

From cannabis to cannabidiol to treat epilepsy, where are we?

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Running Title: Cannabidiol in epilepsy

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Abstract

Background: Several antiepileptic drugs (AEDs), about 25, are currently clinically available for the treatment of patients with epilepsy. Despite this armamentarium and the many recently introduced AEDs, no major advances have been achieved considering the number of drug resistant patients, while many benefits have been indeed obtained for other clinical outcomes (e.g. better tolerability, less interactions). Cannabinoids have long been studied for their potential therapeutical use and more recently phytocannabinoids have been considered a valuable tool for the treatment of several neurological disorders including epilepsy. Among this wide class, the most studied is cannabidiol (CBD) considering its lack of psychotropic effects and its anticonvulsant properties. *Objective:* Analyse the currently available literature on CBD also in light of other data on phytocannabinoids, reviewing data spanning from the mechanism of action, pharmacokinetic to clinical evidences. *Results:* Several preclinical studies have tried to understand the mechanism of action of CBD, which still remains largely not understood. CBD has shown significant anticonvulsant effects mainly in acute animal models of seizures; beneficial effects were reported also in animal models of epileptogenesis and chronic models of epilepsy, although not substantial. In contrast, data coming from some studies raise questions on the effects of other cannabinoids and above all marijuana. *Conclusions:* There is indeed sufficient supporting data for clinical development and important antiepileptic effects and the currently ongoing clinical studies will permit the real usefulness of CBD and possibly other cannabinoids. Undoubtedly, several issues also need to be addressed in the next future (e.g. better pharmacokinetic profiling). Finally, shading light on the mechanism of action and the study of other cannabinoids might represent an advantage for future developments.

Keywords: **Cannabinoids;** Cannabidiol; Epilepsy; Seizures; Preclinical studies; Clinical evidence.

Introduction

Epilepsy is a severe neurological disorder of the central nervous system (CNS) characterized by spontaneous and recurrent seizures (SRS) [1-3]. Its etiology depends on the abnormal balance between excitatory and inhibitory cerebral activity leading to hyperexcitability [4, 5]. However, neither basic mechanisms of seizures and even more epileptogenesis has been yet completely understood [6, 7]. According to several hypotheses, epilepsy can be triggered by a brain insult, an infection, a genetic predisposition, but in some cases the onset of seizures is unprovoked and unpredictable [8, 9]. Epilepsy patients are treated using antiepileptic drugs (AEDs) that are basically oriented to reduce the symptoms since for none of them disease modifying effects have been clinically proven [6, 10], furthermore, they strongly impact on patients quality of life according to their unavoidable burden of side effects [11, 12]. The introduction of the new AEDs has also failed to improve the quality of life of epilepsy patients [12, 13]. Therefore there is no drug able to prevent epilepsy or slow its progression. Nevertheless, it has been demonstrated that treatment during the early phases of the pathology might slow or modify the epileptogenic process and improve the quality of life of epilepsy patients [14]. For this reason, much effort of the researchers has been spent in the identification of new therapies also able to manage epileptogenesis [6] and new potential drugs effective in drug resistant patients [15-17]. Phytocannabinoids (terpenophenolic compounds synthesized by several cannabis species) have been recently reconsidered as a potential therapeutic strategy for epilepsy treatment based on old studies supporting their beneficial effects in neurological disorders including epilepsy [18-20]. Unfortunately, the clinical use of cannabinoid-based therapy still remains limited to only few pathologies [19]. In this article, we have summarized and reviewed the most relevant data on cannabidiol (CBD; representing the current leading compound of this group in epilepsy) spanning from

the mechanism of action, pharmacokinetic to clinical evidences and keeping in mind the articles reporting phytocannabinoids effects in patients with epilepsy.

