INVESTIGATIONAL CANNABINOIDS IN SEIZURE DISORDERS, WHAT HAVE WE LEARNED THUS FAR?

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ABSTRACT

Introduction. Anticonvulsant activity of cannabinoid attracted much attention in the last decade. Cannabinoids that are currently investigated with intention to become drugs for treatment of epilepsy are cannabidiol, cannabidivarin, Δ9-tetrahydrocannabivarin and Δ9-tetrahydrocannabinolic acid.

Areas covered. Topic of this review are results of pre-clinical and clinical studies with investigational cannabinoids. Relevant literature was searched for in MEDLINE, SCOPUS, EBSCO, GOOGLE SCHOLAR and SCINDEX databases.

Expert opinion. Pre-clinical studies confirmed anticonvulsant activity of cannabidiol and cannabidivarin in a variety of epilepsy models. While results of clinical trials with cannabidivarin are still awaited, cannabidiol showed clear therapeutic benefit and good safety in patients with therapy resistant seizures associated with Dravet syndrome and in patients with Lennox-Gastaut syndrome having drop seizures. However, full therapeutic potential of cannabinoids in treatment-resistant epilepsy has yet to be investigated in near future.

Key Words: cannabidiol; cannabidivarin; treatment-resistant epilepsy; Dravet syndrome; Lennox-Gastaut syndrome

1. INTRODUCTION

Cannabinoids are terpenophenolic compounds found in hashish (resin separated from flowers of female plants), leaves, and flower buds of the herb Cannabis sativa L [1]. They are synthetized in acidic form, but under the influence of light or heat carboxyl groups are rapidly lost and neutral forms could be found in the plant material. The most abundant and biologically active natural cannabinoids are Δ9-tetrahydrocannabinol, cannabigerol, cannabichromene and cannabidiol [1, 2]. There are also several hundreds of synthetic cannabinoids, mostly designed for illicit use, which bind for the same receptors as natural ones, but with different affinity and intrinsic efficacy [3]. Endogenous cannabinoids were also discovered, being derivatives of arachidonic acid, N-arachidonylethanolamide (anandamide) and 2-arachidonylglycerol, and acting on the same receptors as plant-derived compounds [4].

Only two types of receptors for cannabinoids are well established to date, CB1 and CB2, both belonging to the G-protein coupled receptors superfamily, although several others were proposed [4, 5]. CB1 receptors are mostly present at nerve terminals (both in central and peripheral nervous system), mediating inhibition of neurotransmitter release, while CB2 receptors could be found on immune cells, being involved in regulation of cytokine release [6]. However, cannabinoids have other binding sites which do not involve CB1/CB2 receptors, but several voltage- or ligand-gated channels and transient potential receptor class channels which are being modulated by these compounds [7].

There is a plethora of cannabinoid pharmacological effects, which could be found in almost every human organ or tissue [8]. Cannabinoids influence memory, cognition, sense of satisfaction, body movement, appetite, sense of pain and perception in general; they exhibit antiemetic, sedative, both anticonvulsant and pro convulsive action [9], and at periphery stimulation of heart, accelerated wound healing, liver-protective and immunosuppressant actions could be observed. Anticonvulsant action of cannabinoids has attracted much attention

recently, and cannabinoid receptors are seen as molecular targets for development of promising anticonvulsants that could help to decrease burden of drug-resistant epilepsy [10].

2. INVESTIGATIONAL CANNABINOIDS

Although there are many preparations with cannabinoids that are extensively used or investigated, just a handful is intended to pass regular preclinical and clinical testing and become investigational (pharmaceutical) products [11], and only some of these substances are being developed as anticonvulsants. Cannabinoids that are currently in the process of development to become pharmaceutical products for treatment of epilepsy are cannabidiol, cannabidivarin, Δ9-tetrahydrocannabivarin and Δ9-tetrahydrocannabinolic acid [12, 13].

