Cannabidiol for the treatment of Lennox-Gastaut syndrome and Dravet syndrome: experts' recommendations for its use in clinical practice in Spain

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Introduction. Cannabidiol (CBD) is one of the main components of the cannabis plant that has demonstrated anti-epileptic seizure effect. Following its clinical development, in September 2019 the European Medicines Agency approved its indication for the adjunctive therapy of epileptic seizures associated with Lennox-Gastaut syndrome (LGS) and Dravet syndrome (DS), combined with clobazam (CLB), in patients of 2 years of age and older.

Aim. To establish recommendations on the use of plant-derived highly purified CBD on which Spanish experts have reached consensus for the treatment of epilepsy in patients with DS and LGS based on their clinical experience and the scientific evidence.

Development. Consensus meeting with the participation of four Spanish neurologists and neuropediatric who are experts in epilepsy secondary to DS and LGS and with clinical experience in the use and management of CBD. They discussed on several topics, including posology (starting dose, dose escalation schema), efficacy (assessment of outcomes and indications for treatment withdrawal), and safety (evaluation, drug-drug interactions, adverse events management).

Conclusions. In order to optimise CBD treatment, a slow dose escalation (≥ 4 weeks) is recommended until the maximum recommended dose or the desire effect is reached. It is also recommended that the concomitant antiseizure medications (ASMs) be reduced in case of adverse events due to interactions, and that the treatment continues for at least 6 months if it is well tolerated. The efficacy and safety of CBD must be assessed individually, considering the benefits and risks for individual patients.

Key words. Adverse events. Cannabidiol. Dravet syndrome. Efficacy. Lennox-Gastaut syndrome. Recommendations. Spain.

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Introduction

In September 2019, the use of a product of purified cannabidiol (CBD) (Epidyolex, GW Pharmaceuticals plc) was approved by the European Medicines Agency (EMA) and the Spanish Agency of Medicines and Medical Devices (AEMPS, by its Spanish acronym) [1,2].

Epidyolex is indicated for use as adjunctive therapy of seizures associated with Lennox-Gastaut syndrome (LGS) or Dravet syndrome (DS), combined with clobazam (CLB) in patients of 2 years of age and older [1,2]. The indication was approved based on four placebo-controlled randomised clinical trials carried out in more than 700 patients who showed an appropriate efficacy and safety profile with regard to both epileptic syndromes [3-6].

In December 2019, after the European approval, the National Institute for Health and Care Excellence (NICE) developed guidelines including recommendations on the use of CBD combined with CLB for treating epileptic seizures associated with DS [7] and LGS [8]. These guidelines were subsequently published in 2020 [9]. Additionally, the Cannabinoids International Experts Panel elaborated a guide regarding the CBD as a therapeutic option for epilepsy, including recommendations on CBD dosing and its use (February 2020) [10]. However, in Spain there are still no guidelines that include this type of recommendations. Since experience in using and managing CBD is limited, such guidelines are helpful in treating these patients in an optimal way [9].

Therefore, the aim of this consensus document is to gather information on the use of CBD in clinical practice in Spain: dose escalation schema, adverse events (AEs) management, and rules for treatment withdrawal.

Development

Consensus meeting with a group of four experts in the epilepsy management (neurologists and neuropediatricians) selected for their experience in treating patients with DS or LGS and managing CBD in

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Spain (use of CBD in clinical trials and open studies and use of CBD as medicine in special situations).

This meeting was convened on 28th October 2020 with the following aims: sharing and collecting the experts' experience; reaching an agreement on several aspects relevant to the management of CBD; and making recommendations that could guide neurologists, neuropediatricians, and epileptologists to optimise CBD treatment and its outcomes.

The experience and recommendations for handling CBD are outlined below.

