New therapeutic approach in Dravet syndrome and Lennox-Gastaut syndrome with cannabidiol

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Introduction. Dravet syndrome (DS) and Lennox-Gastaut syndrome (LGS) are two serious epileptic syndromes with paediatric onset which are refractory to therapy and are associated with an important increase in mortality rates and comorbidities compared to the general population. These pathologies have a strong impact on the lives of patients and their families, because they undergo multiple pharmacological therapies (many of them without specific indication), with frequent changes due to poor efficacy and associated adverse effects. The specialists who care for these patients highlight unmet needs and the lack of specific, safe and effective treatments for better management of the syndrome.

Development. A group of four neurologists specializing in epilepsy has met to review the scientific literature and evaluate the efficacy and safety of oral solution cannabidiol in the treatment of these syndromes, both in randomized clinical trials (CT) and in some observational studies.

Conclusions. Cannabidiol is positioned as an innovative therapy that allows better control of epileptic seizures and comorbidities of DS and LGS, furthermore its efficacy and safety have been evaluated in more than 700 patients. In CTs, cannabidiol significantly reduced the percentage of convulsive seizures and drop seizures compared to placebo in patients with DS and LGS respectively, which could improve their quality of life and that of their family members. The most frequent adverse effects reported were somnolence and decreased appetite. Elevated liver aminotransferase levels were also reported, especially in patients given concomitant sodium valproate. This therapy may allow better control of the epileptic seizures associated with these syndromes.

Palabras clave. Antiepileptic. Cannabidiol. Dravet syndrome. Lennox-Gastaut syndrome. Refractory epilepsy. Severe epilepsy.

Introduction

Dravet syndrome (DS) and Lennox-Gastaut syndrome (LGS) are rare central nervous system diseases [1,2] considered serious epileptic encephalopathies, generally resistant to treatment, that cause different types of epileptic seizures as well as cognitive and behavioural changes [3-6]. The mortality rate among people with epilepsy is two to three times greater than that of the population in general. It is calculated that each year 33,000 deaths are caused by epilepsy, of which 13,000 are avoidable [7].

Both syndromes generally appear in infancy or early childhood, DS in the first year of life [3] and LGS between three and five years of age [8]. They entail a heavy burden for families and carers of patients, as much physically [9-11] and emotionally (disrupted sleep, chronic fatigue and physical pain due to carrying the patient) [10-17] as economically (significant outlay to cover the special needs of the patient and difficulties keeping their job) [10,18]. Early diagnosis is fundamental to begin the treatment as soon as possible and limit the development and progression of the disease. Control of a seizure can reduce the death rate in this group of patients due to Sudden Unexpected Death in Epilepsy (SUDEP) [9,17,19-29].

Treatment can be pharmacological or non-pharmacological (for example, vagal stimulation, surgery and a ketogenic diet). For DS it is recommended to begin the treatment with valproic acid and clobazam used as first-line antiseizure drugs and stiripentol and topiramate in second-line treatment. Other therapeutic options are clonazepam, levetiracetam and zonisamide [9]. For LGS it is recommended to initiate treatment with valproate, lamotrigine or topiramate as first-line drugs. Other effective antiseizure medicines are levetiracetam, clobazam, rufinamide and zonisamide [11]. Specialists highlight the need for new treatments for these syndromes. Highly purified CBD,

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Acknowledgements:
The authors thank Ana Moreno Cerro, MD, on behalf of Springer Healthcare and BioInnova Consulting, for the medical writing of this manuscript.

Funding:
This manuscript has been funded by GW Pharmaceuticals.

Conflict of interests:
V. Villanueva has participated in advisory boards and symposiums sponsored by GSK, UCB, Eisai, Bial, GW Pharmaceuticals, Novartis, Esteve, Arvelle and Newbridge. M. Carreño has participated in advisory boards and symposiums sponsored by UCB, Eisai, Bial, GW Pharmaceuticals, Sanofi and Arvelle. A. Gil Nagel-Rein has participated in advisory boards and symposiums sponsored by Bial, Eisai, Esteve, GW Pharmaceuticals, Medtronic, Sanofi, Stoke, UCB and Zogenix. F.J. López-González has participated in advisory boards and symposiums sponsored by UCB, Bial, Eisai, Esteve, GW Pharmaceuticals, Sanofi and Livanova.

Accepted:
23.04.21.

How to cite this article:
Villanueva V, Carreño-Martínez →

M, Gil-Nagel A, López-González FJ. New therapeutic approach in Dravet syndrome and Lennox-Gastaut syndrome with cannabidiol. Rev Neurol 2021; 72 (Supl 1): S1-10. doi: 10.33588/rn.72S01.2021017.

