Epilepsy and cannabidiol: a guide to treatment

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ABSTRACT – The growing interest in cannabidiol (CBD), specifically a pure form of CBD, as a treatment for epilepsy, among other conditions, is reflected in recent changes in legislation in some countries. Although there has been much speculation about the therapeutic value of cannabis-based products as an anti-seizure treatment for some time, it is only within the last two years that Class I evidence has been available for a pure form of CBD, based on placebo-controlled RCTs for patients with Lennox-Gastaut syndrome and Dravet syndrome. However, just as we are beginning to understand the significance of CBD as a treatment for epilepsy, in recent years, a broad spectrum of products advertised to contain CBD has emerged on the market. The effects of these products are fundamentally dependent on the purity, preparation, and concentration of CBD and other components, and consensus and standardisation are severely lacking regarding their preparation, composition, usage and effectiveness. This review aims to provide information to neurologists and epileptologists on the therapeutic value of CBD products, principally a purified form, in routine practice for patients with intractable epilepsy.

Key words: epilepsy, cannabis, cannabidiol, CBD, oil, guidelines, Dravet, Lennox-Gastaut, Epidiolex, Epidyolex

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The therapeutic potential of cannabis-related products has been suggested for many years (Perucca, 2017), and interest in the subject in recent decades has fluctuated in parallel with perceptions of cannabis and changes in legislation. With the realisation that (-)-trans-∆-9-tetrahydrocannabinol (THC) is a component with prominent psychoactive properties, attention shifted to the potential therapeutic value of cannabidiol (CBD). In recent decades, interest in the therapeutic value of CBD-containing products, as anti-inflammatory, anti-emetic, anti-psychotic, and anti-epileptic treatments, has emerged for a wide range of conditions. However, the supporting data is principally based on anecdotal or *in vitro* experiments with supraphysiological concentrations. In addition, other compounds that may be present in artisanal CBD preparations may have independent physiological effects, leading to inevitable confusion regarding the effectiveness and safety of the preparations.

It is only within the last two years that Class I evidence has become available for a pure form of CBD, based on placebo-controlled RCTs. In the light of this recent evidence, this review aims to provide information on the current status of what is known about CBD as a therapeutic option for epilepsy, which will likely be of value to neurologists and epileptologists. This paper contributes to the following competencies of the ILAE curriculum (Blümcke *et al.*, 2019): "*Demonstrate up-to-date knowledge about the range of pharmacological treatments for epilepsy ; Recommend appropriate therapy based on epilepsy presentation ; Demonstrate up-to-date knowledge about special aspects of pharmacological treatment* ".

Legislation

Laws regarding the use of raw herbal cannabis, cannabis extracts and cannabinoid-based medicines differ between countries (Abuhasira *et al.*, 2018; Specchio *et al.*, 2020). Recreational use of cannabis has been legalised in Canada and Uruguay, as well as 11 states and the District of Columbia in the US. More restricted recreational use has been adopted in Georgia, South Africa, Spain, and The Netherlands. The use of herbal cannabis for medicinal purposes is now authorised in a number of countries, including Argentina, Australia, Canada, Chile, Colombia, Croatia, Ecuador, Cyprus, Germany, Greece, Israel, Italy, Jamaica, Lithuania, Luxembourg, North Macedonia, Norway, the Netherlands, New Zealand, Peru, Poland, Switzerland, and Thailand, as well as a number of states in the US.

Cannabis and cannabis extracts have not been approved by the FDA or the European Medicines Agency (EMA), although cannabinoid-based products have been approved by the FDA as well as by 23 European countries and Canada. In some cases, authorisation is specific to certain indications, while in others the choice of indication may be dictated by the physician (Abuhasira *et al.*, 2018).

In the European Union, CBD, in contrast to THC, is not a controlled substance and according to EU law, CBD products must not contain more than 0.2% THC. Several companies within the EU produce and distribute CBD-based products obtained from inflorescences of industrial hemp varieties. No analytical controls are mandatory and no legal protection or guarantees regarding the composition and quality is required. An obligatory testing and basic regulatory framework to determine the indication area, daily dosage, route of administration, maximum recommended daily dose, packaging, shelf life, and stability is also not required. Much of the ongoing confusion results from whether such products should be regulated as a food, a supplement, or medicine.

It is beyond the scope of this review to provide details for individual countries. However, physicians considering prescribing cannabis related products should be fully aware of the relevant legislation in relation to the heath care service for their specific geographical location. Since the situation can be complex, provision and use of guidelines from recognised national professional associations and or governmental bodies can be extremely helpful. For example, in the UK, such guidelines have been provided by the British Paediatric Neurology Association (BPNA, 2018) and the National Institute for Health and Care Excellence (NICE, 2019). In both, to prescribe a cannabis related product for medicinal use for epilepsy, the prescriber must be on the Specialist Register (Reference: Section 34D of the Medical Act 1983) and the prescription should be made by a consultant paediatric neurologist. Within the UK, responsibility for the prescribing and potential adverse effects of a cannabis related product remain with the prescribing clinician. Thus, clinicians are advised to be aware of the General Medical Council (GMC) guidance on prescribing unlicensed medication (GMC, 2019), and to investigate whether medical protection insurance and hospital indemnity will cover them for prescription of unlicensed cannabis related products. Should a doctor feel under pressure to prescribe a medication that they believe is not in the patient's interests, then paragraph 5d of the GMC guidance "Consent: patients and doctors making decisions together" is relevant (GMC, 2008). It states: "If the patient asks for a treatment that the doctor considers would not be of overall benefit to them, the doctor should discuss the issues with the patient and explore the reasons for their request. If, after discussion, the doctor still considers that the treatment would not be

of overall benefit to the patient, they do not have to provide the treatment. But they should explain their reasons to the patient, and explain any other options that are available, including the option to seek a second opinion".

Artisanal products advertised with CBD content

The known physiologically active components of cannabis include cannabinoids, terpenoids, and flavonoids. Plant or phyto cannabinoids are unique to the cannabis plant. Over a hundred different cannabinoid compounds have been isolated from the cannabis plant, for which various chemovars exist (*Cannabis indica*, *ruderalis*, and particularly *sativa* being the most common). Of these compounds, only 16 exist in meaningful concentrations; these include THC, CBD, cannabichromene (CBC), and cannabigerol (CBG) (as both acid and varin forms). The majority of animal and *in vitro* studies have focussed on THC and CBD, and whereas the effect of THC is less clear and appears to exhibit both proconvulsant and anticonvulsant properties under different conditions, CBD demonstrates clear anti-convulsant properties, making it a focus as a potential treatment for epilepsy.

An abundance of CBD-related products is currently commercially available, ranging extensively in purity, content of effective compounds and price. The global market for these products is considerable and according to the Centre for Medicinal Cannabis (2019) in the UK, at the current rate, the market will be worth one billion pounds/year in 2025.

Importantly, the content of CBD-related products is dependent on the type of cannabis plant as well as the different parts of the plant and growing conditions. Hemp and marijuana may be considered as different varieties of the same cannabis plant; whereas hemp is low in all cannabinoids including THC ($\leq$0.3%), marijuana has a higher THC content (>0.3%).