Posology of cannabidiol: starting dose and dose escalation scheme

As stated in the summary of product characteristics (SmPC) [2], 'the recommended starting dose of CBD is 2.5 mg/kg taken twice daily (5 mg/kg/day) for one week. After one week, the dose should be increased to a maintenance dose of 5 mg/kg twice daily (10 mg/kg/day). Based on individual clinical response and tolerability, each dose can be further increased in weekly increments of 2.5 mg/kg administered twice daily (5 mg/kg/day) up to a maximum recommended dose of 10 mg/kg twice daily (20 mg/kg/day).

Any dose increases above 10 mg/kg/day, up to the maximum recommended dose of 20 mg/kg/day, should be made considering individual benefit and risk and with adherence to the full monitoring schedule'.

Generally, the starting dose of CBD used by the experts is 2.5 mg/kg/day taken once daily, usually at night, instead of 5 mg/kg/day, as indicated in the SmPC [2]. The aim of making the dose escalation slower is to reduce the potential AEs, as it is done when any other new antiseizure medication (ASM) is added to the treatment (polytherapy).

Regarding the concomitant use of clobazam (CLB), it may be administered before adding CBD or be added simultaneously with CBD. It is recommended that CLB dose are reduced slowly for avoiding somnolence.

The recommendation on dose escalation would be to perform a weekly dose increase until reaching maintenance dose. This should be done based on the observed efficacy and tolerability for each patient.

A mean period of time of four weeks is recommended until the dose of 10 mg/kg/day is reached, with weekly dose increments. This dose escalation scheme is slower than that indicated in the SmPC, since the objective is to reduce the potential AEs. This slower dose escalation scheme is similar to that recommended by D'Onofrio G et al [11], with weekly increments of 2.5 mg/kg. During this time, dose adjustments of other concomitant ASMs are usually made.

Potential AEs induced by a fast dose escalation should be considered to avoid losing the potential benefits of CBD. A slower dose escalation throughout a longer period allows to assess the pharmacokinetics (PK) and pharmacodynamics (PD) interactions and to personalise the appropriate titration for each individual patient.

Differences between Dravet syndrome and Lennox-Gastaut syndrome

A slower dose escalation of CBD is suggested for patients with DS, as they usually receive higher doses of CLB than patients with LGS.

Efficacy: definition, time for determination, and treatment withdrawal

The aim of the treatment, and therefore the efficacy assessment, depends on the type and duration of the epileptic seizures (mainly convulsive seizures in the case of DS, or drop seizures in the case of LGS). Thus, experts suggest reviewing the NICE recommendations for DS and LGS that state the following: 'The frequency of drop/convulsive seizures should be checked every 6 months, and CBD should be stopped if a reduction of at least 30%, compared with the 6 months prior to the start of treatment, is not achieved' [7-9].

In specific patients, it is possible that no significant reduction in the frequency of seizures is observed with respect to baseline. However, based on the experience with CBD in the clinical practice and not on the evidence provided by randomized clinical trials, CBD treatment can contribute to other meaningful improvements for the patient and their caregivers. These improvements include changes in epileptic seizure severity and pattern, changes in patients' relationship with their environment, a reduction in emergency room visits, and other factors that are highly valuable for this type of patients in terms of quality-of-life improvements.

Furthermore, factors related to efficacy can be difficult to evaluate on the basis of objective data only, since caregivers do not always fill in the seizure diary and sometimes fail to effectively transfer all factors and the patients' progress to the doctors.

Table I shows the efficacy criteria for CBD treatment defined by the experts in the management of

epilepsy who participated in the consensus meeting on the basis of their experience.

In order to determine the efficacy, it is important to consider the time it should take to reach the dose of 10 mg/kg/day of CBD during the first month. Afterwards, an additional month would be necessary to consolidate and monitor the response, as well as to be aware of any possible AEs that may occur. Therefore, the minimum time period considered for assessing the response is three months.