3. MECHANISM OF ACTION AND PRECLINICAL STUDIES WITH INVESTIGATIONAL CANNABINOIDS

Investigational cannabinoids with anticonvulsant action mostly use mechanisms which do not include CB1 and CB2 receptors. Cannabidiol in vitro antagonize CB1 and CB2 receptor agonists, but it is believed that its anticonvulsant action is associated with at least some of the following mechanisms: stimulation of 5-HT1a receptors, inhibition of glutamate release, inhibition of noradrenaline, dopamine and adenosine reuptake, stimulation of glycine receptors and stimulation and desensitization of transient receptor potential class channels (ankyrin and vanilloid types, i.e. TRPA1, TRPV1 and TRPV2 receptors) [14]. Anticonvulsant effect of cannabidivarin is probably related to its agonistic action on TRPA1, TRPV1 and TRPV2 receptors, similar as that of cannabidiol, while its inhibitory action on diacylglycerol lipase-α, which synthesizes 2-arachidonoylglycerol, an endocannabinoid, remain yet to be connected to anticonvulsant properties [15, 16]. Δ9-tetrahydrocannabivarin is an antagonist of CB1 receptors, and partial agonist of CB2 receptors; an unconfirmed

hypothesis was made that increasing GABA release by blocking CB1 receptors for endocannabinoids is basis for Δ9-tetrahydrocannabivarin anticonvulsant action [17]. Δ9-tetrahydrocannabinolic acid has little affinity and efficacy at CB1 and CB2 receptors [18], and it activates TRPA1 and TRPV4 channels and blocks TRPM8 channels. Δ9-tetrahydrocannabinolic acid also inhibits diacylglycerol lipase alpha, but all this mechanisms of action were not unequivocally connected to anticonvulsant activity [19].

Cannabidiol and cannabidivarin (Figure 1) showed the most prominent effects in certain number of studies on animal models of seizures and epilepsy [20], which justified their later clinical investigation. There is only one study with Δ9-tetrahydrocannabivarin, while Δ9-tetrahydrocannabinolic acid was not tested yet. These studies were concentrated to ability of investigational cannabinoids to protect against seizures (acute induced seizures) or epilepsy (chronic induced seizures, e.g. electrical of chemical kindling) caused by various pro-convulsive agents. Cannabidiol and cannabidivarin in all but one study (rat lamotrigine-resistant amygdala kindling epilepsy model) showed clear protective effect against seizures, induced by either acute or chronic action of pro convulsive substances. However, although epileptogenesis after interference with endocannabinoid system was reported (epileptogenesis relates to drug or else induced transition of neuronal tissue from physiological to state of increased excitability leading to emergence of spontaneous, recurrent seizures) [20, 21], experiences with anti-epileptogenic potential of the investigational cannabinoids were not published to date, probably because such studies are more demanding technically. Pre-clinical studies with investigational cannabinoids are shown in the Table 1 [22, 23, 24, 25, 26, 27, 28, 29, 30, 31].

Special attention in animal studies was given to possible adverse effects of cannabinoids on cognition in immature animals, and it was shown that Δ9-tetrahydrocannabinol impairs cognitive functions in rodents; the effect was persistent even

after long periods of abstinence, and probably involves CB1 receptors [32]. However, this was not repeated consistently with cannabidiol in rodents [33], and there is considerable amount of evidence that in monkeys cannabidiol ameliorate the detrimental effects of tetrahydrocannabinol on learning and memory [34]. Effects of cannabidivarin on cognition in experimental animals is largely unknown [15, 16, 17].

While pro convulsive effect of tetrahydrocannabinol and synthetic agonists of CB1 receptors was observed in numerous studies on rodents [20], cannabidiol and cannabidivarin showed primarily anticonvulsive effects in animal seizure models, as shown in the Table 1. This difference could be explained, as said before, by CB1 blocking effects of cannabidiol and by action of both cannabidiol and cannabidivarin on transient receptor potential class channels [20].

