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Effect Of The Use Of Cannabidiol On The Treatment Of Lennox-Gastaut Syndrome: A Systematic Review

Efeito Do Uso De Canabidiol No Tratamento Da Síndrome De Lennox-Gastaut: Uma Revisão

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ABSTRACT:

Objective: Lennox-Gastaut syndrome is a common and intractable epileptic encephalopathy. It is responsible for about 5% of all childhood epilepsies, causing symptoms such as seizures, behavioral changes and delay in child development. The treatment of this syndrome occurs in a combined way between the physiotherapeutic approach and drug intervention. However, due to the fact that anticonvulsants present high levels of toxicity and effective treatment incapacity, new approaches have been analyzed as a therapeutic intervention proposal, one of them being the use of medicinal plants such as Cannabis sativa. Based on this, this study aims to analyze the effectiveness of cannabidiol in clinical application for patients with Lennox-Gastaut Syndrome, through a systematic review of the literature. To carry out this study published in the last five years, were recruited in the MEDLINE/PubMed, Science Direct, Web of Science, Scopus, BVS/LILACS, SciELO, CAPES Periodicals, CENTRAL and CINAHL Complete databases. descriptors Cannabidiol and Lennox-Gastaut Syndrome, combined by the Boolean operator AND. The review research was registered in PROSPERO with the code CRD42021229584 and followed the criteria of the PICO strategy. From the analysis and careful investigation of the results of the databases, two articles were included in the study, selected from the screening of 540 studies. The discussion of the articles was based on criteria that define the pharmacological parameters, the side effects of cannabidiol and the effects on the quality of life of individuals. Therefore, the study demonstrated that cannabidiol is effective in the clinical condition of patients with Lennox-Gastaut Syndrome, but further studies are needed to more selectively investigate toxicity, optimal dosage, product shelf life, as well as possible drug interactions and effects. collaterals.

KEYWORDS: Cannabis; Quality of life; Naturals Extracts; Lennox-Gastaut

RESUMO:

Objetivo:A síndrome de Lennox-Gastaut é uma encefalopatia epiléptica comum e intratável. É responsável por cerca de 5% de todas as epilepsias infantis, causando sintomas como convulsões, alterações de comportamento e atraso no desenvolvimento infantil. O tratamento para essa síndrome ocorre de forma combinada entre a abordagem fisioterapêutica e a intervenção medicamentosa. No entanto, como os anticonvulsivantes apresentam altos níveis de toxicidade e incapacidade efetiva para o tratamento, novas abordagens têm sido analisadas como proposta de intervenção terapêutica, sendo uma delas o uso de plantas medicinais como a Cannabis sativa. Com base nisso, este estudo tem como objetivo analisar a eficácia do canabidiol em aplicação clínica para pacientes com Síndrome de Lennox-Gastaut, por meio de uma revisão sistemática da literatura. Para a realização deste estudo, foram recrutados artigos publicados nos últimos cinco anos, nas bases de dados MEDLINE / PubMed, Science Direct, Web of Science, Scopus, BVS / LILACS, SciELO, Periódicos CAPES, CENTRAL e CINAHL. os descritores Cannabidiol e Lennox-Gastaut Syndrome, combinados pelo operador booleano AND. A pesquisa de revisão foi registrada no PROSPERO com o código CRD42021229584 e seguiu os critérios da estratégia PICO. A partir da análise e investigação criteriosa dos resultados das bases de dados, foram incluídos no estudo dois artigos, selecionados a partir da triagem de 540 estudos. A discussão dos artigos foi realizada a partir de critérios que definem os parâmetros farmacológicos, os efeitos colaterais do canabidiol e os efeitos na qualidade de vida dos indivíduos. Portanto, o estudo demonstrou que o canabidiol é eficaz na condição clínica de pacientes com Síndrome de Lennox-Gastaut, mas mais estudos são necessários para investigar mais seletivamente a toxicidade, dosagem ideal, validade do produto, bem como possíveis interações medicamentosas e efeitos colaterais.

PALAVRAS-CHAVE: Cannabis; Qualidade de vida; Extratos naturais; Síndrome de Lennox-Gastaut.

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1 INTRODUCTION

Lennox-Gastaut Syndrome (LGS) is a severe and rare epileptic encephalopathy of multifactorial origin[1,2] . Symptoms tend to start before age eight; more than 90% of cases also persist into adulthood[1,2]. It has an incidence for 2 to 100,000 people and is responsible for 5 to 10% of seizures in pediatrics[3,4]. Its pathology is difficult to manage, as it is often resistant to pharmacological treatment[1,5]. The diagnostic criteria for LGS form a triad: (1) multiple types of seizures, mostly generalized, which can be tonic or atonic and evolve over years; (2) presence of intellectual deficit/cognitive impairment; (3) diffusive peak complex and slow beaker on electroencephalogram (EEG)[1].

One of the characteristics of this pathology are falls resulting from seizures (fall crisis), tonic alteration (increase or decrease in muscle tone) and loss of consciousness, which can result in serious injuries[2,3,6].