CBD's pharmacokinetic profile in humans

Several administration routes for CBD such as oral, transdermal, sublingual and inhalation have been examined and suggested. However, to date, several clinical studies in epilepsy, report that CBD has been mainly delivered orally through oil-based formulation, whereas the other administration routes, until now, have only demonstrated lacking importance in clinical practice. CBD after oral administration shows a variable pharmacokinetic profile, as a result of both low water solubility, which leads to an irregular gastrointestinal absorption, and of a significant first-pass metabolism [21]. Keeping with this, the CBD's oral bioavailability has been evaluated around 10%. Moreover, following CBD oral administration, the time (T_{max}) to reach the maximum plasma concentrations (C_{max}) was 90-120 minutes [22]. At odds, the bioavailability of inhaled CBD, evaluated in subjects who smoked cannabis, has been around 31%, whereas the C_{max} has been reached in few minutes after smoking (< 10 min) [23].

The distribution volume of CBD has been evaluated around 30 L/Kg. The high value of this volume is related with the high lipophilicity of CBD, which is responsible for its fast distribution in fat organs including brain and adipose tissue [24]. Furthermore, CBD's affinity toward these organs leads to a half-life of about 24h (range: 18-32h) [25]. The plasma clearance determined after i.v. administration of CBD ranged from 960 to 1560 ml/min. Moreover, CBD results to be highly bound to plasma proteins (> 99%) and about 10% is bound to red blood cells [25].

CBD as well as several other cannabinoids is widely metabolized by cytochrome P450 (CYP450) enzymes in the liver. Particularly, the CYP3A and CYP2C are the isoform of enzymes mainly involved in CBD metabolisms. CBD's metabolites are mainly excreted in

the feces, whereas only a low percentage results excreted in the urine [26]. Furthermore, it has been demonstrated that CBD is able to inhibit many classes of CYP450 enzymes including CYP3A and CYP2C families. This property of CBD leads to drug-drug interactions, which deserve to be further investigated [27]. In particular, drug-drug interaction between CBD and AEDs such as clobazam could also be used to manage refractory epilepsy considering that interactions do not necessarily have a negative impact if properly managed [28].

In this review, we have examined the literature about the effects of CBD treatment in epilepsy. For this purpose, we have considered both preclinical and clinical studies. A PubMed search for MEDLINE was performed to look for studies using the following keywords: “Cannabidiol and epilepsy”, “Cannabidiol and seizure”, “Cannabidiol and epileptogenesis”, “Cannabidiol and animal model of epilepsy”, “Cannabis and epilepsy”, “Cannabis and seizure”, “Cannabis and epileptogenesis” and “Cannabidiol and clinical studies”. The date of our last search was April 20, 2016 and the period of time reviewed was approximately 40 years. Only English language papers were considered.

Looking for CBD’s mechanisms of action in epilepsy

Cannabis contains many compounds, including at least 60 cannabinoids (about 100 is currently suggested) [29]. The two major neuroactive components are Δ^9 -tetrahydrocannabinol (THC) and the nonpsychotropic CBD. [21, 30]. Both CBD and THC have antiseizure effects. The antiseizure effect of THC is still controversial because of its pro- and anti-convulsant properties and the development of psychotropic and tolerance effects, due to these side effects, THC’s clinical trials are limited. [31, 32]. CBD is used in both preclinical and clinical studies [33] since it has antiseizure activity with a good side-

effect profile [34, 35] and no psychotropic effects. To date, the molecular mechanism of CBD action is not yet fully understood [36].

The phytocannabinoids THC acts on the cannabinoid receptor type 1 (CB1) and cannabinoid receptor type 2 (CB2), while CBD has only a low affinity [36]. However, it has been demonstrated that CBD is able to antagonize CB1 and CB2 receptor agonists *in vitro* with unexpectedly high potency [37]. These properties of CBD might explain its lack of psychotropic effects [38, 39].

According to *in vitro* and *in vivo* assays, the therapeutic properties of CBD are independent by the endocannabinoid-signaling pathway and are likely mediated by enzymes, receptors, ion channels, and transporters [21, 36]. **However, should be noted that a dysregulation of the endocannabinoid-signaling pathway could play a key role in the pathogenesis of epilepsy including temporal lobe epilepsy [40, 41].**

The possible molecular mechanisms by which CBD may influence neuronal hyperexcitability are: 1) activation of 5-HT_{1a} receptors [42, 43]; 2) reduction of the synaptic release of glutamate antagonizing G protein-coupled receptor (GPR) 55; 3) stimulation and desensitization of transient receptor potential of vanilloid type 1 (TRPV1) and 2 (TRPV2) channels [44, 45]; 4) inhibition of the synaptic uptake of GABA, noradrenaline, adenosine as well as dopamine [46, 47]; 5) stimulation of $\alpha 3$ and $\alpha 1$ glycine receptors [48, 49]; 6) stimulation and desensitization transient receptor potential of ankyrin type 1 (TRPA1) channel.