This supplement of *Revista de Neurología* has not undergone the peer review process. The veracity of the information contained herein is the sole responsibility of the authors.

Versión en español disponible en neurologia.com

designated as an orphan drug, was approved in 2019 by the European Medicines Agency (EMA) as Epidyolex© (GW Pharma [International] B.V.) for the treatment of seizures associated with Lennox-Gastaut syndrome (LGS), or Dravet syndrome (DS), in conjunction with clobazam, in patients ≥2 years of age [30,31]. This article reviews the most notable aspects of the two syndromes and the most recent developments with regards to their treatment with cannabidiol. It also includes the opinions of the experts who are authors of this article.

Situation regarding Dravet syndrome and Lennox-Gastaut syndrome in Spain

Refractory epilepsies have been defined by the International League Against Epilepsy (ILAE) as those that have not responded after being treated by two appropriately prescribed and tolerated antiseizure drugs, either in monotherapy or combined [32]. Both DS and LGS fall into this category.

Dravet syndrome

According to the ILAE [31], DS is a serious epileptic encephalopathy characterised by refractory seizures that begin during the first year of life (on average between 5 and 8 months [19]). Although its principal manifestation is epilepsy, comorbidities such as learning, speech, attention and behavioural disorders, ataxia, dysarthria, trembling, clinical manifestations of Parkinson's disease like bradykinesia and rigid muscles [33] appear together with frequent hospitalisations. All this means a significant impact on the quality of life of both patients and family members [14,34-37].

DS usually begins with generally febrile epileptic seizures in the first year of life. These are usually prolonged and can develop into hemiconvulsive and generalised tonic-clonic status epilepticus, making in many cases the employment of rescue medication necessary [38]. In fact, death due to status epilepticus, accidents or by SUDEP occur in around 15% of cases [39]. From the first year, other types of seizures (absence, atonic, focal and myoclonic) appear. The disease leads to progressive cognitive deterioration and behavioural disorders [38], frequently accompanied by stereotypic behaviour, social communication disorder and attention deficit disorder with hyperactivity [33]. This progression is in part related to the lack of control of epileptic seizures.

DS is frequently confused with other refractory epilepsies [40] with a low percentage of diagnoses being made in the first visit to a doctor [34]. The lack of standardised clinical guides and the non-existence of public health reference centres [35] are impediments that make that make DS diagnosis difficult. Taking into account that up to around 85% of patients with DS show mutations in the SCN1A gene [9,19,41,42], the carrying out and homogenisation of genetic tests is improving the diagnosis of the disease [34].

The incidence of DS in Europe is one in every 15,000 births [9,43] and the estimated prevalence is one case for every 45,700 inhabitants. Using the Delphi measurement system, the most recent epidemiological study estimates that in Spain the average number of new patients with DS is 73 per year with a prevalence of between 348 and 540 patients [3]. In another study in Spain, 1.4% of 365 children less than 15 years old with epileptic syndromes had DS [44].

DS seriously affects the quality of life of patients and their families [9]. Due to the high frequency of seizures [9], the risk of SUDEP [41] and comorbidities, many patients require supervision 24 hours per day [9]. The high human and economic load that caring for a patient with DS imposes (beyond epileptic seizures) cause frequent relationship problems between couples and family members, withdrawal from work and social activities (for example, leisure time and travel). With regards to the economic impact that comorbidities associated with DS entail, a recent survey carried out in Spain revealed that with more than half of the patients (58-72%), it is the carer themselves who finances the treatment of the comorbidities. To this must also be added the reduction of income through giving up work (in more than a third of carers), the reduction of working hours (in 21% of cases) or time not worked due to caring for children [34].

Currently, standardised guides to diagnose and treat DS do not exist [9]. It takes 9 to 15 months to confirm a diagnosis and the availability of genetic tests is irregular [3]. Moreover, until an appropriate diagnosis is obtained, the patient often receives ineffective therapies that can worsen the seizures and increase the risk of status epilepticus [9].

DS epileptic seizures are refractory to treatment. In general, the benefit achieved with current antiseizure drugs is usually rare [45] and does not result in controlling the seizure in the majority of patients [46]. Furthermore, some antiseizure drugs act by blocking the sodium channels, increasing the frequency and seriousness of the seizure for which they are contraindicated [14,46].

Very few patients respond well to monotherapy for which reason a combination of drugs is usually prescribed. Among the alternatives that can be employed as second-line therapy beyond medication is the ketogenic diet [20,38]. In case of the desired effect not being obtained with therapies applied in the first and second lines, stimulation of the vagus nerve or corpus callosotomy are other possible alternative treatments [3].