4. CLINICAL TRIALS WITH INVESTIGATIONAL CANNABINOIDS

Only two of the investigational cannabinoids were tested in clinical trials on patients with epilepsy until now: cannabidiol and cannabidivarin (Table 2) [13]. Early clinical studies of efficacy and safety of cannabidiol in patients with epilepsy were methodologically invalid and done on very small number of subjects (4 studies with 48 subjects in total), which made authors of a systematic review of this topic [35] to conclude that "No reliable conclusions can be drawn at present regarding the efficacy of cannabinoids as a treatment for epilepsy.". The first clinical trial of acceptable quality with cannabidiol was completed and published just two years ago [36]: it was an open-label, expanded-access study on patients with treatment-resistant epilepsy, conducted at 11 centers in U.S.A. Both safety, tolerability and efficacy were tested in this trial, which enrolled 214 patients, but only 137 of them completed 12-weeks treatment period and were included in efficacy analysis; safety and tolerability were analyzed on 162 of the enrolled patients. The patients were 1 to 30 years old, with severe,

childhood-onset epilepsy resistant to drug treatment, and majority suffered from Dravet (20%) or Lennox-Gastaut (19%) syndrome. Cannabidiol was administered orally, as add-on therapy (the patients continued with current anticonvulsants) starting from 2–5 mg/kg per day (divided in two daily doses) and up-titrated weekly until not further tolerated or maximally 25-50 mg/kg/day. The drug was fairly effective: frequency of motor seizures per month decreased from 30 to 15.8 (median reduction 36.5%), and 39% of patients had a decrease of 50% or more in frequency of motor seizures. However, subgroup analysis showed that patients with Dravet syndrome had the best response (median reduction in motor seizures per month was 49·8%, and 50% patients had a decrease of 50% or more in seizure frequency), while those with Lennox-Gastaut syndrome responded somewhat less beneficially (median reduction 36·8% of seizure frequency and 37% of patients had 50% or more decrease in seizure rate). This effect was achieved on expense of moderate adverse events: the most frequent were somnolence (25%), decreased appetite (19%), diarrhoea (19%), fatigue (13%) and convulsions (11%), while the only prominent serious adverse event was status epilepticus (in 6% of patients). One observation from this study deserves special attention: the patients with concomitant clobazam had better response than others (51% of patients taking clobazam vs. 27% of patients without clobazam had reduction of seizure frequency 50% or more). This finding generated hypothesis that observed beneficial effects could be consequence of interaction between cannabidiol and clobazam [37], which was further strengthened with findings of Geffrey et al [38] who demonstrated that cannabidiol increases serum concentrations of clobazam for 60% and of its metabolite norclobazam for five times.

Encouraged by promising results of this first trial, the same investigator group conducted randomized, double-blind, placebo-controlled trial with cannabidiol on children and young adults (2.3 to 18.4 years old) with Dravet syndrome and treatment-resistant seizures [39]. The trial had 4-week baseline period, then treatment was given for 14-weeks,

and after tapering drugs adverse events were monitored for further 4 weeks. Cannabidiol was administered orally, in daily doses up to 20 mg/kg (divided in two doses), as add-on therapy. In total 120 patients were randomized from 23 sites in U.S.A. and Europe, and 108 patients completed the study protocol. Median monthly convulsive-seizure frequency in cannabidiol group dropped from 12.4 to 5.9 (median reduction 38.9%), while in the placebo group change was much smaller: from 14.9 to 14.1 (median reduction 13.3%). Reduction in convulsive-seizure frequency of 50% or more happened in 43% of the patients with cannabidiol, and in 27% of the patients with placebo. When all types of seizures were taken into account, the median number of seizures per month dropped from 24.0 to 13.7 with cannabidiol group (28.6% adjusted reduction), and from 41.5 to 31.1 with placebo (9% adjusted reduction). However, it is worthy of noting that 66% of patients in cannabidiol group were taking clobazam concomitantly. The most common adverse events observed in this trial were somnolence (36% cannabidiol, 10% placebo), diarrhea (31% cannabidiol, 10% placebo), decreased appetite (28% cannabidiol, 5% placebo) and fatigue (20% cannabidiol, 3% placebo). Serious adverse events were registered in 10 patients with cannabidiol; three of them experienced status epilepticus, but it happened also with three patients in placebo group. Other serious adverse events were related to elevation of serum aminotransferase levels, but all these patients were also taking valproate.

