

Use of cannabidiol for the control of refractory symptoms in convulsive syndromes and neurodegenerative diseases

DOI: 10.5377/alerta.v6i1.15563

Laura Sofía Díaz Rodríguez^{1*}, Alejandra Elizabeth López Mirón², Alberto Armando Romero Olmedo³

1-3. Dr. José Matías Delgado University, Santa Tecla, El Salvador.

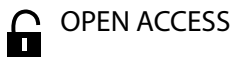
* Correspondence

✉ laura.diazr03@gmail.com

1.  0000-0002-8154-782X

2.  0000-0003-4843-6367

3.  0000-0002-9098-9945



OPEN ACCESS

Uso de cannabidiol para el control de síntomas refractarios en síndromes convulsivos y enfermedades neurodegenerativas

Suggested citation:

Díaz Rodríguez LS, López Mirón AE, Romero Olmedo AA. Use of cannabidiol for the control of refractory symptoms in convulsive syndromes and neurodegenerative diseases. *Alerta*. 2023;6(1):78-85. DOI: 10.5377/alerta.v6i1.15563

Received:

October 3, 2022.

Accepted:

January 19, 2023.

Published:

January 30, 2023.

Author contribution:

DRLS¹, LMAE², ROAA³: creation of the title and research objectives, exhaustive search of information in multiple databases, writing of introduction, development and conclusions of the review article, correction of observations made by advisor and thesis reviewer.

Conflicts of interest:

The authors have no conflict of interest.

Abstract

As part of the alternative therapies for the control of refractory symptoms in advanced diseases, the use of cannabidiol stands out. It has been studied in pathologies such as Alzheimer's disease, Parkinson's disease, and convulsive disorders. Convulsive syndromes are present in all age groups. Within this group, epilepsy is refractory in up to 40 % of patients, who have shown a decrease in the frequency of seizures with the concomitant use of cannabidiol and conventional antiepileptics, with mild side effects such as diarrhea and drowsiness. To determine the use of cannabidiol for the control of refractory neurological symptoms in patients with seizure syndromes and neurodegenerative diseases, a literature search was performed in Pubmed, Scopus, and Embase. Meta-analyses, original articles, systematic and literature reviews, and documents from the Pan American Health Organization, published between 2017 and 2022, were included. The effects of cannabidiol make it an alternative, in addition to conventional therapeutics, for symptom control in neurological disorders, sustainably decreasing the total number of episodes with an acceptable safety profile. There is limited information regarding the use of cannabidiol in neurodegenerative diseases, the reason its effectiveness has not been demonstrated.

Keywords

Cannabidiol, refractory epilepsy, neurodegenerative diseases, neurological manifestations.

Resumen

Como parte de las terapias alternativas para el control de síntomas refractarios en enfermedades avanzadas destaca el uso de cannabidiol. Este se ha estudiado en patologías como enfermedad de Alzheimer, Parkinson y trastornos convulsivos. Los síndromes convulsivos están presentes en todos los grupos etarios. Dentro de este, la epilepsia es refractaria hasta en un 40 % de los pacientes, quienes han demostrado disminución en la frecuencia de convulsiones con el uso concomitante de cannabidiol y antiepilépticos convencionales, con efectos secundarios leves, como diarrea y somnolencia. Con el objetivo de determinar el uso del cannabidiol para el control de síntomas neurológicos refractarios en pacientes con síndromes convulsivos y enfermedades neurodegenerativas, se realizó una búsqueda bibliográfica en Pubmed, Scopus y Embase. Se incluyeron metaanálisis, artículos originales, revisiones sistemáticas y bibliográficas, y documentos de la Organización Panamericana de la Salud, publicados entre 2017 y 2022. Los efectos del cannabidiol lo convierten en una alternativa, adicional a la terapéutica convencional, para el control de síntomas en trastornos neurológicos, disminuyendo de forma sostenida el número total de episodios con un perfil de seguridad aceptable. Existe limitada información respecto al uso de cannabidiol en enfermedades neurodegenerativas, por lo que no se ha evidenciado su efectividad.

Palabras clave

Cannabidiol, epilepsia refractaria, enfermedades neurodegenerativas, manifestaciones neurológicas.

Introduction

Current therapy for advanced diseases is oriented towards symptom control rather than halting their progression. However, this usually has low efficacy, in addition to multiple adverse effects. Therefore, there is a great need for new therapies in order to improve the quality of life of these patients¹. This represents a relevant impact not only in the clinical setting but also in the psychological, social, economic, and/or spiritual spheres, contributing to the increase in total pain².

For these patients, alternatives are continuously being sought to control refractory symptoms, among which the use of cannabidiol (CBD) for the management of neurological symptoms, mainly neuropathic pain and seizures, stands out³. Pharmacological studies show that this is a promising bioactive substance effective for multiple diseases of the nervous system⁴.

