. Of the patients who had adverse events, 61% of the patients in the cannabidiol group and 64% of the patients in the placebo group, the events resolved by the end of the trial.

Common adverse events: Diarrhea (IG 13%; CG 4%), somnolence (IG 14%; CG 8%), pyrexia (IG 1%; CG 1%), decreased appetite (IG 9%; CG 1%), and vomiting (IG 7%; CG 5%).

Adverse events leading to discontinuation: 14% in the cannabidiol group and 1% in the placebo group. The most common treatment-related adverse events that led to withdrawal were collectively reported in three patients and comprised increased alanine aminotransferase and aspartate aminotransferase concentrations (all three patients) and increased gamma-glutamyltransferase concentrations (two patients). Only one patient in the cannabidiol group was withdrawn due to alanine aminotransferase and aspartate aminotransferase elevations

Two cases in the cannabidiol group reported hepatic failure but did not meet the diagnostic criteria for severe liver injury as the events occurred without elevations in bilirubin, and patients had a complete recovery. One patient in the cannabidiol group died due to respiratory failure, which was considered unrelated to treatment. One patient in the placebo group withdrew due to monoplegia that was considered treatment-related. 7% of the patients in the cannabidiol group and 1% in the placebo group had adverse events that led to a dose reduction of the investigational medicinal product. The most common events were vomiting (two patients in the cannabidiol group vs. one in the placebo group) and sedation (two patients in the cannabidiol group).

Serious adverse events: Reported in 23% of the patients in the cannabidiol group and 5% of the patients in the placebo group. Two patients in the cannabidiol group had serious adverse events at the end of the trial: one patient died due to acute respiratory distress syndrome, and one had had ongoing sleep apnea (considered treatment-related) and status epilepticus (not considered treatment-related). Most common serious treatment-related adverse events (occurring in > 3% of patients):

Cannabidiol group: increased alanine aminotransferase concentration (four patients), increased aspartate aminotransferase concentrations (four patients), and increased gamma-glutamyltransferase concentrations (three patients). Pneumonia and acute respiratory failure (two patients on clobazam), pneumonia alone (three patients, two of which on clobazam), and acute respiratory failure (one patient on clobazam). Placebo group: pneumonia alone (one placebo patient on clobazam). Increases in alanine aminotransferase or aspartate aminotransferase (>three times the upper limit of normal), regardless of whether they were reported as adverse events, occurred in one patient in the placebo group and 20 patients in the cannabidiol group; 16 of these patients in the cannabidiol group were on concomitant valproate.

Six patients in the cannabidiol group withdrew from treatment due to adverse events associated with increases in alanine or aspartate aminotransferase concentrations. A seventh patient met the criteria for withdrawal

(alanine aminotransferase concentrations >three times the upper limit of normal, with fatigue and vomiting) but was discontinued for non-compliance.

All elevations in alanine or aspartate aminotransferases resolved either spontaneously during treatment (eight patients in the cannabidiol group versus one in the placebo group), after a reduction in the concomitant valproate dose (three patients in the cannabidiol group), after tapering or cessation of cannabidiol (six patients in the cannabidiol group), or after entry into the open-label extension trial (three patients in the cannabidiol group).

According to Devinsky *et al*. (2018)[20], adverse events were reported in 77 patients (94%) in the 20-mg cannabidiol group (IG20), 56 patients (84%) in the 10-mg cannabidiol group (IG10), and 55 patients (72%) in the placebo group (CG).

Common adverse events: Somnolence (IG20 30%; IG10 21%; CG 5%), decreased appetite (IG20 26%; IG10 16%; CG 8%), diarrhea (IG20 15%; IG10 10%; CG 8%), upper respiratory tract infection (IG20 13%; IG10 16%; CG 14%), and pyrexia (IG20 12%; IG10 9%; CG 16%). Adverse events leading to discontinuation: A total of eight patients discontinued cannabidiol or placebo due to adverse events and were withdrawn from the trial (six in the 20-mg cannabidiol group, one in the 10-mg cannabidiol group, and one in the placebo group). Elevation of serum aminotransferase concentrations was the most common adverse event among these patients, occurring in four of the six patients in the 20-mg cannabidiol group and in the 10-mg cannabidiol group, with maximum elevations in aspartate aminotransferase or alanine aminotransferase concentrations that were 3.2 to 12.2 times the upper limit of the normal range.

