Clin Drug Investig (2016) 36:331–340
DOI 10.1007/s40261-016-0379-x

CURRENT OPINION

# Plant-Derived and Endogenous Cannabinoids in Epilepsy

**Alberto Verrotti[1] · Miriam Castagnino[2] · Mauro Maccarrone[3,4] · Filomena Fezza[4,5]**

Published online: 18 February 2016
© Springer International Publishing Switzerland 2016

**Abstract** Cannabis is one of the oldest psychotropic drugs and its anticonvulsant properties have been known since the last century. The aim of this reveiw was to analyze the efficacy of cannabis in the treatment of epilepsy in adults and children. In addition, a description of the involvement of the endocannabinoid system in epilepsy is given in order to provide a biochemical background to the effects of endogenous cannabinoids in our body. General tolerability and adverse events associated with cannabis treatment are also investigated. Several anecdotal reports and clinical trials suggest that in the human population cannabis has anticonvulsant properties and could be effective in treating partial epilepsies and generalized tonic-clonic seizures, still known as "grand mal." They are based, among other factors, on the observation that in individuals who smoke marijuana to treat epilepsy, cessation of cannabis use precipitates the re-emergence of convulsive seizures, whereas resuming consumption of this psychotropic drug controls epilepsy in a reproducible manner. In conclusion, there is some anecdotal evidence for the potential efficacy of cannabis in treating epilepsy. Though there has been an increased effort by patients with epilepsy, their caregivers, growers, and legislators to legalize various forms of cannabis, there is still concern about its efficacy, relative potency, availability of medication-grade preparations, dosing, and potential short- and long-term side effects, including those on prenatal and childhood development.

**Key Points**

The anticonvulsant properties of cannabis are recognized.

There are few clinical studies on the use of cannabinoids in epileptic patients.

The safety of cannabinoids in treatment of epilepsy remain to be proven.

## 1 Introduction and Historical Issues

Cannabis is one of the oldest psychotropic drugs and its anticonvulsant properties have been known since the last century. In this review we analyze human studies on the use of cannabinoids (CBs) in epilepsy. There are several species of cannabis; the most relevant are *Cannabis sativa*,

A. Verrotti, M. Maccarrone and F. Fezza are equally senior authors.

✉ Alberto Verrotti
averrott@unich.it

✉ Filomena Fezza
Filomena.fezza@uniroma2.it

[1] Department of Pediatrics, University of L'Aquila, Ospedale "San Salvatore", 67100 L'Aquila, Italy

[2] Department of Pediatrics, University of Perugia, Ospedale "Santa Maria della Misericordia", Sant'Andrea Delle Fratte, 06123 Perugia, Italy

[3] Department of Medicine, Campus Bio-Medico University of Rome, Via Alvaro del Portillo 21, 00128 Rome, Italy

[4] European Center for Brain Research/IRCCS Santa Lucia Foundation, Via del Fosso del Fiorano, 65, 00143 Rome, Italy

[5] Department of Experimental Medicine and Surgery, Tor Vergata University of Rome, Via Montpellier 1, 00130 Rome, Italy

*Cannabis indica*, and *Cannabis ruderalis*. *Cannabis sativa*, the most widespread variety, grows in tropical and temperate climates. The two main preparations derived from cannabis are marijuana and hashish. Marijuana is a Mexican term initially attributed to cheap tobacco, but referring today to the dried leaves and flowers of the hemp plant. Hashish, the Arabic name for Indian hemp, is the viscous resin of the plant [1].