Hemp seed oils (from seeds) contain minimal cannabinoids (*i.e.* THC); this depends principally on the extent of washing prior to subsequent processing, as cannabinoids in the flowers and leaves appear to transfer to the outer coating or husk of the seed during harvesting and preparation. Cannabis oils (from flowers and leaves of marijuana) contain variable levels of CBD and THC, depending on the chemovars. CBD-enriched oils (from flowers and leaves of hemp) contain high levels of CBD and some THC. The maximum ratio of CBD to THC that can be achieved without subsequent purification, irrespective of the chemovar, is 20:1, however, it should be noted that THC is significantly more potent (50-100-fold) than CBD. Moreover, for CBD-enriched oils advertised as "high CBD/low THC" content, in order to obtain CBD at similar doses to those used in randomised controlled trials (see below), the meaningful amount of THC may be higher than expected. For a child of 18 kg taking 300 mg CBD/day, this equates to 15 mg THC/day, based on a 20:1 CBD:THC ratio in preparations, which is similar to the maximum daily dosage of marinol or dronabinol, a synthetic Δ-9-THC (prescribed for chemotherapy-induced nausea and vomiting as well as weight loss in cancer or AIDS/HIV patients).

Galenic products are available in the form of cannabis decoction filter bags and cannabis extracts as oils, creams, and supplement capsules. Supplements appear to be the most common form, often referred to as "CBD dietary supplements" or "CBD-enriched oils", obtained from extraction of different *Cannabis sativa L.* chemovars with high CBD content. Of the CBD-enriched oils, there are six main varieties available on the market in Europe: Bedrocan, Bedrobinol, Bediol, Bedica, Bedrolite and Bedropuur (*table 1*).

It is important to emphasise that these products demonstrate significant variation with regards to content, which is dependent not only on the initial source of the plant (*e.g.* the use of fertilisers and pesticides) but also the method by which they are prepared (Carcieri *et al.*, 2018; Pegoraro *et al.*, 2019; Bettiol *et al.*, 2019). There are a number of different methods to prepare such oils, the most common being "supercritical CO_2 extraction". This leads to an extract rich in lipophilic cannabis components plus waxes, however, different biologically active compounds can be isolated during subsequent procedures, including omega-3 fatty acids, vitamins, terpenes, flavonoids, and other phytocannabinoids such as CBC, CBG, cannabidivarin (CBDV), and cannabinol (CBN) as a degradant (according to how the fresh the materials is) (Calvi *et al.*, 2018). Terpenes represent the largest group (with more than 100 different molecules) of cannabis phytochemicals; these can easily cross cell membranes and the blood-brain barrier. Moreover, a synergistic effect between cannabinoids and terpenes has been hypothesised, but not proven (Russo, 2011; Aizpurua-Olaizola *et al.*, 2016; Santiago *et al.*, 2019).

It is also worth mentioning that an adequate dose of CBD based on commercially available CBD-enriched oils (up to 10-20 mg/kg/day), similar to doses used in randomised controlled trials (*see below*), comes at considerable financial cost to the family; in excess of 500 euros per month.

Product labelling

When it comes to CBD-enriched oils, there are major concerns regarding THC, CBD and terpene concentration, as well as appropriate preparation

Table 1. THC and CBD content of CBD-enriched oils and purified CBD preparations.

	Product	THC content	CBD content
CBD-enriched oils	Bedrocan	22%	<1%
	Bedrobinol	13.5%	<1%
	Bediol	6.5%	8%
	Bedica	14%	<1%
	Bedrolite	0.4%	9%
	Bedropuur		<1%
	FM1		
	FM2		
	Pedanios 22/1	22%	<1
	Pedanios 8	8%	8
	Pedanois 1/8	<1%	8
	CBD Crystals 99%		99%
GW Pharmaceuticals plc	Sativex (GW)	51%	49%
	Epidiolex (GW)		>98%

methods and storage conditions. These may vary significantly (Carcieri *et al.*, 2018; Pavlovic *et al.*, 2018), leading to insufficient quality control. Moreover, laboratory analyses have shown that the cannabinoid content is often not reflected on the marketing label (Vandrey *et al.*, 2015).

Based on a report by the Centre for Medicinal Cannabis (2019) in the UK, there is an urgent need for a move towards accurate labelling regarding CBD content, as many products are sold with quantities of CBD which are well below those used in clinical trials. In the study by Bonn-Miller *et al.* (2017), the label accuracy of 84 products was analysed. Overall, CBD concentration ranged from 0.10 to 655.27 mg/mL (median: 9.45 mg/mL; median labelled concentration: 15.00 mg/mL). Of the products tested, 42.85% (*n* = 36) products were under-labelled, 26.19% (*n* = 22) were over-labelled, and 30.95% (*n* = 26) were accurately labelled. The level of CBD in the over-labelled products in the study is similar in magnitude to levels that triggered a warning from the US Food and Drug Administration (FDA) to 14 businesses in 2015-2016, indicating that there is a continued need for federal and state regulatory agencies to take steps to ensure accurate labelling of these consumer products.

Under-labelling is of less concern, as CBD itself does not appear to be susceptible to abuse and there have been no reported serious adverse effects (AEs) at high doses, however, the THC content observed may be sufficient to produce intoxication or impairment, especially among children. Clear labelling regarding the exact concentration of CBD is not yet mandatory, and there is clearly a need to introduce stricter legislation regarding accurate content labelling.

Effectiveness as a treatment for epilepsy

Anecdotal reports have fuelled public interest and, understandably, have inspired families to seek CBD-related products for the treatment of drug-resistant epilepsy (Filloux, 2015). The most well-known report is that of Charlotte, a five-year-old girl in the US who was diagnosed in 2013 with *SCN1A*-confirmed Dravet syndrome, with up to 50 generalised tonic-clonic seizures per day. Following three months of treatment with high-CBD-strain cannabis extract (later marketed as "Charlotte's Web"), her seizures were reported to have reduced by more than 90% (Maa and Figi, 2014). Other anecdotal reports suggesting that CBD may improve seizure control as

well as alertness, mood and sleep have also been documented (Porter and Jacobson, 2013; Hussain *et al.*, 2015; Schonhofen *et al.*, 2018).

A number of studies have investigated the effect of oral cannabis extracts on intractable epilepsy, based on parental reporting. These include the study by Press *et al.* (2015) of 75 patients (23% with Dravet syndrome and 89% with Lennox-Gastaut syndrome) in the US and Tzadok *et al.* (2016) of 74 patients in Israel over an average of six months; 50% seizure reduction was reported in 33%, and 50-75% seizure reduction in 34% in the two studies, respectively. In a retrospective study by Porcari *et al.* (2018) of 108 children with epilepsy in the US, the addition of CBD oil over an average of six months resulted in >50% seizure reduction in 29% patients, with 10% becoming seizure-free.

Based on a meta-analysis (*n*=670), Pamplona *et al.* (2018) provide evidence in support of the therapeutic value of high-content CBD treatments (CBD-rich cannabis extract or purified CBD). The results indicated a favourable effect for both patients with CBD-rich extracts (6.1 mg/kg/day CBD) and purified CBD (27.1 mg/kg/day), which was in fact more pronounced in patients taking the CBD-rich extracts. This may provide evidence in favour of the inclusion of other components within CBD-rich extracts offering beneficial entourage effects.

