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USE OF CANNABIDIOL IN PATIENTS WITH REFRACTORY EPILEPSY: AN INTEGRATIVE REVIEW OF CLINICAL AND THERAPEUTIC EVIDENCE

USO DO CANABIDIOL EM PACIENTES COM EPILEPSIA REFRATÁRIA: REVISÃO INTEGRATIVA DAS EVIDÊNCIAS CLÍNICAS E TERAPÊUTICAS

USO DE CANNABIDIOL EN PACIENTES CON EPILEPSIA REFRACTARIA: REVISIÓN INTEGRADORA DE LA EVIDENCIA CLÍNICA Y TERAPÉUTICA

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ABSTRACT

This study presents an integrative review of the clinical and therapeutic evidence available on the use of cannabidiol (CBD) in patients with refractory epilepsy. This condition is characterized by resistance to conventional antiepileptic treatments, making seizure control a significant challenge for both patients and healthcare professionals. CBD, a non-psychoactive compound derived from *Cannabis sativa*, has shown promising potential in managing epileptic seizures, particularly in syndromes such as Dravet and Lennox-Gastaut. Based on the analysis of recent clinical studies, benefits have been observed regarding seizure frequency reduction, improved quality of life, and an acceptable safety profile when

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used under medical supervision. However, further studies are needed to standardize dosages and assess long-term effects. This review also highlights the importance of developing public policies that regulate access to treatment, ensuring safety and equity in the provision of this therapy.

Keywords: Cannabidiol. Refractory Epilepsy. Adjunct Treatment. Epileptic Syndromes. Quality of Life.

RESUMO

Este estudo apresenta uma revisão integrativa das evidências clínicas e terapêuticas disponíveis sobre o uso do canabidiol (CBD) em pacientes com epilepsia refratária. Essa condição é caracterizada pela resistência aos tratamentos antiepilépticos convencionais, tornando o controle das crises um desafio significativo para pacientes e profissionais de saúde. O CBD, um composto não psicoativo derivado da *Cannabis sativa*, tem demonstrado potencial no manejo das crises epilépticas, especialmente em síndromes como Dravet e Lennox-Gastaut. A partir da análise de estudos clínicos recentes, foram observados benefícios associados à redução da frequência das crises, à melhora na qualidade de vida e a um perfil de segurança aceitável, quando utilizado sob supervisão médica. No entanto, destaca-se a necessidade de estudos adicionais que padronizem as dosagens e avaliem os efeitos a longo prazo. O presente trabalho também ressalta a importância do desenvolvimento de políticas públicas que regulamentem o acesso ao tratamento, assegurando a segurança e equidade na oferta dessa terapia.

Palavras-chave: Canabidiol. Epilepsia Refratária. Tratamento Adjuvante. Síndromes Epilépticas. Qualidade de Vida.

RESUMEN

Este estudio presenta una revisión integradora de la evidencia clínica y terapéutica disponible sobre el uso de cannabidiol (CBD) en pacientes con epilepsia refractaria. Esta enfermedad se caracteriza por la resistencia a los tratamientos antiepilépticos convencionales, por lo que el control de las crisis supone un reto importante tanto para los pacientes como para los profesionales sanitarios. El CBD, un compuesto no psicoactivo derivado del *Cannabis sativa*, ha mostrado un potencial prometedor en el control de las crisis epilépticas, especialmente en síndromes como los de Dravet y Lennox-Gastaut. Según el análisis de estudios clínicos recientes, se han observado beneficios en cuanto a la reducción de la frecuencia de las crisis, la mejora de la calidad de vida y un perfil de seguridad aceptable cuando se utiliza bajo supervisión médica. Sin embargo, se necesitan más estudios para estandarizar las dosis y evaluar los efectos a largo plazo. Esta revisión también destaca la importancia de desarrollar políticas públicas que regulen el acceso al tratamiento, garantizando la seguridad y la equidad en la provisión de esta terapia.