Despite existing treatments, close to 100% of patients with DS have uncontrolled seizures during infancy [47]. For this reason, experts agree on the need to have available in Spain safe new therapeutic options with proven efficacy for better management of epileptic seizures and comorbidities of patients with DS in both paediatric and adult populations [3,35].

Lennox-Gastaut syndrome

LGS is an uncommon refractory epileptic encephalopathy. It is considered one of the most serious epileptic syndromes of infancy and early childhood [4-6]. Between approximately one quarter and one third of LGS cases do not have a clear aetiology, possibly being cases related to genetic factors [8]. Although the incidences (= 2:100.000 children in Europe) and the prevalence (between 0.1 and 0.28 for every 1000 children in Europe) of LGS are low, this syndrome represents between 3% and 10% of all infant and early childhood epilepsies and has a mortality rate of 3-7% [5]. In Spain, the average age of patients with LGS is 18,2 ± 13,5 years, although most common seizures begin at the age of 3,5 ± 2,31 on average (range: 0,1-18 years) [5].

The classic diagnostic criteria for LGS consists of a trio of electroclinical characteristics: multiple types of seizures difficult to control (atonic and absence seizures being the most common), EEG anomalies in the form of slow spike-wave and fast rhythms during sleep and intellectual disability [8,48]. LGS is usually diagnosed between 3 and 5 years of age [8]. At first, the most common seizures are tonic and atonic, known as drop seizures. At least 50% of LGS patients experience these seizures [8]. Other types of seizures can also occur, for example, tonic-clonic (both generalised and unilateral) as well as tonic, atypical absence, atonic and myoclonic seizures [8]. Atypical absence seizures are the second most common type. Nonconvulsive status epilepticus which involves the use of rescue medicine appears in 50-75% of patients with LGS [6].

The most typical variation in the EEG in wakefulness is the presence of generalised slow spike-wave (less than 3 Hz) [5]. The presence of discharges in the form of rapid rhythms during sleep is another characteristic. Intellectual disability, a habitually diagnosed characteristic of LGS, is serious and remains throughout the life of the patient [26,49]. The mortality rate is estimated at between 3% to 25% [50] and among the causes of death are found accidents resulting from seizures and the complications of status epilepticus [25]. Furthermore, patients with LGS are exposed to the risk of SUDEP [15].

The burden for LGS patients includes serious epileptic seizures, physical injuries as a result of these, reduced mobility, incontinence, disrupted sleep, dysphagia and the risk of SUDEP. The burden on family members include sleep disorders, chronic fatigue and pain caused by manually moving the patient [15-18].

The objective of the treatment of LGS is to suppress or reduce the frequency of the most incapacitating seizures. The management of comorbidities in LGS is a fundamental aspect [11]. Therapeutic options are few and some antiseizure medication can cause or exacerbate comorbidities, for example, cognitive deterioration and depression [6]. Among the alternative non-pharmacological therapies are the ketogenic diet, vagus nerve stimulation and surgery (palliative care approach and, on occasions, very aggressive) [5] (Figure). According to Spanish clinical experience, the need to have available more proven effective treatment options for LGS patients is clear.

