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Review Article

Comprehensive Review of the Current Evidence for the Use of Cannabis (Marijuana) in the Treatment of Pediatric Epilepsy

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ABSTRACT:

Epilepsy is a disorder of the central nervous system characterized by periodic loss of consciousness with or without convulsions associated with abnormal electrical activity in the brain. Epilepsy is a common heterogeneous neurological problem in children with a frequency of 4-8 cases per 1000 children. Fifty million people have epilepsies globally; more than half of them are children. The plant Cannabis sativa, commonly known as Marijuana, is composed of more than five hundred compounds. Those that are unique to the cannabis plant are called cannabinoids and the cannabis plant contains approximately eighty cannabinoids. The principal active components of marijuana are Δ9-tetrahydrocannabinol (THC) and cannabidiol Marijuana is currently licensed in fourteen states in the United States and is legal in Canada for use in seizures or epilepsy. The present review article focuses on the use of Marijuana to treat epilepsy in children.

Keywords: Epilepsy, Marijuana, Cannbidiol and THC.

INTRODUCTION

A seizure is a clinical manifestation, resulting from a brief episode of abnormal excessive or synchronous neuronal activity in the brain. Epilepsy is a brain disorder characterized by a chronic predisposition to generate epileptic seizures with secondary neurobiological, cognitive, psychological, and social consequences [1]. It affects about 3 million people in the United States approximately 65 million people worldwide . Epileptic seizures affect 1-2 % of the population and 4% of children. The highest incidence rate (100 per 100,000) is observed in the first year of life, declining to approximately 20 cases per 100,000 per year in adolescence. It exerts a significant physical, psychological, economic and social toll on children and their caregivers. Fifty million people have epilepsies globally; more than half of them are children. The problem is further compounded in developing countries as they add about 75-80% of new cases of epilepsy [2]. The seizures and epilepsies in children are extremely diverse, differing markedly in age of onset, seizure characteristics, associated comorbidities, treatment and prognosis.

CLASSIFICATION OF SEIZURES

ILAE 2010 Classification of Seizures

I. Focal seizures

Descriptors of focal seizures:

A. Without impairment of consciousness or awareness
1. With observable motor or autonomic components
2. Involving subjective sensory or psychic phenomena only
B. With impairment of consciousness or awareness
C. Evolving to a bilateral, convulsive seizure

II. Generalized seizures

A. Tonic-clonic seizures
B. Absence seizures
    1. Typical
    2. Atypical
    3. Absence with special features
        a. Myoclonic absence
        b. Eyelid myoclonia
C. Myoclonic
    1. Myoclonic
    2. Myoclonic atonic
    3. Myoclonic tonic
D. Clonic
E. Tonic
F. Atonic
G. Unknown
    1. Epileptic spasms

Adapted from [3].

TYPES OF SEIZURES

PARTIAL SEIZURES (FOCAL, LOCAL SEIZURES

a) **SIMPLE PARTIAL SEIZURES :**

It is characterized by localized onset of excessive neuronal discharge – a FOCUS. Because only one part of the brain involved in seizure activity there is almost always no impairment of consciousness. Various manifestations, depending upon the cortical brain area involved; seizure may be limited to a single limb or muscle group . Behavioral signs include: sensory hallucinations illusions affecting touch, vision, hearing, smell and taste. A person may see lights, hear buzzing sounds or feel tingling or numbness; and b) Motor: a change in muscle activity in one part of the body without loss consciousness. This includes convulsive movements and jerking.

b) **COMPLEX PARTIAL SEIZURES :**

The type of seizure is frequently referred as temporal lobe epilepsy (TEMPORAL LOBE SEIZURES): the focus is located in the temporal lobe (LIMBIC EPILEPSY). The person performs automatic movements called automatisms