It has been hypothesized that CBD has also many other potential targets mediating its antiepileptic effects, such as: cyclooxygenase (COX), voltage-dependent anion channel 1 (VDAC1), nitric oxide (NO), G protein-coupled receptor (GPR) 18, peroxisome proliferator-activated receptor γ (PPAR- γ), **tumor** necrosis factor (TNF) and fatty acid amide hydrolase (FAAH). However, further studies are necessary to clarify the real efficacy of CBD on

epilepsy patients and unravel its exact mechanism of action. Interestingly, CBD also possesses anxiolytic, antidepressant and antipsychotic properties that might be useful to treat psychiatric symptoms associated with epilepsy. The effects of CBD on cognitive functions represent another important therapeutic aspect to consider in the management of epilepsy patients [50-55].

Besides CBD, there are other cannabinoids that have shown an antiepileptic activity, both in *in vitro* assays and *in vivo* studies, such as cannabichromene (CBC), cannabidivarin (CBDV), and Δ^9 -tetrahydrocannabidivarin (Δ^9 -THCV); although there are no clinical studies proving their efficacy [21]. Among these compounds, the most interesting is currently CBDV, which is the propyl variant of cannabidiol [22, 56]; CBDV has shown anticonvulsant properties through the involvement of specific molecular targets such as TRP channels or diacylglycerol lipase A [45, 57].

Preclinical studies for CBD's antiepileptic effects

In preclinical studies, CBD similarly to many other established AEDs has shown anticonvulsant activity in many acute animal models of seizures [21, 58]. It has been demonstrated that CBD pre-treatment was able to prevent tonic-seizures induced by GABA inhibitors, whereas it failed in case of seizures induced by the glycine antagonists strychnine [59]. On the other hand, CBD (60 mg/kg; i.p.) was not effective against focal seizures with secondary generalization induced by cobalt implantation [60].

Studies in the classically used animal models of epilepsy such as **pentylentetrazole** (PTZ) and maximal electroshock (MES) have demonstrated that CBD better acts on tonic but not clonic seizures. In other words, this may suggest that CBD may act preferentially decreasing the spreading of seizures and partially influencing seizures onset [61, 62]. Moreover, CBD may increase the antiseizure activity of some AEDs (such as phenytoin) but might also

decrease the effects of other AEDs (such as ethosuximide and clonazepam) as demonstrated in the MES model [63, 64]. The drug-drug interaction among AEDs and CBD could be related to the ability of CBD to inhibit several isoforms of cytochrome P450 (CYP450), and this point still needs further clarification [27]. However, A clinical study Geffrey et al. [28]Geffrey et al. (2015)Geffrey et al. (2015)Geffrey et al. (2015)Geffrey et al. [28] has demonstrated that the association of CBD and clobazam (which are both catalyzed by CYP2C9 and CYP3A4 pathway) could be useful to treat children with refractory epilepsy (see Cannabis, cannabidiol and epilepsy: clinical data) [17].

By using the PTZ model of seizures, Jones et al. [65], have observed that a CBD pre-treatment (100 mg/Kg; i.p.) is able to decrease the occurrence of PTZ-induced seizures as well as rats mortality. CBD (0.01-100 μ M) has shown antiepileptiform properties in hippocampal brain slices treated with Mg^{2+} -free and 4-aminopyridine solutions, both displaying epileptic-like activity. The same study has also demonstrated that the mechanisms of actions of CBD in antiepileptiform activity *in vitro* and antiseizure activity *in vivo* are independent from CB1 receptor [65]. Further studies in a PTZ mouse model of seizure have shown that CBD pre-treatment (0.2-200 ng/mouse; i.c.v.) determines anticonvulsant effects, that are mitigated by co-administration of paxilline, an antagonist of voltage and Ca^{2+} activated K^+ (BK) channels [49]. Likewise, in MES induced seizures, CBD pre-treatment (20, 100, and 200 ng/mouse; i.c.v.) induced anticonvulsant effects, which were not affected by co-administration of paxilline. These results suggest that the antiseizure effect of CBD, observed in PTZ model but not in other epilepsy models, could be linked to BK channels. [66, 67].