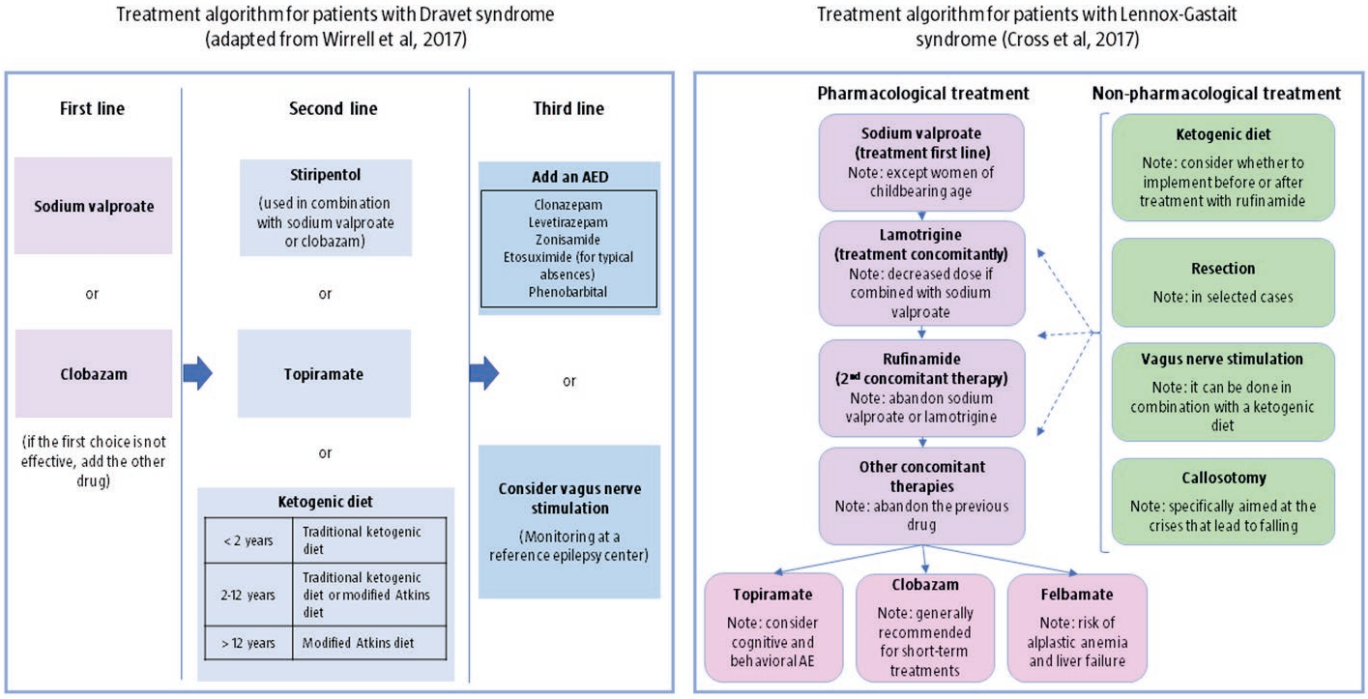
Treatment algorithms for refractory epileptic syndromes

The algorithm proposed by Wirrell et al to manage DS considers three lines of treatment (Figure) [9].

LGS is resistant to treatment in a high percentage of patients [51]. Due to the many kinds of existent seizures in LGS and its comorbidities, the choice of antiseizure drugs is complex and, in many cases, a combination of these [6], often used off-label. The proposed algorithm, before the approval of cannabidiol for the treatment of LGS, includes pharmacological and non-pharmacological treatment (Figure) [11].

Therefore, patients with DS and LGS often find themselves undergoing changeable polytherapy, associated with a limited effect and important adverse effects which reflect non covered important needs.

Figure. Treatment algorithms for Dravet and Lennox-Gastaut syndromes (before approval of cannabidiol).



Cannabidiol in the treatment of Dravet and Lennox-Gastaut syndromes

Cannabidiol (Epidyolex©) is an orally administered antiseizure drug with 100 mg/ml of cannabidiol. Its authorised indication in the EU is as an add-on therapy together with clobazam for epileptic seizures associated with DS and LGS for patients from the age of two. It was authorised by the U.S. Food and Drug Administration (FDA) in 2018 and the European Medicines Agency (EMA) in 2019 [52,53], being the first and only cannabidiol based medication approved by the EMA [30,54]. Cannabidiol is a molecule isolated from the Cannabis sativa plant [52]. It does not have psychoactive properties, that is it does not produce the 'euphoric' effect associated with cannabis and its capacity for abuse is low [52,55]. It is the first drug of a new class of antiseizure medication for the treatment of epilepsy (category ATC N03AX ['Other anti epileptics], code N03AX24) [56].

The joint administration of the cannabidiol oral solution with clobazam increases by three times the plasma concentration of active metabolites of clobazam, N-desmethylclobazam [53], which becomes additionally effective when combined with this drug.

As with the majority of antiseizure medication, the mechanism of action of cannabidiol is not exactly known. It is known that its anticonvulsant properties do not connect to the direct action related to the classic cannabinoid receptors. Furthermore, it has been demonstrated in experimental epilepsy models that it reduces hyperactivity of the neurons through different actions: modulation of intracellular calcium through the receptor connected to the proteins G 55 (GPR55) and the transient receptor potential vanilloid type 1 (TRPV-1) channels, as well as the modulation of the signals caused by adenosine by means of the suppression of cellular recruitment of adenosine through equilibrative nucleoside transporters 1 (ENT-1) [54].

The cannabidiol development programme included four phase 3 clinical trials [4,57-59], two with DS and two with LGS, and an open extension study. Its compassionate use has also been studied (Expanded Access Program). Ten Spanish hospitals participated in this clinical development programme.

