

# Cannabinoids in the Treatment of Epilepsy: Hard Evidence at Last?

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## Review Article

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The interest in cannabis-based products for the treatment of refractory epilepsy has skyrocketed in recent years. Marijuana and other cannabis products with high content in  $\Delta(9)$ -tetrahydrocannabinol (THC), utilized primarily for recreational purposes, are generally unsuitable for this indication, primarily because THC is associated with many undesired effects. Compared with THC, cannabidiol (CBD) shows a better defined anticonvulsant profile in animal models and is largely devoid of adverse psychoactive effects and abuse liability. Over the years, this has led to an increasing use of CBD-enriched extracts in seizure disorders, particularly in children. Although improvement in seizure control and other benefits on sleep and behavior have been often reported, interpretation of the data is made difficult by the uncontrolled nature of these observations. Evidence concerning the potential anti-seizure efficacy of cannabinoids reached a turning point in the last 12 months, with the completion of three high-quality placebo-controlled adjunctive-therapy trials of a purified CBD product in patients with Dravet syndrome and Lennox-Gastaut syndrome. In these studies, CBD was found to be superior to placebo in reducing the frequency of convulsive (tonic-clonic, tonic, clonic, and atonic) seizures in patients with Dravet syndrome, and the frequency of drop seizures in patients with Lennox-Gastaut syndrome. For the first time, there is now class 1 evidence that adjunctive use of CBD improves seizure control in patients with specific epilepsy syndromes. Based on currently available information, however, it is unclear whether the improved seizure control described in these trials was related to a direct action of CBD, or was mediated by drug interactions with concomitant medications, particularly a marked increase in plasma levels of N-desmethyloclobazam, the active metabolite of clobazam. Clarification of the relative contribution of CBD to improved seizure outcome requires re-assessment of trial data for the subgroup of patients not comedicated with clobazam, or the conduction of further studies controlling for the confounding effect of this interaction. (2017;7:61-76)

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## Introduction

The history of human use of the *Cannabis* plant goes back to the dawn of mankind. The plant, which originated in Central Asia or in the foothills of the Himalayas, was initially cultivated in China for fiber and seed production, and in India for resin production.<sup>1</sup> For many centuries, European and East Asian societies have used mostly *Cannabis* strains containing low amounts (< 1% dry weight) of the psychoactive principle 9- $\Delta$ -tetrahydrocannabinol (THC), and their main utilization was for fiber and food. Conversely, African, Middle-Eastern, South Asian, and Southeast Asian societies have

used cannabis primarily for its psychoactive properties, with strains from these regions often containing 5-10% THC.<sup>1</sup>

The first studies on the medical use of cannabis date back to the Chinese Emperor Shen Nung (about 2,700 B.C.).<sup>2</sup> As evidence of the important role of the plant in ancient Chinese culture, archeological excavations in the Xinjiang-Uighur Autonomous Region of China have recently unearthed a 2,700-year-old grave of a shaman which contained a large cache of cannabis, perfectly preserved by climatic and burial conditions, presumably employed as a medicinal or psychoactive agent, or as an aid to divination.<sup>3</sup> Early written records of medical applications can be traced to Sumerian and Akkadian tab-

lets, around 1,800 B.C., which mention the use of a medicinal plant, most likely cannabis, to treat a variety of ailments, including nocturnal convulsions.<sup>2,4</sup> In less ancient times, there are records in the Arabic and Islamic literature which mention explicitly cannabis as a treatment for seizures and epilepsy.<sup>4</sup>

The first detailed modern description of the utility of cannabis-based products as an anti-seizure medication was published in 1843 by W.B. O'Shaughnessy, physician in the Bengal Army and Late Professor of Chemistry and Materia Medica at the Medical College of Calcutta. After testing the behavioral effects of various preparations of *Cannabis indica* in healthy fish, dogs, swines, vultures, crows, horses, deers, monkeys, goats, sheep, cows, and military assistants, he investigated the potential value of extracts of the plant in patients with different disorders, and reported remarkable anti-seizure effects in a 40-days-old baby girl with recurrent convulsive seizures.<sup>5</sup> These observations were taken up by other physicians, including Sir William Gowers, who described the effectiveness of *Cannabis indica* against seizures resistant to bromides.<sup>6</sup>

In the twentieth century the use of cannabis declined somewhat because cultivation of the plant was made illegal in many countries. However, scientific advances on the properties of the plant progressed as chemists and pharmacologists started on work on the chemical characterization of its active ingredients, and on the relationship between their molecular structure and biological activity. While various reports focused on the effects of smoked cannabis on seizure control, it soon became clear that the psychoactive effects of THC limited the applicability of crude cannabis preparations in the treatment of seizures, and attention shifted to the potential utility of non-psychoactive ingredients such cannabidiol (CBD).<sup>2</sup> Although interest in 'medical marijuana' and its individual constituents for the treatment of seizures persisted through the years, it is only in the last decade that preclinical and clinical research into the potential application of cannabis in the treatment of epilepsy has literally exploded (Fig. 1). The purpose of the present article is to review the pharmacological basis of the anti-seizure effects of cannabis and particularly its non-psychoactive constituents, and to discuss critically the expanding range of evidence on the efficacy of these compounds in the management of different seizure types and epilepsy syndromes.

## Chemistry and mechanisms of action

The genus *Cannabis* refers to a flowering plant of which there are three main species, *Cannabis sativa*, *Cannabis indica* and *Cannabis*

*ruderalis*. These plants contain over 100 biologically active chemicals called cannabinoids, with the most abundant and best characterized among those being THC and CBD (Fig. 2).<sup>7</sup> Crude preparations of cannabis include dried leaves, stems and flower pods (marijuana), resins (hashish), and oily extracts (hashish oil), all of which have been used through the centuries mostly for their psychoactive properties. In general, cannabis products derived from *Cannabis sativa* exhibit a higher CBD/THC ratio than products derived from *Cannabis indica*. Different *Cannabis* strains have been bred either to maximize THC

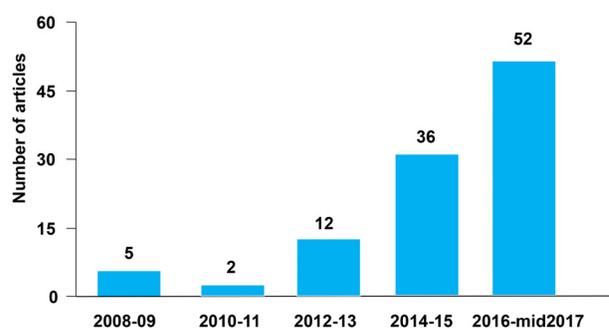


Figure 1. Number of articles retrieved in PubMed by using the search terms 'cannabis and epilepsy', grouped by year of publication.