Serious adverse events: were reported in 33 patients (13 in each cannabidiol group and seven in the placebo group). Among the 26 patients in the cannabidiol groups that had serious adverse events, the events were considered by the investigator to be related to the cannabidiol treatment in seven patients (one patient had multiple events); these events included elevated aspartate aminotransferase concentration (two patients), elevated alanine aminotransferase concentration (one patient), elevated gamma-glutamyltransferase concentration (one patient), somnolence (one patient), increased seizures during weaning (one patient), nonconvulsive status epilepticus (one patient), lethargy (one patient), constipation (one patient), and worsening chronic cholecystitis (one patient). Increases in serum aminotransferase concentrations greater than 3 times the upper limit of the normal range occurred in 14 (9%) of the patients who received cannabidiol (11 in the 20-mg group and 3 in the 10-mg group). Of these 14 patients, 11 (79%; 9 patients in the 20-mg group and 2 in the 10-mg group) were receiving valproic acid concomitantly.

No patient met the criteria for severe drug-induced liver injury, and all cases of elevated aminotransferase concentrations greater than 3 times the upper limit of the normal range resolved either spontaneously during the treatment period (three patients), after entry into the open-label extension trial

(two patients), or after the dose of cannabidiol was tapered, cannabidiol was discontinued, or the those of another antiepileptic drug was reduced (nine patients).

In Devinsky *et al*. (2017)[21], adverse events that emerged during treatment were reported in 93% of the patients in the cannabidiol group and 75% of the patients in the placebo group. Among the patients with adverse events, 89% had events of mild or moderate severity (84% in the cannabidiol group and 95% in the placebo group).

Common adverse events: Diarrhea (IG 31%; CG 10%) vomiting (IG 15%; CG 5%), fatigue (IG 20%; CG 3%), pyrexia (IG 15%; CG 8%), upper respiratory tract infection (IG 11%; CG 8%), decreased appetite (IG 28%; CG 5%), and somnolence (IG 36%; CG 10%). Adverse events leading to discontinuation: In the cannabidiol group, eight patients withdrew from the trial due to adverse events, compared with one patient in the placebo group.

Serious adverse events: Reported in ten patients in the cannabidiol group and three in the placebo group. Elevated levels of liver aminotransferase enzymes (alanine aminotransferase or aspartate aminotransferase level >3 times the upper limit of the normal range) led to withdrawal from the trial of 3 patients in the cannabidiol group and 1 in the placebo group. Overall, elevated aminotransferase levels occurred in 12 patients in the cannabidiol group and one in the placebo group. All these patients were taking a form of valproate. In the other nine cases of raised aminotransferase levels in which the patient continued in the trial, the enzyme levels returned to normal while the patient was receiving cannabidiol.

DISCUSSION

The Lennox-Gastaut syndrome has as its main characteristic the presence of atypical absence seizures, drop seizures, myoclonic seizures, and mental retardation. These seizures usually begin before eight years of age, with a higher incidence from 3 to 5 years[22]. Nearly all children with Lennox-Gastaut syndrome develop learning problems and intellectual disability. Many also show delayed development of motor skills, such as sitting and crawling. Most people with Lennox-Gastaut syndrome need help with activities of daily living[23]. In turn, Dravet syndrome is a rare genetic condition that emerges during the first year of life, with frequent fever-associated seizures (febrile seizures). It is later marked by the emergence of other types of seizures, including myoclonic seizures (involuntary muscle spasms). Furthermore, the status epilepticus may also occur, a potentially lethal seizure with a continuous convulsive activity that requires emergency health care. Children with Dravet syndrome usually show poor motor skills and language development, hyperactivity, and difficulty dealing with other people[24].