Phase 3 clinical trials

The phase 3 double-blind studies, randomised and controlled with placebo, had a four-week basal period, followed by fourteen weeks of treatment (two weeks of dose escalation, twelve weeks of maintenance dose), a progressive ten day dose reduction (10% each day) and a four week period of monitoring to evaluate safety [60]. These studies provided data for more than 700 patients with DS and LGS. The principal objective of the clinical trials was to quantify the percentage of change in a specific type of seizure: with DS it was the reduction in the percentage of convulsive seizures in relation to the basal period and with LGS it was the reduction in the percentage of drop seizures in relation to the basal period. Moreover, safety was also studied in the phase 3 clinical trials [60]. The DS efficacy trial results are shown in Table I. In the GWPCARE1 study, the frequency of convulsive seizures was reduced in the group with cannabidiol (20 mg/kg per day) by an average of –38.9% (interquartile range [RIC]: –69.5 to –4.8) in relation to the basal period. The adjusted mean difference of convulsive seizures amongst the cannabidiol group and the placebo group was from –22.8% (IC95%: –41.1% to –5.4: p = 0.001) [57]. In the GWPCARE2 study, the frequency of convulsive seizures per month was reduced more in the groups with 10 mg/kg per day and 20 mg/kg per day of cannabidiol than in the placebo group. The average difference in convulsive seizures between the 10 mg/kg per day cannabidiol group and the placebo group was from –29.8% (CI 95%: –46.2% to –8.4%; p = 0.0095), whilst between the 20 mg/kg per day cannabidiol group and the placebo group it was from –25.7% (CI 95%: –43.2% to –2.9%; p = 0.0299).

The efficacy results of the phase 3 LGS studies are shown in Table II. In the GWPCARE3 study, the reduction in the frequency of drop seizures was greater in the groups treated with cannabidiol than in the placebo group. The estimated average difference between the 20 mg/kg per day cannabidiol group and the placebo group was 21.6 (CI 95%: 6.7-34.8; p = 0.005) and the estimated average difference between the 10 mg/kg per day cannabidiol group and the placebo group was 19.2 (CI 95%: 7.7 to 31.2; p = 0.002) [59]. In the GWPCARE4 study, the reduction in drop seizures with cannabidiol (20 mg/kg per day) for 14 weeks of treatment was 43.9% (RIC: -69.6 to -1.9). The estimated average difference between the group treated with cannabidiol and the placebo group was 17.21 (CI 95%: –30.32 to –4.09; p = 0.0135) during a period of 14 weeks of treatment and 19.45 (CI 95%: –33.05 to –4.68; p = 0.0096) during the 12 weeks of maintenance [4].

Table I. Efficacy results of cannabidiol oral solution in clinical trials of patients with Dravet syndrome.

	Outcome	Measure	Result
GWPCARE1 [57,60]	Primary outcome	Percentage of seizure frequency change	20 mg/kg/day of cannabidiol: –38.9% (IQR: –69.5 to –4.8), observable from the first month Placebo: –13.3% (IQR: –52.5% to 20.2%)
	Secondary outcome, during the treatment period (14 weeks)	≥25% reduction in the frequency of seizures	OR= 2,10 (CI95%: 1,01-4,35; p = 0,05)
		≥50% reduction in the frequency of seizures	OR= 2,00 (CI95%: 0,93-4,30; p = 0,08)
		≥75% reduction in the frequency of seizures	OR = 2,21 (CI 95%: 0,82-5,95; p = 0,11)
		100% reduction in seizures	Cannabidiol 5% vs 0% placebo Difference 4.9 (CI95%: –0.5 to 10.3; p = 0.08)
		Non-convulsive seizures reduction	Non-significant results available in the publication
		Total seizures reduction	Difference between groups –19.2% (CI95%: –39.25 to –1.17; p = 0.03)
GWPCARE2 [58]	Primary outcome	Percentage of change (reduction) in convulsive seizures during the treatment period compared to baseline	20 mg/kg/day: –45,7% (CI95%: –34,2% to –55,2%) 10 mg/kg/day: –48,7% (CI95%: –37,9% to –57,6%) Placebo: 26,9% (CI95%: –11,9% to 39,4%)
	Secondary outcome, during the treatment period (14 weeks)	Percentage of change (reduction) in total seizures during the treatment period compared to baseline	20 mg/kg/day: –47.3% (CI95%: –36.9% to –56.0%) 10 mg/kg/day: –56.4% (CI95%: –47.8% to –63.6%) Placebo: 29.7% (CI95%: 16.0%-41.1%)
		Participants with a ≥50% reduction from baseline in the frequency of convulsive seizures during the treatment period	20 mg/kg/day: (29/66) 49.3% 10 mg/kg/day: (33/67) 43.9% Placebo: (17/65) 26.2%

CI: confidence interval; IQR interquartile range; OR: *odds ratio*.