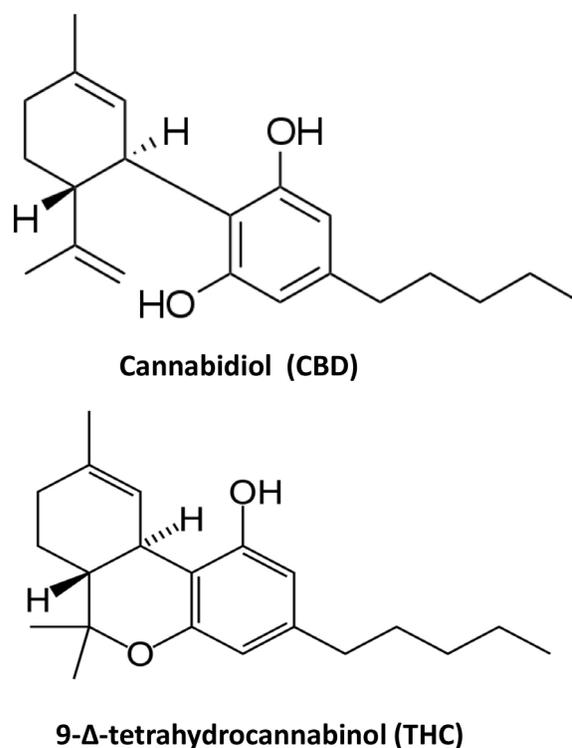


Figure 2. Chemical structure of cannabidiol and 9-Δ-tetrahydrocannabinol.

content or, conversely, to reduce THC content and increase the concentration of CBD and other non-psychoactive ingredients.<sup>8</sup>

Many biological actions of cannabinoids are mediated by their interaction with two closely related receptors, cannabinoid receptor type 1 (CB1) and 2 (CB2), although a variety of other receptors and targets are also involved in the effects of these compounds.<sup>9-13</sup> Both the CB1 and the CB2 receptors belong to the class of  $G_{i/o}$ -coupled metabotropic receptors and are widely distributed throughout the central nervous system (CNS), with CB1 receptors being localized primarily in neurons and CB2 receptors being expressed in microglia and, to a greater extent, in the immune system.<sup>9</sup> The discovery of cannabinoid receptors in the CNS led to a search for endogenous substances interacting with these receptors and to the identification of so-called 'endogenous cannabinoids', the most important of which are the arachidonic acid derivatives anandamide (2-arachidonoylethanolamide) and 2-arachidonoyl glycerol.<sup>9</sup> Extensive evidence has now accumulated that endocannabinoids play an important role in the control in synaptic transmission and the regulation of the rate of neuronal firing.<sup>13-17</sup> In the CNS, CB1 receptors are expressed pre-synaptically on both glutamatergic and GABAergic interneurons, and activation of these receptors results in inhibition of synaptic transmission, including glutamate release.<sup>9,10,16</sup> An involvement of endocannabinoid signaling pathways in the pathophysiology of epilepsy (and the possibility of targeting these pathways for therapeutic purposes) is suggested by a number of experimental and clinical observations. Experimentally, many studies reviewed in recent articles<sup>10,14,16,17</sup> have demonstrated that endogenous cannabinoids systems are altered in a variety of models of seizures, epilepsy and epileptogenesis, whereas external modulation of these systems can prevent or modulate seizure activity. Clinically, observations implicating a role of endocannabinoid systems in epilepsy include the finding of reduced anandamide concentrations in the cerebrospinal fluid of individuals with new-onset temporal lobe epilepsy;<sup>18</sup> demonstration of downregulation of CB1 receptors and related molecular components in glutamatergic neurons from surgical samples of epileptic human hippocampus;<sup>19</sup> demonstration of sprouting of CB1-receptor expressing GABAergic axons (or increased expression of CB1-receptors on these fibers) in sclerotic human hippocampi;<sup>20</sup> and PET evidence of differential changes in CB1 receptor availability in the seizure onset zone and in the insula of patients with temporal lobe epilepsy and hippocampal sclerosis.<sup>21</sup>

Cannabinoids have numerous and complex pharmacological properties. In experimental models, for example, THC displays com-

plex psychoactive effects, variable anticonvulsant effects, and analgesic, cognitive, muscle relaxant, anti-inflammatory, appetite stimulant, and antiemetic activity.<sup>9,12,22</sup> On the other hand, CBD is mostly devoid of adverse psychoactive effects and possesses anti-convulsant, analgesic, anti-anxiety, antiemetic, immune-modulating, anti-inflammatory, neuroprotectant, and anti-tumorigenic properties.<sup>9,12,22</sup> In the case of THC, anti-seizure activity seems to be mediated to an important extent by its partial agonist action on the CB1 receptor, which is also primarily involved in the expression of psychoactive effects.<sup>9,13,23</sup> CBD, on the other hand, has very weak affinity for the CB1 and CB2 receptors and its anti-seizure activity at clinically relevant concentrations is considered to be mediated by other mechanisms,<sup>13,24,25</sup> possibly including functional agonism or antagonism at multiple 7-transmembrane receptors, ion channels, and neurotransmitter transporters (Table 1).<sup>24-35</sup> In particular, an effect on adenosine reuptake and antagonism of G protein-coupled receptor 55 (GPR55) have been recently suggested to play an important role in CBD anti-seizure activity.<sup>36</sup>

**Table 1.** A list of targets and actions reported for CBD based on results of studies in different experimental models and systems<sup>24-36</sup>

Receptor/target	Action of CBD at the indicated receptor/target
CB1	Non-competitive antagonist
CB2	Inverse agonist
TRPV1-3	Agonist
TRPV4	Agonist
TRPM8	Antagonist
TRPA1	Agonist
$\alpha 1$ , $\alpha 3$ glycine	Agonist
5-HT <sub>1a</sub>	Agonist
GPR55	Antagonist
PPAR- $\gamma$	Agonist
TNF $\alpha$	Modulator
Voltage-gated T-type calcium channels	Antagonist
Resurgent sodium current	Inhibition
VDAC1	Modulator
Adenosine reuptake	Inhibitor
Adenosine A <sub>1</sub> and A <sub>2</sub> receptors	Modulator
Anandamide reuptake	Inhibitor
Fatty acid amide hydrolase	Inhibitor

The list is not exhaustive and not all reported actions may be relevant to anti-seizure activity.

CBD, cannabidiol; CB1, cannabinoid type 1 receptor; CB2, cannabinoid type 2 receptor; TRPV1-3, transient receptor potential of vanilloid types 1-3; TRPV4, transient receptor potential of vanilloid type 4; TRPM8, transient receptor potential of the melastatin type 8; TRPA1, transient receptor potential of ankyrin type 1; 5-HT<sub>1a</sub>, serotonin receptor, subtype 1A; GPR55, G protein-coupled receptor 55; PPAR- $\gamma$ , nuclear peroxisome proliferator-activated receptor  $\gamma$ ; VDAC1, voltage-dependent anion-selective channel protein type 1.