It is recommended that treatment would be followed for at least 3 months so that the efficacy of CBD can be determined. However, this period of time is not enough to establish efficacy in terms of seizure reduction or other relevant efficacy parameters that depend on the type of epileptic seizures and syndrome: the response is assessed earlier in LGS patients than in DS patients.

Therefore, waiting until the 6th month of CBD treatment is generally recommended, having reached the maximum recommended dose of 10 mg/kg/day and having a good tolerability profile.

During the first 6 months, it is usually advisable to assess the result with the 10 mg/kg/day dose of CBD. If the drug is well tolerated and the response is not enough, the dose should be gradually increased to 20 mg/kg/day, or until the desired effect is reached. In each case, the benefit and risk should always be considered, and the established follow-up criteria should be complied with.

Since these patients have limited therapeutic options and they are usually treated with several ASMs, they should be individually evaluated. Before stopping treatment, it is recommended that the dose of CBD and/or other ASMs are adjusted, considering the risk-benefit balance.

The information provided by caregivers (expectations, epileptic seizure frequency, QoL improvement, concomitant medication, current situation compared to pre-treatment situation…) is very useful to evaluate the efficacy and treatment tolerability profile.

This information, together with each patient´s profile, the pathology or associated comorbidities, and the therapeutic objectives set by the physician, is the basis on which it is decided whether to continue or stop treatment.

Differences between Dravet syndrome and Lennox-Gastaut syndrome

According to the experts' experience, clinical response to CBD treatment seems to take longer to become evident in DS patients compared to LGS patients. However, the observed efficacy seems to be more striking in DS patients. The aetiology of LGS is very heterogeneous, so the pathophysiological and genetic mechanisms should be considered to assess the efficacy.

Table I. Efficacy criteria for cannabidiol treatment.

Efficacy criteria[a], listed in descending order of relevance	
% of reduction in drop seizures or seizures with motor a component (convulsions)	It is the most important criteria, since convulsions or seizures with a motor component and drop seizures have a high impact on the quality of life of patients The efficacy goal of the reduction in seizures depends on the baseline situation of each patient In some cases (e.g. LGS patients with a high number of nocturnal seizures or drop seizures), a reduction of up to 50-70% in total seizures could be considered an excellent result even if total control of said seizures were not achieved.
Reduction in generalised tonic-clonic seizures and drop seizures	These are the most life- threatening seizures and the ones that have the highest impact on the quality of life of patients Generalised tonic-clonic seizures can lead to status epilepticus and can be associated with a higher risk of sudden unexpected death in epilepsy (SUDEP) in DS patients Controlling drop seizures is essential in LGS patients. The morbidity and mortality rates for trauma is very high and this gives rise to anxiety in patients' family members and caregivers
Reduction or improvement in the severity of other types of seizures	Reduction in other types of seizures (atypical absences, minor motor seizures, or myoclonic seizures) and night tonic seizures: • LGS: reduction of ≥ 30% in atypical absences • DS: reduction of ≥ 30% in partial complex seizures
Changes in seizures semiology and reduction in rescue medication	• Duration of the seizures: achieve a reduction in their duration (e.g.: they used to last 5 minutes and now they last 30 seconds) • Onset: it should be slower. It is important when it comes to drop seizures, since caregivers should be aware of possible falls so that injuries due to trauma can be reduced. • Intensity It is essential to reduce the 'rescue medication' (mainly benzodiazepines) administered by patients' caregivers in order to avoid status epilepticus. Many AEs are reduced. The collection of this information weekly by caregivers is very relevant and helpful for the physicians when it comes to optimising the treatment
Increase in seizure-free days	The increase in seizure-free days is a parameter highly valued by caregivers. More seizure-free days allow them to carry out more activities, reassure the confidence of the patients' families, and improve their QoL
Cognitive improvement: improvement in alert or attention, which involves an improvement in the QoL	Improvement in QoL: recovery of school days and daily living activities. Reinforcement of family confidence QoL scales needed to assess these changes (for example CAVE, LQOL scales) It is difficult to assess whether the patient is alert or more participative, by using scales because there are not specific scales for DS or LGS. The reports of the educational centre caregivers are very helpful
Reduction in the number of concomitant ASMs or their doses	DS or LGS patients are generally polymedicated If the dose or the number of concomitant ASMs got to be reduced, treatment-related AEs would be reduced