Palabras clave: Cannabidiol. Epilepsia Refractaria. Tratamiento Adjunto. Síndromes Epilépticos. Calidad de Vida.

1 INTRODUCTION

Epilepsy is one of the most common neurological diseases, characterized by recurrent epileptic seizures that can significantly impact the quality of life of patients and their families. It is estimated that about 50 million people worldwide are affected by this condition, making it a global public health problem (Kanner; Bicchi, 2022). Although most individuals are able to control seizures with conventional antiepileptic drugs (EAMs), approximately 30% develop refractory or drug-resistant (RE) epilepsy, a condition that represents a therapeutic challenge and demands more effective clinical alternatives (Aneja; Jain, 2014; Dalic; Cook, 2016).

Refractory epilepsy is defined by the persistence of epileptic seizures, even with the appropriate use of two or more MAEs in therapeutic doses. This condition is associated with an increased risk of morbidity and mortality, cognitive and psychiatric impairments, and relevant social and economic limitations (Dalic; Cook, 2016; Silva et al., 2018). In this scenario, efforts are intensified in the search for new pharmacological options, highlighting the growing therapeutic interest in *Cannabis sativa*, especially cannabidiol (CBD), one of its main bioactive compounds.

Cannabidiol, unlike tetrahydrocannabinol (THC), does not have psychoactive effects, and is considered a promising therapeutic agent for several neurological and psychiatric conditions (Devinsky et al., 2014; Oak; Tannús, 2019). Its pharmacology has been widely studied, revealing complex mechanisms of action, with emphasis on the modulation of neuronal excitability, neurogenic inflammation and neuroprotection. Its effects include interaction with voltage-gated sodium channels and action on receptors of the endocannabinoid system (Ghovanloo et al., 2018; Sait et al., 2020; Huang et al., 2021).

Several clinical studies have evaluated the efficacy and safety of CBD in patients with refractory epilepsy, especially in severe pediatric epileptic syndromes, such as Dravet syndrome and Lennox-Gastaut syndrome (Bebin et al., 2018; Devinsky et al., 2017). The randomized clinical trial conducted by Devinsky et al. (2017) was a pioneer in demonstrating a significant reduction in seizure frequency in patients with Dravet syndrome treated with CBD, compared to placebo, laying the groundwork for its regulatory approval in several countries.

Additionally, data from expanded access programs and observational studies corroborate the clinical efficacy and good tolerability of cannabidiol in the long term, with a favorable safety profile and positive impact on patients' quality of life (Devinsky et al., 2019; Sands et al., 2019; Spezzia, 2022). However, relevant challenges remain, such as variability

in clinical responses, potential drug interactions, especially with clobazam, and the high cost of treatment (Rogawski, 2020; Uliel-Sibony et al., 2021).

In Brazil, the therapeutic use of cannabidiol was recently regulated by the Ministry of Health, with a specific indication for refractory epilepsies in children and adolescents, representing a significant advance in the incorporation of this therapy into the public health system (Brasil, 2021). At the same time, there has been a significant increase in the judicialization of access to medicine, evidencing both the interest of the population and the logistical and economic obstacles to its wide availability (Gurgel et al., 2019).

This integrative review aims to synthesize the available clinical and therapeutic evidence on the use of cannabidiol in patients with refractory epilepsy, contributing to the updating of scientific knowledge and subsidizing clinical practice, as well as the formulation of public health policies. Methodologically, the study adopts established guidelines for integrative reviews (Lakatos; Marconi, 2003; Whittemore; Knafl, 2015), covering clinical trials, observational studies, and recent systematic reviews (Lattanzi et al., 2021; Santos et al., 2019; Stockings et al., 2020).

1.1 REFRACTORY EPILEPSY: THERAPEUTIC CHALLENGES

Adequate control of epileptic seizures is essential to prevent the neurological and social consequences associated with the disease. However, refractory epilepsy imposes substantial limitations, since conventional treatments are insufficient to achieve complete or significant seizure remission in a significant subgroup of patients (Aneja; Jain, 2014; Dalic; Cook, 2016). This condition is related to a higher risk of injury, hospitalizations, development of comorbidities, and impaired quality of life (Kanner; Bicchi, 2022).