## Pharmacological profile in experimental models of seizures and epilepsy

Among the many active principles found in the cannabis plant, THC is the most widely investigated for its many actions, including its psychoactive effects and risks associated with overdose and abuse. THC shows some anticonvulsant effects in certain seizure models, but there have also been studies suggesting a proconvulsant effect.<sup>14,37</sup> Although it is plausible that THC may contribute to the anti-seizure activity reported for medical marijuana and other cannabis preparations, its adverse psychotropic properties<sup>37</sup> and inconsistent activity in seizure models render it undesirable for development for the treatment of epilepsy.<sup>38</sup> Therefore, most cannabinoid research efforts in epilepsy have focused on the characterization of non-psychoactive agents, particularly CBD and cannabidiol (CBDV), and the present review will focus especially on these compounds.

### CBD

In preclinical studies, CBD has been found to be active in a variety of seizure models, including seizures induced by maximal electroshock<sup>39-41</sup> and by pentylenetetrazole in rats and mice,<sup>42-44</sup> audiogenic seizures in rats<sup>45</sup> and seizures induced by 3-mercaptopropionic acid, bicuculline, picrotoxin, cocaine and isoniazid (but not strychnine) in mice.<sup>39,45,46</sup> In addition, CBD shows protective activity in pilocarpine models of temporal lobe seizures and in the penicillin and cobalt models of focal seizures in rats,<sup>47-49</sup> and increases the afterdischarge threshold while reducing afterdischarge amplitude and duration in electrically evoked kindled seizures in rats.<sup>50</sup> CBD also inhibits epileptiform potentials induced by a  $Mg^{2+}$ -free medium and 4-aminopyridine in hippocampal brain slices.<sup>42</sup>

Recently, the anticonvulsant profile of CBD was re-evaluated using a refocused screening protocol developed by the National Institute of Neurological Disorders and Stroke (NINDS)-funded Epilepsy Therapy Screening Program.<sup>41</sup> In this investigation, CBD given intraperitoneally (i.p.) produced a dose-dependent protection against maximal electroshock-induced seizures in mice ( $ED_{50}$  83.5 mg/kg) and rats ( $ED_{50}$  88.9 mg/kg), and was also found to be effective in the 6 Hz 44 mA seizure model ( $ED_{50}$  164 mg/kg), and in the corneal kindling model ( $ED_{50}$  119 mg/kg) in mice. These effects were observed at doses that did not cause motor impairment. No protection, however, was attained in the lamotrigine-resistant amygdala kindled rat at doses up to 300 mg/kg.

As discussed above, the molecular actions involved in CBD an-

ti-seizure activity do not appear to be mediated by a direct effect on cannabinoid receptors, but the precise mechanisms of action have not been ascertained. In various studies, CBD has been reported to exhibit a range of other activities which suggest potential utility in many other conditions, including anxiety, mood disorders, psychosis, fear, trauma-related conditions, tobacco and opioid addiction, inflammatory diseases, neurodegenerative disorders, and as a tool to counteract the undesired psychotropic effects of THC.<sup>32,51-56</sup>

### CBDV

CBDV, another cannabinoid present in the cannabis plant, has been the focus of many recent studies. Like CBD, CBDV is virtually devoid of psychoactive effects and shows protecting activity *in vitro* against epileptiform potentials induced by 4-aminopyridine and  $Mg^{2+}$ -free conditions in rat hippocampal slices and, *in vivo*, against seizures induced by maximal electroshock, pentylenetetrazole, and audiogenic stimulation.<sup>57</sup> In an early study, CBDV was not found to protect against pilocarpine-induced seizures at doses up to 200 mg/kg i.p., but potentiated the effect of valproic acid and phenobarbital in this model.<sup>57</sup> In a subsequent study by the same group, however, inhibition of pilocarpine-induced seizures was observed after administration of a CBDV-rich cannabis extract.<sup>58</sup> The mechanisms responsible for the anti-seizure effects of CBDV do not seem to involve an action on cannabinoid receptors.<sup>25,29</sup> Like CBD, CBDV acts as an agonist for the transient receptor potential (TRP) channels TRPV1, TRPV2, TRPA1, and as an antagonist for TRPM8.<sup>28,30,59</sup> These actions, however, have been considered unlikely to contribute to its anticonvulsant activity.<sup>29,36</sup> CBDV also inhibits diacylglycerol lipase  $\alpha$ , the primary enzyme involved in the synthesis of 2-arachidonoylglycerol.<sup>28</sup> Again, the potential contribution of this effect to its anticonvulsant activity has not been established.

### 9- $\Delta$ -tetrahydrocannabinolic acid

In the cannabis plant, most cannabinoids are synthesized in their acidic form. These acidic cannabinoids undergo decarboxylation to their neutral counterparts (e.g., CBD and THC) under the influence of auto-oxidation, light and heat. In most common extraction and delivery methods, plant materials are exposed to heat, resulting in the conversion of the acidic forms to the neutral constituents.<sup>60</sup> However, some cannabis products may retain some content in acidic cannabinoids, particularly cannabidiolic acid (CBDA) and 9- $\Delta$ -tetrahydrocannabinolic acid (THCA). THCA has been found to possess anticonvulsant activity in preliminary preclinical investigations, and be

devoid of adverse psychoactive effects.<sup>61</sup> Interest in THCA been rekindled recently by the fact that it is sometimes used for anti-seizure purposes in the USA, where it can be more readily available and/or affordable than CBD. One specific concern is that accidental exposure to heat of artisanal THCA preparations may result in partial conversion to THC.<sup>61</sup>

## Pharmacokinetics and drug interactions

### CBD

Following administration to healthy subjects of a single 400 mg oral dose encapsulated in gelatin capsules, CBD was found to be rapidly absorbed, with mean peak plasma concentrations of 114 to 181 ng/mL being attained at about 1.5 to 3 hours.<sup>62</sup> Following oral administration, CBD shows a high interindividual pharmacokinetic variability. Its oral bioavailability is low, in the order of 6%<sup>37</sup> or 10%,<sup>63</sup> due in part to extensive first-pass metabolism.<sup>37</sup> Bioavailability appears to be higher (in the range of 11 to 45%) after inhalation in cannabis smokers.<sup>64</sup> In a study conducted with an oromucosal spray of nabiximols (a formulation containing THC and CBD in an approximately 1:1 ratio, which is approved in some countries for the treatment of symptoms of spasticity associated with multiple sclerosis), co-administration with food resulted in a mean 5-fold increase in CBD bioavailability.<sup>65</sup> It is unclear whether a similar effect also occurs with oral formulations.