The safety profile of the oral cannabidiol solution (Epidyolex©, GW Pharmaceuticals) in participant patients in the trials is shown in Table III. In general, the oral cannabidiol solution (Epidyolex©) was well tolerated during clinical development with the majority of reported adverse effects being mild or moderate. The most common adverse effects in the trials were somnolence, decreased appetite, diarrhoea, pyrexia, fatigue and vomiting. The most

Table II. Efficacy results of cannabidiol oral solution in clinical trials of patients with Lennox-Gastaut syndrome.

	Outcome	Measure	Result
GWPCARE3 [59,60]	Primary outcome	Percentage of drop seizures change	20 mg/kg/day: –41.9% 10 mg/kg/day: –37.2% Placebo: –17.2%
	Secondary outcome, during the treatment period (14 weeks)	>25% reduction in the frequency of drop seizures	20 mg/kg/day vs placebo: OR=2.11 (CI95%–1.1-4.04) 10 mg/kg/day vs placebo: OR=2.22 (CI95%–1.15-4.28)
		≥50% reduction in the frequency of drop seizures	20 mg/kg/day vs placebo: OR=3.85 (CI95% –1.75-8.47, p< 0.001) 10 mg/kg/day vs placebo: OR=3.27 (CI95%–1.47-7.26, p-0.003)
		≥75% reduction in the frequency of drop seizures	20 mg/kg/day vs placebo: OR=12.33 (CI95%–2.76-55.13, p< 0.001) 10 mg/kg/day vs placebo: OR=4.55 (CI95%–0.93-22.22, p-0.003)
		100% reduction in drop seizures	Results not included in the publication
		Reduction in other seizures than drop seizures	20 mg/kg/day vs placebo: 22.4 (CI95% x 2.2-40.1) 10 mg/kg/day vs placebo: 28.3 (CI95% 10.5-43.8)
		Reduction in total seizures	20 mg/kg/day vs placebo: 18.8 (CI95% x 4.4-31.8, p. 0.009) 10 mg/kg/day vs placebo: 19.5 (CI95% x 7.5-30.4, p-0.002)
GWPCARE4 [4,60]	Primary outcome	Percentage of change in drop seizures	20 mg/kg/day: –43.9% (IQR: –69% -1.9%) Placebo: –21.8% (IQR: –45.7% to 1.7%)
	Secondary outcome, during the treatment period (14 weeks)	>25% reduction in the frequency of drop seizures	OR= 2,30 (CI95%: 1,24-4,26; p = 0,0081)
		≥50% reduction in the frequency of drop seizures	OR= 2,57 (CI95%: 1,33-4,97; p = 0,0043)
		≥75% reduction in the frequency of drop seizures	OR = 2,75 (CI 95%: 1,07-7,01; p = 0,0273)
		100% reduction in drop seizures	Non-significant results
		Reduction in other seizures than drop seizure	Estimated difference –26.1 (CI95%: –46.1 to –8.3 p = 0.0044)
		Reduction in total seizures	Estimated difference –21.1 (CI95%: –33.3 to –9.4; p = 0.0005)

CI: confidence interval; IQR interquartile range; OR: *odds ratio.*

frequent cause of treatment discontinuation was the increase in transaminases.

Extension study

After completing the double-blind period of the phase 3 studies (GWPCARE 1, 2, 3 and 4), patients were offered the opportunity to participate in the open extension phase of the studies to evaluate along with tolerability, the long-term effectiveness of the oral cannabidiol solution. The principal conclusions are that long term treatment with the oral cannabidiol solution shows an acceptable safety profile and that a clinically relevant reduction in the frequency of seizures in patients with DS and LGS is achieved that is maintained over time [61,62]. With DS, between weeks 1 and 12 the reduction in the percentage of convulsive seizures was 38%, 43% between weeks 13 and 24 and 44% between weeks 37 and 48 [61]. In LGS, between weeks 1 and 12 the reduction in the percentage of convulsive seizures was 48%, 56% between weeks 13 and 24 and 60% between weeks 37 and 48 [63]. The safety profile observed after four years of treatment is comparable to that seen in previous trials of Epidyolex. Decreased appetite and diarrhoea were frequent, weight decreased was, subsequently, observed [64].

Compassionate use and clinical practice

In 2014 the FDA authorised a program of compassionate use (Early Access Program, EAP) [63-66] with the objective of facilitating access to treatment prior to its approval. This programme provided longer term efficacy and safety data that did not differ from the existing data already mentioned in the above-mentioned studies and can predict better the results in clinical practice. The results with most published cases include 58 patients with DS and 94 with LGS [66]. During the 12 weeks of treatment, epileptic motor seizures were reduced by 50% or more in 53% of the patients, by 75% or more in 23% of the patients and by 100% in 6% of the patients. The most common adverse effects were Somnolence (30%) and diarrhoea (24%). The authors consider that the oral cannabidiol solution has an acceptable safety profile.