In 1839, O'Shaughnessy, a British physician and surgeon working in India, discovered the analgesic, appetite-stimulant, antiemetic, muscle relaxant, and anticonvulsant properties of cannabis; the publication of his observations quickly led to the expansion of the medical use of cannabis [2]. In 1854, cannabis was listed in the United States Dispensatory [3], and since then was sold freely in pharmacies in Western countries. However, after prohibition of alcohol was lifted, the American authorities banned cannabis, which was considered to be responsible for insanity, moral and intellectual deterioration, violence, and various crimes. Thus in 1937, under pressure from the Federal Bureau of Narcotics and against the advice of the American Medical Association, the US government introduced the *Marihuana Tax Act*: a tax of US$1 per ounce was collected when marijuana was used for medical purposes and US$100 per ounce when it was used for unapproved purposes [4]. In 1942, cannabis was removed from the United States Pharmacopoeia, thus losing its therapeutic legitimacy [5]. Great Britain and most European countries banned cannabis by adopting the 1971 Convention on Psychotropic Substances instituted by the United Nations [6]. Despite its illegality, patients have continued to obtain cannabis on the black market for self-medication. In 1978, in response to the success of a lawsuit filed by a glaucoma patient who had begun treating himself by smoking marijuana after losing a substantial part of his vision, the US Government created a compassionate program for medical marijuana: 20 people suffering from debilitating diseases legally received marijuana cigarettes from the National Institute on Drug Abuse, after approval by the US Food and Drug Administration (FDA). This program was closed to new candidates in 1991 by President Bush, but still recently seven people continued to receive their marijuana [7]. In Canada, 14 years after the 1988 arrest of Terrance Parker (an Ontario patient who had discovered that marijuana consumption relieved his epileptic attacks, contrary to conventional drugs) and 1 year after the Ontario Court of Appeal ruled that discretionary regulation of marijuana use for medical purposes was contrary to the principles of the Canadian Charter of Rights and Freedoms, the Government of Canada decided to draft new regulations [8]. Thus, since 30 July 2001 the *Marihuana Medical Access Regulations* (MMAR) allow Canadian patients suffering from a serious disease to be eligible for therapeutic consumption of marijuana. As of April 2005, 821 people were thus authorized to possess marijuana for medical purposes and 363 physicians had supported a request for authorization of possession [9].

The therapeutic applications of cannabis and its derivatives have been studied by various world bodies, including the Scientific Committee of the House of Lords in Great Britain (1998), the Institute of Medicine in the USA (1999), and the Senate Special Committee on Illegal Drugs in Canada (2002). Since 2003, medicinal cannabis, in standard CB concentrations, is sold in pharmacies in The Netherlands by medical prescription [10]. Various Western countries have authorized and conducted clinical trials on cannabis and its derivatives. Thus, for example, since 1999 Health Canada, in collaboration with the Canadian Institutes of Health Research, has established a Medical Marihuana Research Program [11]. Cannabinoid research has increased exponentially in the last 15 years, in particular evaluating the therapeutic applications of cannabis and its derivatives. In March 2014 the Canadian federal government brought forward the Marihuana for Medical Purposes Regulation, replacing the previous MMAR [12]. In response to physicians' concerns, most of the regulatory medical colleges in Canada have published recommendations for prescribing medical marijuana [13].

## 2 The Endocannabinoid System

Cannabis contains more than 460 known chemicals, more than 60 of which are grouped under the name CBs [14]. The major psychoactive ingredient of cannabis is delta-9-tetrahydrocannabinol, commonly known as THC (Fig. 1a). Other CBs present in Indian hemp include delta-8-tetrahydrocannabinol, cannabinol, cannabidiol (CBD) (Fig. 1a), cannabicyclol, cannabichromene, and cannabigerol, but they are present small quantities and have no significant psychotropic effects compared to THC [15]. In mammals it is now well established that most CBs carry out their function principally through specific receptors, called type 1 and type 2 cannabinoid receptors ($CB_1R$ and $CB_2R$, respectively) [16]. Immediately afterwards, an entirely new endogenous system of bioactive lipids (termed "endocannabinoids" [eCBs]) (Fig. 1b), their receptor targets (including CBRs), and metabolic enzymes responsible for eCBs synthesis and degradation was discovered: the so called "endocannabinoid system" (ECS) [17].