Overall, the studies on CBD-enriched oils indicate a 50% reduction in seizures in roughly 30-40% patients. However, it should be emphasised that these are uncontrolled studies with heterogeneous CBD preparations, the CBD content of which varied significantly (estimated at <0.02-50 mg/kg/day). In the study of Press *et al.* (2015), the effect of cannabis extracts was investigated in a cohort of paediatric patients with epilepsy in a single tertiary epilepsy centre in Colorado, where the law on cannabis-related products is more relaxed. Interestingly, the overall responder rate (47%) for patients who had moved to Colorado for treatment was greater than that (22%) of those who were already living in Colorado, indicating a possible positive reporting bias and the need for appropriately controlled studies.

Adverse events

The studies described above reported AEs in 40-50% patients, including increased seizure frequency, gastrointestinal disturbances/diarrhoea, appetite alteration, weight changes, nausea, liver dysfunction, pancreatitis and, particularly, somnolence and fatigue. More serious effects included developmental regression, abnormal movements and status epilepticus.

More long-term effects regarding cannabis-derived products have generally been gathered based on indirect evidence, however, no hard conclusions can be drawn, mainly due to methodological limitations (dosage of THC and other cannabis-derived products, duration of exposure, concordant addiction to other drugs, genetic factors, psychiatric comorbidity, *etc.*). Long-term data from studies on prenatal and adolescent exposure to cannabis products indicate, however, a possible negative and lasting effect on cognitive and, particularly, behavioural functions (Lagae, 2020). Moreover, the externalisation of behavioural problems and a decrease in IQ have been reported as a result of chronic cannabis use. Clearly, long-term studies using large childhood epilepsy cohorts are needed on the chronic use of CBD and cannabis-related products.

Purified CBD (Epidiolex/Epidyolex®)

A purified preparation of CBD is available from GW Pharmaceuticals plc, under the name of Epidiolex/Epidyolex® (>98% CBD). Interest has so far largely focussed on Epidiolex as an add-on drug for cases of epilepsy. Another product, Sativex® (also known as Nabiximol) (51% THC, 49% CBD), made by the same company as a refined extract, has been approved for cases of neuropathic pain, spasticity, overactive bladder and other symptoms of multiple sclerosis in some countries.

Purified CBD has been shown to demonstrate positive effects against a wide spectrum of seizures and epilepsy based on animal models (Rosenburg *et al.*, 2017a). While the precise mechanism of action of CBD in the control of epileptic seizures in humans remains unknown, recent evidence suggests a role in modulating intracellular Ca^{2+} (including effects on neuronal Ca^{2+} mobilisation via GPR55 and TRPV1) and modulating adenosine-mediated signalling (Gray and Whalley, 2020).

In 2017 and 2018, the first randomised controlled trials for pharmaceutically prepared Epidiolex were published for Dravet syndrome and Lennox-Gastaut syndrome, respectively (Devinsky *et al.*, 2017; Thiele *et al.*, 2018), and in June 2018, the FDA approved CBD as an add-on antiepileptic drug for patients with Lennox-Gastaut syndrome or Dravet syndrome over the age of two. Epidiolex was also later approved by the EMA in September 2019 for patients over two years of age with Dravet syndrome and Lennox-Gastaut syndrome, in conjunction with clobazam. However, accessibility to Epidiolex outside of Europe and the US remains variable (*e.g.* only patients involved in RCTs may be eligible), due to a lack of approval and legal reform by central agencies. While such reform is clearly welcomed, it cannot come fast enough for those who may benefit.

Table 2. Possible AED/CBD interactions.

Enzyme inducer (↓)	Enzyme inhibitor (↑)	CBD as an enzyme inhibitor (↑)
Carbamazepine Phenytoin	Valproate* Stiripentol Felbamate	Clobazam** Topiramate Rufinamide Zonisamide Eslicarbamazepine Perampanel Lamotrigine?

*Associated with a significant risk of elevated transaminases. **Associated with a significant risk of elevated N-desmethylclobazam, which may cause e.g. sedation.

Pharmacology and drug interactions

As a therapeutic drug, the pharmacokinetic profile of CBD exhibits low bioavailability, significant protein binding (99% protein binding capability), and interactions with various metabolic pathways in the liver, including CYPs that are susceptible to pharmacogenetic variability and drug interactions. However, as CBD interacts with many enzymes, it is cleared quickly and is therefore less susceptible to modulation by drugs that affect metabolising enzymes. Moreover, the pharmacokinetic profile of CBD seems relatively unaffected by inhibitors and inducers or genetic background. The bioavailability of oral oil formulations is limited (<6%) due to extensive first pass metabolism in the liver (Bialer *et al.*, 2017, 2018).

CBD may exhibit numerous interactions with AEDs (Johannessen Landmark and Patsalos, 2010; Johannessen and Johannessen Landmark, 2010; Johannessen Landmark *et al.*, 2012, 2016; Patsalos, 2013a, 2013b) including both potent enzyme inducers (such as carbamazepine and phenytoin) and inhibitors (such as stiripentol, felbamate and valproate) (*table 2*), however, the clinical significance of these interactions may not be meaningful. The most obvious and clinically significant interaction between CBD and other concomitantly used drugs, based on clinical trials, is that with clobazam. CBD, via enzyme inhibition (CYP2C19), may lead to an increase (up to five-fold) in its less potent metabolite, N-desmethylclobazam (Geffrey *et al.*, 2015; Devinsky *et al.*, 2018a), leading to toxicity (principally manifesting as sedation [Gaston *et al.*, 2017]), which may occur at even low levels (1 mg/kg/day) (unpublished observations; Johannessen Landmark). In addition, concurrent clobazam may lead to increased 7-hydroxy-cannabidiol (an active metabolite of CBD) (Morrison *et al.*, 2019), which arguably may lead to better seizure control by boosting the effect of CBD, however, studies with and without clobazam are needed to confirm this.

Other AEDs with a similarly increased effect, concomitant with CBD, may include topiramate, rufinamide, zonisamide and eslicarbazepine (Gaston *et al.*, 2017; Franco and Perucca, 2019). There are therefore still a number of unanswered questions regarding the pharmacology of CBD (Johannessen Landmark and Brandl, 2020; Brodie and Ben-Menachem, 2018).