(picking at clothes, lip smacking. Seizures last between 30 sec and 3 min, and is followed by a state of confusion. It is characterized by impairment of consciousness, amnesia, and postictal confusion. The patient does not remember seizures. EEG (Electro Encephalo Gram) shows have a bizarre activity over the anterior temporal lobe during the seizure. An AURA is a sensation(s) felt by patient immediately preceding an epileptic seizure (unusual smell, sensory illusions) this is a focal phenomena that warns the patient of the impending attack. It is a very small focal seizure and its location determines the signs. AURAS represent anything the brain is capable of manifesting: limbic = psychic (déjà vu) ; amygdale = smell ; motor cortex = twitching hand ; sensory cortex = tingling foot ; optical lobe ; visual phenomena.

c) PARTIAL SEIZURES SECONDARILY GENERALIZED :

Partial seizures can progress to become generalized seizures (secondarily generalized). The type of seizure is characterized by a loss or impaired consciousness and convulsive movements. A sensory or motor aura may precede the seizure. An aura may be felt as a tingling or movement of a limb can spread throughout the body (generalized seizure).

A secondary generalized seizure may be difficult to distinguish from generalized tonic-clonic seizures.

GENERALIZED SEIZURES (BILATERAL SYMMETRICAL)

a) ABSENCE SEIZURES (PETIE MAL):

Brief loss of consciousness, occur in childhood. Generalized 3 Hz synchronized spike and wave discharge in the EEG. No aura. Seizure is observed as a freeze or blank staring. Seizures are generalized from the beginning, and the entire cortex is involved. Frequently the attack may involve clonic movements, ranging from blinking eyelids to a jerking of the entire body. The seizure lasts less than one minute.

b) TONIC CLONIC SEIZURES (GRAND MAL) :

Major convulsions, seizure begins with a sudden loss of consciousness, maximal tonic spasm of all body musculature, followed by clonic jerking, postictal depression. Tonic phase (30 sec): body becomes regid and fall. Clonic phase (2-3 min) body experiences rhythmic jerks, followed by relaxation. Postictal state (10 min): body becomes limp, and the person remains unresponsive. In some patients the seizures preceded by a prodrome – a feeling of tenseness or depression well before the seizure (several hours). Immediately prior to the seizure, the patient will experience an aura.

c) MYOCLONIC SEIZURES :

Single or multiple myoclonic jerks of the neck and shoulder flexor muscles (no loss of consciousness). Rare often associated with permanent neurological damage.Does not respond well to drug therapy.

d) ATONIC SEIZURES (DROP ATTACKS) :

Loss of postural tone with sagging of the neck or falling (brief loss of consciousness).Does not respond well to drug therapy [4].

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PATHOPHYSIOLOGY OF EPILEPSY

Seizures are paroxysmal manifestations of the cerebral cortex. A seizure results when a sudden imbalance occurs between the excitatory and inhibitory forces within the network of cortical neurons. The basic physiology of a seizure episode is detected to in an unstable cell membrane or its surrounding/adjacent supportive cells. The seizure originates from the grey matter of any cortical or sub cortical area [5]. As abnormality of potassium conductance, a defect in the voltage activated ion channels, or a deficiency in the membrane ATPase linked to ion transport may cause neuronal membrane unstable and cause a seizure. Certain neurotransmitters (e.g. glutamate, aspartate, acetyl choline, norepinephrine, histamine, corticotrophin releasing factor, purines, peptides, cytokines and steroid hormones) enhance the excitability and propagation of neuronal activity, whereas a-amino butyric acid (GABA) and dopamine inhibit neuronal activity and propagation. During a seizure, the demand for blood flow to the brain increases to carry off CO_2 and to bring substrate for metabolic activity of the neurons, as the seizure prolongs, the brain suffers more from ischemia that may result in neuronal destruction and brain damage. Mutation in several genes may be linked to some types of epilepsy [6].