CBD is one of the many derivatives of the cannabis plant, and unlike tetrahydrocannabinol (THC), it lacks psychoactive and intoxicating effects⁵. Although its mechanism of action is not well defined, since the 1990 decade it has been suggested that its effect is related to an endogenous cannabinoid system.

This system called endocannabinoid, influences different physiological processes through transmitters (anandamide and 2-arachidonylglycerol) that activate receptors, mainly CB1 and CB2; the CB1-type is located in the central nervous system and affects cognitive functions, such as memory, motor control, sensory and visceral perceptions, and pain. CB2-type receptors are located in the peripheral nervous system and mainly affect the control of neuropathic pain and the control of immune functions⁶. Although CBD has no direct action on CB1 and CB2 receptors, it can have a protective effect on endocannabinoid system alterations⁷.

The pharmacokinetics of CBD depends on the route of administration, being oral the most used, although it exists in inhaled, transdermal, and intravenous presentations⁸. Given some evidence of neuroprotective, cardioprotective, and anti-inflammatory effects, possible medicinal uses have been attributed to it⁹. In some countries, in recent years, it has been used as a complementary treatment in pathologies such as Alzheimer's disease, Parkinson's disease, Multiple Sclerosis, neuropathic pain, and convulsive disorders that are difficult to treat¹⁰, as well as anxiety and schizophrenia⁴.

This narrative article aims to determine the use of cannabidiol for the control of refractory neurological symptoms in patients with seizure syndromes and neurodegenerative diseases. The information was searched in Pubmed, Scopus, and Embase, through the Hinari platform in Spanish and English. Metaanalyses, original articles, systematic and literature reviews, as well as information from portals of organizations such as the Pan American Health Organization (PAHO/WHO), published between 2017 and 2022, were consulted. Boolean operators OR, AND, and NOT were used with the keywords: Epilepsies, Seizure Disorder, Drug-Resistant Epilepsy, Epileptic Syndromes, Lennox Gastaut Syndromes, Dravet Syndrome, Neurodegenerative Disease, Alzheimer Disease, Parkinson Disease, Cannabidiol, CBD, Neurological Manifestations, Neurologic Symptoms, Pain, Dyskinesias, Seizures, among others.

Discussion

Refractory neurological symptoms in seizure syndromes and neurodegenerative diseases

Neurodegenerative diseases represent one of the leading causes of morbidity and mortality worldwide in older adults; although, they can begin at an earlier age¹¹; within this age group, dementia stands out, defined by the WHO as a syndrome characterized by the progressive deterioration of cognitive function, which affects 50 000 000 people per year¹².

Alzheimer's disease is the most common form of dementia, accounting for 60-70 % of cases worldwide¹², 10 % start before the age of 65¹³; It is characterized by cognitive impairment and behavioral disturbances; symptoms develop gradually and higher cortical functions deteriorate as time progresses¹⁴. These patients suffer from amnesia, behavioral changes, depression, anxiety, impaired vision, and language disorders¹⁵. As the disease progresses, symptom management becomes more complex¹⁶.

Parkinson's disease is the second most common neurodegenerative disease¹⁷ and affects 6 300 000 individuals annually¹⁸. It is detected in 1 % of people aged over 65 years, although it can be present early in patients under 40 years old¹⁹.

Parkinson's disease is characterized by motor manifestations, such as tremors, bradykinesia, altered postural reflexes and rigidity, and non-motor manifestations, such as sleep and behavioral disorders, cognitive

or autonomic dysfunction, pain, among others, which are associated to damaged structures of the nervous system²⁰. The most common symptom in this condition is tremor, which is present in more than 70 % of patients; these are unilateral, approximately between 4-6 Hz, and frequent in distal parts of the extremities²¹. Similarly, pain is common in these patients, mostly myalgia, cervicalgia, and lumbago, which worsens as the disease progresses; it is associated with stiffness and dyskinesia²².

Sleep disorders also present in these conditions; there may be difficulty in falling asleep or staying asleep, suffering nightmares, or even self-injurious behavior or aggressive behavior towards family members during sleep²³. As the disease progresses, the control of these symptoms becomes more complex, as they no longer respond to conventional therapies, being classified as refractory to treatment²⁴.

On the other hand, seizure syndromes are a group of disorders present in all age groups, epilepsy being the main one, which affects 50 000 000 people worldwide²⁵. According to the International League Against Epilepsy (ILAE) it is defined as the presence of two or more unprovoked seizures at least 24 hours apart²⁶. The ILAE defines refractory epilepsy as "epilepsy in which there has been failure of two trials of appropriately chosen and adequately tolerated antiepileptic drugs, in monotherapy or in combination, to achieve sustained seizure freedom"²⁷. It is found in 30 to 40 % of these patients²⁸.