Another small (n=34), dose-escalating, randomized clinical trial, aimed primarily to study pharmacokinetics and safety, was conducted on treatment resistant children with Dravet syndrome (age range 4-10 years) [40]. Three doses of cannabidiol were tested (5, 10, and 20 mg/kg/day) for 3 weeks, and compared to placebo. The following adverse events were more frequent in the groups receiving cannabidiol when compared to placebo: pyrexia, decreased appetite, somnolence, sedation, vomiting, abnormal behavior and ataxia. However, only occurrence of decreased appetite was dose dependent. Five patients had serious adverse

events, pyrexia (n=2) and convulsions (n=2) (type of the fifth serious adverse event was not reported), but one patient with convulsions was from the placebo group. None of the patients taking cannabidiol had new seizure types or worsening of clinical status [40].

Recently results from a randomized, double-blind, placebo-controlled phase 3 trial comparing efficacy and safety of cannabidiol in patients with Lennox-Gastaut syndrome and seizures were published [41]. At 24 study sites in U.S.A. and Europe in total 171 patients (2-55 years old) with Lennox-Gastaut syndrome and at least two drop (atonic) seizures per week were randomized to receive either oral cannabidiol 20 mg/kg/day (n=86) or placebo (n=85) for 14 weeks, as add-on therapy. The study protocol was completed by 72 patients in cannabidiol group and by 84 patients in placebo group. Cannabidiol led to median reduction in number of drop seizures per month of 43.9%, and placebo group achieved 21.8% reduction; the observed difference was statistically significant. Percentage of patients with reduction of seizure frequency for 50% or more was 44% in the cannabidiol group and 24% in the placebo group (significant difference). Majority of adverse events were mild or moderate, similar to those observed in other studies with cannabidiol: diarrhea, somnolence, pyrexia, decreased appetite, and vomiting. The adverse events caused withdrawal from the treatment to 12 patients taking cannabidiol and one patient taking placebo.

Another randomized, multicenter, placebo controlled, double-blind trial involving patients suffering from Lennox-Gastaut syndrome and drop seizures (2-48 years of age) had three study arms: oral cannabidiol 20 mg/kg/day, oral cannabidiol 10 mg/kg/day and placebo, all as add-on therapy and for 14 weeks [42]. In total 225 patients were randomized, and majority of them completed the study protocol (66 in cannabidiol 20 mg/kg/day group, 71 in cannabidiol 10 mg/kg/day group and 73 in placebo group). After 14 weeks of treatment, cannabidiol 20 mg/kg/day was associated with median reduction in number of drop seizures per month of 47%, cannabidiol 10 mg/kg/day with reduction of 40% and placebo group

achieved 19% reduction; the observed difference was statistically significant. Percentage of patients with reduction of seizure frequency for 50% or more was 45% in the cannabidiol 20 mg/kg/day group, 40% in the cannabidiol 10 mg/kg/day group and 13% in the placebo group (significant difference). Again diarrhea (cannabidiol 20 mg/kg/day 15%, cannabidiol 10 mg/kg/day 10% and placebo 8%), somnolence (cannabidiol 20 mg/kg/day 31%, cannabidiol 10 mg/kg/day 21% and placebo 5%), pyrexia (cannabidiol 20 mg/kg/day 12%, cannabidiol 10 mg/kg/day 9% and placebo 16%) and decreased appetite (cannabidiol 20 mg/kg/day 26%, cannabidiol 10 mg/kg/day 16% and placebo 8%) were the most frequent adverse events.

Cannabidivarin is currently tested in two phase II clinical trials aimed to evaluate its pharmacokinetics, safety and tolerability compared to placebo, as add-on therapy in patients with inadequately controlled focal seizures (age 18-65 years). The studies are registered at Clinicaltrials.gov [43, 44], and their current status is “completed”, but the results are not published yet. The study “A” compares cannabidivarin with placebo in three groups: the patients on inducer antiepileptic drugs (AED), the patients on inhibitor AED, and the patients on AED that neither induce nor inhibit cytochromes. Primary outcomes of this study are pharmacokinetic parameters of the AEDs and secondary incidence of adverse events. The study “B” compares cannabidivarin (800 mg twice daily) with placebo as add-on treatment for 8 weeks in patients with inadequately controlled focal seizures. This study is aimed to investigate pharmacokinetics, efficacy and safety of cannabidivarin, and main study outcomes are percentage change in focal seizure frequency and incidence of adverse events. Although the authors of these studies made some preliminary announcements in a recent publication [13] that inducers and inhibitors of cytochromes do not affect pharmacokinetics of cannabidivarin, true results await publishing.