AE: adverse event; ASMs: antiseizure medications; CAVE: quality of life scale in childhood epilepsy; CBD: cannabidiol; DS: Dravet syndrome; LGS: Lennox-Gastaut syndrome; QoL: quality-of-life. [a] They can be easily quantified/identified by physicians and/or caregivers.

Table II. AEs commonly reported associated with the use of cannabidiol and recommendations on their management.

Common AEs and recommendations for their management		
Transaminase's elevation		This is the AE that most concerns, since the underlying molecular mechanism is unknown at this time; it is mainly related to concomitant treatment with VPA These elevations of the liver enzymes are generally transient and dose-dependent, and they normalise after ASMs dose adjustment or, sometimes, spontaneously. Following two weeks from VPA dose adjustments, a blood test is repeated Recommendations: • Perform a laboratory blood test: – Prior to starting treatment with CBD (serum transaminases [ALT and AST] and total bilirubin levels) – Following one month from the start of CBD treatment • Monitor blood VPA concentrations (without exceeding 95-100 mg/L levels), if possible
Somnolence		It is the most common and easily detectable AE. In children, it can be expressed as irritability or motor coordination difficulties. It is mainly related to co-adjuvant treatment with CLB and brivaracetam The improvement in symptomatology guides dose adjustments
Gastrointestinal events	Severe diarrhoea	Diarrhoea is a difficult to manage AE Recommendation: Take CBD in combination with food in order to reduce the osmolarity effect of sesame oil
	Loss of appetite	It is mainly detected in DS patients, since they often have anorexia and prior malnutrition, and they are prone to previous loss of appetite
	Vomiting	Mainly when combining CBD with VPA
Hyperammonaemia		This AE has been mostly observed in patients on concomitant VPA treatment. In patients with CBD and VPA, it can be associated with encephalopathy +/- vomiting, regardless the transaminases elevation or VPA levels. It is essential to detect it. Recommendation: • Add ammonium to the initial laboratory blood test following one month from the start of CBD treatment. • Assess the high risk in pediatric patients with GGT>50 UI/L • L-carnitine prophylaxis (100 mg/kg/day [2-3 doses] in pediatric patients [from the age of 2 years old onward]). It does not need an extra follow-up, and sometimes it is maintained for a long time. • In case of higher ammonium levels, the L-carnitine dose should be adjusted to 100-150 mg/kg/day.

AE: adverse event; ASMs: antiseizure medications; CBD: cannabidiol; CLB: clobazam; DS: Dravet syndrome; LGS: Lennox-Gastaut syndrome; VPA: valproic acid.

Safety: monitoring and management of adverse events

Prior to starting treatment with cannabidiol, it is required to obtain serum transaminases (ALT and AST) and total bilirubin levels [1].

After the first 4 weeks with CBD treatment (the dose of 10 mg/kg/day having been reached), it is recommended that a control visit including a blood test be made to study potential AEs –e.g. liver transaminases elevation, somnolence, hyperammonaemia, loss of appetite, other gastrointestinal (GI)AEs…–.

Table II shows the most reported AEs that are related to the use of CBD, as well as some clarifications and recommendations for their management. The most common AEs, according to the SmPC, are somnolence, decreased appetite, diarrhoea, pyrexia, fatigue, and vomiting [2].

Differences between Dravet syndrome and Lennox-Gastaut syndrome

Overall, tolerance to treatment seems to be worse in DS patients, probably because they received higher doses of CLB, they are usually younger than LGS patients, and they often have pronounced nutritional problems. Specifically, DS patients tend to present more AEs (mainly GI) than LGS patients. Caregivers of DS patients have reported loss of appetite and other nutritional problems (12) that could justify what experts perceived in their clinical practice (13): DS patients are generally thinner and shorter than LGS patients.