The Lennox Gastaut syndrome is a severe form of epilepsy in childhood, affecting two to 5 % of children with epilepsy. It has been characterized by multiple daily seizures of different types, such as tonic-clonic, clonic, absence seizures, and generalized seizures, among others, which cause intellectual disability in this children²⁹.

In addition, the Dravet syndrome, also known as severe myoclonic epilepsy of infancy, is an intractable form of epileptic encephalopathy with early onset in childhood, presenting its first seizure episode between five and eight months of age, with an incidence of one in 15 000 to one in 40 000³⁰. Both syndromes are treatment-refractory epilepsies that present cognitive impairment and are associated with high mortality in these patients³¹.

Use of Cannabidiol in patients with seizure syndromes

The use of CBD for the treatment of refractory symptoms in seizure syndromes has

been studied by multiple researchers. One of the main ones is Dr. Orrin Devinsky who, since 2015, has participated in double-blind randomized clinical trials to assess the effectiveness of this molecule³². Wrede *et al.* found that CBD in concomitant therapy with anti-epileptic drugs decreased the frequency of seizure episodes in patients with treatment-refractory epilepsies³³.

Miller *et al.* identified that 68 % of patients who obtained additional therapy with another CBD drug showed improvement according to the Caregiver Global Impression of Change (CGIC) scale³⁴. This is a tool designed in 1976 to assess the severity, global improvement, and therapeutic response of a disease, which is a Likert-type scale implemented by the patient's caregiver and is used in psychiatric disorders, neurodegenerative diseases, and seizure disorders³⁵. The CGIC has been the primary instrument in multiple clinical trials on Cannabidiol in patients with seizure syndromes to assess the reduction in frequency and duration of seizures identified by caregivers³⁶.

CBD as an add-on therapy to antiepileptic drugs has been studied in the short and long term, and there is only one drug worldwide that contains highly purified cannabidiol, approved by the Food and Drug Administration (FDA) and the European Medicines Agency (EMA), indicated as an adjuvant in epilepsies refractory to treatment. Devinsky *et al.* evaluated patients with Dravet syndrome (DS) for 14 weeks, finding a decrease in seizure frequency from 12.4 to 5.9 episodes per month, where the adjusted median difference was -22.8 seizures with a 95 % confidence interval (95 % CI) of -41.1 to -5.4 ($p < 0.01$)³⁷. In turn, Francesco *et al.* studied for 12 weeks the use of CBD in patients with SD, where 40.2 % of them experienced a decrease greater than or equal to 50 % in seizure frequency³⁸.

On the other hand, the use of CBD added to their antiepileptic drugs was studied for 14 weeks in patients with Lennox-Gastaut Syndrome (LGS), reducing the frequency of monthly seizures by 37.2 % at a dose of 10 mg/kg/day³⁹, and 42.8 % at 20 mg/kg/day⁴⁰, compared to 21.8 % with placebo. This difference was significant from the first week of treatment⁴¹. However, according to Klotz *et al.* the treatment is shown to be more effective in patients with a higher frequency of seizures⁴².

Scheffer *et al.* studied long-term patients with SD, previously included in the Miller *et al.* clinical trial, concluding that after three years, the percentage reduction per month in total seizures was 49-55 % from

week 12. An estimated 85 % of caregivers who completed the CGIC found improvement every 12 weeks⁴³. On the other hand, Thiele *et al.* evaluated the effectiveness of cannabidiol in patients with LGS for 48 weeks. The median reduction in seizure drop frequency from baseline was 48.2 % at weeks one through 12, with a decrease from a median of 80.0 seizures per month at baseline to 37.7 per month, and was maintained for 48 weeks. In 6.3 % of the patients, no more seizure episodes were evidenced during the last 12 weeks, and 2.2 % had no more seizures during the entire study. Similarly, 72 % of their caregivers reported improvement based on the CGIC⁴⁴.

Regarding the safety of CBD, the most common adverse effects were pyrexia, somnolence, hyporexia, sedation, vomiting, and ataxia. Severe adverse effects such as seizures occurred in only five patients, one of whom was in the placebo group. In addition, six patients receiving valproate as an antiepileptic drug, presented elevation of transaminases up to three times their normal value, four of whom presented concomitant nosocomial symptoms⁴⁵.

In the same way, Szaflarski *et al.* investigated the use of CBD in patients with epilepsy refractory to treatment over a period of 48 weeks at doses between two and 50 mg/kg/day, showing that the most common adverse effects were diarrhea (29 %), somnolence (22 %) and seizure (17 %), being less frequent at doses lower than 10 mg/kg/day⁴⁶.

In a study conducted with 84 patients, tolerance was generated in 25 % in a range between three and 24 months, with an average dose of 12.6 mg/kg/day, unrelated to demographic characteristics or to their baseline treatment⁴⁷. Moreover, during the study by Szaflarski *et al.* an increase in CBD dose was needed between 12 and 48 weeks to maintain the initial response to treatment. However, no patient reported an increment in seizure episodes or the appearance of a new type of seizure^{48,45}. In turn, the percentage of adverse effects, such as drowsiness, was higher in the group of patients with CBD, thus requiring a dose adjustment in the same group³⁴.