CBD is highly bound to plasma proteins (> 99%)<sup>63</sup> and is extensively metabolized by cytochrome P450 (CYP) enzymes, particularly CYP3A4 and CYP2C19,<sup>66</sup> and glucuronyltransferases.<sup>67</sup> The major metabolic pathway involves hydroxylation and oxidation at C-7, followed by further hydroxylation in the pentyl and propenyl groups.<sup>68</sup> The major oxidized metabolite identified is cannabidiol-7-oic acid containing a hydroxyethyl side chain. The elimination of CBD follows a biphasic pattern, with an initial half-life of about 6 hours which partly reflects distributive processes. Because of its very high lipophilic properties, CBD distributes extensively into tissues, from which it is slowly released, resulting in a late-phase terminal half-life of about 24 hours.<sup>63</sup> In a safety and pharmacokinetic study in patients with Dravet syndrome, 27 children aged 4 to 10 years received CBD doses of 5, 10 or 20 mg/kg/day in addition to pre-existing antiepileptic drugs (AEDs).<sup>69</sup> On treatment day 22, exposures to CBD and its major metabolites were found to increase dose-proportionally.

The clearance of CBD has been reported to be increased after

co-administration with the enzyme inducer rifampicin.<sup>70</sup> It would be expected that enzyme inducing AEDs such as carbamazepine and phenytoin also accelerate CBD metabolism and reduce CBD levels at steady state. Conversely, CBD levels have been found to be increased by the CYP3A4 inhibitor ketoconazole, but not by the CYP2C19 inhibitor omeprazole.<sup>70</sup>

In studies conducted on liver isozymes, CBD has been shown to inhibit the activity of CYP1A1, CYP1A2, CYP1B1, CYP2D6, CYP3A4, and CYP2C19 enzymes.<sup>71-75</sup> There is also evidence of CBD acting as an inhibitor of transporter systems, such as BCRP and the ABC transporter multidrug resistance-related protein 1.<sup>67</sup> Some of these *in vitro* effects occur at concentrations above those found within the clinically used dose range. However, at least one clinically important interaction mediated by inhibition of drug metabolism has been reported. In a group of 13 patients with epilepsy aged 4 to 19 years, addition of CBD (initial dose 5 mg/kg/day, titrated up to a target dose of 25 mg/kg/day) resulted in an increase in the plasma levels of concomitantly administered clobazam by 60 ± 80% (mean ± standard deviation). More importantly, the plasma concentration of the active metabolite of clobazam, N-desmethyl-clobazam, increased by 500 ± 300% (95% confidence interval [CI]: +90 to +610%) at 4 weeks after starting CBD.<sup>76</sup> Ten of the 13 patients experienced side effects, most commonly drowsiness, which resolved after lowering the clobazam dose. This interaction, which was considered to be mediated by inhibition of CYP2C19, is particularly relevant because clobazam is frequently used in epileptic encephalopathies for which CBD appears to be a promising new treatment. In a safety and pharmacokinetic study in children with Dravet syndrome, there were minimal changes in clobazam levels, but concentrations of N-desmethyl clobazam increased independently of CBD dose, except for patients on stiripentol in whom N-desmethyl-clobazam levels appeared to be unaffected by CBD.<sup>69</sup> There were no demonstrable effects on other AEDs (valproic acid, topiramate, stiripentol, levetiracetam).<sup>69</sup> Serum levels of concomitant AEDs were also measured in another study which assessed 39 adults and 42 children started on CBD at a dose of 5 mg/kg/day, increased according to clinical response up to a maximum of 50 mg/kg/day.<sup>77</sup> In the latter study, increases in the levels of N-desmethyl-clobazam, topiramate, and rufinamide were reported with increasing CBD doses. In adults, there were also increases in serum levels of zonisamide and eslicarbazepine. The results of this study are difficult to interpret, because of the confounding effects of changes in the dose of comedications. Serum clobazam levels, for example, decreased during CBD coadministration, primarily due to a re-

duction in clobazam dose. In any case, assessment of the data suggested that changes in serum levels of concomitant AEDs during CBD administration were generally minor, with the exception of clobazam and N-desmethylclobazam levels.<sup>77</sup> In fact, occurrence of sedation as a result of the interaction with clobazam often led to a decrease in clobazam dose.

CBD may also be involved in pharmacodynamic interactions, i.e. interactions which occur at the site of action. In particular, acutely administered CBD may antagonize some of the effects of THC at CB1 receptor sites,<sup>78-80</sup> an observation which may explain why patients taking marijuana with higher CBD content are less likely to develop adverse THC-related psychotropic symptoms, and may tolerate higher THC doses.<sup>37,81</sup> Studies in animal models, however, suggest that after prolonged exposure molecular interactions between CBD and THC may be more complex than previously thought, and may involve superadditive effects on some measures.<sup>82</sup> Terpenoids contained in cannabis extracts may also interact with the action of CBD and other cannabinoids.<sup>83</sup>

The observation has been made that elevations in liver enzymes associated with CBD treatment occur much more frequently among patients comedicated with valproate than among patients comedicated with other AEDs.<sup>77,84-86</sup> It is unclear whether the mechanism underlying this interaction is pharmacokinetic or pharmacodynamic in nature.<sup>87</sup>

## CBDV

The pharmacokinetics of CBDV have not been reported in detail. In a recently completed Phase I study, healthy subjects were given single oral doses ranging between 25 and 800 mg, as well as multiple doses of 800 mg once daily over 5 days.<sup>36</sup> Peak plasma concentrations and areas under the plasma concentration-time curve were found to be dose proportional. The 7-hydroxy- and 6-hydroxy-metabolites could be detected shortly after dosing.

## Clinical evidence of efficacy and safety: exploratory studies

### Marijuana and oral cannabis extracts

As discussed in the introductory section of this article, evidence of cannabis being used in the treatment of seizure disorders dates back thousands of years, and cannabis preparations had a role in the treatment of epilepsy by neurologists in the late nineteenth century. Although use of cannabis in epilepsy declined in the twentieth cen-

tury due to legal restrictions and the gradual introduction of AEDs, observations suggesting anti-seizure activity continued to be reported. In 1975, Consroe et al.<sup>88</sup> described a 24-year-old patient with seizures uncontrolled despite therapy with phenobarbital and phenytoin, who became seizure-free after starting to smoke marijuana. A few other reports suggestive of beneficial effects on seizures of marijuana smoking appeared in the subsequent decades,<sup>89-92</sup> including an interesting epidemiological study which found a reduced risk of a first seizure among illicit cannabis users.<sup>93</sup> There have been however, also reports of marijuana smoking precipitating or aggravating seizures.<sup>94,95</sup>