Experts' opinions

After review of the results obtained in the clinical development programme, the oral cannabidiol so-

lution is considered an effective innovative therapy that may allow the health professional to focus on some of the needs not covered in patients with DS and LGS and their families beyond seizures such as behavior, cognition etc. The effectiveness of the cannabidiol oral solution is not limited to the reduction of seizures but also to improving quality of life, as much for the patients as for their families, by potentially reducing the number of visits to emergency rooms and the use of other health services. All this contributes to the well-being of the patient and family environment.

The adverse effects registered during the clinical trials with the oral cannabidiol solution must be interpreted in the context of the disease, its treatment and the formulation of the oral solution.

Conclusions

The management of patients with DS and LGS is very complicated due to the wide variety of seizures that can occur and their refractoriness to different treatments used. The likelihood of achieving complete control of seizures decreases in proportion to the number of drugs tried.

The oral cannabidiol solution (Epidyolex©, GW Pharmaceuticals) is an innovative medicine with a structure distinct to other antiseizure drugs habitually used for the treatment of seizures in these syndromes. It has a multimodal mechanism of action whose efficacy and safety profile has been evaluated in more than 700 patients with DS and LGS.

The absence of effective pharmacological options for the treatment of patients with DS and LGS clearly constitutes an unmet need. The clinical contribution of the oral cannabidiol solution covers therapeutic needs, alleviating the impact of these syndromes and their consequences, providing improvements in quality of life, both for patients and their families.

Table III. Tolerability results of cannabidiol oral solution in phase 3 clinical trials in patients with Dravet syndrome or Lennox-Gastaut syndrome.

	Patients	Side effects
GWPCARE1 [57,60]	Dravet syndrome	Observed in 5% or more of the patients in one of the branches of the study: • 20 mg/kg/day of cannabidiol: somnolence (36%), diarrhoea (31%), decreased appetite (28%), fatigue (20%), vomiting (15%), pyrexia (15%), lethargy (13%), infections (11%), convulsion (11%). • Placebo: somnolence (10%), diarrhoea (10%), pyrexia (8%), infections (8%), decreased appetite (5%), vomiting (5%), lethargy (5%), convulsion (5%). Patients with GOT, GPT or GGT levels greater than 3 times the normal upper limit: • 20 mg/kg/day: 12 patients (3 were withdrawn from the study for this reason and 9 continued the treatment with cannabidiol in the study, normalizing their GOT/GPT levels). • Placebo: 1 patient, who was withdrawn from the study for this reason. All patients with abnormal liver function in both the cannabidiol group and the placebo group were being treated with valproate.
GWPCARE2 [58]	Dravet syndrome	Observed in 5% or more of the patients in one of the branches of the study: • 20 mg/kg/day of cannabidiol: Decreased appetite (27.54%), diarrhoea (26.09%), somnolence (23.19%), fatigue (20.29%), pyrexia (20.29%), vomiting (15.94%), nasopharyngitis (11.59%), status epileptic (10.14%), aggression (8.70%), irritability (7.25%), upper respiratory tract infections (5.80%), lower respiratory tract infections (5.80%), toxicity to various agents (5.80%), convulsion (5.80%), tremor (5.80%), abnormal behavior (5.80%). • 10 mg/kg/day: Pyrexia (23.44%), somnolence (21.88%), diarrhoea (17.19%), decreased appetite (15.63%), fatigue (7.81%), status epileptic (7.81%), vomiting (6.25%), nasopharyngitis (6.25%). • Placebo: Pyrexia (16.92%), decreased appetite (16.92%), somnolence (13.85%), diarrhoea (12.31%), status epileptic (12.31%), fatigue (10.77%), nasopharyngitis (7.69%), vomiting (6.25%), convulsion (6.25%). Patients with GOT, GPT or GGT levels greater than 3 times the normal upper limit: • 20 mg/kg/day: 8 patients with GOT elevation, 8 with GPT and 4 with GGT. • 10 mg/kg/day: 3 patients with GOT elevation, 3 with GPT and 4 with GGT. • Placebo: 3 patients with GGT elevation.
GWPCARE3 [59,60]	Lennox-Gastaut syndrome	Observed in 5% or more of the patients in one of the branches of the study: • 20 mg/kg/day of cannabidiol: Somnolence (30%), decreased appetite (26%), diarrhoea (15%), upper respiratory tract infections (13%), pyrexia (12%), vomiting (12%), nasopharyngitis (11%). • 10 mg/kg/day: Somnolence (21%), decreased appetite (16%), upper respiratory tract infections (16%), diarrhoea (10%), status epileptic (10%), pyrexia (9%). • Placebo: Pyrexia (16%), upper respiratory tract infections (14%), vomiting (12%), decreased appetite (8%), nasopharyngitis (7%) somnolence (5%). Patients with GOT, GPT or GGT levels greater than 3 times the normal upper limit: • 20 mg/kg/day: 11 patients with GOT or GPT elevation, 9 of them were being treated with valproate and in 4, treatment was discontinued for this reason. • 10 mg/kg/day: 3 patients with GOT or GPT elevation, 2 of them were being treated with valproate and in 1, treatment was discontinued for this reason. In 2 patients with GOT elevation, 1 with GPT elevation and 1 with GGT elevation was considered to be related to cannabidiol. All GOT/GPT elevations were resolved (in 3 patients spontaneously, in 2 after entering the open-label extension phase, and by 9 after reducing or discontinuing the dose of cannabidiol or reducing the dose of another antiseizure drug). Placebo: No case.