Multiple pharmacokinetic and pharmacodynamic interactions of this molecule with the most widely used antiepileptic drugs have been identified, such as brivaracetam, clobazam, lacosamide, gabapentin, oxcarbazepine, phenobarbital, pregabalin, topiramate, among others⁴⁹. Clobazam is one of the most studied first-line drugs, since CBD increases sedation by prolonging the half-life of its metabolite N-desmethyl-

clobazam⁵⁰. Similarly, it decreases the anti-convulsant action of levetiracetam at doses of 100 mg/kg⁴⁹. In turn, it has been found that the concomitant use of cannabidiol with valproic acid can increase serum levels of liver enzymes⁴⁶⁻⁵⁰.

It is important to highlight that the effectiveness of CBD in convulsive syndromes does not only imply a reduction in the number of episodes or their length, but also reduces the need for emergency services, contributing to the wellbeing of the patient and his or her environment³¹. Thus, 40 % of parents report an improvement in the alertness of patients, as well as in social and language skills with the use of this molecule⁴⁷.

Use of Cannabidiol in patients with neurodegenerative diseases

Cannabidiol, having antioxidant and anti-inflammatory action, is considered a neuroprotective agent as an alternative complementary treatment in neurodegenerative diseases. In turn, its efficacy has been studied in the control of symptoms such as spasticity, pain⁵¹, and movement disorders such as chorea in patients with Huntington's disease⁵².

Through scales such as the Brief Psychiatric Rating Scale (BPRS) and the Parkinson Psychosis Questionnaire (PPQ), it has been possible to determine a decrease in psychotic symptoms in patients with Parkinson's disease, applying doses between 150 and 400 mg/day of oral CBD together with conventional antiparkinsonian drugs with mild side effects⁵³. Likewise, it improves mobility, emotional wellbeing, cognitive capacity and communication, in addition to achieving a reduction in general malaise with doses of 300 mg/day⁵⁴.

Among the side effects reported were somnolence, hyporexia, weight loss and diarrhea at doses of 1280 mg/day or 50 mg/kg/day. However, there are not enough clinical trials evaluating safety as well as effectiveness in patients with a history of cannabis use⁵⁵.

Leehey *et al.* describe moderate adverse effects, such as drowsiness, fatigue, diarrhea and in some cases hepatotoxicity in patients with Parkinson's disease, using doses of about 1600 mg/day. However, diarrhea has been associated more with sesame oil used as an excipient, since its frequency is independent of the dose⁵⁶.

In addition, multiple clinical trials in animals have been developed to evaluate the effectiveness of CBD combined with Tetrahydrocannabinol (THC) for the control of anxiety, agitation and depression in

Alzheimer's disease⁵⁷. In the case of Amyotrophic Lateral Sclerosis (ALS) the effect of combined cannabidiol was studied in animals; however, low doses of THC were used to reduce the psychoactive effects; being an effective molecule for the control of refractory symptoms. More research in humans is needed to prove its effectiveness in these pathologies⁵⁸.

Conclusions

Cannabidiol's effects make it a complementary and adjuvant therapeutic alternative for symptom control in certain neurological disorders. CBD has been mainly studied in seizures refractory to conventional treatments, showing improvement in the total number of seizures in the short and long term, from the beginning of its implementation, as well as its safety in these time periods. Adverse effects are mild to moderate, such as anemia, gastrointestinal symptoms, somnolence and ataxia, and are directly proportional to the dose administered.

Additional short and long-term treatment with CBD in disorders such as Dravet syndrome and Lennox Gastaut syndrome showed a sustained reduction in total seizures. Adverse effects were more common with concomitant use of clobazam. It is important to emphasize that, though it is an alternative therapy, it does not replace conventional antiepileptic treatment, even when studies of the use of isolated and purified cannabidiol are still lacking, it alone does not control seizure episodes. There are few studies evaluating the development of tolerance with the use of CBD in refractory epilepsy, therefore more research is needed.

Furthermore, despite the fact that there is no clear evidence at the moment to support the effectiveness of cannabidiol management in patients with Parkinson's disease, there are researchers who support that cannabis derivatives, such as CBD, can alleviate motor and non-motor symptoms in the initial stages of treatment, without causing severe adverse effects. The main limitation to justify the use of cannabidiol in neurodegenerative diseases is the small number of investigations that establish the relationship between the mechanisms of action and its clinical effects.

Acknowledgements

The authors would like to thank the Dr. José Matías Delgado University for the support and constant assistance throughout the process of conducting this research.

Funding

The authors declare they have not received any incentive or monetary support.