Several factors contribute to pharmacological resistance, including the etiological heterogeneity of epilepsy, alterations in the pharmacokinetic and pharmacodynamic processes of drugs, as well as the modulation of drug transporters and neuronal receptors (Younus; Reddy, 2018). In view of this scenario, the incorporation of alternative and complementary therapies becomes imperative in order to expand the therapeutic options for patients who do not have a satisfactory response to conventional regimens.

1.2 CANNABIDIOL: HISTORY, PHARMACOLOGY AND THERAPEUTIC POTENTIAL

The medicinal use of *Cannabis sativa* dates back millennia, with historical records that show its use in the relief of various symptoms (Gontiès; Araújo, 2003). Contemporary science

has resumed this interest, especially after the identification of phytocannabinoids and the endocannabinoid system in the human body, allowing the elucidation of the molecular mechanisms involved in their therapeutic effects (Devinsky et al., 2014).

Among the main compounds studied, cannabidiol (CBD) stands out for its non-psychoactive profile and for having anticonvulsant, anti-inflammatory, antioxidant, and neuroprotective properties (Carvalho; Tannús, 2019; Peixoto et al., 2020). Its mechanism of action is multifactorial, involving the modulation of ion channels, serotonergic receptors, components of the endocannabinoid system, and pathways related to neuroinflammation (Ghovanloo et al., 2018; Sait et al., 2020).

Preclinical studies have shown that CBD is able to reduce neuronal excitability and prevent the spread of epileptic seizures, which justifies its investigation in controlled clinical trials (Huang et al., 2021; Younus; Reddy, 2018). This evidence supported the development of purified pharmaceutical formulations of cannabidiol for therapeutic use.

1.3 CLINICAL EVIDENCE OF THE USE OF CANNABIDIOL IN REFRACTORY EPILEPSY

Clinical trials and observational studies demonstrate that cannabidiol (CBD) can reduce both the frequency and severity of epileptic seizures in patients with refractory epilepsies, especially in specific difficult-to-control syndromes (Bebin et al., 2018; Devinsky et al., 2017). Although variation in clinical response is observed, a significant proportion of patients show considerable improvement in seizure control (Carvalho et al., 2021; Pietrafusa et al., 2019).

It is relevant to highlight that the efficacy of CBD seems to be enhanced when administered in association with certain drugs, such as clobazam, due to pharmacokinetic interactions that increase the concentration of the active metabolite (Rogawski, 2020; Uliel-Sibony et al., 2021). However, there are still controversies regarding its efficacy alone and safety profile, and the reported adverse effects are generally mild to moderate, including somnolence, diarrhea, and changes in liver levels (Darina; Langley, 2023; Sands et al., 2019).

1.4 FINAL CONSIDERATIONS AND RELEVANCE OF THE REVIEW

In view of the growing scientific production on the subject and the demand for therapeutic alternatives in the management of refractory epilepsy, the present integrative review proposes to compile and critically analyze the available evidence on the use of cannabidiol, with the aim of guiding clinical professionals, researchers, and public policy

makers. This integrative approach allows the identification of gaps, trends, and consensus in the specialized literature, in addition to fostering the debate about the incorporation of CBD into clinical practices and health systems (Crossetti, 2012; Whittemore; Knafl, 2015).

2 METHODOLOGY

The present integrative review was conducted with the objective of gathering and critically analyzing the available scientific evidence on the use of cannabidiol (CBD) in patients with refractory epilepsy, considering clinical and therapeutic aspects. The methodology adopted strictly followed the precepts described by Whittemore and Knafl (2015), which propose an update of the integrative review method, expanding its capacity for synthesis, critical evaluation, and integration of the included studies.