LGS manipulation addresses antiepileptic strategies, as well as the preservation of cognitive function, consisting of pharmacological treatment, usually composed of anticonvulsants associated with polypharmacy, and non-pharmacological treatment such as vagal stimulation, ketogenic diets or even palliative surgical treatment for patients in whom antiepileptic drugs are used. did not have the desired effect[5,7,8].

Among the treatment approaches for epileptic seizures is Cannabidiol (CBD) which is a Phyto cannabinoid derived from Cannabis Sativa and has potentially new multimodal mechanisms of action capable of reducing the frequency of seizures in vitro and in vivo, being effective and safe in drug-resistant treatment for epilepsy[9,10].

Therefore, this study seeks to analyze, from a systematic review of the literature, whether cannabidiol is effective in clinical application for patients with Lennox-Gastaut Syndrome. Among the reasons that justify this type of study, very important in current issues and still little addressed in everyday life, there is the possibility of contributing with relevant information to clinical practice and to the scientific community, providing scientific evidence in a totally safe way for field application in populations with Lennox-Gastaut Syndrome.

2 METHODS

2.1 PROTOCOL AND REGISTRY

The review protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO) in February 9, 2021 (CRD42021229584).

2.2 CRITERIA FOR TO CONSIDER STUDIES FOR TO REVIEW

The research question was: “What is the effect of cannabidiol use on the symptoms of individuals diagnosed with Lennox-Gastaut Syndrome?” Following the criteria of the PICO strategy, P (population, patient or problem): Lennox-Gastaut Syndrome (LGS); I (Intervention): Use for cannabidiol (CBD) extract; C (control or comparative intervention): Use

of others drugs, use of other natural extracts, or interventions based on placebo control; and O (outcome): reduction in symptoms.

2.3 TYPES OF STUDIES

This review included randomized controlled trials that reported use of CBD for people with LGS, without language restriction and in the last five years of publication, interventions that addressed CBD, CBD-associated therapy, CBD extract, pharmacokinetic or pharmacointeractive applicability of CBD. The primary outcome was a reduction in Lennox-Gastaut Syndrome symptoms. Studies that did not address the use of CBD in LGS were excluded, other types of studies, animal studies, uncontrolled clinical trial, quasi-experimental studies, duplicate studies, dissertation theses and clinical trial protocol were excluded.

2.4 ELECTRONIC SEARCH

Nine databases were used to search for appropriate documents that matched the objectives of this study. The National Library of Medicine (MEDLINE/PubMed), Science Direct, Web of Science, Scopus, Virtual Health Library – Latin American and Caribbean Health Science Literature (BVS/LILACS), Scientific Electronic Library Online (SciELO), Periódicos CAPES, Cochrane Central Register of Controlled Trials (CENTRAL) and Cinahl Information Systems (CINAHL Complete) were included using the combination of the following descriptors: < cannabidiol >, < Lennox Gastaut syndrome > and search terms and Boolean operations (< cannabidiol > [Termos MeSH] AND < Lennox Gastaut Syndrome >).

We performed a search for articles in the aforementioned data (databases), using the following protocol: step 1) analysis of articles titles; step 2) reading abstracts of articles that were identified in stage 1; step 3) reading of the article in its entirety after selection in step 2; and finally analyzing the article references of those that were read in full. Databases were searched for studies carried out until March 2021.

The level of agreement of inclusion/ exclusion between two groups (doubles) of researchers who examined the studies was obtained using the Kappa test. The Kappa test analyzes the agreement between the articles that were included and excluded by researchers. Kappa values below 0 are classified insignificant; of 0.01 to 0.20 are considered fair consent; 0.21 to 0.40 as moderate consent; 0.61 to 0.80 as a strong agreement; and from 0.81 to 0.99 as almost perfect agreement.

2.5 RESEARCH OTHERS RESOURCES

Free hand search, gray literature, references list, World Wide Web and personal collections of articles were performed by the authors using search terms and Boolean operators [(cannabidiol) AND (Lennox Gastaut Syndrome)] and studies dealing with interventions that addressed CBD, CBD-associated therapy, CBD extract, pharmacokinetic or

pharmacointeractive applicability of CBD.

2.6 STUDIES SELECT

Our review was performed according to the guidelines for systematic reviews and meta-analyses (PRISMA)[11] and followed the recommendations the International Peer Review of Electronic Search Strategies (PRESS) guideline[12.] Electronic searches were performed to identify the largest number of articles on CBD for LGS. Specific search strategies were developed for each database.

2.7 EXTRACTION AND DATA MANAGEMENT

A spreadsheet was created to collect information specific to our review, contained: author; year of publication; study design; participants, age; objectives; LGS level; assessment instrument; intervention; result; limitations; conclusions.

The analyses of selected articles were performed independently by for four authors according to the type of study selected, type of participants (age, gender, presence or absence comorbidities), type of intervention used (cannabidiol), as well as the type of control group (others intervention, placebo or non-intervention), randomization and blinding of participants, period and frequency, measured time points, results. A fifth reviewer adjusted discrepancies and disagreements.