In particular, $CB_1R$ occurs mostly in the central nervous system (CNS), with high levels in the hippocampus, and $CB_2$ is found mainly in the periphery; $CB_1R$ is also expressed by non-neuronal cells and $CB_2R$ by neurons

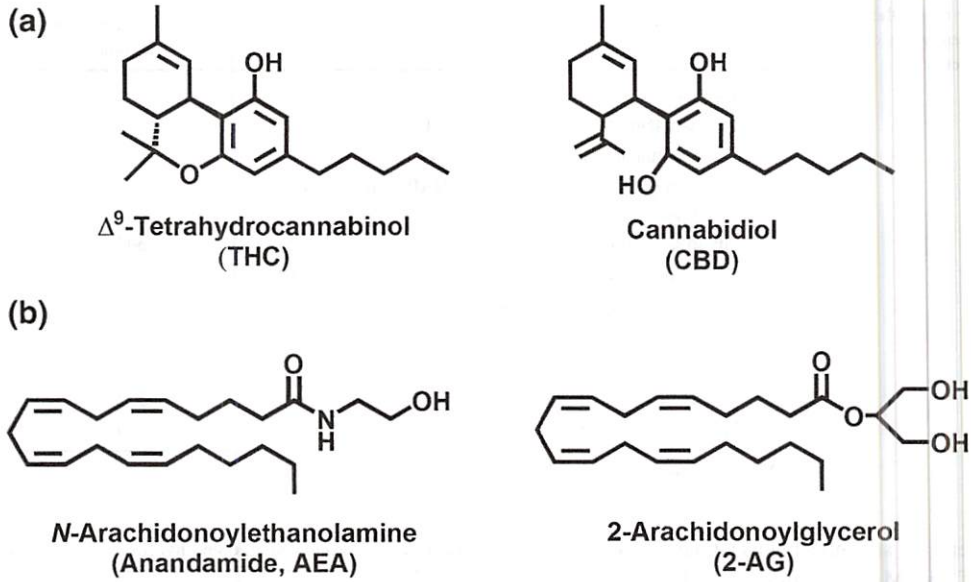


**Fig. 1** Chemical structures of THC (delta-9-tetrahydrocannabinol), CBD (cannabidiol), and two prominent endocannabinoids, AEA and 2-AG

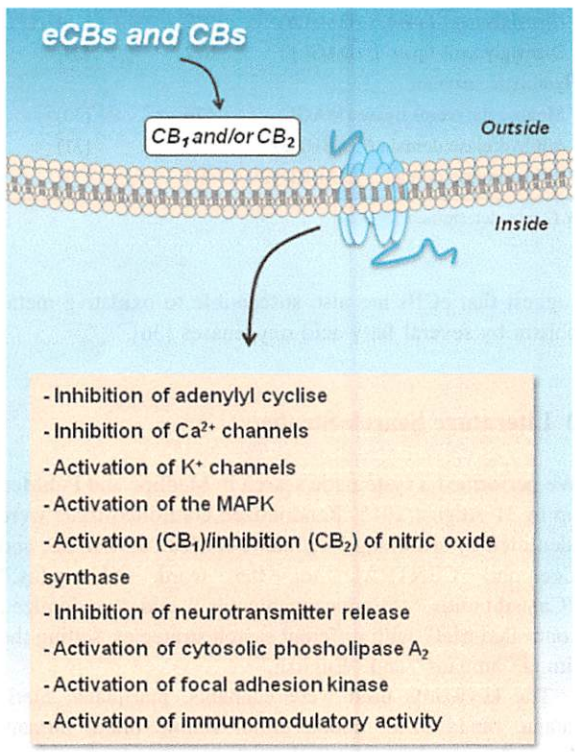


**Fig. 2** Main signaling pathways triggered by (endo)cannabinoids

upon brain insult [18]. $CB_1R$ and $CB_2R$ have relatively low sequence homology (almost 50 %) and both act by inhibiting adenylyl cyclase (AC) and by activating Gi/o proteins and mitogen-activated protein kinase (MAPK) [16].

In addition to the orthosteric site for the specific agonist, $CB_1R$ has allosteric sites that other ligands can bind in order to increase or attenuate receptor activation [19]. $CB_1R$ action is coupled to p42/p44 MAPK and nitric oxide synthase (NOS) and was found to regulate voltage-dependent ion channels and activate Jnk and p38 MAP kinases, focal adhesion kinase and cytosolic phospholipase $A_2$ [16]. CBs can also activate $CB_1R$ via a G protein-independent pathway that involves G protein-coupled receptor kinase-3 and β-arrestin-2, required for desensitization and development of tolerance [16].