2.1 TYPE OF STUDY

The integrative review is characterized by allowing the systematic analysis of multiple types of studies, quantitative, qualitative and theoretical, favoring a comprehensive understanding of the investigated phenomenon (Crossetti, 2012; Lee; Fracolli, 2008). This methodological approach was chosen for its ability to encompass the complexity of the use of cannabidiol in refractory epilepsy, whose evidence base is composed of randomized clinical trials, systematic reviews, case reports, as well as experimental and pharmacological studies (Devinsky et al., 2017; Silva et al., 2018).

2.2 SEARCH AND SELECTION PROCEDURES

The bibliographic search was carried out in the electronic databases PubMed, SciELO, Web of Science and LILACS, using the following descriptors in Portuguese and English: "cannabidiol", "refractory epilepsy", "drug-resistant epilepsy", "cannabidiol and epilepsy", "drug-resistant epilepsy", "medical cannabis" and "CBD and seizures". The Boolean operators "AND" and "OR" were used in combination, in order to expand the scope and sensitivity of the search.

The time frame comprised publications between the years 2014 and 2023, with the aim of contemplating the most recent advances and the growing scientific interest in the use of CBD as a therapeutic alternative for difficult-to-control forms of epilepsy (Devinsky et al., 2014; Silva et al., 2018).

2.3 INCLUSION AND EXCLUSION CRITERIA

Original studies, systematic reviews, meta-analyses, and case reports investigating the use of cannabidiol in patients with refractory epilepsy, both in pediatric and adult populations, published in Portuguese, English, or Spanish, were included in this review. Technical and normative documents, such as CONITEC reports (2021) and clinical guidelines, were also considered with the aim of contextualizing the regulatory and care aspects of the therapeutic use of CBD.

Articles that exclusively addressed non-drug-resistant forms of epilepsy, studies related to the recreational use of *Cannabis sativa*, publications without peer review, as well as those whose full text was not available for analysis were excluded.

2.4 STAGES OF THE REVIEW

The conduct of the review followed five fundamental steps:

1. **Identification of the problem and formulation of the guiding question**: What is the efficacy and safety of cannabidiol in the treatment of patients with refractory epilepsy? (Lakatos & Marconi, 2003).
2. **Literature search and selection of studies**: As detailed above, the search was performed with double independent review to minimize bias. The titles and abstracts were initially evaluated and, later, the full texts were read for the final decision of inclusion.
3. **Data extraction and organization**: Relevant information was extracted into spreadsheets, containing author, year, type of study, population, CBD dose, clinical outcomes, and main findings. Extraction was performed by two independent reviewers, with disagreements resolved by consensus.
4. **Critical analysis of the included studies**: Each article was evaluated for methodological quality, level of evidence and validity of the results, based on criteria adapted from the GRADE scale and the PRISMA statement (Liberati et al., 2009). Randomized controlled trials (RCTs) were prioritized for the analysis of therapeutic evidence (Devinsky et al., 2017; Bebin et al., 2018).
5. **Synthesis of results and discussion**: The extracted data were grouped into thematic categories that include: clinical efficacy of CBD, adverse effects, pharmacological mechanisms, drug interactions, and regulatory and social aspects.

2.5 QUALITY CONTROL AND BIAS

The methodological rigor of the review was ensured through the use of the PRISMA statement for systematic and integrative reviews, adapted to the context (Liberati et al., 2009; Whittemore & Knafl, 2015). Double screening and independent extraction reduced the risk of selection and interpretation bias, ensuring greater reliability.

To assess the risk of bias of the included clinical studies, criteria such as randomization, blinding, sample size, and follow-up were used (Devinsky et al., 2017; Sands et al., 2019). In addition, the heterogeneity of the studies was considered in the analysis of the synthesis of the results.

2.6 ETHICAL ASPECTS

As this is an integrative review based on published literature, there was no need for approval by a research ethics committee, as advised by the Brazilian National Health Council. However, the research respected ethical principles of integrity, transparency and correct attribution of sources.