Cannabidiol as co-adjuvant treatment: dose and drug-drug interactions management

CBD is mainly metabolised in the liver via CYP450 and UDP-glucuronosyltransferase (UGT) enzyme [2]. These enzymes are also involved in the metabolism of other drugs, such as CLB and valproic acid (VPA). The known drug-drug interactions with other ASMs are described below and recommendations for the management of each of them are made.

Clobazam-cannabidiol

CBD can induce an increase in the levels of the active metabolite of CLB (norclobazam; N-CLB) [14,15] up to 3-4 times the usual levels [16]. This promotes a CLB accumulation and a progressive increase in AEs, mainly in somnolence and ataxia [17-18]. CLB can also induce an increase in the levels of CBD, since it inhibits the glucuronidation pathway [16].

The use of stiripentol (STP) seems to reduce the CLB-CBD interaction [16]. The increase in the N-CLB levels promoted by the CLB-CBD combination is not observed when CBD is added to the CLB-STP combination [14,15]. This fact can be explained due to the basal levels of CLB, which are lower when CBD is initiated with the CLB-STP

combination or by means of a saturation effect of inhibition by STP.

CLB is more frequently used in patients with DS; in patients with LGS, CLB is used in cases of drop seizures or atypical absence, and its use is limited in case of tonic seizures. The combination CLB-CBD is effective.

The doses of CLB used are not very high: 0.20-0.25 mg/kg/day as a single dose at night, or divided into two, one in the morning and one at night (pediatrics), or 5-15 mg once a day (ideally at night in order to improve tolerability and reduce somnolence) compared to 20-40 mg/day dose with optimal effect reported in other patients [19].

Recommendations on the concomitant use of clobazam

Before starting CBD, it is advisable to determine blood levels of CLB and active metabolite (N-CLB) levels, which is responsible for toxicity. This control could be avoided by virtue of the limitations imposed in some of the laboratories of the centres where patients are being treated. In this case, it is essential that a correct interpretation of the symptomatology related to AEs be made to be able to appropriately adjust the dose.

In case of somnolence following CBD addition, CLB dose can be slowly reduced until a balanced situation is reached.

In patients with high prior CLB doses, it is recommended that the daily dose of CLB be reduced by 25% at the beginning.

Valproic acid-cannabidiol

Mitochondrial β-oxidation and glucuronidation are the primary routes of VPA metabolism [20].

No relevant *in vivo* drug-drug interactions have been observed with the active metabolites of CBD and VPA. However, plasma transaminases elevation is frequently observed with CBD-VPA combination [21].

In clinical practice, those patients with high doses of VPA receiving CBD can show elevated VPA plasma levels above 100 mg/L. It is advisable to assess the PK interaction between CDB and VPA by the determination of plasma levels of both drugs, thus facilitating the individual management and follow-up of patients. Additionally, it is advisable to analyse basal VPA doses of patients with transaminases elevation to be able to understand the underlying mechanism of this process.

Mitochondrial β-oxidation also seems to be implicated in the ammonium ion elevation detected with the use of VPA [22,23]. This elevation occurs concomitantly of the increase of gamma-glutamyl transferase (GGT) levels. Therefore, the quantification of the GGT elevation is useful since it would allow to identify a potential risk of hyperammonaemia. In this case, L-carnitine treatment (50-100 mg/kg/day) should be considered. Supplementation with this amino acid allows to reduce the risk of ammonium elevation secondary to VPA treatment, especially common in children < 6 years old on polytherapy (especially in the presence of CYP450 enzyme inducers).