The clinical impact of such interactions in the individual patient is difficult to predict. Patients should be systematically questioned about efficacy, tolerability and adherence, and serum concentrations should be measured if possible and dosages adjusted accordingly to optimise each patient's treatment.
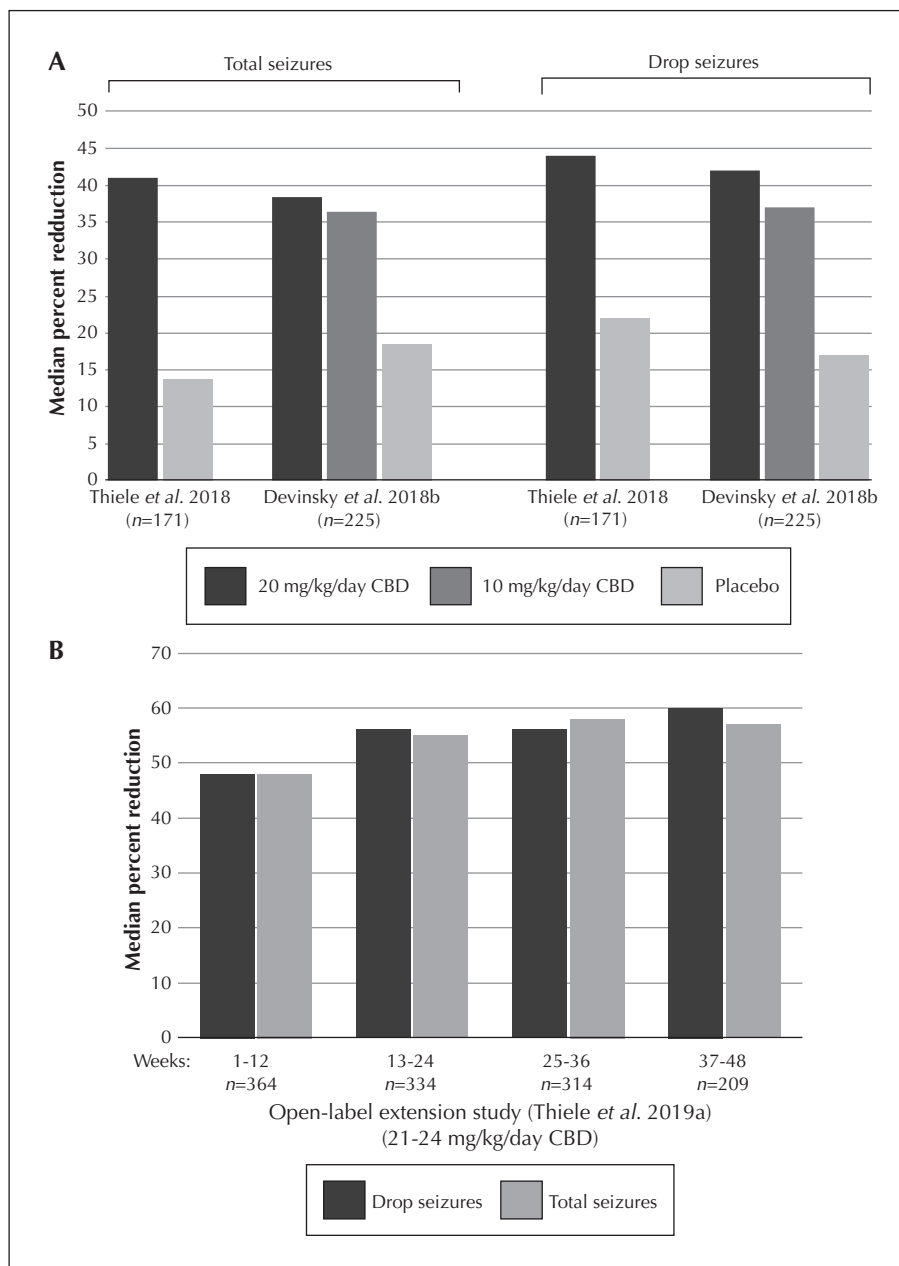
Efficacy as a treatment for epilepsy

The first trials for purified CBD (Epidiolex) were launched as an expanded access programme in 2014 for patients with significant medically refractory epilepsy in the form of an open-label, non-controlled trial for compassionate use (Devinsky *et al.*, 2016). Patients (*n*=214) with intractable seizures (at least four weekly) were monitored over a 12-week period (relative to a four-week baseline) with initial CBD doses of 2.5-5 mg/kg/day, increasing weekly to 25 or 50 mg/kg/day. Overall, a 36.5% median reduction of motor seizures was reported (49.8% for Dravet syndrome patients), and five patients were free of all motor seizures (of the patients with motor and atonic seizures, 39% and 56% showed a >50% reduction of seizures, respectively). This programme was continued and interim data on >600 patients over a 96-week period were published in 2018 by Szaflarski *et al.*, revealing a reduction of median monthly convulsive seizures by 51% (52% with ≥50% seizure reduction) and total seizures by 48% at 12 weeks, with similar results over the 96-week period.

With these very encouraging results, shortly after the initial launch of this programme, controlled trials for Epidiolex were established for Dravet syndrome (Devinsky *et al.*, 2017) and Lennox-Gastaut syndrome (Thiele *et al.*, 2018; Devinsky *et al.*, 2018b). For further details regarding these trials, refer to Nabbout and Thiele (2020).

Lennox Gastaut syndrome

In the two Lennox-Gastaut syndrome double-blind placebo-controlled trials, patients (*n*=171 and 225) were administered CBD at 20 mg/kg/day (GWPCARE4; Thiele *et al.*, 2018) or 10 or 20 mg/kg/day (GWPCARE3; Devinsky *et al.*, 2018b) over a 14-week treatment period (including a titration phase of two weeks starting with a dose of 2.5 mg/kg/day, titrated to 10 or 20 mg/kg/day), and data were compared relative to a four-week baseline observation period. CBD in an oral solution or

Figure 1. Median percent reduction of Lennox-Gastaut syndrome total seizures and monthly drop seizures based on the two controlled trials (Thiele *et al*., 2018; Devinsky *et al*., 2018b) (A), and the open-label extension study (Thiele *et al*., 2019a) (B).

placebo was administered as add-on to current AEDs. For CBD at 20 mg/kg/day, the median percentage reduction in total seizure frequency was 41% (vs 13.7% placebo) and 38.4% (vs 18.5% placebo), and monthly median decrease in drop seizures was reported to be 44% (vs 22% placebo) and 42% (vs 17% placebo) in the two trials, respectively. At 10 mg/kg/day, the median percentage reduction in total seizure frequency was similar at 36.4% (vs 18.5% placebo), and monthly median decrease in drop seizures was 37% (vs 17% placebo).

Lennox-Gastaut syndrome patients who enrolled in these RCTs were also invited to enter an open-label study (GWPCARE5; Thiele *et al*., 2019a). The interim data after 48 weeks of treatment revealed a 48-60% median decrease in drop seizure frequency and a 48-57% median decrease in monthly total seizure frequency relative to baseline (*figure 1*).