2.7 SCOPE SCAN

Refractory epilepsy, also called drug-resistant epilepsy, is characterized by the failure to achieve control of epileptic seizures even after the adequate use of two or more antiepileptic drugs in therapeutic doses (Aneja; Jain, 2014; Dalic; Cook, 2016). The choice of cannabidiol as the focus of this review is justified by the growing evidence base supporting its therapeutic potential, either as monotherapy or as an adjuvant regimen, especially in difficult-to-manage severe epileptic syndromes, such as Dravet syndrome and Lennox-Gastaut syndrome (Devinsky et al., 2017; Pietrafusa et al., 2019).

2.8 JUSTIFICATION OF THE METHOD

The choice for integrative review, to the detriment of strict systematic review, was based on the need to contemplate different types of evidence, including experimental studies aimed at elucidating the pharmacological mechanisms of cannabidiol (Ghovanloo et al., 2018; Sait et al., 2020), as well as analyses regarding the social and legal aspects of medical cannabis use (Abuhasira et al., 2018; Gurgel et al., 2019).

This methodological approach enabled a holistic understanding of the application of cannabidiol in refractory epilepsy, integrating clinical, pharmacological, and contextual data, in order to support future research, therapeutic decisions, and public policy formulations.

3 RESULTS

The present integrative review analyzed a comprehensive set of clinical studies, systematic reviews, and case reports that investigated the use of cannabidiol (CBD) in patients with refractory epilepsy, with an emphasis on its therapeutic efficacy, safety profile, and mechanisms of action. The available body of evidence points out that CBD plays a relevant role as an adjuvant therapy in cases of epilepsy resistant to conventional treatment, especially in severe epileptic syndromes, such as Dravet and Lennox-Gastaut syndromes.

3.1 CLINICAL EFFICACY OF CANNABIDIOL IN REFRACTORY EPILEPSY

Randomized controlled clinical studies constitute the main evidence base on the use of cannabidiol (CBD) in the treatment of refractory epilepsy. The pioneering study by Devinsky et al. (2017) evaluated the efficacy of CBD in patients with Dravet syndrome, a severe form of childhood epilepsy resistant to traditional medications. The results showed an average reduction of 39% in the frequency of seizures among patients treated with cannabidiol, compared to 13% in the placebo group, with significant effects already in the first weeks of treatment. This is a reference study, both for its methodological robustness and for its clinical impact, showing a reduction in generalized tonic-clonic seizures, which are particularly difficult to control.

Similarly, Bebin et al. (2018) presented data from an expanded access program with pediatric and adult patients, confirming the maintenance of anticonvulsant effects in the long term, with a reduction in seizure frequency ranging between 40% and 50% after months of continuous treatment. These findings were corroborated by Sands et al. (2019), who highlighted not only the durability of the therapeutic response, but also the improvement in the quality of life of patients and their families.

Additionally, recent systematic reviews emphasize the efficacy of cannabidiol not only in Dravet syndrome, but also in other refractory epileptic encephalopathies, such as Lennox-Gastaut syndrome and developmental epilepsies associated with rare genetic conditions (Carvalho et al., 2021; Lattanzi et al., 2021). The meta-analysis conducted by Stockings et al. (2020) reinforces these findings, demonstrating the efficacy of CBD in significantly

reducing seizure frequency, especially tonic-clonic seizures and absence seizures, the latter often associated with elevated neurological morbidity in these patients.

3.2 MECHANISMS OF ACTION AND PHARMACOLOGICAL INTERACTIONS

The anticonvulsant effect of cannabidiol (CBD) is not directly mediated by the classical endocannabinoid system, but results from multiple mechanisms, including ion channel modulation, as well as anti-inflammatory and neuroprotective actions. In *vitro studies* show that CBD inhibits voltage-gated sodium channels, with emphasis on the Nav1.4 channel, which is essential in the regulation of neuronal excitability (Huang et al., 2021; Sait et al., 2020). Ghovanloo et al. (2018) also demonstrated that CBD reduces the current of these channels, which contributes to the stabilization of the neuronal membrane and the reduction of hyperexcitability characteristic of epileptic seizures.