Clinical trials with cannabidiol did not point to significant risk of cognitive impairment. In an open-label clinical trial on children with treatment-resistant epilepsy (n=48)

cannabidiol improved quality of life, especially in cognitive domain, as both memory and other cognitive functions showed better scores on Quality of Life in Childhood Epilepsy scale [45].

The abovementioned clinical trials with investigational cannabinoids resulted at the end of 2017 with acceptance of U.S. Food and Drug Administration (FDA) to make priority review of New Drug Application (NDA) for Epidiolex (cannabidiol) submitted by the GW Pharmaceuticals, for seizures associated with Lennox-Gastaut or Dravet syndrome [46].

5. PHARMACOKINETICS AND DRUG-DRUG INTERACTIONS OF CANNABINOIDS USED IN TREATMENT OF EPILEPSY

Oral bioavailability of cannabidiol and cannabidivarin is very low (about 6%) due to erratic absorption and first pass metabolism [12]. After oral administration cannabidiol achieves maximum plasma concentration in about 3 hour's time. Cannabidiol is highly liposoluble, and therefore bound for plasma protein in high percent, has large volume of distribution (32 L/kg) and penetrates well to brain. Only 5% of orally taken cannabidiol is excreted in urine as unchanged drug [47]; the rest is metabolized mainly by the cytochrome P450 (CYP) isoenzymes 2C19 and 3A4 [40]. Main metabolite of cannabidiol is 7-COOH-cannabidiol, but 6-OH-cannabidiol could also be found in plasma. Cannabidivarin is also metabolized in liver to 7-COOH and 6-OH metabolites, but details are not published yet [13]. The elimination half-life of cannabidiol is about 3 hours [48]

Cannabidiol inhibits CYP2C19 and therefore interacts with metabolite of anticonvulsant clobazam, N-desmethylclobazam, increasing its plasma concentration for 1.6 times on average [40]. Phenitoin is also significant substrate for CYP2C19, which imply theoretical possibility that cannabidiol could increase plasma concentrations of this

anticonvulsant [49]. In clinical trials with cannabidivarin significant interactions with other anticonvulsants were not observed [13].

6. CONCLUSION

Among the four investigational cannabinoids tested for anticonvulsant activity (cannabidiol, cannabidivarin, Δ9-tetrahydrocannabivarin and Δ9-tetrahydrocannabinolic acid) only cannabidiol and cannabidivarin showed promising effect in animal studies and were advanced to clinical trials. While results of clinical trials with cannabidivarin are still awaited, cannabidiol showed clear therapeutic benefit and good safety in patients with therapy resistant seizures associated with Dravet syndrome and in patients with Lennox-Gastaut syndrome having drop (atonic) seizures. Thanks to hard evidence of efficacy and safety from clinical trials, nearly marketing authorization of cannabidiol for Dravet syndrome is expected.

7. EXPERT OPINION

Possible role of cannabinoids in control of seizures attracted much interest in the last decade, and four of them (cannabidiol, cannabidivarin, Δ9-tetrahydrocannabivarin and Δ9-tetrahydrocannabinolic acid) became investigational drugs, i.e. were intended to pass preclinical and clinical studies. Results of preclinical investigations favored cannabidiol and cannabidivarin as efficient anticonvulsants, which then entered clinical trials. Cannabidiol reached phase III clinical trials and showed clear therapeutic benefit with good safety in patients with Dravet syndrome and treatment-resistant seizures, as well as in patients with Lennox-Gastaut syndrome and drop seizures. However, since preclinical testing of Δ9-tetrahydrocannabivarin and Δ9-tetrahydrocannabinolic acid was not completed and cannabidivarin only reached phase II clinical trials, complete picture of antiepileptic potential of investigational cannabinoids is still missing.