Based on the patient or caregiver Clinical Global Impression (CGI) scale, overall improvements were reported in patients of each trial: 58% patients (compared to 34% in the placebo group) in the study of

Thiele *et al.* (2018), 57% and 66% in the 20 mg/kg/day and 10 mg/kg/day group, respectively (compared to 44% in the placebo group) in the study of Devinsky *et al.* (2018b), and 88% at 24 weeks (also similar at 38 and 48 weeks) in the open-label study of Thiele *et al.* (2019a).
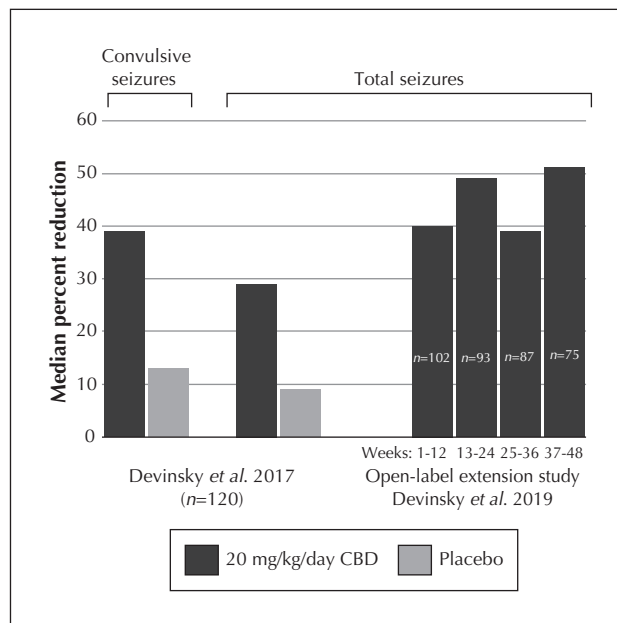
Dravet syndrome

For Dravet syndrome, two trials involved an initial double-blind placebo-controlled trial (*n*=120) (GWP-CARE1B; Devinsky *et al.*, 2017) and a later open-label extension programme (GWPCARE5; Devinsky *et al.*, 2019). An additional trial has also recently been completed (GWPCARE2; Miller *et al.*, 2019). For the former, similar to the Lennox-Gastaut syndrome trials, patients were administered 20 mg/kg/day CBD over a 14-week treatment period, and data were compared relative to a four-week baseline period. For the open-label extension programme, a subset of these patients together with participants from the recently completed GWP-CARE2 trial were enlisted (*n*=189) and followed over 48 weeks. For the controlled trial, during the treatment period, the median percent reduction of convulsive seizures and total seizures was 39% and 29% in the CBD arm relative to 13% and 9% in the placebo arm, respectively. The difference in median percent reduction in non-convulsive seizures was not significant. During the open-label extension programme, the median percent reduction of total seizures continued at between 39% and 51% over a 48-week period (*figure 2*).

As part of the expanded access programme mentioned above, the long-term effect of add-on CBD at up to 25-50 mg/kg/day over a period of 144 weeks was reported for Dravet syndrome and Lennox-Gastaut syndrome patients (Laux *et al.*, 2019). Monthly major motor seizures were reduced by 50% and total seizures by 44%, with consistent reductions in both seizure types across the treatment period, thus supporting CBD as a long-term treatment option.

Based on the patient or caregiver CGI scale, overall improvements were reported for both trials: 62% patients (compared to 34% in the placebo arm) in the study of Devinsky *et al.* (2017), and 85% at 48 weeks in the open-label study of Devinsky *et al.* (2019).

Tuberous sclerosis complex

A clinical trial (GWPCARE6) for Epidiolex as add-on treatment in patients with tuberous sclerosis complex (TSC) was completed earlier this year and has also revealed promising results (Thiele *et al.*, 2019b). Patients were randomised into two groups with Epidiolex (25 or 50 mg/kg/day) or placebo. Of the 201 patients who completed the study, total seizure frequency was decreased by 48% (*p*=0.0013),

Figure 2. Median percent reduction of Dravet syndrome total seizures and convulsive seizures based on the controlled trial of Devinsky *et al.* (2017) and the open-label extension programme of Devinsky *et al.* (2019).

48% (*p*=0.0018) and 27%, and 50% seizure reduction in 36% (*p*=0.0692), 40% (*p*=0.0245), and 22% in the 20 mg/kg/day, 50 mg/kg/day and placebo groups, respectively. An overall improvement, based on the caregiver CGI scale, was reported for 69% (*p*=0.0074), 62% (*p*=0.580) and 40% in the three groups, respectively. In conclusion, Epidiolex significantly reduced seizures in TSC patients. The therapeutic effect of the lower 25 mg/kg/day concentration was similar to that of the higher 50 mg/kg/day dose, and since the latter was associated with more AEs (see below), the 25 mg/kg/day dose would therefore be indicated for these patients.

Other syndromes

Based on an open-label trial for compassionate use, CBD was tested as a treatment for CDKL5 deficiency disorder and Aicardi, Doose, and Dup15q syndromes over a 12-week period (*n*=55) (Devinsky *et al.*, 2018c). The mean decrease in convulsive seizure frequency was 51.4% (*n*=35). Studies are underway to evaluate CBD efficacy for a broader range of epilepsy syndromes and more than 20 trials are currently listed at ClinicalTrials.gov.

Overall, evidence from open-label studies suggests a favourable effect of CBD as an add-on treatment for a number of severe epileptic conditions and the controlled trials for Lennox-Gastaut syndrome, Dravet syndrome and TSC provide a clearer picture

of the positive effect of CBD, in some cases even correlating with seizure freedom. A general positive trend for quality of life (particularly in Lennox-Gastaut syndrome patients), sleep behaviour (particularly in Dravet syndrome patients) and adaptive behaviour was reported. There were also particular improvements in the socialisation domain and communication domain for Dravet syndrome and Lennox-Gastaut syndrome patients, respectively. In the prospective, open-label clinical study by Rosenberg *et al.* (2017b), in which caregiver-reported quality of life (*n*=48) was evaluated for a subset of patients treated with CBD for 12 weeks, improvements (in energy/fatigue, memory, control/helplessness, other cognitive functions, social interactions, behaviour and global QOL) were not related to changes in seizure frequency or AEs, suggesting that CBD may have beneficial effects on patient QOL, distinct from anti-seizure effects, however, this should be confirmed in controlled studies.

Adverse effects

In contrast to artisanal CBD-related products, the AEs associated with purified CBD have been more clearly demonstrated based on the open-label trials and, particularly, the randomised, double-blind placebo-controlled trials (Anciones and Gil-Nagel, 2020).

Based on the collective data from the controlled trials, AEs were frequently reported (86% in CBD groups and 76% in placebo groups), however, the vast majority of AEs were mild and moderate. These included somnolence, decreased appetite, pyrexia and diarrhoea, followed by other less frequent AEs such as vomiting, fatigue and upper respiratory infections (*table 3*). Most AEs appeared within the first two weeks of treatment. Serious AEs were far less common (affecting 19% of CBD groups and 9% of placebo groups). These included, in particular, somnolence, pyrexia, convulsion, rash, lethargy and elevated transaminases (>three times the normal upper limit). The latter occurred in 16% patients in the CBD groups and 1% in the placebo groups. Moreover, in >79-100% of the cases with elevated transaminases, patients were concomitantly taking valproate.

No seizure worsening, suicidal ideation or deaths related to the treatment were reported. It should be emphasised, however, given the novelty of Epidiolex, that long-term AEs are currently unknown.

In the recent TSC trial with the higher dose of 50 mg/kg/day CBD (Thiele *et al.*, 2019b), AEs were common but similarly overall reported as mild and moderate (93%, 100% and 95% in the 25 mg/kg/day; 50 mg/kg/day and placebo groups, respectively). The most common AEs were diarrhoea, decreased appetite, and somnolence, and treatment discontinuation due to AEs occurred in 11%, 14% and 3%, respectively. Elevated liver enzymes were reported in 12% (*n*=9) and 25% (*n*=18) in the 25 mg/kg/day and 50 mg/kg/day, respectively (of those, 81% were also taking valproate).