2.8 ASSESSMENT OF METHODOLOGICAL QUALITY AND RISK OF BIAS IN INCLUDED STUDIES

Standard quality assessment criteria (Kmet checklist) were applied to assess the methodological quality of each study selected for inclusion. Risk scale and trend were reported, in relation to grade or level of quality. The checklist includes topics such as: question and purpose of the study description; study design; description of the method of selection groups and variable information sources, including sample size; randomization and blinding; exposure results and measures; analytical methods; controlled to confuse; detailed results and conclusions on the line.

A score was used to classify methodological quality rating: > 80% was considered strong quality; 70 to 79%, good quality; 50 to 69%, reasonable quality and < 50% was considered poor methodological quality.

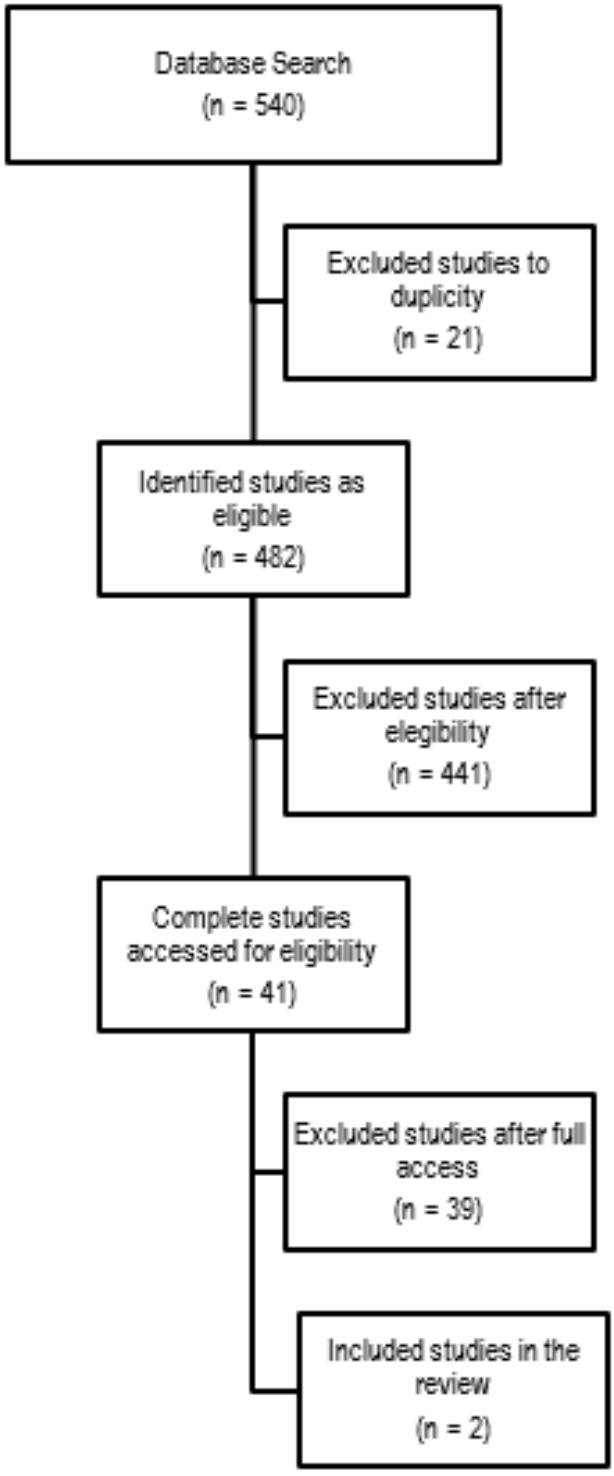
The Review Manager software (version 5.3 RevMan) was used to analyze the risk of bias in the selected studies. The assessment of the risk of bias is based on the establishment of individualized methodological quality of randomized controlled trial (RCT). According to the Cochrane manual, bias is defined as a systematic error, or deviation from the truth, in results or differences, in terms of selection, performance, detection, friction, communication and other biases and the researchers rate the studies as high, low or clear risks of bias for each domain.

Four researchers independently performed the methodological quality checklist and risk of bias tool and a fifth researcher adjusted the discrepancies and disagreements.

3 RESULTS AND DISCUSSION

The selection process found 540 studies. After excluding duplicates and screening abstracts, 41 studies were selected. A total of 2 studies met the inclusion criteria[25,27]. The entire process is described in Figure 1. There was a high level of agreement on inclusion/exclusion between the two investigators who reviewed the studies (Kappa > 83%). The detailed search strategy for each database is available in Appendix 1.

Figura 1: Flowchart of systematic search of review literature



According to the selected variables, the following data were obtained, shown in table 1.