Experiences with antiepileptic activity of investigational cannabinoids to date are encouraging, as efficacy against treatment resistant seizures was clearly demonstrated, while in the same time the drugs exhibited minimal toxicity. Clinical trials were concentrated on seizures in Dravet and Lennox-Gastaut syndromes, yet there are many other types of treatment-resistant seizures for which beneficial effect of investigational cannabinoids could be expected. The ultimate goal should be investigation of full antiepileptic potential of all investigational cannabinoids. As the first step in achievement of this goal, further clinical trials with cannabidiol and cannabidivarin in other types of treatment-resistant seizures are necessary as well as progress with pre-clinical testing of Δ9-tetrahydrocannabivarin and Δ9-tetrahydrocannabinolic acid. However, while it is reasonable to expect results of pre-clinical testing soon, quite a time would be necessary to conduct clinical trials, as patients with treatment-resistant seizures comprise a heterogenic group, and actually a number of parallel clinical trials with difficult-to-recruit patients would be necessary to get the whole picture.

The first what we could expect in near future are results of current phase II clinical trials of cannabidivarin in patients with inadequately controlled focal seizures. If they are beneficial, larger phase III clinical trials would probably be undertaken in the same patient population. Testing of both cannabidiol and cannabidivarin in other treatment-resistant seizure types should follow, and cannabidiol brings the greatest expectations as its effects were the most persuasive to date.

8. ARTICLE HIGHLIGHTS BOX

- There are four investigational cannabinoids: cannabidiol, cannabidivarin, Δ9-tetrahydrocannabivarin and Δ9-tetrahydrocannabinolic acid

- Both cannabidiol and cannabidivarin were clearly protective against seizures in a variety of pre-clinical models of epilepsy; Δ9-tetrahydrocannabivarin and Δ9-tetrahydrocannabinolic acid are not tested yet
- Cannabidiol demonstrated clear efficacy against treatment-resistant seizures in clinical trials on patients with Dravet and Lennox-Gastaut syndromes
- Cannabidiol also demonstrated good safety in clinical trials to date
- Results of phase II clinical trials of cannabidivarin in patients with treatment-resistant focal seizures are about to be published in close future
- There is significant potential of cannabidiol in other types of treatment-resistant seizures that should be explored in future pre-clinical and clinical trials

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Figure 1. Molecular structures of cannabidiol and cannabidivarin.

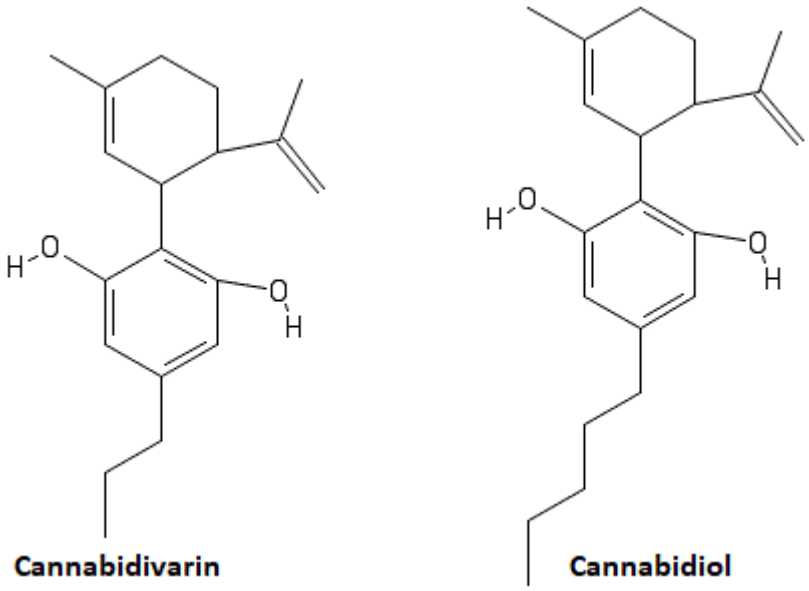

Table 1. Published preclinical studies of cannabinoids related to seizures and epilepsy.