In a recent study, the antiseizure effects of CBD (10-50 mg/kg; i.v.) have been evaluated in a chronic model of epilepsy, which has been obtained by PTZ administration for 28 consecutive days. In this study, rats pre-treated with CBD (20 and 50mg/Kg) showed a

reduction of PTZ-induced seizures, and a lower neuronal death in CA1 and CA3 hippocampal regions. The analysis of the morphological changes of hippocampal neurons, by immunohistochemistry and glial fibrillary acidic protein (GFAP), has shown that CBD is able to decrease hippocampal astrocytic hyperplasia after PTZ. Furthermore, the hippocampal expression of N-methyl-D-aspartic acid (NMDA) receptor subunit 1 is also reduced in rats treated with CBD [68].

CBD antiepileptic properties have also been tested in other animal models, such as temporal lobe epilepsy (the pilocarpine model) and partial epilepsy (penicillin model) [69]. In the pilocarpine rat model, CBD pre-treatment (1 and 100mg/kg; i.p.) decreased the occurrence of tonic-clonic seizures, without influencing the percentage of mortality. In the penicillin model of seizures, CBD treatment (≥ 10 mg/kg; i.p.) reduced both tonic-clonic seizures and mortality. Another important aspect of this study is that CBD treatment has minimal side effects on motor performances at anticonvulsant doses as highlighted by several behavioral tests. Hosseinzadeh et al. [70] have also studied CBD's antiseizure/antiepileptogenic effects in the pilocarpine rat model. In this study the researchers have administered CBD in two different treatment schedules. The first group of rats received five consecutive days of CBD injections (100 ng; i.c.v.) started at the onset of the silent phase after pilocarpine-induced status epilepticus. The second group received a single injection of CBD (100 ng; i.c.v.) at the beginning of the chronic phase after the development of pilocarpine-SE induced chronic epilepsy. In both groups, CBD was able to reduce seizures. Moreover, in the silent phase, the repeated administrations of CBD delayed the onset of spontaneous recurrent seizures (SRS) probably by increasing autophagy and antioxidant defense in hippocampal cells, therefore suggesting possible antiepileptogenic effects [70]. This latter point is also supported by the demonstrated neuroprotective effect of CBD, which has been evaluated in hypoxic-ischemic (HI) newborn pigs. The administration of CBD (0.1 mg/kg, i.v) prevented edema as well as

seizures onset in newborn pigs after hypoxic-ischemic damage. Apparently, the neuroprotective effect of CBD, involved CB2 and 5HT1A receptors. In particular, it was suggested that CBD acts as an agonist of 5HT1A receptors, and as modulator of CB2 receptors by increasing the levels of endocannabinoids in the brain [43, 71, 72].

CBDV, the propyl variant of CBD, has anticonvulsant activity as suggested by both *in vitro* assays and *in vivo* preclinical studies. Hill et al. [73] have reported antiseizure effects of CBDV (1-100 μ M) in hippocampal slice models of epilepsy induced by administration of 4-AP and Mg^{2+} -free solutions. In a further study, using the same Mg^{2+} -free model, it has been demonstrated that the antiepileptiform effects of CBDV could be related to an activation and desensitization of TRPV1 channels [45]. CBDV pre-treatment (1 hour before seizure induction) possesses not dose-dependent antiseizure properties in several animal models of epilepsy including PTZ (CBDV = 100 mg/kg; i.p.), audiogenic (CBDV = 50 mg/kg; i.p.) and MES (CBDV = 100 mg/kg; i.p.) [73]. At odds, in some studies, CBDV alone was not effective while it was able to potentiate AEDs effects. Briefly, CBDV (200 mg/kg; i.p.) has not shown any effects on pilocarpine-induced acute seizures, but it induces a decrease of seizures, only when combined with other AEDs such as phenobarbital or valproate [73]. CBDV (400 mg/kg, p.o.) effects on acute PTZ-induced seizures in rats was correlated to an increased expression of epilepsy-related genes such as Egr1, Fos, BDNF, Arc and Ccl4 [74]; CBD and CBDV might therefore differ both in their antiepileptic effects and their mechanisms of action.