For medicinal use, oral intake provides a more easily controllable route of drug delivery than inhalation. Therefore, particularly during the last twenty years, users of cannabis for seizure control have generally preferred oral preparations. At the same time, increasing realization that CBD is superior to THC in safety and potential anti-seizure activity has resulted in preferential use of whole plant preparations or cannabis-based oil or liquid extracts enriched in CBD content. A number of such products are accessible in many countries and states under widely different legal and regulatory scenarios.<sup>87,96</sup> In some settings, users obtain their cannabis from local growers, purchase it online or they grow the plant and process the product themselves.<sup>61</sup> Therefore, it is not surprising that many preparations lack adequate quality validation, and that some marketed products when tested are found to have contents of individual cannabinoids wildly different from those stated in their label,<sup>97,98</sup> and some may even contain potentially harmful contaminants.<sup>99</sup> This situation raises concerns about consistency in dosing and risk of adverse effects, including toxic effects resulting from psychoactive constituents such as THC. In this regard, a recent report described two children with manifestations suggestive of THC intoxication, including seizure exacerbation, in whom clinical symptoms remitted after switching their treatment from a CBD-enriched edible cannabis preparation to a formulation of purified CBD.<sup>100</sup> In some countries, well standardized products are accessible, which typically differ in their relative content of CBD and THC. In Israel, for example, available medical cannabis products approved for epilepsy have standardized CBD/THC ratios of 2:1, 5:1, and 20:1, with the latter being the preparation most commonly used.<sup>101</sup>

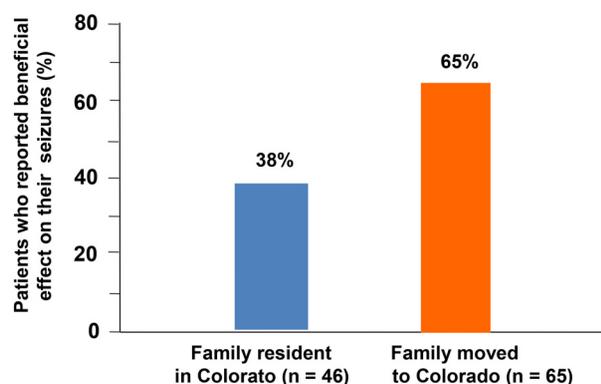
Evidence about the efficacy and safety of oral cannabis preparations is mostly based on surveys and case reports, including the widely publicized story of Charlotte, a little girl with SCN1A-confirmed Dravet syndrome, who experienced a remarkable improvement in her

seizures after being switched to a CBD-enriched extract.<sup>102</sup> One of the first surveys targeted a Facebook group of approximately 150 parents in the USA supporting the use of CBD-enriched cannabis in their children with drug refractory seizures.<sup>103</sup> There were only 19 respondents, with most of the children having a diagnosis of Dravet syndrome and Doose syndrome. Over 80% of parents in this small and possibly biased sample considered their child to have fewer seizures while on CBD-enriched cannabis, at estimated doses up to 25 mg/kg/day for CBD and up to 0.8 mg/kg/day for THC. Two children were free from seizures. Parents also reported other beneficial effects, including improved alertness, and improved mood and sleep. Side effects included drowsiness and fatigue. Another online survey was directed to parents who used CBD-enriched cannabis products for the treatment of their children's epilepsy.<sup>104</sup> There were 117 respondents (including parents of 53 children with infantile spasms and Lennox-Gastaut syndrome), with 85% reporting a reduction in seizure frequency in their children, and 14% reporting complete seizure freedom. The median duration of therapy was 6.8 months, and the median estimated CBD dosage was 4.3 mg/kg/day. Many responders reported that their children showed improved sleep, alertness and mood. In a very recent web-based survey from Australia targeting people with epilepsy nationwide, 137 of the 976 respondents reported to be using, or having previously used, cannabis products for the treatment of their seizures.<sup>105</sup> Use of these products increased with increasing number of AEDs used in the past, suggesting that patients with the most drug resistant seizures were more likely to access cannabis therapy. Products were perceived as helpful in managing seizures in 71% of children and 89.5% of adults, and almost one half of respondents reported to have been able to reduce their concomitant AEDs. Interestingly, only 6.5% of responders stated that they used cannabis because it was recommended by their physician, and the majority of the products used were obtained from illegal suppliers, without knowledge of their precise composition. Positive results with cannabis use were also reported in another recent online survey directed to parents of children with refractory epilepsy in Mexico.<sup>106</sup>

In addition to web-based surveys, there have several reports based on chart reviews. In one such report from the USA, use of artisanal cannabis in 272 children and adults with a variety of seizure types was associated with at least 50% seizure reduction in 55% of cases, with 10% achieving seizure freedom, and there was no indication of improvement being preferentially associated with a specific seizure type or syndrome.<sup>61</sup> In a retrospective survey of 75 children and ado-

lescents with refractory epilepsy from Colorado, where use marijuana for medical purposes was legalized in 2,000, one third of patients experienced a > 50% seizure reduction after starting therapy with oral cannabis, with the highest apparent benefit being reported in those with Lennox-Gastaut syndrome.<sup>107</sup> Adverse events were reported in almost one half of the cases and included increased seizures (13%) and somnolence/fatigue (12%), but there were also reports of improved alertness or behavior in one third of the cases. Comparable findings were reported in a similar report from Colorado, which included data from 119 patients (it is unclear whether this population partly overlapped with that described in the earlier report by the same group).<sup>108</sup> In the latter study, the proportion of patients who showed >50% seizure reduction was 24% and, interestingly, one third of those who did not report any seizure improvement continued to take cannabis therapy, presumably because of other perceived benefits. The average duration of cannabis use in this cohort was 11.7 months (range 0.3 to 57 months) and overall 71% of patients discontinued cannabis therapy during the study period. Another report from Israel included 74 patients with highly drug resistant epilepsies secondary to various etiologies (mostly epileptic encephalopathies), treated with a CBD dose of 1 to 20 mg/kg/day using an oil product containing CBD and THC in a 20:1 ratio.<sup>109</sup> Almost 90% of the patients were cognitively impaired and one half were less than 10 years of age. Unlike other studies, therapy in the Israeli setting was generally prescribed by a physician, and the fact that 81% of the patients received relatively low doses (less than 10 mg/kg/day) was attributed to the fact that most patients kept the oil drops sublingually for several minutes, which would be expected to result in higher bioavailability.<sup>102</sup> About one half of the patients reported at least a 50% reduction of their seizures, but five reported seizure aggravation leading to treatment withdrawal. As in previous reports, many patients reported improvements in behavior, alertness, language, communication, motor skills and sleep. Thirty-four (45%) patients reported adverse events, including somnolence/fatigue (22%), seizure aggravation (18%), gastrointestinal symptoms and irritability (7%).