References

1. Stone NL, Murphy AJ, England TJ, O'Sullivan SE. A systematic review of minor phytocannabinoids with promising neuroprotective potential. *Br J Pharmacol.* 2020; 177(19):4330-52. DOI: [10.1111/bph.15185](https://doi.org/10.1111/bph.15185)
2. López Sánchez JR, Rivera-Largacha S. Historia del concepto de dolor total y reflexiones sobre la humanización de la atención a pacientes terminales. *Rev. Cienc. salud.* 2018;16(2): 339-354. DOI: [10.12804/revistas.urosario.edu.co/revsalud/a.6773](https://doi.org/10.12804/revistas.urosario.edu.co/revsalud/a.6773)
3. Chirinos J. Cannabis y cannabinoides: Uso Clínico Y Perspectivas. *Academia Nacional de Medicina-Anales* 2018. 2018; (25) 124-133. Available in: <https://anmperu.org.pe/sites/default/files/anales-2018/25-Cannabis-y-cannabinoides-Uso-Clinico-Y-Perspectivas-pag-124-a-133.pdf>
4. Ożarowski M, Karpiński TM, Zielińska A, Souto EB, Wielgus K. Cannabidiol in Neurological and Neoplastic Diseases: Latest Developments on the Molecular Mechanism of Action. *IJMS.* 2021;22(9):4294. DOI: [10.3390/ijms22094294](https://doi.org/10.3390/ijms22094294)
5. Freeman TP, Hindocha C, Green SF, Bloomfield MAP. Medicinal use of cannabis based products and cannabinoids. *BMJ.* 2019; (365):e1141. DOI: [10.1136/bmj.11141](https://doi.org/10.1136/bmj.11141)
6. Grotenhermen F. Clinical Pharmacodynamics of Cannabinoids. *Journal of Cannabis Therapeutics.* 2004;4(1):29-78. DOI: [10.1300/J175v04n01_03](https://doi.org/10.1300/J175v04n01_03)
7. Batalla A, Bos J, Postma A, Bossong MG. The Impact of Cannabidiol on Human Brain Function: A Systematic Review. *Front. Pharmacol.* 2021;11(618184). DOI: [10.3389/fphar.2020.618184](https://doi.org/10.3389/fphar.2020.618184)
8. Kis B, Ifrim FC, Buda V, Avram S, Pavel IZ, Antal D, *et al.* Cannabidiol—from Plant to Human Body: A Promising Bioactive Molecule with Multi-Target Effects in Cancer. *IJMS.* 2019;20(23):e5905. DOI: [10.3390/ijms20235905](https://doi.org/10.3390/ijms20235905)
9. Britch SC, Babalonis S, Walsh SL. Cannabidiol: pharmacology and therapeutic targets. *Psychopharmacology.* 2021;238(1):9-28. DOI: [10.1007/s00213-020-05712-8](https://doi.org/10.1007/s00213-020-05712-8)
10. Maroon J, Bost J. Review of the neurological benefits of phytocannabinoids. *Surg Neurol Int.* 2018;9(1):91-91. DOI: [10.4103/sni.sni_45_18](https://doi.org/10.4103/sni.sni_45_18)
11. Erkinen MG, Kim M-O, Geschwind MD. *Clinical Neurology and Epidemiology*