Table 1: Synthesis of articles obtained in the bibliographic survey of this article

Author/Year	Title	Objective	Methodology	Results	Conclusion
(THIELE et al., 2018)	Cannabidiol in patients with seizures associated with Lennox-Gastaut syndrome (GWPCARE4): a randomized, double-blind, placebo-controlled phase 3 trial.	To evaluate the safety and efficacy of using Cannabidiol compared to placebo as adjuvant therapy to antiepileptic treatments in the control of seizures associated with Lennox-Gastaut Syndrome.	A sample of 171 individuals was recruited from 24 clinical centers and subsequently randomly allocated to the Cannabidiol group (n = 86) or to the placebo group (n = 85), all of whom received at least one dose of the proposed treatment in the study.	There was a mean percentage reduction in the frequency of seizures, with a monthly drop of 43.9% (IQR −69 • 6 to −1 • 9) in the intervention group (cannabidiol), and a drop of 21.8% (IQR −45 • 7 to 1 • 7) in the placebo group, with a mean difference of -17.21 between groups in the 14-week treatment period. Most adverse effects occurred mildly or moderately in 86% of patients in the intervention group and in 69% of individuals in the control group (placebo).	The use of cannabidiol is effective and has good tolerance in the treatment of patients who present seizures associated with Lennox-Gastaut Syndrome.
(DEVINSKY et al., 2018).	Effect of Cannabidiol on Drop Seizures in the Lennox–Gastaut Syndrome	To evaluate the efficacy and safety of cannabidiol associated with a conventional antiepileptic medication regimen in the treatment of seizures in patients with Lennox-Gastaut Syndrome.	A total of 225 patients from 30 clinical centers were recruited and assigned to the Cannabidiol 10 mg/Kg group (n = 73), Cannabidiol 20 mg/Kg group (n = 76) and placebo group (n = 76), in which 2 daily doses of the proposed treatment were administered for 14 weeks.	There was a mean percentage reduction in seizures of 37.2% in the group that received 10 mg/kg cannabidiol, 41.9% in the 20 mg/kg cannabidiol group, and 17.2% in the placebo group (p = 0.005 for the 20 mg cannabidiol group vs. placebo group, and p = 0.002 for the 10 mg cannabidiol group vs. placebo group) during the treatment period. Adverse effects were more present in the group with the highest dose of cannabidiol and 9% of patients who received cannabidiol had high concentrations of hepatic aminotransferase.	The addition of cannabidiol (10 mg/Kg or 20 mg/Kg) to conventional antiepileptic treatment resulted in reductions in the frequency of seizures when compared to placebo treatment of individuals with Lennox-Gastaut Syndrome.

For a more accurate analysis of the selected articles, the discussion was divided into three criteria: pharmacological parameters, side effects caused by the use of the drug and benefits presented in patients who adopt the treatment of LGS through drugs based on Cannabidiol.

3.1 CRITERIA 1. PHARMACOLOGICAL PARAMETERS

Approximately 1000 receptors called Phytocannabinoids are found in the Cannabis Sativa plant[13,14]. In the last century, two of these numerous substances were isolated, Tetrahydrocannabinol (THC) and Cannabidiol (CBD), which despite being similar in some aspects, both differ in their function and pharmacology, since CBD does not have psychoactive properties, which, in turn, makes it a great therapeutic enhancer when compared to THC[15,16].

Cannabidiol is a lipid substance, linked to proteins, with low water solubility, in addition to having anti-inflammatory and anticonvulsant properties[10,14]. Despite having little affinity with CB1 receptors (found in the Central Nervous System, linked to motor control and cognition) and CB2 (linked to the immune system), CBD is able to indirectly modulate the Endocannabinoid System (ECS) and block Anandamide (similar component to THC), increasing its capacity to activate CB1 and CB2 receptors that are G protein-coupled. These receptors have the function of regulating the body's psychic and immune activity, helping to reduce seizures[10,14,16].

The CBD is able to decrease the release of calcium between cells and neuronal hyperexcitability in the epithelial tissue, in addition to desensitizing the transient receptor potential vanilloid type 1 (TRPV1) channels, which play an important role in the transmission of painful stimuli, leading to a decrease in extracellular calcium[18-20]. It is also able to increase the concentration of adenosine, thus decreasing neuronal activity. This increase can activate presynaptic receptors (A1 and A2), which contributes to the anti-inflammatory and neuroprotective action. In addition, CBD tends to model GABA (gamma aminobutyric acid) receptors when given at low concentrations[18,20].

It is suggested that the potential anti-inflammatory capacity of CBD may be linked to several mechanisms, such as cytokine modulation and arachidonic acid manipulation. In addition to having antioxidant properties, it influences neutrophils and interacts with microglial cells, which induce CB2 receptors[18,21-23]. The 2-arachidonylglycerol (2-AG), which is produced in case of inflammation, will activate these cells through CB2, taking them to the inflamed site. In this way, CBD can antagonize this circuit, thus having an anti-inflammatory effect[21-23].

When compared to approved antiepileptic drugs, CBD is structurally unique and has potentially new multimodal mechanisms of action[10,24]. Newer antiepileptics seek to increase outcomes and reduce these seizures. So far, the use of CBD has proven to be safe and has shown good results[10,24]. There are no data on the use of this substance in the long term, however, it is known that its prolonged use can have harmful effects on the users' lives[24].

3.2 CRITERIA 2. CANNABIDIOL SIDE EFFECTS 3.3 CRITERIA

Studies suggest that using cannabidiol as adjunct therapy to existing antiepileptic drug regimens can significantly reduce seizure frequency in patients with Lennox-Gastaut syndrome[9,10,26]. However, the results also indicate that cannabidiol can lead to additional adverse events, which in general appears to be well tolerated [25,26].