In two of the studies included, there was a prevalence of patients with less than 18 years, with a mean age of 15.5 and 16.0[19,20]. Even though the inclusion criteria established patients with Lennox-Gastaut syndrome with age from 2 to 55 years, while in the study by Devinsky *et al.* (2017) the inclusion criterion established patients with Dravet syndrome

with age from 2 to 18 years, with a mean age of 9.7.

In the study by Cunha *et al.* (1980)[25], patients and volunteers, throughout the entire experimental period, tolerated cannabidiol very well, and no signs of toxicity or serious side effects were detected on examination. Four of the eight subjects that received cannabidiol remained almost free of convulsive seizures during the experiment, and other three patients showed partial improvement in their clinical condition. It is seen that the benefits of cannabidiol against epilepsy have been reported since 1980.

The three articles, written by Thiele *et al.* (2018), Devinsky *et al.* (2018) and Devinsky *et al.* (2017)[19-21] showed that all parameters and outcomes observed in these studies were also positive, and the group that received cannabidiol obtained a significant improvement regarding seizure reduction. Devinsky *et al.* (2014)[26] affirmed that the use of cannabidiol reduced the frequency of convulsive seizures, showing a safety profile in the population with highly treatment-resistant epilepsy (Devinsky *et al.*, 2016)[27]. Examples of highly resistant epilepsy are the Lennox-Gastaut syndrome and the Dravet syndrome[28,29].

Cannabidiol is safe and well-tolerated in humans at high doses and with chronic use. However, it showed potential drug metabolism interactions, cytotoxicity, and decreased receptor activity[30-32]. Diarrhea, somnolence, pyrexia, decreased appetite, vomiting, and upper respiratory tract infection were the most common adverse events reported. Another very cited adverse event was elevated concentrations of the alanine aminotransferase, aspartate aminotransferase, and gamma-glutamyltransferase enzymes[19-21]. These serum transaminases are clinical laboratory markers of liver injury[33].

For safety reasons, six patients were withdrawn from treatment in the study by Thiele *et al.* (2018)[19] due to increased serum levels of alanine aminotransferases and aspartate aminotransferase. In Devinsky *et al.* (2018)[20] this increase was observed in 14 patients, but these were not withdrawn as they did not meet the criteria for severe liver injury. In Devinsky *et al.* (2017)[21], the elevation of the serum level of these enzymes was observed in 12 patients, but only three withdrew from the trial. In the three studies, it was observed that the patients who had elevated levels of alanine aminotransferases, aspartate aminotransferase, and gamma-glutamyltransferase were receiving valproic acid concomitantly, a drug that is also harmful to the liver, thus constituting a drug-interaction[34].

The benefit of cannabidiol was confirmed with the FDA (Food and Drug Administration) approval of the first drug made with cannabidiol, 99% pure, oral (Epidiolex, GW Pharmaceuticals, London, UK), indicated for the treatment of seizures associated with two rare and severe forms of epilepsy in patients with two years of age or more, the Lennox-Gastaut syndrome and the Dravet syndrome. The sector responsible for the manufacturing and commercialization of this drug used the studies by Thiele *et al.* (2018), Devinsky *et al.* (2018) and Devinsky *et al.* (2017)[19-21] as the scientific basis for the approval by the FDA. GW Pharmaceuticals

was responsible for providing the cannabidiol samples in the three studies and is the company that currently provides this drug in the United States of America[35,36].

CONCLUSION

This systematic review allowed to affirm that the administration of cannabidiol as a complementary anticonvulsant medication is capable of satisfactorily reducing epileptic seizures, especially when epilepsy is resistant to pharmacological treatment. When comparing the therapeutic and adverse effects produced by cannabidiol, the benefits to the patient are more relevant. Although the results are promising, to conduct new clinical trials to identify the effects obtained in continuous treatment is necessary. The execution of new studies, will enable other countries to approve its commercialization and cannabidiol can be purchased by all patients with refractory epilepsy.

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