In addition to the isolated mechanisms, Rogawski (2020) highlights that the association of CBD with clobazam can enhance its therapeutic efficacy. This pharmacokinetic interaction promotes an increase in plasma levels of the active metabolite of clobazam, amplifying the anticonvulsant effect of the combination. Without this association, the efficacy of CBD alone may be lower, which reinforces the importance of individualized evaluation of drug interactions in clinical management.

3.3 SAFETY PROFILE AND ADVERSE EVENTS

In terms of safety, cannabidiol (CBD) has shown a generally favorable profile. The most frequently reported adverse events include drowsiness, fatigue, diarrhea, and changes in appetite, most of which are mild, moderate, and transient (Devinsky et al., 2017; Bebin et al., 2018). It is important to highlight that, in some cases, intensified sleepiness was associated with interaction with benzodiazepines, which requires close clinical monitoring (Carvalho; Tannús, 2019).

Long-term follow-up studies show that CBD treatment is generally well tolerated, with low discontinuation rates related to adverse effects (Devinsky et al., 2019; Darina; Langley, 2023). Uliel-Sibony et al. (2021) observed that there is no significant development of tolerance to cannabidiol over time, which allows the maintenance of its therapeutic efficacy, a crucial aspect in both pediatric and adult patients with chronic epilepsy.

Despite the positive safety profile, some authors stress the need for additional studies on the side effects of CBD in special populations, such as the elderly and individuals with

multiple comorbidities. In addition, the importance of standardizing cannabis-based products is highlighted, in order to ensure consistency in the concentration and purity of the active ingredients (Abuhasira et al., 2018; Medeiros et al., 2020).

3.4 REGULATORY ASPECTS AND ACCESS TO TREATMENT

The use of cannabidiol (CBD) as a therapeutic alternative for refractory epilepsy has advanced significantly in the regulatory sphere. In Brazil, the National Health Surveillance Agency (Anvisa) has approved the use of CBD-based medicines for children and adolescents with refractory epilepsy, in accordance with the recommendations of the Ministry of Health (Brasil, 2021). This regulatory framework represents the official recognition of the efficacy and safety of cannabidiol for this indication, in addition to contributing to the expansion of access to treatment in the context of the public health system.

However, Gurgel et al. (2019) highlight that, despite regulatory advances, access to CBD is still limited by economic, bureaucratic, and structural barriers. Many patients depend on court decisions to obtain medicines, which highlights the phenomenon of judicialization of health. This context reveals not only inequalities in access to innovative therapies, but also the urgency of implementing more equitable and inclusive public policies, which guarantee the regular and affordable supply of these drugs to the population.

3.5 COMPLEMENTARY CLINICAL EVIDENCE AND REAL-WORLD USE

Clinical case reports and observational studies contribute in a relevant way to complement the findings of randomized controlled trials. Oliveira et al. (2020) described the significant improvement of a patient with Zellweger syndrome after the introduction of cannabidiol as an adjuvant therapy, observing a reduction in the frequency of epileptic seizures and an improvement in cognitive performance. These reports reinforce the applicability of CBD in different refractory epileptic conditions, including in rare and complex conditions.

Studies of "real-world" use also demonstrate that, even in patients with a history of multiple treatment failures, CBD can represent an effective and safe option. Darina and Langley (2023) showed that patients undergoing cannabidiol therapy maintained adherence to treatment and achieved partial or total control of seizures over several years, even in polypharmacy regimens. These findings reinforce the importance of longitudinal follow-up and therapeutic personalization in the management of refractory epilepsy.

3.6 LIMITATIONS OF CURRENT EVIDENCE AND FUTURE DIRECTIONS

Despite the promising evidence, some methodological limitations are still evident in part of the studies analyzed, including small sample size, heterogeneity of the populations evaluated, in addition to variations in the formulations and dosages used of cannabidiol. Silva et al. (2018) highlight the need for randomized, multicenter clinical trials with more robust samples, in order to consolidate the efficacy and safety of CBD in the treatment of refractory epilepsy.