Overall, review of the available studies suggests that CBD-enriched cannabis may have anti-seizure effects, but the quality of the evidence does not allow to draw firm conclusions. Studies were generally retrospective, and based on patient or parenteral reports without adequately structured data collection. Many of the patients surveyed used unspecified products whose composition and dosage was unknown. Moreover, estimates of apparent efficacy could be af-



**Figure 3.** Proportion of patients reporting beneficial anti-seizure effects from cannabis products in relation to whether patients' family resided originally in Colorado or moved to Colorado in order to access cannabis therapy.<sup>108</sup>

affected by patients' selection bias, reporting bias, and other confounders such as the natural course of the disease, regression to the mean phenomena, and placebo effects.<sup>110</sup> In particular, placebo effects are known to be strongly influenced by expectations,<sup>111</sup> and the broad media exposure associated with cannabis products is a strong generator of positive expectations. An indication that patient or parental expectations may have a strong impact on the outcome of cannabis treatment is provided by a comparison of perceived improvement among patients included in the Colorado surveys.<sup>107,108</sup> Specifically, outcomes of cannabis therapy were significantly better when families moved their residence to Colorado in order to access the medication compared with families already residing in Colorado (Fig. 3). Although there could be alternative explanations for this finding, it is plausible that patients with high expectations/motivations, leading them to relocate to another state, were those who responded best.

### Purified cannabidiol

The first studies of pure CBD in the treatment of drug-resistant epilepsy date back to the late 70s and the 80s and explored oral doses in the range of 200 to 300 mg/day.<sup>112-115</sup> Despite the fact that all four studies included placebo as a control, only one trial was truly double-blind, the largest sample size was only 15 patients, critical details were lacking, and there were other methodological shortcomings.<sup>37</sup> These trials were evaluated in a Cochrane review which included a systematic literature search up to September 2013, and the conclusion was reached that 'no reliable conclusions can be drawn at present regarding the efficacy of cannabinoids as a treatment for epi-

lepsy'.<sup>116</sup> Similar conclusions were reached in a 2014 report of the Guideline Development Subcommittee of the American Academy of Neurology.<sup>117</sup>

To date, the largest exploratory study of the tolerability and anti-seizure activity of CBD relates to a recent physician-sponsored expanded-access programme at 11 epilepsy centres in the USA.<sup>84</sup> A total of 214 patients aged 1-30 years with severe, childhood-onset, drug resistant epilepsy received an oil-based liquid formulation of 99% pure CBD at an initial dose of 2-5 mg/kg/day, up-titrated until intolerance or to a maximum dose of 25 mg/kg or 50 mg/kg per day, depending on study site. Tolerability and safety were analysed for the group of 162 patients who achieved at least 12 weeks of follow-up—this included 33 patients with Dravet syndrome and 31 patients with Lennox-Gastaut syndrome. In this group, adverse events were reported in 128 (79%) patients, the most common being somnolence (25%), decreased appetite (19%), diarrhea (19%), fatigue (13%), and convulsion (11%). Adverse events leading to discontinuation of treatment occurred in 5 patients (3%). An explorative assessment of efficacy was performed in a subgroup of 137 patients, after excluding patients with less than 12-week follow-up (n = 52), patients with no motor seizures (n = 21), and patients who were aged less than one year or had a severe progressive metabolic disease (n = 3). In those 137 patients, there was a median 35% decrease in total seizures, with the greatest seizure reduction being recorded in patients with focal seizures (-55%, n = 42) and atonic seizures (-54%, n = 32). Nine patients (7%) were free from all seizures during the last 4 weeks of follow-up. It is of interest that a reduction in motor seizures by 50% or greater was observed in 51% of patients comedicated with clobazam (n = 70), compared with 27% of those not receiving clobazam (n = 67). Patients on clobazam, however, were also more likely to develop adverse effects, particularly somnolence and fatigue. These differences in outcome in relation to type of comedication may be explained by the increase in plasma clobazam and N-desmethylclobazam levels caused by CBD.<sup>76</sup> Additional analyses in the efficacy patient set showed that patients with Dravet syndrome (n = 32) had a 43% median reduction in all seizures, whereas for patients with Lennox-Gastaut syndrome (n = 30) median reduction in total seizures was 36%. In a subgroup of children evaluated with a caregiver-filled quality of life questionnaire, CBD therapy was associated with improved scores for energy/fatigue, memory, control/helplessness, other cognitive functions, social interactions, behavior, and global quality of life, which did not correlate with changes in seizure frequency.<sup>118</sup> Outcome data from a larger cohort of 261 children and

young adults from the same program (including 44 with Dravet syndrome and 40 with Lennox-Gastaut syndrome) have also been reported in summary form.<sup>36</sup> Convulsive seizure rate for the whole cohort decreased by a median of 48% compared with baseline, whereas atonic seizures in patients with Lennox-Gastaut syndrome decreased by 71.1%. Overall, the main value of these studies is in providing a preliminary characterization of CBD safety profile. Data concerning improvement in seizure control, however, are difficult to assess in view of the uncontrolled nature of the observations.

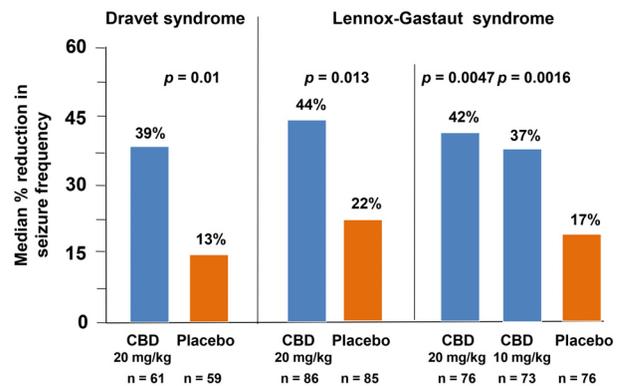
Smaller uncontrolled studies and case reports have also suggested that CBD could be of value in the treatment of patients with drug-resistant seizures associated with tuberous sclerosis complex,<sup>119,120</sup> febrile infection-related epilepsy syndrome (FIRES),<sup>121</sup> Sturge-Weber syndrome<sup>122</sup> and malignant migrating partial seizures in infancy.<sup>123</sup>

## Well controlled randomized trials

The recent flurry of research focused on the potential usefulness of cannabinoids in epilepsy has resulted in the completion of three well controlled randomized trials, all of which evaluated a liquid proprietary oral formulation of CBD.<sup>85,86,124</sup> Of these trials, only one has been published in detail.<sup>85</sup>