Models of seizures and epilepsy			
Drug	Experimental model	Observed effects	Reference
Cannabidiol	mouse 6 Hz 44 mA seizure model	dose-dependent protection	[22]
	mouse maximal electroshock (MES) seizure model	dose-dependent protection	[22, 23]
	mouse corneal kindling epilepsy model	dose-dependent protection	[22]
	rat maximal electroshock (MES) seizure model	dose-dependent protection	[22]
	rat lamotrigine-resistant amygdala kindling epilepsy model	not protective	[22]
	intrahippocampal pilocarpine-induced status epilepticus (SE) rat model	protective effect	[24]
	pentylenetetrazole-induced epilepsy in rats	dose-dependent protection	[25, 26]
	mouse pentylenetetrazole-induced seizure model	protective effect	[23, 27]
	rat pilocarpine model of temporal lobe seizure	protective effect	[28]
	rat penicillin model of partial seizure.	protective effect	[28]
Cannabidivarin	rat pilocarpine model of temporal lobe seizure	dose-dependent protection	[15]
	pentylenetetrazole-induced	dose-dependent	[15, 29, 30]

	epilepsy in rats	protection	
	audiogenic seizures in mice	dose-dependent protection	[15, 30]
	mouse maximal electroshock (MES) seizure model	dose-dependent protection	[30]
Δ9-tetrahydrocannabivarin	pentylenetetrazole-induced epilepsy in rats	protective effect	[31]

Table 2. Clinical studies with investigational cannabinoids in epilepsy.

Investigational drug and comparator	**Type of epilepsy**	**Observed effect**	**Type of the study and total number of evaluated patients**	**Reference**
Cannabidiol	Treatment – resistant, majority Dravet (20%) or Lennox-Gastaut (19%) syndrome	Frequency of motor seizures per month decreased from 30 to 15.8, and 39% of patients had a decrease of 50% or more in frequency of motor seizures	Open-label, expanded-access study, n = 137	[33]
Cannabidiol vs. placebo	Dravet syndrome with treatment-resistant seizures	Monthly convulsive-seizure frequency - median reduction 38.9% with cannabidiol, 13.3% with placebo. Reduction in convulsive-seizure frequency of 50% or more in 43% of the patients with cannabidiol, and in 27% with placebo.	Randomized, double-blind, placebo-controlled trial, n = 108	[36]
Cannabidiol vs. placebo	Lennox-Gastaut syndrome with drop (atonic) seizures	Monthly drop seizures frequency - reduction 43.9% with cannabidiol, 21.8% with placebo. Reduction of seizure frequency for 50% or more 44% with cannabidiol and in 24% with placebo.	Randomised, double-blind, placebo-controlled phase 3 trial, n = 156	[37]
Cannabidiol 20 mg/kg/day vs. cannabidiol 10 mg/kg/day vs.	Lennox-Gastaut syndrome with drop (atonic) seizures	Monthly drop seizures frequency - 47% reduction with cannabidiol 20	Randomized, multicenter, placebo controlled,	[38]

placebo		mg/kg/day, 40% reduction with cannabidiol 10 mg/kg/day and 19% reduction with placebo. Reduction of seizure frequency for 50% or more 45% with cannabidiol 20 mg/kg/day, 40% with cannabidiol 10 mg/kg/day and 13% with placebo.	double-blind trial, n = 210	
Cannabidivarin with placebo in three groups: the patients on inducer antiepileptic drugs, the patients on inhibitors, and the patients on neither inducers nor inhibitors	Inadequately controlled focal seizures	Pharmacokinetic parameters of anticonvulsants and incidence of adverse events – results not yet published.	Randomized, placebo controlled, double-blind trial, phase II	[39]
Cannabidivarin vs. placebo	Inadequately controlled focal seizures	Percentage change in focal seizure frequency and incidence of adverse events	Randomized, placebo controlled, double-blind trial	[40]