Narrative review article

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

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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 patients[1]. 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 pain[2].

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 out[3]. Pharmacological studies show that this is a promising bioactive substance effective for multiple diseases of the nervous system[4].

CBD is one of the many derivatives of the cannabis plant, and unlike tetrahydrocannabinol (THC), it lacks psychoactive and intoxicating effects[5]. 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 CB19-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 functions[6]. Although CBD has no direct action on CB1 and CB2 receptors, it can have a protective effect on endocannabinoid system alterations[7].

The pharmacokinetics of CBD depends on the route of administration, being oral the most used, although it exists in inhaled, transdermal, and intravenous presentations[8]. Given some evidence of neuroprotective, cardioprotective, and anti-inflammatory effects, possible medicinal uses have been attributed to it[9]. 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 treat[10], as well as anxiety and schizophrenia[4].

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 age[11]; 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 year[12].

Alzheimer's disease is the most common form of dementia, accounting for 60-70 % of cases worldwide[12], 10 % start before the age of 65[13]; It is characterized by cognitive impairment and behavioral disturbances; symptoms develop gradually and higher cortical functions deteriorate as time progresses[14]. These patients suffer from amnesia, behavioral changes, depression, anxiety, impaired vision, and language disorders[15]. As the disease progresses, symptom management becomes more complex[16].

Parkinson's disease is the second most common neurodegenerative disease[17] and affects 6 300 000 individuals annually[18]. It is detected in 1 % of people aged over 65 years, although it can be present early in patients under 40 years old[19].

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 system[20]. 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 extremities[21]. Similarly, pain is common in these patients, mostly myalgia, cervicalgia, and lumbago, which worsens as the disease progresses; it is associated with stiffness and dyskinesia[22].

Sleep disorders are 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 sleep[23]. 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 treatment[24].

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 worldwide[25]. According to the International League Against Epilepsy (ILAE) it is defined as the presence of two or more unprovoked seizures at least 24 hours apart[26]. 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 patients[28].

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 children[29].

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 40 000[30]. Both syndromes are treatment-refractory epilepsies that present cognitive impairment and are associated with high mortality in these patients[31].

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 molecule[32]. Wrede *et al.* found that CBD in concomitant therapy with antiepileptic drugs decreased the frequency of seizure episodes in patients with treatment-refractory epilepsies[33].

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) scale[34]. 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 disorders[35]. 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 caregivers[36].

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. Denvinsky *et al.* evaluated patients with Davet 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 frequency[38].

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/day[39], and 42.8 % at 20 mg/kg/day[40], compared to 21.8 % with placebo. This difference was significant from the first week of treatment[41]. However, according to Klotz *et al.* the treatment is shown to be more effective in patients with a higher frequency of seizures[42].

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 weeks[43]. 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 CGIC[44].

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 symptoms[45].

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/day[46].

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 treatment[47]. 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 group[34].

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 others[49]. Clobazam is one of the most studied first-line drugs, since CBD increases sedation by prolonging the half-life of its metabolite N-desmethylclobazam[50]. Similarly, it decreases the anticonvulsant action of levetiracetam at doses of 100 mg/kg[49]. In turn, it has been found that the concomitant use of cannabidiol with valproic acid can increase serum levels of liver enzymes[46-50].

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 environment[31]. 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 molecule[47].

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, pain[51], and movement disorders such as chorea in patients with Huntington's disease[52].

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 effects[53]. Likewise, it improves mobility, emotional wellbeing, cognitive capacity and communication, in addition to achieving a decrease in general malaise with doses of 300 mg/day[54].

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 use[55].

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 dose[56].

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

Alzheimer's disease[57]. 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 pathologies[58].

Conclusion

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.

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