In a previous study, it was reported that, the most frequent adverse events that led to withdrawal from the trial were transient elevations in liver enzymes[27]. About 61% of patients allocated to the cannabidiol group and 64% to the placebo group had adverse events resolved during the study[27]. They report that no adverse events related to so-called stoned-like effects were reported in the trial, which is consistent with a previous trial that sought to assess liability for cannabidiol abuse in people who smoke marijuana. Furthermore, it was observed that the proportion of patients who withdrew due to adverse events was similar or lower than those associated with the use of other antiepileptic drugs[27].

In the study by BRODIE & BEN-MENACHEM (2018)[10], the main adverse effects identified by the use of Cannabidiol were drowsiness, reduced hunger, intestinal disorder and fatigue, which corroborates the previous study[25]. It was also observed that CBD can influence the inhibition of some liver enzymes, such as CYP2C19, as has already been shown in the literature[27.] CYP2C19 is responsible for controlling the metabolism and organization of drugs; it is suggested that such effects may be associated with prolonged use of the drug, which can also lead to memory loss, failure in cognitive activities and liver problems, as it is metabolized in the liver28.

CBD does not show a cure; however, it is necessary and necessary to have reasonable expectations about its usefulness as an antiepileptic drug[10,27]. The misconception that CBD is free from adverse effects can be attributed to its derivation from a natural source, since natural extracts have a low level of toxicity for humans when contrasted with other therapies normally presented and chosen today, such as the drugs[10]. Therefore, adequate monitoring is necessary to supervise and manage the optimal dose, side effects, product validity and possible drug interactions[24].

3.3 CRITERIA 3. EFFECTS ON THE QUALITY OF LIFE OF INDIVIDUALS

Several studies have shown that the use of CBD is effective for treating seizures [9,10,24,25]. Furthermore, despite being used medicinally since ancient times, the mechanism of action and therapeutic potential of CBD have been without legitimacy, making further controlled studies necessary to indicate its safety and determine optimal doses in order to avoid toxicity and reduce its effectiveness[24]. Thus, with the increase in studies and evidence of improvements offered to pathologies, it is expected that countries will have greater acceptance, in order to open more paths for science regarding the medicinal use of cannabis[24].

Medical use and CBD treatment are associated with statistically and clinically important increases in adult patients enrolled in expanded activity[29]. From this perspective, cannabidiol presented advantages that are partially independent of the improvements observed in other measures, that is, the medication alon e cannot increase the Quality of Life[29]. It was from this study that significant improvements in severity, mood and adverse events were demonstrated for adult participants diagnosed with refractory epilepsy after treatment with CBD[29-31].

Among the studies, an open screening of cannabidiol in patients with childhood epilepsy of various causes

showed improvements in several components of quality of life[32,33]. What differs from the study by DEVINSKY et al. (2018), which after a general assessment of quality of life, showed no significant difference between cannabidiol and placebo[25].

On the other hand, a study produced in 2018 showed that the use of CBD had a positive outcome in the global impression of the patient and caregiver about the change in the duration of the seizures and the change in sleep interruption and daytime sleepiness, in quality of life and adaptive behaviors[27]. It also shows that the number of hospital admissions due to epilepsy was recorded and cognitive function was assessed during the analysis[27]. In addition, in this study it was included a response analysis, ie, the proportion of patients who achieved a ≥25%, ≥50%, ≥75% or 100% reduction in baseline fall seizures, and percentage change in the frequency of non-fall, convulsive (tonic-clonic, tonic, clonic or atonic), non-convulsive (myoclonic, countable focal, other focal or absence seizures) and individual seizure types[27].

Furthermore, despite the marginalization of Cannabis sativa, several studies that demonstrate and point to the need for CBD-based antiepileptic drugs in the market are taken into account[25]. Therapy with this alternative appears to improve results. Based on this, a study of children found that cannabidiol had positive effects on QoL that appeared to be at least somewhat independent of seizure control[33].

Finally, analyzing the treatment using CBD in children and adolescents with severe epilepsy, ROSENBERG et al. (2017) reported improvements in fatigue, memory, proprioception, sleep, as well as in cognitive and behavioral factors, thus influencing the increase in QoL[29].

3.4 ASSESSMENT OF THE QUALITY OF STUDIES

According to the standard quality assessment criteria (Kmet checklist), the two articles included in this systematic review presented reasonable methodological quality.

Assessment of the methodological quality of studies was performed using the Cochrane risk of bias tool for randomized trials. Based on this tool, both included articles (100%) present a quality risk of the included studies and presented in Figures 2 and 3. The included articles (100%) have 3 evaluated questions: blinding of the outcome evaluation, incomplete outcome data and selective reporting.

Figure 2: . Assessment of the methodological quality.