Overall, CBD and CBDV possess antiepileptic efficacy in a variety of preclinical *in vitro* and *in vivo* models, which clearly supports their further development in clinical studies.

Cannabis, cannabidiol and epilepsy: clinical data

In contrast to the large available amount of preclinical data, the current supportive clinical evidence for the use of cannabinoids in human epilepsy is rather limited (Table 1). Most data

concerning the clinical effects of marijuana in human patients have been gathered from anecdotal cases, phone or online surveys, epidemiological studies, and a few clinical trials.

The evidence extrapolated from anecdotal cases is not univocal. A small case series in 1949 reported treatment with a tetrahydrocannabinol (THC) homolog, up to 4 mg/day, in five institutionalized children with refractory epilepsy and intellectual disability, with two of them achieving a significant improvement in seizure control [75]. A case report of a young man with epilepsy, having previously been seizure-free for six months, describes tonic-clonic seizure recurrence after frequent marijuana smoking over a three week-period [76]. Marijuana smoking, in conjunction with therapeutic doses of phenobarbital and diphenylhydantoin, was reported as effective in controlling seizures in one young case with epilepsy [77]. Another case report showed evidence of reduction of complex partial seizures following marijuana use [77, 78]. A small case series on the therapeutic application of THC in children with various neurological conditions, including epilepsy and intellectual disability, showed some evidence of anticonvulsive effects. The doses ranged from 0.04 to 0.12 mg/kg body weight a day. In most cases treatment was discontinued and there was no any worsening following the withdrawal [79]. Two adult cases with focal epilepsy, with previously reported benefit from frequent marijuana smoking, experienced significant increase in seizure frequency, documented by video-EEG telemetry in the setting of marijuana discontinuation upon admission to the epilepsy monitoring unit [80]. A young girl with Dravet syndrome (*SCN1A*-positive) was started on adjunctive therapy with a high concentration of THC, given in conjunction with her prescribed clobazam, and had subsequent dramatic (>90%) reduction of the frequency of her convulsive seizures. The effect had persisted for about 20 months, and she was been successfully weaned from her other antiepileptic drugs [81]. A 10-month-old boy, affected by malignant migrating partial seizures in infancy (MMPS), was started on adjunctive treatment with CBD (25 mg/mL at 10

mg/kg/day divided twice daily, up to 25 mg/kg/day twice daily). His seizure frequency decreased from 10-20 per day to five per week with up to nine days of clinical seizure freedom and he made some developmental gains [82]. **Very recently, the use of CBD oil, in the management of an 18 year old male affected by super refractory status epilepticus (SRSE) in the setting of new-onset refractory status epilepticus (NORSE) syndrome, was reported. CBD oil was added to the current AEDs treatment regimen. CBD treatment (started at 2.5 mg/Kg/day and increased up to a maximum of 24 mg/Kg/day) was not able to reduce focal and generalized seizures. Therefore, in agreement with both the family and clinical recommendation, AEDs and sedating drugs were reduced, whereas CBD oil administration continued. Unfortunately, the patient died after treatment withdrawal [83].**

A telephone survey was conducted in 2001 in order to determine the prevalence of marijuana use and the beliefs regarding the effects of marijuana on seizures in patients with epilepsy. Of the 136 interviewed subjects, 28 (21%) had used marijuana in the past year. In the logistic regression analysis, seizure frequency, longer disease duration, and other illicit drug use were predictors of frequent marijuana use. The majority of active users reported beneficial effects on seizures (68% of active cannabis users reported reduced seizure severity, and 54% observed decreased seizure frequency). Twenty-four percent of all subjects believed marijuana was effective to treat epilepsy [84].