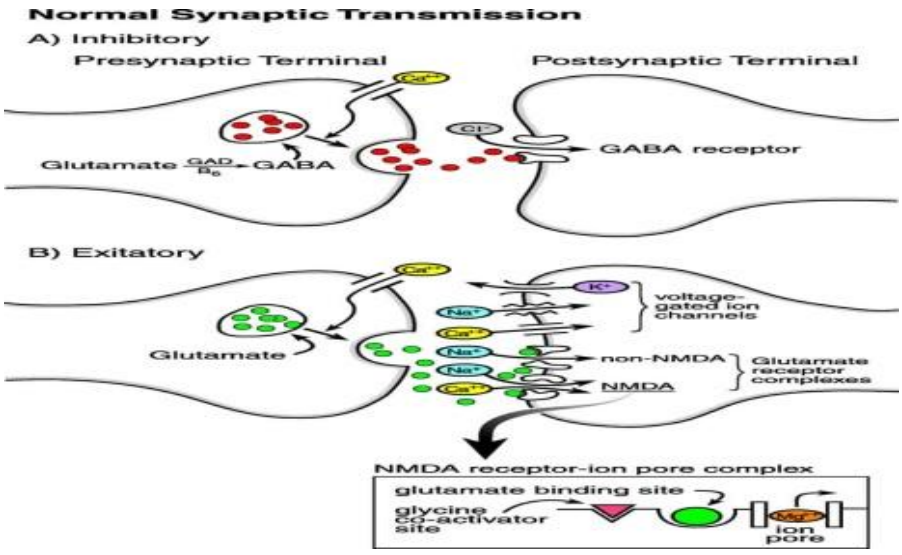

Figure1: The patho physiology of epileptic seizures

Adapted from Pathophysiology of epileptic seizures [7].

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ANTIEPILEPTIC DRUGS:

Table 1: Antiepileptic drugs, Mechanism, Pediatric dosing information and side effects

Drug	Mechanism of action	Clinical Efficacy	Dose(mg/kg body weight/ day	Side effects
Vigabatrin (1989)	GABA potentiation	Focal seizures	150-200 Daily or twice daily	Drowsiness, lethargic, confusion, appetite, irritation loss of peripheral vision
Carmabazepine(1964)	Na^+ channel blockade	Broad Spectrum	10–30 [in 2 divided dose]	Hepatotoxicity Ataxia, diplopia, rash, school performance worsening
Clonazepam (1968)	Allosteric modulation of GABA-A receptor	Absence/ Myoclonic	0.1–0.3	Fatigue, sedation,drowsiness,ataxia,aggression,hyperkinesias,hypersalivation
Diazepam (1963)	Allosteric modulation of GABA-A receptor	Status epilepticus	1mo-4yr 0.1-0.3 5-12yr 0.1-0.3 13yr 5-10	Dizziness, confusion
Ethosuximide (1958)	T-type Ca^{+2} channel blockade	Absence seizures	20-30 [in 2 divided dose]	Abdominal discomfort, hiccups headaches, sedation
Phenobarbital (1912)	Allosteric modulation of GABA-A receptor	Broad Spectrum	<5 yr, 3-5 >5 yr, 2-3	Sedation, ataxia, oseomalasia, perodoxical hypersensitivity in children
Phenytoin (1938)	Inhibition of voltage gated Na^+ channels	Broad Spectrum	< 3 yr, 8-10 >3 yr, 4-7 in 2 divided dose	Nystagmus,ataxia,anorexia,dyspepsia,nausea,aggression,depression,paradoxical seizures, megaloblasic anemia, hyperglycemia
Primidone (1954)	Allosteric modulation of GABA-A receptor	Partial/ generalized	10-30	Sedation, ataxia, oseomalasia, hypersensitivity in children
Valproic acid (1967)	GABA synthesis and Na^+ channel blockade	Broad Spectrum	10–60 [in 2–3 divided dose]	Nausea, weight loss, alopecia
Newer Generation				
Felbamate	$Na^{+,}$ Ca^{+2} and NMDA	Partial/ generalize	30-60 in 2 divided	Anorexia, vomiting, insomnia, somnolence, aplastic anemia,