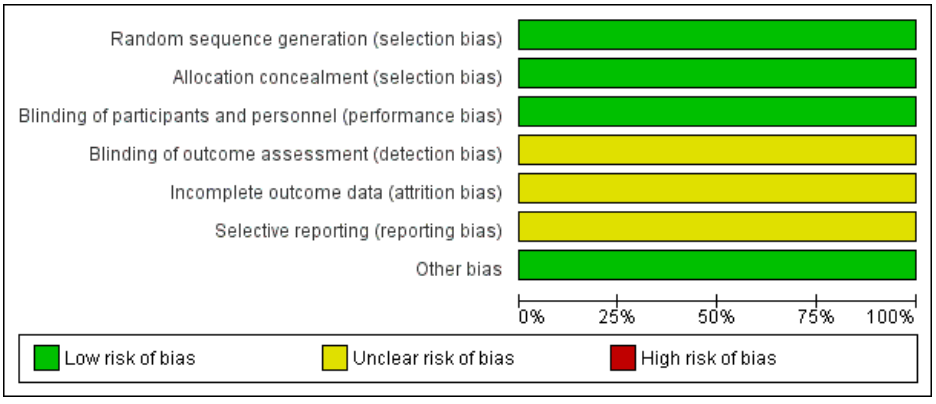
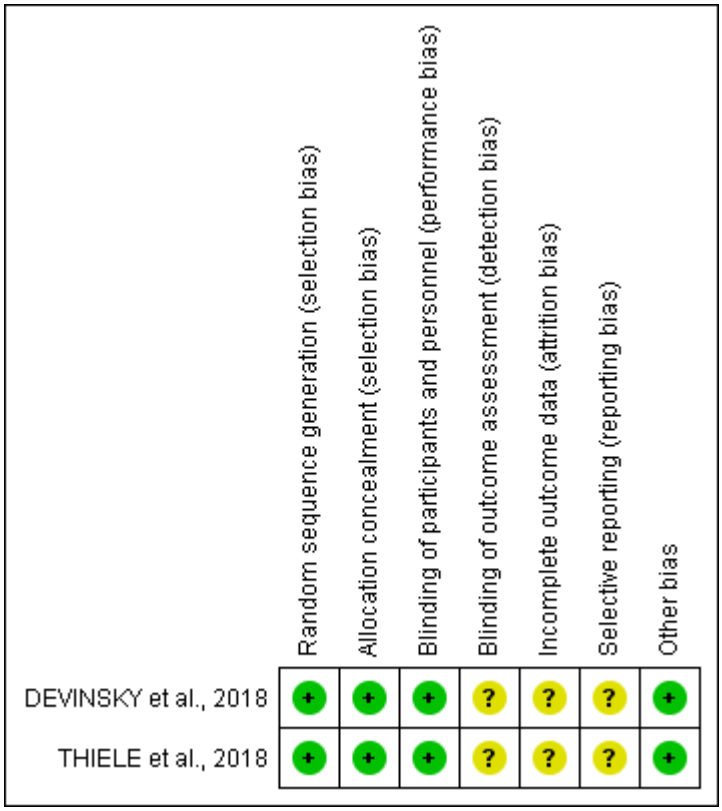


Figure 2: . Assessment of the methodological quality.



LIMITATIONS OF STUDIES

We searched the main databases, including all available evidence, however, we are aware of the existence of others that could also have eligible studies, for example, in gray literature. This fact introduces a potential limitation of the results for the study. In addition, due to the limited number of studies included, it was not possible to explore potential sources of heterogeneity. We were also unable to perform meta-analyses and deepen the analyzes related to the use of cannabidiol in the condition studied.

4 CONCLUSION

The therapeutic potential of Cannabidiol has beneficial effects in reducing the frequency of seizures in individuals with GLS. In general, CBD was well tolerated, causing transient adverse effects, thus constituting a favorable therapeutic resource for the treatment of this condition. It is also observed that CBD shows responsiveness in patients with LGS, although the mechanisms by which this occurs are not clearly presented.

In addition, in many cases, the use of CBD provides and offers improvements in the quality of life. On the other hand, some complications and interferences can occur during prolonged treatment, making multidisciplinary management

and referral of these patients essential and considerable, in order to provide and obtain the necessary support for the changes that occur during implanted therapy.

Therefore, there is a need for further studies in order to more closely investigate the levels of toxicity, the ideal dosage, the shelf life of the product, the possible drug interactions and the possible side effects that it may present.

4 REFERENCES

[1] Camfield PR. Definition and natural history of Lennox-Gastaut syndrome. Epilepsia. 2011 Aug;52 Suppl 5:3-9. doi: 10.1111/j.1528-1167.2011.03177.x.

[2] Asadi-Pooya AA. Lennox-Gastaut syndrome: a comprehensive review. Neurol Sci. 2018 Mar;39(3):403-414. doi: 10.1007/s10072-017-3188-y.

[3] Trevathan E, Murphy CC, Yeargin-Allsopp M. Prevalence and descriptive epidemiology of Lennox-Gastaut syndrome among Atlanta children. Epilepsia. 1997 Dec;38(12):1283-8. doi: 10.1111/j.1528-1157.1997.tb00065.x.

[4] Goldsmith IL, Zupanc ML, Buchhalter JR. Long-term seizure outcome in 74 patients with Lennox-Gastaut syndrome: effects of incorporating MRI head imaging in defining the cryptogenic subgroup. Epilepsia. 2000 Apr;41(4):395-9. doi: 10.1111/j.1528-1157.2000.tb00179.x.