Recommendations for use

CBD is administered orally as an oil solution. In open-label studies, doses mostly up to 25 mg/kg/day were used, and in the controlled studies, higher doses up to 50 mg/kg/day were used. The studies on Lennox-Gastaut syndrome, however, show that a significant proportion of children respond to doses of as little as 10 mg/kg/day. Therefore a "start slow" and "increase on a case-by-case basis" strategy is recommended. A starting dose of 5 mg/kg/day, divided in two doses, would appear to be adequate. This dose should be increased to 10 mg/kg/day after two weeks of treatment. Thereafter, the individual's response should be carefully observed. The required observation time strictly depends on baseline seizure frequency before the administration of CBD. If the drug is well tolerated but not sufficiently effective, the dose should be slowly increased in increments of 5 mg/kg/day, as long as it is tolerated, up to a maximum of 20-25 mg/kg/day (*table 4*).

As mentioned above, special care should be taken if both CBD and clobazam are administered, since the addition of CBD may lead to an increase (up to five-fold) in its less potent metabolite, N-desmethylclobazam. A toxic benzodiazepine level may manifest as fatigue, somnolence, ataxia, a decrease in cognitive function or behavioural changes. Clinically, these are difficult to distinguish from the possible AEs of CBD itself and monitoring of clobazam/N-desmethylclobazam levels is therefore recommended. Baseline therapeutic drug monitoring should be performed before administration of CBD and subsequently after each increase. If a significant increase in benzodiazepine level is observed, the dose of clobazam should be reduced (and then checked), according to an estimate based on linear kinetics. Like CBD, however, stiripentol inhibits the same P450 subtype 2C19 (CYP2C19), and an increase in benzodiazepine level may not, therefore, occur if the patient is already on stiripentol (Devinsky *et al.*, 2018b). It is highly recommended to follow serum concentrations of all drugs when initiating CBD as a basis for appropriate dosage adjustment. This includes psychotropic drugs (mood stabilisers, antidepressants, and antipsychotics) in order to reveal possible pharmacokinetic interactions or reasons for poor clinical effects or observed AEs.

Table 3. Adverse events based on randomised, double-blind, placebo-controlled trials (the most frequent adverse events are highlighted in grey).

	Dravet syndrome				Lennox-Gastaut syndrome			
	Devinsky *et al.*, 2017		Devinsky *et al.*, 2018a		Devinsky *et al.*, 2018b		Thiele *et al.*, 2018	
	CBD (*n*=61)	Placebo (*n*=59)	CBD (*n*=27)	Placebo (*n*=7)	CBD (*n*=149)	Placebo (*n*=76)	CBD (*n*=86)	Placebo (*n*=85)
[CBD] mg/kg/day	20	-	5, 10 or 20-		10 or 20	-	20	-
Reported AEs (%)	93	75	74	86	89	72	86	69
Reported serious AEs (*n*)	10	3	5	1	26	13	20	4
Withdrawn (*n*)	8	1	2	-	7	1	12	1
Somnolence (*n*)*[a]	22	6	5	1	39	4	25	15
Decreased appetite (*n*)	17	3	5	0	32	6	19	3
Pyrexia (*n*)*	9	5	6	0	16	12	12	8
Diarrhoea (*n*)	19	6			19	6	27	10
Elevated transaminases (*n*)*[b]	12	1	6	-	14	0	20	1
Vomiting (*n*)	9	3	3	0	10	9	15	18
Fatigue (*n*)	12	2	1	2				
Upper respiratory infections (*n*)	7	5			21	11		
Pharyngitis (*n*)			3	2	12	5		
Convulsion (*n*)*	7	3	1	2				
Sedation (*n*)			4	0				
Ataxia (*n*)			3	0				
Rash (*n*)*			2	0				
Non-specified pneumonia (*n*)			2	0				
Lethargy (*n*)*	8	3						
Status epilepticus (*n*)	3	3			11	3	1	1

*Serious adverse events reported in ≤2 patients per RCT. [a]Majority of patients were also taking clobazam. [b]>79% patients were taking valproate (transaminases were elevated >3 times the upper normal limit).

Table 4. Guide to CBD dosing.

1	Start low (5 mg/kg/day), increase to 10 mg/kg/day after two weeks
2	Review clinical response and adverse effects at 10 mg/kg/day
3	Remain on this dose if effective, otherwise increase dose in steps of 5 mg/kg/day if CBD is well tolerated
4	Stop at 20-25 mg/kg/day, and withdraw CBD if ineffective

Pharmacogenetic testing for *CYP2C19* could be performed if a poor metabolizer genotype is suspected based on unexpectedly high levels of CBD relative to the dose.

Finally, biochemical markers of toxicity should be measured, particularly regarding liver enzymes in conjunction with valproate (Gaston *et al.*, 2017; Devinsky *et al.*, 2018a). In the controlled studies, increased liver enzymes led to withdrawal of CBD if levels were more than three times the upper normal limit in the presence of any symptoms (fever, rash, nausea, abdominal pain or increased bilirubin) or eight times higher in the absence of such symptoms. In rare cases, an increase

in enzymes was observed with 20 mg/kg/day CBD without concomitant use of valproate, but not with lower doses of CBD. Overall, the increase in liver enzymes was reversible in about half the cases, without taking any action; in the remaining cases, CBD was withdrawn, leading to normalisation of levels (Devinsky *et al.*, 2018b). A mild increase in enzyme levels may be observed over a few weeks before taking any action, however, as levels become too high, CBD or valproate should be withdrawn or reduced, according to the benefit of each.

Conclusions

Given the range of, and easy access to CBD-enriched oils on the market, alongside the fallacious perception that "natural" products may be safer with fewer AEs than conventional AEDs, it is clear to see why such products are popular. However, analytical controls for CBD-enriched products are not mandatory, leaving consumers with no legal protection or guarantees about the composition and quality of the product they are acquiring. Currently, CBD-enriched products are not subject to any obligatory testing or basic regulatory framework to determine the indication area, daily dosage, route of administration, maximum recommended daily dose, packaging, shelf life or stability. The content of these products is therefore highly variable and although components other than CBD are present which may even be beneficial, there is currently no way this can be ascertained or controlled.

In contrast, purified CBD, in the form of Epidiolex/Epidyolex, is a standardised pharmaceutical preparation that is subject to minimal variability. Based on controlled trials, Epidiolex appears to be an effective treatment option for patients with Dravet syndrome, Lennox-Gastaut syndrome and TSC and has a relatively good safety profile, although it should be emphasised that, at least from the controlled trials, CBD does not outperform other drugs and will by no means represent a silver bullet for everyone. It does, however, add to the arsenal of available add-on drugs against these severe forms of epilepsy, in some cases offering substantial benefits.