	blockade		doses	hepatotoxicity
Fosphenytoin	Prodrug of phenytoin	Status epilepticus, tonic clonic	4-8 in 2 divided doses	Burning/tingling sensations, groin pain, dizziness, drowsiness
Gabapentin (1993)	GABA turn over and Ca^{+2} channel inhibition	Partial(add -on)	30-60 3 times daily	Somnolence, dizziness, ataxia, fatigue, diplopia, paraeshesia Amnesia
Lamotrigine(1990)	Na^{+} channel blockade	Broad Spectrum	0.2–15 in 2 divided dose	Drowsiness,diplopia,headache,ataxia,insomnia,tremor,aggression,irritability
Levetiracetam (2000)	SV2 Protein and modulate neurotransmitters	Partial/ generalized	10 Increase weekly to 15-45 in 2 divided doses	Sedation, behavior problem
Oxcarbazepine(1990)	$Na^{+,}$ Ca^{+2} channel blockade	Partial/ generalized	20-40 [in 2 divided doses]	Sedation, headache, ataxia, hyponatremia [rare]
Pregabalin (2004)	GABA turn over and Ca^{+2} channel inhibition	Partial(add -on)	Not used in children	Appetite, Increased Nervousness, renal disfunction
Tiagabine	Blockade of GABA uptake	Partial(add -on)	15-45 in 2 divided doses	Stupor or spike wave stupor, Weakness
Topiramate (1995)	Increase GABA and inhibits Ca^{+2} channel	Broad Spectrum	Initial dose 0.5-1 Maintenance dose 5-9	Dizziness, somnolence, ataxia, confusion, fatigue, paresthesias, speech difficulities, diplopia, impaired concentration and nausea,
Zonisamide(2000)	$Na^{+,}$ Ca^{+2} channel blockade	Partial/ generalized	4-5	Rash, renal calculi, hypohidrosis, Irritability, photosensitivity, weight loss
Stiripentol (2002)	GABA potentiation, Na+ channel blocker	Dravet syndrome	50 divided into2-3 doses/day	Few minor CNS effects of drug interaction
Rufi namide (2004)	Na+ channel blockade	Lennox-Gastaut syndrome	25-35	headache, dizziness, fatigue, somnolence, and nausea
Lacosamide (2008)	Enhanced slow inactivatio	Partial seizures	2–8	irritability, oral tics, and prolonged crying

	n of voltage gated Na+ channels			
Eslicarbazepine acetate (2009)	Na+ channel blocker	Focal seizures with secondary generalized tonic clonic seizures	15–30	Dizziness, headache, aomnolence
Perampanel (2012)	Glutamate (AMPA) Antagonist	Partial seizures	Not used in children	Dizziness, sleepiness, fatigue, irritability

[8,9,10].

***MARIJUANA* (*CANNABIS SATIVA*):**

The plant ***Cannabis sativa***, commonly known as ***marijuana***, is composed of more than five hundred compounds. Those that are unique to the cannabis plant are called cannabinoids. Marijuana consists of more than 421 components and 60 pharmacologically active cannabinoids. The two best-described cannabinoids are THC and cannabidiol (CBD). The principal active components of marijuana are Δ9-tetrahydrocannabinol (THC) and cannabidiol [4,5]. THC and Cannabidiol exert different physiological effects. In recent years, medical uses of cannabis have focused on cannabidiol, because of its non-psychoactive nature and also because of its promise in treating seizures and other diseases . Marijuana is currently licensed in fourteen states in the United States and is legal in Canada for use in seizures or epilepsy [11].