In USA, a survey was presented to parents belonging to a Facebook group dedicated to sharing information about the use of cannabidiol-enriched cannabis to treat their child's seizures. 16/19 parents reported a reduction in seizure frequency while taking medical marijuana; others reported beneficial effects like improved sleep and mood. Drowsiness and fatigue were reported by some parents. Thirteen children had Dravet syndrome, four had Doose syndrome, and one each had Lennox-Gastaut syndrome and idiopathic epilepsy [85]. A study, conducted between 2008 and 2010 at an epilepsy outpatient clinic in Berlin, aimed

to assess the prevalence of cannabis and other illicit drug use among epilepsy patients and the effects of illicit drug use on epilepsy. They systematically interviewed 310 patients with epilepsy; of these, 63 (20.3%) had consumed cannabis after their epilepsy was diagnosed. Most of them (53, 84.1%) did not observe any effect on the disease [86].

An online survey of parents who administered CBD-enriched cannabis preparations for the treatment of their children with epilepsy, including infantile spasms or Lennox–Gastaut syndrome, was conducted in 2014. Eighty-five percent of all parents reported a reduction in seizure frequency, and 14% reported complete seizure freedom. The median duration of CBD treatment was 6.8 months and the median dosage was 4.3 mg/kg/day. Also improvement in sleep, alertness, and mood during CBD treatment, was reported. The most frequent side effects were increased appetite and weight gain [87]. A retrospective chart review of children attending the neurology service at the Children's Hospital of Colorado included 75 patients or caregivers who had started taking oral cannabis extracts for refractory epilepsy. Of these, 57% reported improvement to either seizure duration or frequency. The responder rate varied based on the type of epilepsy: it was 23% in cases with Dravet syndrome, 0% in cases with Doose syndrome, and 89% in cases with Lennox-Gastaut syndrome. However, there was a discrepancy in responder rate between patients with preexisting residency in Colorado and those patients who had moved to Colorado seeking oral cannabis treatments, finding that the latter were more than 3 times as likely to report a >50% seizure reduction than those who had a preexisting care in Colorado. Many of the families reported also improved behavior/alertness, language and motor skills. The most common adverse events were increased seizures or new seizures, somnolence/fatigue and GI symptoms [88].

A further online survey was conducted by the journal “Epilepsia” (official journal of the international league against epilepsy; ILAE) in 2014 to seek opinions about the use of medical marijuana and cannabidiol (CBD) for people with epilepsy. Of 776 who started the

poll, 529 (68%) completed all of the questions. A minority of epileptologists and general neurologists from Europe and North America said that there were sufficient safety (34%) and efficacy (28%) data to use medical marijuana for epilepsy. The survey asked: “Would you advise patients with severe, catastrophic epilepsy who have not responded to approved therapy to try medical marijuana?”. The 48% of epileptologists and general neurologists said that such patients should be advised to try medical marijuana. Different opinions were gathered by patients and the public; almost all of them said that there were sufficient safety (96%) and efficacy (95%) data, and 98% would recommend medical marijuana in cases of severe epilepsy. Also most general physicians, basic researchers, nurses, and allied health professions sided more with patients, replied that there were sufficient safety (70%) and efficacy (71%) data, and 83% said that severe cases should be advised to try medical marijuana. Regarding the question: “What is your opinion about having pharmacologic grade compounds containing CBD available to us in epilepsy patients?”, the majority (78%) responded: “Yes, such compounds should be available”, with no differences comparing specialists, general medical personal, and patients and the public. This survey proves a wide diversity of opinion on the use of medical marijuana and CBD in epilepsy, with more general physicians, basic researchers, allied health personal, patients and the public, supporting its use compared with medical specialists [89].

A recent retrospective multicenter study described the effect of CBD-enriched medical cannabis on 74 children and adolescent with refractory epilepsy. The median duration of treatment was 5.5 months, with a follow-up of 10 months. The CBD dosage ranged from 1 to 20 mg/kg/die. Most of the patients (89%) reported reduction in seizure frequency. Also among patients affected by epileptic encephalopathies with or without known genetic mutations, 66% had more than a 25% reduction in seizure frequency, with 51% reporting between 50 and 100% reduction in seizure frequency. In 7% of patients there was an

aggravation of seizures, which led to CBD withdrawal. Improvement in behavior and alertness, language, communication, motor skills and sleep, is also reported. The most common adverse reactions were somnolence, fatigue, gastrointestinal disturbances and irritability [90].