- of the Major Neurodegenerative Diseases. Cold Spring Harb Perspect Biol. 2018;10(4):e033118. DOI: [10.1101/cshperspect.a033118](https://doi.org/10.1101/cshperspect.a033118)
12. OMS. Demencia. Organización Mundial de la Salud. 2020. [accessed June 21, 2022]. Available in: <https://www.who.int/es/news-room/fact-sheets/detail/dementia>
 13. Gumus M, Multani N, Mack ML, Tartaglia MC. Progression of neuropsychiatric symptoms in young-onset versus late-onset Alzheimer's disease. GeroScience. 2021;43(1):213-223. DOI: [10.1007/s11357-020-00304-y](https://doi.org/10.1007/s11357-020-00304-y)
 14. Knapskog A-B, Engedal K, Selbæk G, Øksengård A-R. Alzheimers sykdom - diagnostikk og behandling. Tidsskriftet. 2021.141(7). DOI: [10.4045/tidsskr.20.0919](https://doi.org/10.4045/tidsskr.20.0919)
 15. Atri A. The Alzheimer's Disease Clinical Spectrum. Medical Clinics of North America. 2019;103(2):263-293. DOI: [10.1016/j.mcna.2018.10.009](https://doi.org/10.1016/j.mcna.2018.10.009)
 16. Xiong Y, Lim C-S. Understanding the Modulatory Effects of Cannabidiol on Alzheimer's Disease. Brain Sciences. 2021;11(9):1211. DOI: [10.3390/brainsci11091211](https://doi.org/10.3390/brainsci11091211)
 17. Saavedra Moreno JS, Millán PA, Buritica Henao OF. Introducción, epidemiología y diagnóstico de la enfermedad de Parkinson. Acta Neurol. Colomb. 2019;35(3 supl. 1):2-10. DOI: [10.22379/24224022244](https://doi.org/10.22379/24224022244)
 18. R. Condor I, Atencio Paulino JI, Contreras Cordova CR. Características clínico epidemiológicas de la enfermedad de parkinson en un hospital nacional de la sierra peruana. Revista de la Facultad de Medicina Humana. 2019;19(4):14-21. DOI: [10.25176/RFMH.v19i4.2342](https://doi.org/10.25176/RFMH.v19i4.2342)
 19. Radhakrishnan D, Goyal V. Parkinson's disease: A review. Neurol India. 2018;66(7):26-35. DOI: [10.4103/0028-3886.226451](https://doi.org/10.4103/0028-3886.226451)
 20. Marín D, Hans C, Ibarra M, Gámez M. Enfermedad de Parkinson: fisiopatología, diagnóstico y tratamiento. Revista de la Universidad Industrial de Santander. 2018;50(1):79-92. DOI: [10.18273/revsal.v50n1-2018008](https://doi.org/10.18273/revsal.v50n1-2018008)
 21. Jagadeesan AJ, Murugesan R, Vimala Devi S, Meera M, Madhumala G, Vishwanathan Padmaja M, et al. Current trends in etiology, prognosis and therapeutic aspects of Parkinson's disease: a review. Acta Biomed. 2017;88(3):249-262. DOI: [10.23750/abm.v88i3.6063](https://doi.org/10.23750/abm.v88i3.6063)
 22. Pérez de la Cruz S. Effectiveness of aquatic therapy for the control of pain and increased functionality in people with Parkinson's disease: a randomized clinical trial. Eur J Phys Rehabil Med. 2017;53(6): 825-832. DOI: [10.23736/S1973-9087.17.04647-0](https://doi.org/10.23736/S1973-9087.17.04647-0)
 23. Stefani A, Högl B. Sleep in Parkinson's disease. Neuropsychopharmacol. 2020;45(1):121-128. DOI: [10.1038/s41386-019-0448-y](https://doi.org/10.1038/s41386-019-0448-y)
 24. Ng JSC. Palliative care for Parkinson's disease. Ann. Palliat. Med. 2018;7(3):296-303. DOI: [10.21037/apm.2017.12.02](https://doi.org/10.21037/apm.2017.12.02)
 25. OPS. Epilepsia. Organización Panamericana de la Salud. 2022. [accessed June 22, 2022]. <https://www.paho.org/es/temas/epilepsia>
 26. Beghi E. The Epidemiology of Epilepsy. Neuroepidemiology. 2020;54(2):185-191. DOI: [10.1159/000503831](https://doi.org/10.1159/000503831)
 27. López González FJ, Rodríguez Osorio X, Gil-Nagel Rein A, Carreño Martínez M, Serratos Fernández J, Villanueva Haba V, et al. Epilepsia resistente a fármacos. Concepto y alternativas terapéuticas. Neurología. 2015;30(7):439-446. DOI: [10.1016/j.nrl.2014.04.012](https://doi.org/10.1016/j.nrl.2014.04.012)
 28. Xue-Ping W, Hai-Jiao W, Li-Na Z, Xu D, Ling L. Risk factors for drug-resistant epilepsy: A systematic review and meta-analysis. Medicine. 2019;98(30):e16402. DOI: [10.1097/MD.00000000000016402](https://doi.org/10.1097/MD.00000000000016402)
 29. Amrutkar C, Riel-Romero RM. Lennox Gastaut Syndrome. Treasure Island (FL). StatPearls. 2022. 9 p.
 30. Anwar A, Saleem S, Patel UK, Arumaithurai K, Malik P. Dravet Syndrome: An Overview. Cureus. 2019;11(6):e5006. DOI: [10.7759/cureus.5006](https://doi.org/10.7759/cureus.5006)
 31. Villanueva V, Carreño Martínez, Gil-Nagel Rein A, López González FJ. Cannabidiol en los síndromes de Dravet y Lennox-Gastaut: un nuevo abordaje terapéutico. RevNeurol. 2021;72(1):S1-S10. DOI: [10.33588/rn.72S01.2021017](https://doi.org/10.33588/rn.72S01.2021017)
 32. Perucca E. Cannabinoids in the Treatment of Epilepsy: Hard Evidence at Last? J Epilepsy Res. 2017;7(2):61-76. DOI: [10.14581/je.r.17012](https://doi.org/10.14581/je.r.17012)
 33. Von Wrede R, Helmstaedter C, Surges R. Cannabidiol in the Treatment of Epilepsy. Clin Drug Investig. 2021;41(3):211-220. DOI: [10.1007/s40261-021-01003-y](https://doi.org/10.1007/s40261-021-01003-y)
 34. Miller I, Scheffer IE, Gunning B, Sanchez-Carpintero R, Gil-Nagel A, Perry MS, et al. Dose-Ranging Effect of Adjunctive Oral Cannabidiol vs Placebo on Convulsive Seizure Frequency in Dravet Syndrome: A Randomized Clinical Trial. JAMA Neurol. 2020;77(5):613-621. DOI: [10.1001/jamaneurol.2020.0073](https://doi.org/10.1001/jamaneurol.2020.0073)
 35. Kolevzon A, Ventola P, Keary CJ, Heimer G, Neul JL, Adera M, et al. Development of an adapted Clinical Global Impression scale for use in Angelman syndrome. J Neurodevel Disord. 2021;13(1):1866-1955. DOI: [10.1186/s11689-020-09349-8](https://doi.org/10.1186/s11689-020-09349-8)
 36. Nabbout R, Thiele EA. The role of cannabinoids in epilepsy treatment: a