Another relevant aspect refers to the in-depth investigation of the neurophysiological mechanisms of CBD, with the aim of developing more specific formulations and reducing the occurrence of adverse effects. Additionally, the therapeutic potential of cannabidiol in other neurological conditions often associated with epilepsy, such as mood and anxiety disorders, should be explored (Pimentel et al., 2017; Younus; Reddy, 2018).

3.7 FINAL CONSIDERATIONS

In summary, the integrated results of this review indicate that cannabidiol (CBD) is a valid, safe and effective therapeutic alternative for patients with refractory epilepsy, especially in severe epileptic syndromes of genetic or structural origin. Its use should be conducted under strict medical monitoring, with attention to possible drug interactions and the individual clinical characteristics of each patient.

The incorporation of CBD into the therapeutic arsenal represents a significant advance in the treatment of resistant epilepsy, contributing to the reduction of the frequency and severity of seizures, in addition to promoting improvements in the quality of life and overall functioning of patients. Such benefits are especially relevant in the pediatric and adolescent population, which traditionally faces greater therapeutic challenges and morbidity associated with the disease.

4 DISCUSSION

The use of cannabidiol (CBD) in the treatment of refractory epilepsy has been shown to be a promising therapeutic alternative, especially in patients who do not respond adequately to conventional treatments with antiepileptic drugs (EAMs). Refractory, or drug-resistant, epilepsy is defined by the failure to control epileptic seizures even after the proper use of at least two MAEs, a condition that affects approximately 30% of patients with epilepsy (Aneja; Jain, 2014; Dalic; Cook, 2016). In this context, CBD, a non-psychoactive component

of *Cannabis sativa*, has aroused growing interest in the scientific community due to its anticonvulsant potential and relatively favorable safety profile (Devinsky et al., 2014; Oak; Tannús, 2019).

Several clinical studies and systematic reviews have consolidated the evidence on the efficacy of CBD in specific epileptic syndromes, such as Dravet and Lennox-Gastaut syndromes, considered models of severe refractory epilepsy (Devinsky et al., 2017; Lattanzi et al., 2021). A notable example is the seminal study by Devinsky et al. (2017), published in the *New England Journal of Medicine*, which demonstrated a significant reduction in seizure frequency in patients with Dravet syndrome treated with CBD, compared to placebo. These findings were corroborated by extension studies, which indicated maintenance of the efficacy and safety of the treatment in the long term (Devinsky et al., 2019; Bebin et al., 2018).

The present integrative review reinforces the efficacy of CBD in reducing seizures in patients with refractory epilepsy, especially when associated with drugs such as clobazam, which potentiate the effects of cannabidiol (Rogawski, 2020). The pharmacological interaction between CBD and clobazam seems to be a key factor for therapeutic success, since CBD raises plasma levels of the active metabolite of clobazam, contributing to better seizure control (Santos; Scherf; Mendes, 2019; Gaston; Szaflarski, 2018). On the other hand, when used alone, CBD can have reduced efficacy and, in some cases, even aggravate seizures, which highlights the importance of close monitoring and individualized dose adjustment (Rogawski, 2020).

In addition to efficacy, the safety profile of CBD has been widely discussed in the literature. The most frequently reported adverse effects are generally mild and include fatigue, diarrhea, changes in appetite, and drowsiness, with a low incidence of serious adverse events (Bebin et al., 2018; Szaflarski et al., 2018). Even so, constant clinical follow-up is essential, considering that CBD can interact with other medications, requiring therapeutic adjustments to avoid toxicity (Kanner; Bicchi, 2022). The absence of the typical psychoactive effects of tetrahydrocannabinol (THC), another compound in cannabis, makes CBD a safer option, especially for children and adolescents, the group most affected by refractory forms of epilepsy (Carvalho et al., 2021; Medeiros et al., 2020).