Up to date, only a few placebo-controlled trials that involve the use of CBD as a treatment for epilepsy have been conducted. A Cochrane systematic review of randomized, controlled clinical trials was conducted over the use of CBD-enriched therapies for the treatment of human epilepsy [35]. They identified only four studies meeting their efficacy criteria, with a total sample of 48 participants in clinical studies, randomized to placebo or to 200-300 mg of CBD per day [91-94].

In all four studies, patients with uncontrolled seizures were randomized into either placebo or CBD groups. The dose of CBD ranged from 200 to 300 mg. Of the four studies, two had reported a difference in seizure frequency between the two groups [91, 92]. In the first study, eight patients were included in the experimental group; of these, four became seizure-free during the treatment phase (8-18 weeks), three reported an improvement in seizure frequency, and one did not have any benefit. The clinical condition of the seven placebo patients remained unchanged whereas the condition of one patient clearly improved. Drowsiness was reported by four patients in the CBD-group [91]. In the second study, four patients were included in the add-on CBD-group vs five in the placebo group (on their habitual AED treatment). Two of the four patients became seizure-free for 12 months, one reported partial improvement in seizure frequency, and one did not show any clinical benefit. The clinical condition of the five placebo patients remained unchanged. No side effects were reported [92]. Two more recent studies suggested little or no difference in seizure frequency between placebo and CBD-groups [93, 94]. One study included 12 patients with uncontrolled seizures and intellectual disability [93]. Few details are provided but no differences in seizure

frequency between the two groups emerged. Mild drowsiness was reported as side effect. The other study was only reported in an International Conference on Cannabis and Cannabinoids: 12 patients were treated with placebo for six months followed by CBD or placebo for 12 months, with a cross-over design. No relevant reduction in seizure frequency was reported [94].

These trials do not provide sufficient and consistent data to prove the effectiveness of treatment with CBD in epilepsy. They only show short-term tolerability of CBD-enriched treatments, with only minor side effects such as drowsiness. However they do not provide data on the safety of long-term treatment with CBD as the exposure to CBD ranged from one to 12 months.

A systematic review to determine the efficacy of medical marijuana in several neurologic conditions concluded that, given the lack of Class I–III studies, data are insufficient to support or refute the efficacy of cannabinoids for treatment of epilepsy. Recently, clinical studies exploring the additive effects of CBD to usual AED regimens, in both children and adults, have significantly increased. In 2014, a prospective observational study described the efficacy of treatment with 25 mg/kg/day of CBD in addition to the habitual AEDs. Of 23 children and young adults with refractory epilepsy, nine had more than 50% reduction in seizure frequency [95, 96]. Very recently, one clinical study showed a significant pharmacodynamics interaction between CBD and clobazam [28], requiring a clobazam dose reduction.

Fifteen clinical trials on the use of cannabinoids in epilepsy are currently registered in ClinicalTrials.gov. Of these, eight studies use the plant-derived CBD, Epidiolex (GWP42003: GWPharmaceuticals), four studies use the synthetic CBD (Insys Therapeutics), and three studies use the propyl variant of CBD (GWP42006: GWPharmaceuticals). The studies that have been using Epidiolex include patients with refractory epilepsy, including Dravet,