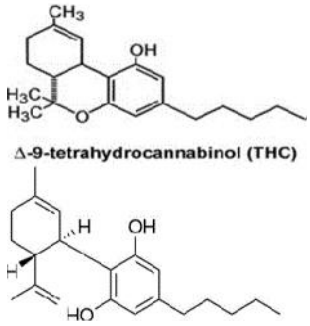

Figure 2: Chemical structure of cannabidiol.

MECHANISM OF ACTION OF CANNABINOIDS IN SEIZURES:

CBD is used in both preclinical and clinical studies[12]. since it has antiseizure activity with a good side-effect profile [13,14]. and no psychotropic effects. To date, the molecular mechanism of CBD action is not yet full understood [15]. The

phytocannabinoids THC acts on the cannabinoid receptor type 1 (CB1) and cannabinoid receptor type 2 (CB2), while CBD has only a low affinity[16].However, it has been demonstrated that CBD is able to antagonize CB1 and CB2 receptor agonists *in vitro* with unexpectedly high potency[17].These properties of CBD might explain its lack of psychotropic effects [18,19]. A key role in the pathogenesis of epilepsy including temporal lobe epilepsy[20,21].The possible molecular mechanisms by which CBD may influence neuronal hyperexcitability are: 1) activation of 5-HT1a receptors [22,23]. ; 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[24, 25]. 4) inhibition of the synaptic uptake of GABA, noradrenaline, adenosine as well as dopamine [26, 27]. 5) stimulation of □3 and □1 glycine receptors[28 29]. 6) stimulation and desensitization transient receptor potential of ankyrin type 1 (TRPA1) channel.

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 [30,31]. It has been demonstrated that CBD pretreatment was able to prevent tonic-seizures induced by GABA inhibitors, whereas it failed in case of seizures induced by the glycine antagonist's strychnine [32].Studies in the classically used animal models of epilepsy such as pentylenetetrazole (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 [33, 34].

However, A clinical study Geffrey *et al*. [35]. 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) [36].

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. Furthermore, the hippocampal expression of N-methyl-D-aspartic acid (NMDA) receptor subunit 1 is also reduced in rats treated with CBD[37].

CBD antiepileptic properties have also been tested in other animal models, such as temporal lobe epilepsy (the pilocarpine model) and partial epilepsy (penicillin model) [38]. 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*. [39]. 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 [39].

CBDV, the propyl variant of CBD, has anticonvulsant activity as suggested by both *in vitro* assays and *in vivo* preclinical studies. Hill *et al*. [40]. have reported antiseizure effects of CBDV (1-100 μM) in hippocampal slice models of epilepsy induced by administration of 4-AP and Mg2+-free solutions. In a further study, using the same Mg2+-free model, it has been demonstrated that the antiepileptic form effects of CBDV could be related to an activation and desensitization of TRPV1 channels [41]. 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.

CLINICAL DATA: CANNABIS, CANNABIDIOL AND EPILEPSY

Table2: CLINICAL EVIDENCE OF CBD IN THE PHARMACOLOGICAL MANAGEMENT OF EPILEPSY.

Study Design	Subjects	Dose	Duration	Results	Refs
Survey	117 parents of children with epilepsy	4.3 mg/kg/day (median dosage)	6.8 months (median duration of treatment)	85% of parents reported reduction In seizure frequency, whereas 14% of parents reported complete seizure freedom	[42].
Retrospective Study	75 patients with refractory epilepsy		5.6 months (median observation period)	57% reported improvement to either seizure duration or frequency	[43].
Retrospective multicenter study	74 children/ adolescent with refractory epilepsy	1 to 20 mg/kg/die (doses range)	5.5 months (median duration of treatment)	89% reported reduction in seizure Frequency	[44].
Prospective/ Placebocontrolled Trials	15 patients with uncontrolled seizures (8 treated and 7 Placebo)	200-300 mg/ Kg/day	8-18 weeks (treatment phase)	4 of 8 became seizure-free 3 of 8 reported seizures reduction 1 did not show clinical benefit	[45].
Prospective/ placebocontrolled trials	9 adults with uncontrolled seizures (4 treated and 5 placebo)	200 mg/Kg/day	3 months	2 of 4 became seizure-free 1 reported partial improvement in seizure frequency 1 did not show clinical benefit	[46].