- critical review of efficacy results from clinical trials. *Epileptic Disord.* 2020;22(1):23-28. DOI: [10.1684/epd.2019.1124](https://doi.org/10.1684/epd.2019.1124)
37. Devinsky O, Cross JH, Laux L, Marsh E, Miller I, Nabbout R, *et al.* Trial of Cannabidiol for Drug-Resistant Seizures in the Dravet Syndrome. *N Engl J Med.* 2017;376(21):2011-2020. DOI: [10.1056/NEJMoa1611618](https://doi.org/10.1056/NEJMoa1611618)
 38. Iannone LF, Arena G, Battaglia D, Bisulli F, Bonanni P, Boni A, *et al.* Results From an Italian Expanded Access Program on Cannabidiol Treatment in Highly Refractory Dravet Syndrome and Lennox-Gastaut Syndrome. *Front. Neurol.* 2021;12(673135):1-9. DOI: [10.3389/fneur.2021.673135](https://doi.org/10.3389/fneur.2021.673135)
 39. Privitera M, Bhathal H, Wong M, Cross JH, Wirrell E, Marsh ED, *et al.* Time to onset of cannabidiol (CBD) treatment effect in Lennox-Gastaut syndrome: Analysis from two randomized controlled trials. *Epilepsia.* 2021;62(5):1130-1140. DOI: [10.1111/epi.16878](https://doi.org/10.1111/epi.16878)
 40. Devinsky O, Patel AD, Cross JH, Villanueva V, Wirrell EC, Privitera M, *et al.* Effect of Cannabidiol on Drop Seizures in the Lennox-Gastaut Syndrome. *N Engl J Med.* 2018;378(20):1888-1897. DOI: [10.1056/NEJMoa1714631](https://doi.org/10.1056/NEJMoa1714631)
 41. Thiele EA, Marsh ED, French JA, Mazurkiewicz-Beldzinska M, Benbadis SR, Joshi C, *et al.* Cannabidiol in patients with seizures associated with Lennox-Gastaut syndrome (GWPCARE4): a randomised, double-blind, placebo-controlled phase 3 trial. *The Lancet.* 2018;391(10125):1085-1096. DOI: [10.1016/S0140-6736\(18\)30136-3](https://doi.org/10.1016/S0140-6736(18)30136-3)
 42. Klotz KA, Grob D, Hirsch M, Metternich B, Schulze-Bonhage A, Jacobs J. Efficacy and Tolerance of Synthetic Cannabidiol for Treatment of Drug Resistant Epilepsy. *Front. Neurol.* 2019;10(1313): e01313. DOI: [10.3389/fneur.2019.01313](https://doi.org/10.3389/fneur.2019.01313)
 43. Scheffer IE, Halford JJ, Miller I, Nabbout R, Sanchez-Carpintero R, Shiloh-Malawsky Y, *et al.* Add-on cannabidiol in patients with Dravet syndrome: Results of a long-term open-label extension trial. *Epilepsia.* 2021;62(10):2505-2517. DOI: [10.1111/epi.17036](https://doi.org/10.1111/epi.17036)
 44. Thiele E, Marsh E, Mazurkiewicz-Beldzinska M, Halford JJ, Gunning B, Devinsky O, *et al.* Cannabidiol in patients with Lennox-Gastaut syndrome: Interim analysis of an open-label extension study. *Epilepsia.* 2019;60(3):419-428. DOI: [10.1111/epi.14670](https://doi.org/10.1111/epi.14670)
 45. Devinsky O, Patel AD, Thiele EA, Wong MH, Appleton R, Harden CL, *et al.* On behalf of the GWPCARE1 Part A Study Group. Randomized, dose-ranging safety trial of cannabidiol in Dravet syndrome. *Neurology.* 2018;90(14):1204-1211. DOI: [10.1212/WNL.0000000000005254](https://doi.org/10.1212/WNL.0000000000005254)
 46. Szaflarski JP, Bebin EM, Comi AM, Patel AD, Joshi C, Checketts D, *et al.* Long-term safety and treatment effects of cannabidiol in children and adults with treatment-resistant epilepsies: Expanded access program results. *Epilepsia.* 2018;59(8):1540-1548. DOI: [10.1111/epi.14477](https://doi.org/10.1111/epi.14477)