### Double-blind trial in Dravet syndrome

As an indication of the high interest of the medical community in the application of cannabinoids to epilepsy management, the first randomized placebo-controlled double-blind trial of CBD in Dravet syndrome was published in the *New England Journal of Medicine* in May 2017.<sup>85</sup> In this trial, conducted at 23 centers in the USA and Europe, 120 patients with an established diagnosis of Dravet syndrome (mean age 9.8 years, range 2.3 to 18.4 years) were randomized to receive placebo or 20 mg/kg/day CBD in two divided daily administrations. All patients had at least 4 convulsive seizures during a preceding 4-week baseline, and CBD or placebo were added on to pre-existing medications, which included clobazam in 65% of cases. The duration of treatment was 14 weeks, including a 2-week-titration phase. Compared with baseline, the median monthly frequency of convulsive seizures (defined as the sum of tonic-clonic, tonic, clonic, and atonic seizures) decreased from 12.4 to 5.9 in the CBD group, and from 14.9 to 14.1 in the placebo group. Median percent changes in seizure frequency are shown in Fig. 4. The adjusted median difference in change in seizure frequency between the CBD and the placebo group (primary endpoint) was -22.8% (95% CI: -41.1 to -5.4,  $p =$



**Figure 4.** Median percent reduction in seizure frequency in the three randomized adjunctive-therapy placebo-controlled efficacy trials of cannabidiol (CBD) reported to date in patients with Dravet syndrome<sup>85</sup> and Lennox-Gastaut syndrome.<sup>86,124</sup> For patients with Dravet syndrome, seizure frequency refers to convulsive seizures. For patients with Lennox-Gastaut syndrome, seizure frequency refers to drop seizures. P values refer to comparisons between each CBD group and corresponding placebo group. n refers to number of patients randomized into each group. For further details, see text.

0.01). The proportion of patients with  $\geq 50\%$  reduction in convulsive seizures frequency was 43% in the CBD group compared with 27% in the placebo group. Non-convulsive seizures were not significantly affected by CBD therapy. Three patients (5%) became seizure-free during the treatment period in the CBD group, compared with none in the placebo group.

Adverse events deemed to be related to the study treatment were reported in 75% of patients in the CBD group and 36% of those in the placebo group. Somnolence, diarrhea, and decreased appetite were the most common CBD-associated adverse events (Table 2). Eighteen of the 22 CBD-treated patients who developed somnolence were on clobazam comedication. Adverse events appeared mostly during the first two weeks of therapy, and there were instances in which the dose of CBD or other medications were reduced. No information, however, was reported on how often the dose of concomitant clobazam was reduced. Eight patients in the CBD group discontinued the trial prematurely due to adverse events (in three cases, marked elevation of liver enzymes), compared with one patient in the placebo group who also had a marked elevation in liver enzymes. Overall, elevated aminotransferases levels occurred in 12 patients in the CBD group and one in the placebo group, all of whom were on concomitant valproate therapy. In the nine patients with raised aminotransferases who did not discontinued treatment, liver enzymes reverted to normal on continuation of therapy.

**Table 2.** Adverse events most commonly reported in the randomized double-blind placebo-controlled trial of CBD in comparison with placebo in patients with Dravet syndrome<sup>85</sup>

Adverse event	Percentage of patients with adverse event	
	CBD group (n = 61)	Placebo group (n = 59)
Somnolence	36%	10%
Diarrhea	31%	10%
Decreased appetite	28%	5%
Fatigue	20%	3%
Vomiting	15%	5%
Fever	15%	8%
Lethargy	13%	5%
Convulsion	11%	5%
Upper respiratory tract infection	11%	8%

Only events occurring with a frequency > 10% in either group are listed.  
CBD, cannabidiol.

Overall, this trial provides for the first time robust evidence that CBD added-on to pre-existing AED treatment reduces the frequency of convulsive seizures in children and young adults with Dravet syndrome. The data also emphasize the need for caution in interpreting results from previous uncontrolled trials—although median convulsive seizure frequency (primary endpoint) decreased by a statistically significantly greater extent in the CBD group compared with the placebo group, the proportion of patients with  $\geq 50\%$  reduction in convulsive seizure frequency did not differ significantly between groups, and more than one quarter of patients allocated to placebo had their seizure frequency reduced by one-half or more during the trial. Interestingly, no significant differences between groups were found in sleep scores, behavioral adaptation (Vineland-II) scores, and Quality of Life in Childhood Epilepsy scores, even though duration of treatment was relatively short and possibly insufficient to determine changes in these parameters. A major weakness in the presentation of the trial results is the failure to report changes in plasma concentrations of concomitant AEDs and, most notably, clobazam and N-desmethyclobazam. In view of the fact that 66% of patients in the CBD group were on clobazam comedication, and evidence from a previous study indicating that N-desmethyclobazam levels increase by 500% on average after adding CBD,<sup>76</sup> the reported data do not allow to determine whether the reported improvement in seizure frequency can be ascribed to a direct action of CBD, or is simply a consequence of increased plasma levels of comedication.

### Double-blind trials in Lennox-Gastaut syndrome

Two well controlled double-blind trials in patients with Lennox-Gastaut syndrome have been completed, but results to date have only been reported in summary form.<sup>86,124</sup>

In the first trial, 171 patients (mean age 15 years) with uncon-

trolled drop seizures (median baseline monthly frequency 74) were randomized to receive adjunctive treatment with CBD oral solution 20 mg/kg/day or placebo for a period of 14 weeks (2-week titration and 12-week maintenance).<sup>86</sup> Fourteen patients (16%) in the CBD group and one patient (1%) in the placebo group withdrew prematurely. Compared with placebo, CBD treatment was associated with a greater median percent reduction in monthly drop seizures (44% vs. 22%;  $p = 0.0135$ , Fig. 4) and a greater proportion of patients with a  $\geq 50\%$  seizure reduction (44% vs. 24%;  $p = 0.0043$ ). Adverse events were reported in 86% of CBD and 69% of placebo patients, the most common being diarrhoea, somnolence, pyrexia, decreased appetite, and vomiting. Treatment-related serious adverse events were reported in nine CBD patients and one placebo patient. Elevations in transaminases occurred mostly in patients on concomitant valproate therapy and all resolved.

In the second trial, 225 patients with Lennox-Gastaut syndrome (mean age 16 years, median number of drop seizures per month at baseline 85) were randomized to three groups and allocated to two doses of CBD (10 or 20 mg/kg/day) or placebo.<sup>124</sup> Enrolled patients were receiving a median of 3 concomitant AEDs. Duration of the trial was 14 weeks (2-week titration and 12-week maintenance). The reduction in monthly frequency of drop seizures was significantly greater in the CBD 20 mg/kg group (42%) and 10 mg/kg group (37%) than in the placebo group (17%;  $p = 0.0047$  and  $0.0016$ , respectively, Fig. 4). The proportion of patients with a  $\geq 50\%$  decrease in drop seizure frequency was also significantly greater in the 20 and 10 mg/kg groups (40% and 36%, respectively) than in the placebo group (15%;  $p = 0.0006$  and  $p = 0.0030$ , respectively). Total seizures were also significantly reduced in both CBD groups compared with placebo. Adverse events were reported in 94% of patients allocated to 20 mg/kg, 84% of those allocated to 10 mg/kg, and 72% of

placebo patients, the most common being somnolence and decreased appetite. Serious treatment-related adverse events occurred in five patients in the 20 mg/kg group, two patients in the 10 mg/kg group, and no patients on placebo patients. Some elevations in transaminases were seen. Of 212 completers, 99% entered an open-label extension study.