Given the range of different seizure types associated with Dravet syndrome, Lennox-Gastaut syndrome and TSC, CBD would appear to have a favourable effect on a large spectrum of convulsive (consistent with preclinical data), rather than non-convulsive seizures (Devinsky *et al.*, 2017), namely clonic, myoclonic, myoclonic-astatic, and generalised tonic-clonic seizures. It should be noted, however, that the effect of CBD on specific types of seizures was not described in detail in the controlled trials and further studies will therefore be required to address this. Other forms of intractable epilepsy cases have been investigated in open-label trials (CDKL5 deficiency disorder and Aicardi, Dup15q and Doose syndromes; Devinsky *et al.*, [2018c]), and more than 20 trials are currently listed at ClinicalTrials.gov (including Rett syndrome and other forms of intractable epilepsy). Although these syndromes collectively represent a small fraction of the epilepsy population, clinical trials in the future may lead to CBD or indeed other cannabinoids being indicated more broadly across the spectrum of epilepsy syndromes. □

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References

Abuhasira R, Shbiro L, Landschaft Y. Medical use of cannabis and cannabinoids containing products - Regulations in Europe and North America. *Eur J Intern Med* 2018; 49: 2-6.

Aizpurua-Olaizola O, Soydaner U, Ȯztüȓk E, *et al*. Evolution of the cannabinoid and terpene content during the growth of cannabis sativa plants from different chemotypes. *J Nat Prod* 2016; 79: 324-31.

Anciones C, Gil-Nagel A. Adverse effects of cannabinoids. *Epileptic Disord* 2020; 22(Suppl. 1): S29-32.

Bettiol A, Lombardi N, Crescioli G, *et al*. Galenic preparations of therapeutic cannabis sativa differ in cannabinoids concentration: a quantitative analysis of variability and possible clinical implications. *Front Pharmacol* 2019; 9: 1543.

Bialer M, Johannessen SI, Levy RH, Perucca E, Tomson T, White HS. Progress report on new antiepileptic drugs: a summary of the Thirteenth Eilat Conference on New Antiepileptic Drugs and Devices (EILAT XIII). *Epilepsia* 2017; 58(2): 181-221.

Bialer M, Johannessen SI, Koepp MJ, *et al*. Progress report on new antiepileptic drugs: a summary of the Fourteenth Eilat Conference on New Antiepileptic Drugs and Devices (EILAT XIV). II. Drugs in more advanced clinical development. *Epilepsia* 2018; 59: 1842-66.

Blümcke I, Arzimanoglou A, Beniczky S, Wiebe S. Roadmap for a competency-based educational curriculum in epileptology: report of the Epilepsy Education Task Force of the ILAE. *Epileptic Disord* 2019; 21: 129-40.

Bonn-Miller MO, Loflin MJE, Thomas BF, Marcu JP, Hyke T, Vandrey R. Labeling accuracy of cannabidiol extracts sold online. *JAMA* 2017; 318(17): 1708-9.

BPNA. *Guidance on the use of cannabis-based products for medicinal use in children and young people with epilepsy.* 2018. https://bpna.org.uk/userfiles/BPNA_CBPM_Guidance_Oct2018.pdf.

Brodie MJ, Ben-Menachem E. Cannabinoides for epilepsy: What do we know and where do we go? *Epilepsia* 2018; 59: 291-6.

Calvi L, Pentimalli D, Panseri S, *et al*. Comprehensive quality evaluation of medical Cannabis sativa L. inflorescence and macerated oils based on HS-SPME coupled to GC-MS and LC-HRMS (q-exactive orbitrap®) approach. *J Pharm Biomed Anal* 2018; 150: 208-19.

Carcieri C, Tomasello C, Simiele M. Cannabinoids concentration variability in cannabis olive oil galenic preparations. *J Pharm Pharmacol* 2018; 70(1): 143-9.

Centre for Medicinal Canabis. *UK CBD Requires Better Regulation and Reform as Industry Moves Towards Billion Pound Sector Status.* 2019. https://www.thecmcuk.org/uk_cbd_requires_better_regulation.

Devinsky O, Marsh E, Friedman D, *et al*. Cannabidiol in patients with treatment-resistant epilepsy: an open-label interventional trial. *Lancet Neurol* 2016; 15(3): 270-8.

Devinsky O, Cross JH, Laux L, *et al*. Trial of cannabidiol for drug-resistant seizures in the Dravet syndrome. *N Engl J Med* 2017; 376(21): 2011-20.

Devinsky O, Patel AD, Thiele EA, *et al*. Randomized, dose-ranging safety trial of cannabidiol in Dravet syndrome. *Neurology* 2018a; 90: e1204-11.

Devinsky O, Patel AD, Cross JH, *et al*. Effect of cannabidiol on drop seizures in the Lennox-Gastaut syndrome. *N Engl J Med* 2018b; 378(20): 1888-97.

Devinsky O, Verducci C, Thiele EA, *et al*. Open-label use of highly purified CBD (Epidiolex®) in patients with CDKL5 deficiency disorder and Aicardi, Dup15q, and Doose syndromes. *Epilepsy Behav* 2018c; 86: 131-7.

Devinsky O, Nabbout R, Miller I, *et al*. Long-term cannabidiol treatment in patients with Dravet syndrome: an open-label extension trial. *Epilepsia* 2019; 60(2): 294-302.

Filloux F. Cannabinoids for paediatric epilepsy? Up in smoke or real science? *Transl Pediatr* 2015; 4: 271-82.

Franco V, Perucca E. Pharmacological and Therapeutic Properties of Cannabidiol for Epilepsy. *Drugs* 2019; 79(13): 1435-54.

Gaston TE, Bebin EM, Cutter GR, *et al*. Interactions between cannabidiol and commonly used antiepileptic drugs. *Epilepsia* 2017; 58: 1586-92.

Geffrey AL, Pollack SF, Bruno PL, Thiele EA. Drug-drug interaction between clobazam and cannabidiol in children with refractory epilepsy. *Epilepsia* 2015; 56: 1246-51.

GMC. *Consent: patients and doctors making decisions together.* 2008. https://www.gmc-uk.org/ethical-guidance/ethical-guidance-for-doctors/consent.

GMC. *Prescribing unlicensed medicines.* 2019. https://www.gmc-uk.org/ethical-guidance/ethical-guidance-for-doctors/prescribing-and-managing-medicines-and-devices/prescribing-unlicensed-medicines.

Gray RA, Whalley B. Working mechanisms of cannabinoids. *Epileptic Disord* 2020; 22(Suppl. 1): S10-5.

Hussain SA, Zhou R, Jacobson C, *et al*. Perceived efficacy of cannabidiol-enriched cannabis extracts for treatment of pediatric epilepsy: a potential role for infantile spasms and Lennox-Gastaut syndrome. *Epilepsy Behav* 2015; 47: 138-41.

Johannessen SI, Johannessen Landmark C. Antiepileptic drug interactions: basic principles and clinical implications. *Current Neuropharm* 2010; 8: 254-67.

Johannessen Landmark C, Patsalos PN. Drug interactions involving the new second and third-generation antiepileptic drugs. *Exp Rev Neurother* 2010; 10: 119-40.

Johannessen Landmark C, Brandl U. Pharmacology and drug interactions of cannabinoids. *Epileptic Disord* 2020; 22(Suppl. 1): S16-22.

Johannessen Landmark C, Johannessen SI, Tomson T. Host factors affecting antiepileptic drug delivery: pharmacokinetic variability. *Adv Drug Deliv Rev* 2012; 64: 896-910.