Recommendations on the concomitant use of valproic acid

Do a slow CBD titration, reducing the VPA dose according to both tolerability and the basal control of the liver function. In case of high doses of VPA, a preventive reduction in the VPA dose would be appropriate.

Determine the levels of VPA, avoiding overcoming the safe doses of 1,000 mg/day (in adults). In children, try to use a range of 30-35 mg/kg/day.

Stiripentol-cannabidiol

When CBD was combined with STP, a minor increase was observed in STP levels, corresponding to 28% for the maximum plasma concentration (C_{max}), and to 55% for the area under the curve (AUC) [2].

It has been reported that STP-CLB combination promotes a CLB levels alteration [17]. Probably, STP induces enzyme saturation (CYP450) and then, when CBD is added to STP-CLB combination, N-CLB levels have already reached a plateau and, therefore, additional alterations in CLB and N-CLB levels are not detected.

Recommendations on the concomitant use of STP

Assess the clinical effect of STP since the determination of plasma levels are not usually available. For this purpose, the AEs possibly related to STP must be monitored: somnolence, appetite loss, weight loss, ataxia, and tremor [24].

Rufinamide-cannabidiol

As reported by Gaston et al [25], the combination of CBD with rufinamide (RFM) increases plasma levels of RFM (ranges > 35-40 mg/L). This situation could induce AEs, mainly GI AEs.

Recommendation on the concomitant use of rufinamide

Monitor the reported AEs possibly related to RFM: aggravation of seizures, appetite loss, fatigue, behavioural changes, nausea, vomiting... [26].

Phenobarbital-cannabidiol

Phenobarbital is not commonly used, but when it is used in combination with CBD, its level may increase (this increase has already been reported [27], although not in a generalised way [28]). There are often drug-drug interactions and other problems due to broad-spectrum enzyme induction [29,30].

Recommendations on the concomitant use of phenobarbital

Determine the levels of phenobarbital, monitoring the possible reported AEs: sedative, behavioural, and mood effects [29].

Brivaracetam-cannabidiol

It has been reported that CBD can increase the levels of brivaracetam (BRV) [31], or produce a PD interaction of somnolence potentiation and sedative AEs.

In LGS patients, BRV-CBD combination produces somnolence events that are more severe than those observed with CLB. This can be explained due to a PD interaction that enhances an effect that is common for both drugs (CBD and BRV) [2,32,33].

Recommendations on the concomitant use of brivaracetam

Since the plasma levels of CBD and BRV are not usually available; the PD interaction must be monitored by assessing the presence of somnolence and the severity of the same.

Clonazepam-cannabidiol

Clonazepam (CZP) is not commonly used in DS and LGS patients; the use of CLB being preferable when benzodiazepines have to be used [34]. Perhaps CZP is used more frequently in LGS patients than in DS patients; but even so, its use is rare.

Taking into account the specifications of the SmPC (the mandatory use of CLB combined with CBD) and that the use of two benzodiazepines is not recommended in epilepsy due to the risk of complex and unpredictable PD effect, in patients receiving CZP who require starting CBD, it is advisable to replace CZP with CLB. This change of drugs can be difficult [35], with the risk of seizures control decompensation or the occurrence of severe AEs that sometimes require hospitalisation in the intensive care unit.

Recommendations on the concomitant use of clonazepam

Gradually withdraw CZP and then CLB.

Try to ensure that the two ASMs do not coincide in time, since this would involve a high risk of sedative AEs, paradoxical behavioural reactions, and sleep pattern alterations.

If the withdrawal of CZP is not possible due to the worsening of the seizures, a dose reduction would be advisable.

If AEs increase, CLB dose should be reduced.

Diazepam-cannabidiol

Diazepam is a rescue medication with an important accumulative effect. It uses the same metabolic pathway as CZP. In some patients with frequent severe seizures, an excessive use of diazepam can be detected, up to several times a week.

Recommendations on the concomitant use of diazepam

Warn caregivers to avoid the abuse of diazepam and reassess the frequency, severity, or duration of seizures in which it should be used.