Overall the results of these trials demonstrate that at dosages of 10 to 20 mg/kg/day CBD is superior to placebo in reducing the frequency of drop seizures in patients with Lennox-Gastaut syndrome. Published reports, however, provide no information on concomitant therapies, and most notably whether, and to what extent, the clinical improvement on CBD therapy could be related to elevation in serum concentrations of other medications, most notably clobazam and N-desmethyclobazam.

## Conclusions and future perspectives

The interest in cannabis preparations in the treatment of epilepsies, particularly drug refractory childhood epilepsies, has skyrocketed in recent years. Marijuana and other cannabis products with moderate to high THC content utilized primarily for recreational purposes are generally unsuitable for this indication, not only because evidence for an anti-seizure activity of THC is equivocal and risk of seizure aggravation cannot be excluded,<sup>101</sup> but also because THC is associated with many undesired effects, including addiction liability, psychiatric disorders, cognitive and motor impairment<sup>125-127</sup> and, possibly, also cardiovascular toxicity.<sup>128</sup> The maturing brain is also more vulnerable to the adverse effects of marijuana,<sup>126,129,130</sup> and there is evidence of THC impairing structural and functional connectivity during brain development.<sup>126,129,130</sup> Discontinuation of THC after prolonged exposure can also lead to withdrawal manifestations<sup>131,132</sup> and cases have been reported of seizure exacerbation after marijuana cessation in people with epilepsy.<sup>133</sup>

Compared with THC, CBD shows a better defined anticonvulsant profile in animal models considered to be predictive of efficacy against focal and generalized seizures. Moreover, CBD is largely devoid of adverse psychoactive effects, and is considered to lack the abuse liability associated with THC-containing products.<sup>134</sup> In the last decade, this has led to an increasing use of CBD-enriched extracts as a potential treatment for epilepsy, particularly in children. Improvement in seizure control, often associated with additional benefits on sleep and behaviour, have been reported in a sizeable proportion of cases,<sup>87</sup> but interpretation of these data is made diffi-

cult by the uncontrolled nature of the observations. Additionally, as discussed in this article, there are concerns about the quality and variability of many of the products used,<sup>98</sup> particularly because cannabis treatment is often initiated spontaneously by patients or caregivers without adequate medical supervision.<sup>105</sup>

Evidence concerning the potential anti-seizure efficacy of cannabinoids reached a turning point in the last 12 months, with the completion of the first high-quality placebo-controlled trials of a purified oil-based liquid CBD preparation in patients with Dravet syndrome and Lennox-Gastaut syndrome.<sup>85,86,124</sup> The results of these studies demonstrate that, at a dosage of 20 mg/kg/day, CBD added on to pre-existing AED treatment is superior to placebo in reducing the frequency of convulsive (tonic-clonic, tonic, clonic, and atonic) seizures in patients with Dravet syndrome, and the frequency of drop seizures in patients with Lennox-Gastaut syndrome. In the latter patients, a dosage of 10 mg/kg/day treatment was also superior to placebo. Therefore there is now for the first time class 1 evidence that CBD improves seizure control when added on to other AEDs in patients with two difficult-to-treat epileptic encephalopathies. Available data, however, do not allow to conclude that CBD *per se* has anti-seizure activity. At least for the trial published in full,<sup>85</sup> a majority of patients were receiving concomitant clobazam therapy, and it is unclear whether the reported seizure benefits, as well as adverse effects, were related to a direct action of CBD, or were mediated by a previously described 5-fold elevation in plasma N-desmethyclobazam levels. For the two studies in Lennox-Gastaut syndrome, the proportion of patients on concomitant clobazam therapy was not reported, but it is likely to have been significant because clobazam is a frequently used comedication in patients with this syndrome. Clarification of the independent effects of CBD would require re-assessment of trial data for the subgroup of patients not comedicated with clobazam, or the conduction of further studies after excluding such patients or, alternatively, adjusting blindly clobazam dosages to maintain unaltered concentration of N-desmethyclobazam. Additional well controlled studies are also desirable to determine the potential value of CBD in other seizure types and epilepsy syndromes, including refractory focal epilepsies.

One of the reasons for the utilization of cannabis products to have become so popular among patients and their caregivers is that these products are generally regarded as causing fewer adverse effects compared with traditional AEDs, partly out of the misperception that remedies derived from natural products are unlikely to be harmful. In a survey carried out by *Epilepsia*, 96% of respondents among the

general public felt that there was sufficient safety evidence about cannabis products, whereas only 34% of physicians considered this to be the case.<sup>135</sup> In fact, in the randomized controlled trials conducted to date the tolerability profile of CBD was relatively benign, with somnolence, decreased appetite and gastrointestinal symptoms being the most common treatment-emergent adverse events. Although these results are encouraging, further studies are required to evaluate the safety profile of CBD and other cannabis products in greater detail, particularly after long-term exposure and whenever these products are used in subpopulations potentially at risk. Elevations of liver enzymes have been frequently observed, especially in patients comedicated with valproate, and although they were generally reversible, close observation for signs suggestive of hepatic toxicity is advisable. Nabiximols, an oromucosal spray formulation containing approximately equal amounts of THC and CBD, has been commercially available in several countries for a number of years and has a relatively extensive safety record.<sup>68</sup> However, the maximum approved daily CBD dose in nabiximols is considerably lower than the CBD doses used in epilepsy trials, and experience of nabiximols in pediatric age is limited because the product is not recommended for use 'below 18 years of age due to lack of safety and efficacy data'.<sup>68</sup> As discussed above, prolonged exposure of the immature brain to THC has been shown to cause deleterious effects on brain connectivity, and there is some evidence of prolonged recreational use of marijuana in adolescence being associated with neuropsychological decline and lower academic performance scores.<sup>136,137</sup> There are also special concerns for risks to the offspring of mothers who use marijuana during pregnancy.<sup>138,139</sup> Although these findings may be specific for THC and other psychoactive cannabinoids, adequate safety data for young children exposed to long-term CBD therapy are not yet available.<sup>24</sup> Another area where limited data is available relates to the risk of rebound seizures following abrupt or rapid discontinuation of treatment. Unlike THC, CBD is not associated with the development of tolerance after repeated administration in various seizure models, and there is no evidence of a withdrawal syndrome developing after CBD discontinuation.<sup>12</sup>

These are exciting times for research in cannabinoids. After almost four millennia of their documented medical use in the treatment of seizure disorders, we are very close to obtaining conclusive evidence of their efficacy in some severe epilepsy syndromes. The era of evidence-based prescription of a cannabis product is within our sight.

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