Johannessen Landmark C, Johannessen SI, Tomson T. Dosing strategies for antiepileptic drugs: from a standard dose for all to individualised treatment by implementation of therapeutic drug monitoring. *Epileptic Disord* 2016; 18: 367-83.

Lagae L. Long-term effects of cannabinoids on development/behavior. *Epileptic Disord* 2020; 22(Suppl. 1): S33-37.

Laux LC, Bebin EM, Checketts D, *et al*. Long-term safety and efficacy of cannabidiol in children and adults with treatment resistant Lennox-Gastaut syndrome or Dravet syndrome: Expanded access program results. *Epilepsy Res* 2019; 154: 13-20.

Maa E, Figi P. The case for medical marijuana in epilepsy. *Epilepsia* 2014; 55(6): 783-6.

Miller I, Perry S, Saneto R, *et al*. Cannabidiol (CBD; 10 and 20 mg/kg/day) significantly reduces convulsive seizure frequency in children and adolescents with Dravet syndrome (DS): Results of a dose-ranging, multicenter, randomized, double-blind, placebo-controlled trial (GWPCARE2). *Neurology* 2019; 93(5): e532.

Morrison G, Crockett J, Blakey G, Sommerville K. A Phase 1, Open-Label, Pharmacokinetic Trial to Investigate Possible Drug-Drug Interactions Between Clobazam, Stiripentol, or Valproate and Cannabidiol in Healthy Subjects. *Clin Pharmacol Drug Dev* 2019; 8(8): 1009-31.

Nabbout R, Thiele E. The role of cannabinoids in epilepsy treatment: a critical review of efficacy results from clinical trials. *Epileptic Disord* 2020; 22(Suppl. 1): S23-8.

NICE. *Cannabis-based medicinal products*. 2019. https://www.nice.org.uk/guidance/ng144.

Pamplona FA, da Silva LR, Coan AC. Potential clinical benefits of CBD-rich cannabis extracts over purified CBD in treatment-resistant epilepsy: observational data meta-analysis. *Front Neurol* 2018; 12(9): 759.

Patsalos PN. Drug interactions with the newer antiepileptic drugs (AEDs)-Part 1: pharmacokinetic and pharmacodynamic interactions between AEDs. *Clin Pharmacokinet* 2013a; 52: 927-66.

Patsalos PN. Drug interactions with the newer antiepileptic drugs (AEDs)-Part 2: pharmacokinetic and pharmacodynamic interactions between AEDs and drugs used to treat non-epilepsy disorders. *Clin Pharmacokinet* 2013b; 52(12): 1045-61.

Pavlovic R, Nenna G, Calvi L. Quality traits of "cannabidiol oils": cannabinoids content, terpene fingerprint and oxidation stability of European commercially available preparations. *Molecules* 2018; 20(2): 5.

Pegoraro CN, Nutter D, Thevenon M, Ramirez CL. Chemical profiles of cannabis sativa medicinal oil using different extraction and concentration methods. *Nat Prod Res* 2019; 12: 1-4.

Perucca E. Cannabinoids in the treatment of epilepsy: hard evidence at last? *J Epilepsy Res* 2017; 7(2): 61-76.

Porcari GS, Fu C, Doll ED, Carter EG, Carson RP. Efficacy of artisanal preparations of cannabidiol for the treatment of epilepsy: practical experiences in a tertiary medical center. *Epilepsy Behav* 2018; 80: 240-6.

Porter BE, Jacobson C. Report of a parent survey of cannabidiol-enriched cannabis use in pediatric treatment-resistant epilepsy. *Epilepsy Behav* 2013; 29(3): 574-7.

Press CA, Knupp KG, Chapman KE. Parental reporting of response to oral cannabis extracts for treatment of refractory epilepsy. *Epilepsy Behav* 2015; 45: 49-52.

Rosenberg EC, Patra PH, Whalley BJ. Therapeutic effects of cannabinoids in animal models of seizures, epilepsy, epileptogenesis, and epilepsy-related neuroprotection. *Epilepsy Behav* 2017a; 70(Pt B): 319-27.

Rosenberg EC, Louik J, Conway E, Devinsky O, Friedman D. Quality of Life in Childhood Epilepsy in pediatric patients enrolled in a prospective, open-label clinical study with cannabidiol. *Epilepsia* 2017b; 58(8): e96-100.

Russo EB. Taming THC: potential cannabis synergy and phytocannabinoid-terpenoid entourage effects. *Br J Pharmacol* 2011; 163: 1344-64.

Santiago M, Sachdev S, Arnold JC, McGregor IS, Connor M. Absence of Entourage: Terpenoids Commonly Found in Cannabis sativa Do Not Modulate the Functional Activity of Δ9-THC at Human CB1 and CB2 Receptors. *Cannabis Cannabinoid Res* 2019; 4(3): 165-76.

Schonhofen P, Bristot IJ, Crippa JA. Cannabinoid-based therapies and brain development: potential harmful effect of early modulation of the endocannabinoid system. *CNS Drugs* 2018; 32(8): 697-712.

Specchio N, Pietrafusa N, Cross HJ. Source of cannabinoids: what is available, what is used, and where does it come from? *Epileptic Disord* 2020; 22(Suppl. 1): S1-9.

Szaflarski JP, Bebin EM, Comi AM, *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): 1540-8.

Thiele EA, Marsh ED, French JA. Cannabidiol in patients with seizures associated with Lennox-Gastaut syndrome (GWPCARE4): a randomised, double-blind, placebo-controlled Phase 3 trial. *Lancet* 2018; 391(10125): 1085-96.

Thiele E, Marsh E, Mazurkiewicz-Beldzinska M. Cannabidiol in patients with Lennox-Gastaut syndrome: interim analysis of an open-label extension study. *Epilepsia* 2019a; 60(3): 419-28.

Thiele E, Bebin M, Hari Bhathal H, *et al*. *Cannabidiol (CBD) Treatment in Patients with Seizures Associated with Tuberous Sclerosis Complex: A Randomized, Double-blind, Placebo-Controlled Phase 3 Trial (GWPCARE6)*. AES meeting, Baltimore 2019.

Tzadok M, Uliel-Siboni S, Linder I. CBD-enriched medical cannabis for intractable pediatric epilepsy: the current Israeli experience. *Seizure* 2016; 35: 41-4.

Vandrey R, Raber JC, Raber ME, Douglass B, Miller C, Bonn-Miller MO. Cannabinoid dose and label accuracy in edible medical cannabis products. *JAMA* 2015; 313(24): 2491-3.

TEST YOURSELF

(1) What are the groups of known physiologically active components of cannabis?

(2) What is the maximum ratio of CBD to THC in artisanal products advertised with CBD content?

(3) What is the effect of THC on seizures?

(4) Epidiolex has been shown to be efficacious for which epileptic syndromes based on RCTs?

(5) Based on RCTs, what are the main adverse effects of Epidiolex?

(6) Which adverse effect is associated with clobazam in combination with Epidiolex?

(7) Which adverse effect is associated with valproate in combination with Epidiolex?

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com, under the section "The EpiCentre".