Conclusions

After the discussion meeting on the CBD management, the following recommendations were made:

- Perform a slower dose escalation of at least 4 weeks until the minimum effective dose of 10 mg/kg/day, recommended in the SmPC, is reached. Then, gradually increase the dose based on both tolerability and the effect on the control of seizures, up to a maximum dose of 20 mg/kg/day, as recommended in the SmPC.
- Wait for at least 6 months before establishing the effectiveness of CBD, considering that sometimes its effectiveness can be evidenced after 3 months.
- In case of CBD interactions with other ASMs, consider reducing the total doses of the other ASMs, if possible; and let CBD exert its action, avoiding AEs due to the drug total burden.
- In case of AEs, assess the balance between the benefits (higher efficacy) and tolerability of the AEs. It can be different depending on patients, pathologies, concomitant ASMs, and patients' responses.

The recommendations included in this article were made based on the shared experience of the experts in the treatment of epilepsy who have an extensive experience in the use of CBD, considering the most relevant factors for the patient's management. This approach ensures that all recommendations are prac-

tical and feasible for their implementation in daily practice now that CBD is available. These recommendations are intended to help achieve the maximum benefit from treatment, considering possible situations that could compromise patient safety.

All the information included in these guidelines is aligned with currently available scientific evidence. However, one of their possible limitations is that some of the recommendations may have been based on limited evidence, so it would be necessary to review them in the future, once more experience with the drug has been gained. Additionally, the application of some of the recommendations (e.g., the determination of some drug plasma levels) will depend on the availability of resources in each hospital. Eventually, other aspects related to the management of CBD that require assessment may exist and they may have not been included in these guidelines. All this should give rise to new projects that aim to generate more comprehensive and up to date practice guidelines in the near future.

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Cannabidiol para el tratamiento del síndrome de Lennox-Gastaut y del síndrome de Dravet: recomendaciones de expertos sobre su uso en la práctica clínica en España

Introducción. El cannabidiol (CBD) es uno de los componentes principales de la planta del cannabis que ha demostrado efecto ante las crisis epilépticas. Tras su desarrollo clínico, obtuvo su aprobación por la Agencia Europea del Medicamento en septiembre de 2019 para el tratamiento de las crisis epilépticas asociadas con el síndrome de Lennox-Gastaut (SLG) y el síndrome de Dravet (SD), en combinación con el clobazam (CLB), en pacientes a partir de los dos años.

Objetivo. Establecer unas recomendaciones de manejo del CBD derivado de la planta altamente purificado consensuadas por expertos españoles en el tratamiento de la epilepsia para su uso en pacientes con SD y SLG, basándose en su experiencia clínica y en la evidencia científica.

Desarrollo. Reunión de consenso de un grupo de cuatro neurólogos y neuropediatras españoles expertos en el manejo de la epilepsia asociada al SD y el SLG y con experiencia clínica en el uso de CBD. Se debatió sobre diferentes áreas, incluyendo la posología (dosis de inicio, pauta de escalada), la eficacia (valoración de resultados e indicaciones para la suspensión del tratamiento) y la seguridad (evaluación, interacciones entre fármacos, manejo de efectos adversos).

Conclusiones. Para optimizar el tratamiento con CBD, se recomienda una pauta lenta de escalada de dosis (de cuatro semanas o más) hasta alcanzar la dosis máxima recomendada o el efecto deseado, reducir los fármacos anticrisis epilépticas concomitantes si aparecen efectos adversos por interacciones y mantener el tratamiento al menos seis meses si se tolera. La eficacia y la seguridad del CBD deben evaluarse de forma individual, considerando el beneficio y el riesgo para cada paciente.

Palabras clave. Cannabidiol. Efectos adversos. Eficacia. España. Recomendaciones. Síndrome de Dravet. Síndrome de Lennox-Gastaut.