[5] Verrotti A, Striano P, Iapadre G, Zagaroli L, Bonanni P, Coppola G, Elia M, Mecarelli O, Franzoni E, Liso P, Vigevano F, Curatolo P. The pharmacological management of Lennox-Gastaut syndrome and critical literature review. Seizure. 2018 Dec;63:17-25. doi: 10.1016/j.seizure.2018.10.016.

[6] Ferlazzo E, Adjien CK, Guerrini R, Calarese T, Crespel A, Elia M, Striano P, Gelisse P, Bramanti P, di Bella P, Genton P. Lennox-Gastaut syndrome with late-onset and prominent reflex seizures in trisomy 21 patients. Epilepsia. 2009 Jun;50(6):1587-95. doi: 10.1111/j.1528-1167.2008.01944.x.

[7] Michoulas A, Farrell K. Medical management of Lennox-Gastaut syndrome. CNS Drugs. 2010 May;24(5):363-74. doi: 10.2165/11530220-000000000-00000.

[8] Amrutkar C, Riel-Romero RM. Lennox Gastaut Syndrome. 2021 Aug 9. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 Jan–.

[9] Billakota S, Devinsky O, Marsh E. Cannabinoid therapy in epilepsy. Curr Opin Neurol. 2019 Apr;32(2):220-226. doi: 10.1097/WCO.0000000000000660.

[10] Brodie MJ, Ben-Menachem E. Cannabinoids for epilepsy: What do we know and where do we go? Epilepsia. 2018 Feb;59(2):291-296. doi: 10.1111/epi.13973.

[11] Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analy-

ses: The PRISMA statement. BMJ. 2009;339(7716):332-336. doi:10.1136/bmj.b2535

[12] McGowan J, Sampson M, Salzwedel DM, Cogo E, Foerster V, Lefebvre C. PRESS Peer Review of Electronic Search Strategies: 2015 Guideline Statement. J Clin Epidemiol. 2016 Jul;75:40-6. doi: 10.1016/j.jclinepi.2016.01.021

[13] Andre CM, Hausman JF, Guerriero G. Cannabis sativa: The Plant of the Thousand and One Molecules. Front Plant Sci. 2016;7:19. Published 2016 Feb 4. doi:10.3389/fpls.2016.00019

[14] Atakan Z. Cannabis, a complex plant: different compounds and different effects on individuals. Ther Adv Psychopharmacol. 2012;2(6):241-254. doi:10.1177/2045125312457586

[15] Rosenberg EC, Patra PH, Whalley BJ. Therapeutic effects of cannabinoids in animal models of seizures, epilepsy, epileptogenesis, and epilepsy-related neuroprotection. Epilepsy Behav. 2017 May;70(Pt B):319-327. doi: 10.1016/j.yebeh.2016.11.006

[16] Katona I. Cannabis and Endocannabinoid Signaling in Epilepsy. Handb Exp Pharmacol. 2015;231:285-316. doi: 10.1007/978-3-319-20825-1_10.

[17] Silvestro S, Mammana S, Cavalli E, Bramanti P, Mazzon E. Use of Cannabidiol in the Treatment of Epilepsy: Efficacy and Security in Clinical Trials. Molecules. 2019 Apr 12;24(8):1459. doi: 10.3390/molecules24081459.

[18] Franco V, Perucca E. Pharmacological and Therapeutic Properties of Cannabidiol for Epilepsy. Drugs. 2019 Sep;79(13):1435-1454. doi: 10.1007/s40265-019-01171-4.

[19] Muller C, Morales P, Reggio PH. Cannabinoid Ligands Targeting TRP Channels. Front Mol Neurosci. 2019 Jan 15;11:487. doi: 10.3389/fnmol.2018.00487.

[20] Vilela LR, Lima IV, Kunsch ÉB, Pinto HPP, de Miranda AS, Vieira ÉLM, de Oliveira ACP, Moraes MFD, Teixeira AL, Moreira FA. Anticonvulsant effect of cannabidiol in the pentylenetetrazole model: Pharmacological mechanisms, electroencephalographic profile, and brain cytokine levels. Epilepsy Behav. 2017 Oct;75:29-35. doi: 10.1016/j.yebeh.2017.07.014.

[21] Laprairie RB, Bagher AM, Kelly ME, Denovan-Wright EM. Cannabidiol is a negative allosteric modulator of the cannabinoid CB1 receptor. Br J Pharmacol. 2015 Oct;172(20):4790-805. doi: 10.1111/bph.13250.

[22] Tham M, Yilmaz O, Alaverdashvili M, Kelly MEM, Denovan-Wright EM, Laprairie RB. Allosteric and orthosteric pharmacology of cannabidiol and cannabidiol-dimethylheptyl at the type 1 and type 2 cannabinoid receptors. Br J Pharmacol. 2019 May;176(10):1455-1469. doi: 10.1111/bph.14440.

[23] Thomas A, Baillie GL, Phillips AM, Razdan RK, Ross RA, Pertwee RG. Cannabidiol displays unexpectedly high potency as an antagonist of CB1 and CB2 receptor agonists in vitro. Br J Pharmacol. 2007 Mar;150(5):613-23. doi: 10.1038/sj.bjp.0707133.