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Table III. Tolerability results of cannabidiol oral solution in phase 3 clinical trials in patients with Dravet syndrome or Lennox-Gastaut syndrome. *(cont.)*

GWPCARE4 [4,60]	Lennox-Gastaut syndrome	Observed in 5% or more of the patients in one of the branches of the study: • 20 mg/kg/day of cannabidiol: Diarrhoea (19%), somnolence (15%), pyrexia (13%), decreased appetite (13%), vomiting (10%). • Placebo: Diarrhoea (8%), somnolence (9%), pyrexia (8%), vomiting (5%), decreased appetite (2%). Patients with GOT, GPT or GGT levels greater than 3 times the normal upper limit: • 20 mg/kg/day: 20 patients had GOT/GPT elevation, 16 of whom were in concomitant treatment with valproate. All GOT/GPT elevations in the study were resolved spontaneously during treatment (8 in the cannabidiol group and one in placebo), after dose reduction of valproate (3 in the cannabidiol group), after ending the dose of cannabidiol (6) or after entering the open-label extension phase (3). 4 patients with GOT elevation also had GPT elevation. 3 of these 4 patients also had GGT elevation. • Placebo: 1 patient with GOT/GPT elevation

GGT: γ- glutamiltransferase; GOT: glutamic-oxaloacetic transaminase; GPT: glutamic-pyruvic transaminase.

grupo%20de%20enfermedades=S-ndrome-de-Lennox-Gastaut&title=S%EDndrome%20de%20Lennox-Gastaut&search=Disease_Search_Simple. [25.06.2020].

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Cannabidiol en los síndromes de Dravet y Lennox-Gastaut: un nuevo abordaje terapéutico

Introducción. Los síndromes de Dravet (SD) y Lennox-Gastaut (SLG) son dos síndromes epilépticos graves y de inicio en la edad pediátrica, refractarios al tratamiento, asociados a un notable incremento en las tasas de mortalidad y comorbilidades respecto a la población general. Suponen un fuerte impacto en la vida de los pacientes y sus familiares, ya que los pacientes están sometidos a múltiples terapias farmacológicas (muchas sin indicación específica), con cambios frecuentes debido a la escasa eficacia y a los efectos adversos. Los especialistas que les atienden destacan las necesidades no cubiertas y la falta de tratamientos específicos, seguros y eficaces para un mejor manejo de la enfermedad.

Desarrollo. Se ha reunido un grupo formado por cuatro neurólogos especialistas en epilepsia para hacer una revisión de la literatura científica y evaluar los resultados de eficacia y seguridad de la solución oral de cannabidiol en el tratamiento de estos síndromes, tanto en ensayos clínicos aleatorizados como en diversos estudios observacionales.

Conclusiones. El cannabidiol se sitúa como una terapia innovadora que permite un mejor control de las crisis epilépticas y comorbilidades del SD y el SLG; además, su eficacia y seguridad han sido evaluadas en más de 700 pacientes. En los ensayos clínicos redujo significativamente el porcentaje de crisis convulsivas y de caída en comparación con placebo en los pacientes con SD y SLG, respectivamente, y puede mejorar su calidad de vida y la de sus familiares. Los efectos adversos más frecuentes fueron la somnolencia y la disminución del apetito. También se notificaron niveles elevados de aminotransferasas hepáticas, especialmente en pacientes tratados concomitantemente con ácido valproico. Esta terapia podría permitir un mejor control de las crisis epilépticas asociadas a estas patologías.

Palabras clave. Anticrisis. Cannabidiol. Epilepsia grave. Epilepsia refractaria. Síndrome de Dravet. Síndrome de Lennox-Gastaut.