The discussion about CBD's mechanisms of action expands the understanding of its therapeutic potential. Cannabidiol acts on multiple molecular targets related to neuronal excitability, including the modulation of ion channels, such as the voltage-gated sodium channels Nav1.4, which influence the propagation of brain electrical activity (Sait et al., 2020;

Huang et al., 2021). The inhibition of these channels contributes to the stabilization of the neuronal membrane, reducing the hyperexcitability characteristic of epileptic seizures (Ghovanloo et al., 2018). In addition, CBD has anti-inflammatory and neuroprotective properties that can improve the brain microenvironment in patients with chronic epilepsy (Younus; Reddy, 2018; Pietrafusa et al., 2019).

Despite the advances, there are important challenges to be faced in the use of CBD for refractory epilepsy. Variability in individual response and regulatory issues still limit access to and standardization of treatments (Abuhasira; Shbiro; Landschaft, 2018; Gurgel et al., 2019). In Brazil, for example, the National Health Surveillance Agency (Anvisa) authorized the use of CBD-based products for specific cases, but the high cost and the need for specialized prescription restrict its reach (Brasil, 2021).

The legal demand for access to cannabidiol has grown, indicating a gap between public policies and actual clinical needs (Gurgel et al., 2019). Thus, it is essential that health policies expand access to CBD with quality assurance, so that more patients with refractory epilepsy can benefit from this emerging therapeutic resource.

In addition, the literature points to the need for clinical studies with greater methodological rigor and larger samples, which evaluate the efficacy of CBD in other forms of refractory epilepsy in addition to the syndromes already studied (Lattanzi et al., 2021; Stockings et al., 2020). The inclusion of data on quality of life, cognitive and neuropsychiatric effects is also essential to understand the full impact of treatment (Crippa; Hallak; Zuardi, 2020).

According to the integrative review methodology, which gathers evidence from multiple studies with scientific rigor, it was possible to identify that cannabidiol constitutes an important but complementary therapeutic advance in the management of refractory epilepsy (Whittemore; Knafl, 2015; Crossetti, 2012). It does not replace traditional medications, but it represents a valuable option for patients who do not respond to them, contributing to the reduction of seizure frequency and improving prognosis (Lu et al., 2023; Darina; Langley, 2023).

Finally, the importance of multidisciplinary follow-up for the management of CBD treatment is highlighted, involving neurologists, psychiatrists, pharmacists and nursing professionals trained to monitor adverse effects, drug interactions and respond to the needs of patients (Lopes; Fracolli, 2008; Peixoto et al., 2020). The education of patients and family

members is also essential to ensure adherence and correct use of the medication (Caraballo; Valenzuela; Dermijian, 2022).

In summary, the use of cannabidiol in patients with refractory epilepsy presents robust clinical evidence supporting its efficacy and safety, especially in severe epileptic syndromes. Recent scientific and regulatory advances offer new perspectives for treatment, but still require additional research to optimize protocols, expand access, and ensure the best quality of life for these patients.

5 CONCLUSION

The integrative analysis of the available clinical and therapeutic evidence indicates that cannabidiol (CBD) has significant potential as an adjuvant option in the control of epileptic seizures, especially in difficult-to-manage syndromes. The studies analyzed demonstrate relevant reductions in the frequency of seizures and improvements in the quality of life of patients, with a safety profile considered acceptable when used under medical monitoring.

Despite the advances, important challenges persist, such as variability in individual response, possible drug interactions, and the lack of standardization regarding doses and formulations. There is also evidence of the need for additional long-term investigations confirming the sustained efficacy and safety of the treatment in different populations.

In addition to the clinical aspects, the importance of formulating public policies that ensure regulated and safe access to CBD is highlighted, promoting equity and responsibility in the use of this emerging therapy.

In this way, cannabidiol is consolidated as a promising therapeutic tool in the management of refractory epilepsy, especially for patients who do not obtain a satisfactory response to conventional treatments. Its inclusion in clinical protocols requires rigorous multidisciplinary follow-up, focusing on efficacy, safety, and improved quality of life. The advancement of research and the strengthening of health policies will be fundamental for its consolidation as a viable and effective alternative in the fight against resistant epilepsy.

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