 47. Uliel-Sibony S, Hausman-Kedem M, Fattal-Valevski A, Kramer U. Cannabidiol-enriched oil in children and adults with treatment-resistant epilepsy-does tolerance exist? *Brain and Development.* 2021;43(1):89-96. DOI: [10.1016/j.braindev.2020.06.018](https://doi.org/10.1016/j.braindev.2020.06.018)
 48. Szaflarski JP, Bebin EM, Cutter G, DeWolfe J, Dure LS, Gaston TE, *et al.* Cannabidiol improves frequency and severity of seizures and reduces adverse events in an open-label add-on prospective study. *Epilepsy & Behavior.* 2018;87:131-136. DOI: [10.1016/j.yebeh.2018.07.020](https://doi.org/10.1016/j.yebeh.2018.07.020)
 49. Gilmartin CGS, Dowd Z, Parker APJ, Harijan P. Interaction of cannabidiol with other antiseizure medications: A narrative review. *Seizure.* 2021;86:189-196. DOI: [10.1016/j.seizure.2020.09.010](https://doi.org/10.1016/j.seizure.2020.09.010)
 50. Gaston TE, Bebin EM, Cutter GR, Liu Y, Szaflarski JP, the UAB CBD Program. Interactions between cannabidiol and commonly used antiepileptic drugs. *Epilepsia.* 2017;58(9):1586-1592. DOI: [10.1111/epi.13852](https://doi.org/10.1111/epi.13852)
 51. Fernández-Ruiz J, Sagredo O, Pazos MR, García C, Pertwee R, Mechoulam R, *et al.* Cannabidiol for neurodegenerative disorders: important new clinical applications for this phytocannabinoid?: Cannabidiol and neurodegenerative disorders. *Br J Clin Pharmacol.* 2013;75(2):323-333. DOI: [10.1111/j.1365-2125.2012.04341.x](https://doi.org/10.1111/j.1365-2125.2012.04341.x)
 52. Consroe P, Laguna J, Allender J, Snider S, Stern L, Sandyk R, *et al.* Controlled clinical trial of cannabidiol in Huntington's disease. *Pharmacology Biochemistry and Behavior.* 1991;40(3):701-708. DOI: [10.1016/0091-3057\(91\)90386-G](https://doi.org/10.1016/0091-3057(91)90386-G)
 53. Rieder CR. Cannabidiol in Parkinson's disease. *Braz. J. Psychiatry.* 2020;42(2):126-127. DOI: [10.1590/1516-4446-2019-0810](https://doi.org/10.1590/1516-4446-2019-0810)
 54. Ferreira-Junior NC, Campos AC, Guimarães FS, Del-Bel E, Zimmermann PM da R, Brum Junior L, *et al.* Biological bases for a possible effect of cannabidiol in Parkinson's disease. *Braz. J. Psychiatry.* 2020;42(2):218-224. DOI: [10.1590/1516-4446-2019-0460](https://doi.org/10.1590/1516-4446-2019-0460)
 55. Babalonis S, Haney M, Malcolm RJ, Lofwall MR, Votaw VR, Sparenborg S, *et al.* Oral cannabidiol does not produce a signal for abuse liability in frequent marijuana smokers. *Drug and Alcohol Dependence.* 2017;172:9-13. DOI: [10.1016/j.drugalcdep.2016.11.030](https://doi.org/10.1016/j.drugalcdep.2016.11.030)
 56. Leehey MA, Liu Y, Hart F, Epstein C, Cook M, Sillau S, *et al.* Safety and Tolerability of Cannabidiol in Parkinson Disease: An Open

Label, Dose-Escalation Study. Cannabis and Cannabinoid Research. 2020;5(4):326-336.

[DOI: 10.1089/can.2019.0068](https://doi.org/10.1089/can.2019.0068)

57. Pagano C, Navarra G, Coppola L, Avilia G, Bifulco M, Laezza C. Cannabinoids: Therapeutic Use in Clinical Practice. IJMS. 2022;23(6): e1422-0067. [DOI: 10.3390/ijms23063344](https://doi.org/10.3390/ijms23063344)
58. Urbi B, Broadley S, Bedlack R, Russo E, Sabet A. Study protocol for a randomised, double-blind, placebo-controlled study evaluating the Efficacy of cannabis-based Medicine Extract in slowing the disease pRegression of Amyotrophic Lateral sclerosis or motor neurone Disease: the EMERALD trial. BMJ Open. 2019;9(11):e029449. [DOI: 10.1136/bmjopen-2019-029449](https://doi.org/10.1136/bmjopen-2019-029449)