Prospective/ placebocontrolled trials	12 patients with uncontrolled seizures (6 treated and 6 placebo)	200-300 mg/ Kg/day	3 weeks	No significant difference in seizure between placebo and CBD-groups	[47].
Prospectiverandomized/ double-blind placebocontrolled trials	12 patients with uncontrolled seizures (crossover design)	300 mg/ Kg/day	12 patients treated with placebo for 6 months followed by CBD or placebo for 12 months	No significant difference	[48].
Open label and uncontrolled study and both efficacy and safety	214 included patients with refractory childhood-onset epilepsy 137 (64%) were included in the efficacy analysis and 162 (76%) were Included in the safety and tolerability analysis.	25 mg/kg or 50 mg/kg per day	Monthly	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).	[49].
first randomized phase 3 clinical trial	120 patients (average age 10 years)	20mg/kg/day	59 received placebo	Significantly reduced convulsive seizures in comparison to placebo.	[50].
Survey	A 10-month-old boy, affected by malignant migrating partial seizures in infancy (MMPS),	CBD (25 mg/mL at 10 mg/kg/day divided twice daily, up to 25 mg/kg/day Twice daily).	nine days	clinical seizure freedom and He made some developmental gains.	[51].
Survey	Nineteen children: Of these, thirteen children had Dravet syndrome, four had Doose syndrome, one had Lennox-Gastaut syndrome and the other had idiopathic epilepsy.	250mg a day	Two weeks	Sixteen (84%) parents reported a reduction in their child's seizure and three parents reported no change. Of the sixteen with the positive outcome, two (11%) reported complete seizure freedom, eight (42%) reported a greater than 80% reduction in seizure frequency, and six (32%) reported a 25–60% seizure reduction. (85)	[52].

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 Δ9- tetrahydrocannabidivarin (Δ9-THCV); although there are no clinical studies proving their efficacy [53]. CBDV has shown anticonvulsant properties through the involvement of specific molecular targets such as TRP channels or diacylglycerol lipase A [54, 55].

The drug called Epidiolex is an oral solution containg highly purified cannabidiol. Epidiolex was approved by FDA for patients age 2 who suffer from Lennox- Gastaut and Dravet syndromes [55].

CONCLUSION

Initiating antiepileptic drug (AED) treatment after a first seizure remains a controversial issue because of our lack of understanding of the underlying mechanisms of brain injury and the subsequent processes that lead to injured brain becoming epileptic. Current treatment for established epilepsy requires long-term treatment with drugs that have obvious limitations.

Moreover, current AEDs, including new generation drugs have considerable side effects, both acute and chronic. Second-generation AEDs (gabapentin, lamotrigine, levetiracetam, oxcarbazepine, pregabalin, tigabine, zonisamide) may be better tolerated but are no more effective than traditional AEDs. Because of our lack of understanding of the underlying mechanism of action of AEDs attempts to rationally prescribe and combine AEDs in different types of seizures and epilepsy syndromes have largely failed [56]. Preclinical studies suggest that naturally occurring cannabinoids (phytocannabinoids) have anticonvulsant effects which are mediated by the endocannabinoid system [57]. Cannabidiol (CBD) and cannabidivarin have shown antiseizure effects in both in vivo and in vitro models. In contrast to tetrahydrocannabinol (THC), CBD does not produce euphoric or intrusive psychoactive side effects when used to treat seizures [58].Cannabinoids have been proposed as an adjunctive treatment for epilepsy[58]. and parents of children with epilepsy report using CBD products [59-61,]. There are a number of phase III human trials underway of CBD as an adjunctive therapy for treatment resistant child and adult epilepsies [62, 63].

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