Lennox–Gastaut and Sturge–Weber syndromes. A recent multicentric open-label trial included patients with refractory childhood-onset epilepsy (including Dravet and Lennox-Gastaut syndromes), with stable AED doses before study entry. Patients were given oral cannabidiol at 2-5 mg/kg per day, up-titrated until a maximum dose of 25 mg/kg or 50 mg/kg per day. Of the 214 included patients, 137 (64%) were included in the efficacy analysis and 162 (76%) were included in the safety and tolerability analysis. For all seizure types, 51 (37%) of patients had a reduction of 50% or more, 30 (22%) patients had a response of 70% or more, and 11 (8%) had a response of 90% or more. The median reduction in monthly motor seizures was 36.5% (IQR 0-64.7). Adverse events were reported in 128 (79%) of the patients within the safety group. The most common adverse events were: somnolence, decreased appetite, diarrhea, fatigue, and convulsion (n=18 [11%]). Serious adverse events possibly related to cannabidiol use were reported in 20 (12%) patients, the most common of which was status epilepticus. The results suggest moderate efficacy and adequate safety profile in patients with refractory epilepsy [95]. However this was an open label and uncontrolled study and both efficacy and safety need to be assessed through blinded, randomized controlled trials. **As widely reported in literature, to provide reliable scientific evidence on efficacy and safety of CBD, powered double-blind randomized, placebo-controlled clinical studies are needed [20]. Regarding to this unmet need, GW Pharmaceuticals has recently provided the preliminary results of CBD's effects (Epidiolex) against Dravet syndrome, in the first randomized phase 3 clinical trial. This study enrolled 120 patients (average age 10 years) affected by this severe myoclonic epilepsy of infancy. Of these patients, 61 were treated with CBD at 20mg/kg/day, whereas 59 received placebo. CBD or placebo was co-administered together with the current AEDs treatment regimens. In this study, starting on the first month of treatment, CBD significantly reduced convulsive seizures in comparison to placebo. The anticonvulsive effect of CBD was maintained throughout the**

period of treatment. Furthermore, CBD resulted well tolerated in this clinical trial. The most common side effects were: somnolence, decreased appetite, diarrhea, fatigue, and convulsion (<http://www.gwpharm.com>).

Conclusion

Marijuana has long been used in traditional medicine or as a remedy for several pathologies despite its psychotropic effects; its effectiveness has been therefore recognized. Our current knowledge and technologies now permit to separate the various constituents of the plant extracts and identify their mechanisms of action and effects to be transferred to clinical practice following the standard drug development procedure. Considering the current need of more effective therapies in several clinical settings including epilepsy, this warrants further studies. Based on this background, several *in vivo* and *in vitro* studies have been recently performed to define CBD and other cannabinoids effects in epilepsy. CBD is indeed able to reduce seizures in a similar fashion than other AEDs in animal models; furthermore it seems to possess less side effects when compared to some other AEDs [58, 64]. Moreover, in different animal models, CBD has also demonstrated beneficial effects on cognitive performance as well as on mood disorders. These properties might also represent a further advantage in the treatment of patients with epilepsy considering that psychiatric comorbidities together with side effects affect quality of life and adherence more than seizures themselves [11, 12]. From the preclinical point of view, the main drawback concerning CBD is the scant information on its effects in chronic models of epilepsy while its effects on acute models of seizures are confirming its efficacy; furthermore, considering the neuroprotective effects that these drugs might possess, properly designed preclinical studies in epileptogenesis models are completely lacking.

The antiepileptic effects of CBD have been verified in patients with drug-resistant epilepsies; therefore the epileptologists, the neurologists and the families believed that CBD is a new and

safer AED. CBD use can be also considered in some particular cases like “catastrophic” infancy and childhood epileptic syndromes, for example the above-mentioned Dravet, MMPS and Lennox–Gastaut syndromes. On the other hand, there are not sufficient studies in humans proving the efficacy for its use while its safety and tolerability is more convincingly determined [35]. Furthermore, the current knowledge on CBD pharmacokinetic and above all its effects on liver enzymes (i.e. induction or inhibition) is not completely clear.

Data on patients with epilepsy are scarce and somehow difficult to interpret considering that different cannabinoid preparations were used in the trials, the optimal doses and the safety profile were also not always clearly defined. Another important aspect is that there are not sufficient studies regarding the effects (also adverse) related to the long-term use of the drug, such as motor dysfunctions, psychiatric disorders, impairment of neuropsychological functions and risk of addiction [18]. In order to address these issues, placebo-controlled, double-blind and multicentered clinical trials, using a relevant number of patients with similar clinical backgrounds, are necessary to have a better knowledge of the efficacy and safety use of CBD and derivatives. Finally, it will be extremely relevant to further study other cannabinoids and their mechanisms of action in order to use this data as a springboard for the development of effective drugs in epilepsy and other human diseases.

Conflict of interest

There are no conflicts of interest to be disclosed

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None

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