[24] Chen KA, Farrar MA, Cardamone M, Lawson JA. Cannabis for paediatric epilepsy: challenges and conundrums. Med J Aust. 2018 Feb 19;208(3):132-136. doi: 10.5694/mja17.00699.

[25] Devinsky O, Patel AD, Cross JH, Villanueva V, Wirrell EC, Privitera M, Greenwood SM, Roberts C, Checketts D, VanLandingham KE, Zuberi SM; GWPCARE3 Study Group. Effect of Cannabidiol on Drop Seizures in the Lennox-Gastaut Syndrome. N Engl J Med. 2018 May 17;378(20):1888-1897. doi: 10.1056/NEJMoa1714631.

[26] Koo CM, Kim SH, Lee JS, Park BJ, Lee HK, Kim HD, Kang HC. Cannabidiol for Treating Lennox-Gastaut Syndrome and Dravet Syndrome in Korea. J Korean Med Sci. 2020 Dec 28;35(50):e427. doi: 10.3346/jkms.2020.35.e427.

[27] Thiele EA, Marsh ED, French JA, Mazurkiewicz-Beldzinska M, Benbadis SR, Joshi C, Lyons PD, Taylor A, Roberts C, Sommerville K; GWPCARE4 Study Group. Cannabidiol in patients with seizures associated with Lennox-Gastaut syndrome (GWPCARE4): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet. 2018 Mar 17;391(10125):1085-1096. doi: 10.1016/S0140-6736(18)30136-3.

[28] Gonçalves J, Rosado T, Soares S, et al. Cannabis and Its Secondary Metabolites: Their Use as Therapeutic Drugs, Toxicological Aspects, and Analytical Determination. Medicines (Basel). 2019;6(1):31. Published 2019 Feb 23. doi:10.3390/medicines6010031

[29] Rosenberg EC, Louik J, Conway E, Devinsky O, Friedman D. Quality of Life in Childhood Epilepsy in pediatric patients enrolled in a prospective, open-label clinical study with cannabidiol. Epilepsia. 2017 Aug;58(8):e96-e100. doi: 10.1111/epi.13815.

[30] Strzelczyk A, Schubert-Bast S. Expanding the Treatment Landscape for Lennox-Gastaut Syndrome: Current and Future Strategies. CNS Drugs. 2021 Jan;35(1):61-83. doi: 10.1007/s40263-020-00784-8.

[31] Raucci U, Pietrafusa N, Paolino MC, Di Nardo G, Villa MP, Pavone P, Terrin G, Specchio N, Striano P, Parisi P. Cannabidiol Treatment for Refractory Epilepsies in Pediatrics. Front Pharmacol. 2020 Sep 29;11:586110. doi: 10.3389/fphar.2020.586110.

[32] Stockings E, Zagic D, Campbell G, Weier M, Hall WD, Nielsen S, Herkes GK, Farrell M, Degenhardt L. Evidence for cannabis and cannabinoids for epilepsy: a systematic review of controlled and observational evidence. J Neurol Neurosurg Psychiatry. 2018 Jul;89(7):741-753. doi: 10.1136/jnnp-2017-317168.

[33] Gaston TE, Szaflarski M, Hansen B, Bebin EM, Szaflarski JP; UAB CBD Program. Quality of life in adults enrolled in an open-label study of cannabidiol (CBD) for treatment-resistant epilepsy. Epilepsy Behav. 2019 Jun;95:10-17. doi: 10.1016/j.yebeh.2019.03.035.

APPENDIX 1

Appendix 1. search strategy

Search	Query	Records retrieved
MEDLINE (Pubmed)	("cannabidiol"[MeSH Terms] OR "cannabidiol"[All Fields] OR "cannabidiolic"[All Fields]) AND ("lennox gastaut syndrome"[MeSH Terms] OR ("lennox"[All Fields] AND "gastaut"[All Fields] AND "syndrome"[All Fields]) OR "lennox gastaut syndrome"[All Fields])	150
Science Direct	("cannabidiol"[MeSH Terms] OR "cannabidiol"[All Fields] OR "cannabidiolic"[All Fields]) AND ("lennox gastaut syndrome"[MeSH Terms] OR ("lennox"[All Fields] AND "gastaut"[All Fields] AND "syndrome"[All Fields]) OR "lennox gastaut syndrome"[All Fields])	149
BVS	Cannabidiol e Lennox-Gastaut Syndrome	44
Web of Science	Cannabidiol e Lennox-Gastaut Syndrome	13
Cochrane Library	Cannabidiol in Title Abstract Keyword AND Lennox-Gastaut Syndrome	57
EMBASE	("cannabidiol"[MeSH Terms] OR "cannabidiol"[All Fields] OR "cannabidiolic"[All Fields]) AND ("lennox gastaut syndrome"[MeSH Terms] OR ("lennox"[All Fields] AND "gastaut"[All Fields] AND "syndrome"[All Fields]) OR "lennox gastaut syndrome"[All Fields])	25
Scielo	Cannabidiol e Lennox-Gastaut Syndrome	2
Scopus	Cannabidiol e Lennox-Gastaut Syndrome	55
Periódicos CAPES	Cannabidiol e Lennox-Gastaut Syndrome	45
Total		**540**