$CB_2R$ also modulates AC and promotes p38 and p42/44 MAPK activation, and it stimulates phosphatidylinositol-3-kinase (PI3K), ceramide production and gene transcription [16]. $CB_2R$ has been shown to increase apoptosis through a process associated with internalization of the receptor and ceramide-dependent signalling [20, 21]. A substantial difference between $CB_1R$ and $CB_2R$ is that the latter poorly modulates calcium and potassium channels and inhibits (rather than activating) NOS [16]. The main signalling pathways of CB1R and $CB_2R$ are shown in Fig. 2.

Nevertheless, much pharmacological and biochemical data suggest that some cannabinoids (i.e., CBD and synthetic analogues of CBD, such as Abnormal-CBD) and eCBs might also interact with other molecular targets, including non-CB1/non-CB2 receptors, receptor GPR55 [16], and various ion channels [16]. In particular, the intracellular signaling initiated by GPR55 is associated with an alteration in cytoplasmic calcium changes and

**Table 1** Major biosynthetic and hydrolytic enzymes of antiepileptic agents

| Name (abbreviation) | Amino acids (human) | References |
|---|---|---|
| Biosynthetic enzymes | | |
| $Ca^{2+}$-dependent *N*-acyltransferase (NAT) | N.D. | [20] |
| $Ca^{2+}$-independent *N*-acyltransferase (iNAT) | 279 | [21] |
| *N*-Acyl-phosphatidyl ethanolamines (NAPE)-hydrolyzing phospholipase D (NAPE-PLD) | 393 | [22] |
| α/β-hydrolase domain 4 (ABHD4) | 342 | [23] |
| Protein tyrosine phosphatase, non-receptor type 22 (PTPN22) | 807 | [24] |
| Glycerophosphodiester phosphodiesterase (GDE1) | 331 | [25] |
| Hydrolytic enzymes | | |
| Fatty acid amide hydrolase (FAAH-1) | 579 | [26] |
| Fatty acid amide hydrolase (FAAH-2) | 532 | [27] |
| *N*-Acylethanolamine-hydrolyzing acid amidase (NAAA) | 359 | [28] |

*N.D.* not determined

involves several $G_\alpha$ subunits, but as a final result lead to the activation of the MAPK pathways and release of transcription factors [16]. Other potential receptors activated by eCBs are peroxisome proliferator-activated receptor (PPAR) α and γ [16].

The main eCBs are two ω3-fatty acids containing lipid molecules, anandamide (*N*-arachidonoylethanolamine, AEA) and 2-arachidonoylglycerol (2-AG) (Fig. 1b). Much like many other bioactive molecules, the actions of eCBs are regulated by their levels, and therefore by a balance between biosynthetic and degradative mechanisms. The principal metabolic enzymes for AEA and 2-AG have been intensely investigated [17], and are summarized in Tables 1 [22–30] and 2 [31–33], respectively.

In particular, AEA is produced from enzymatic hydrolysis of *N*-arachidonoyl-phosphatidylethanolamine (NArPE) via type D phospholipase (NAPE-PLD), NArPE can be formed by the action of yet-unidentified $Ca^{2+}$-dependent (NAT) or $Ca^{2+}$-independent (iNAT) *N*-acyltransferase [34, 35]. Recent studies have reported additional enzymatic pathways for AEA biosynthesis (Table 1) [22, 23], supporting the proposal that the endogenous levels of this eCB are regulated by a complex system [17].

Biosynthesis of 2-AG appears somewhat simpler (Table 2) [31]. The best synthetic pathway is the hydrolysis of membrane phospholipids through the action of phospholipase C, producing 1-acyl-2-arachidonoylglycerol (DAG), which can be converted to 2-AG by two different *sn*-1-selective DAG lipases, named DAGLα and DAGLβ [31]. The main enzymes responsible for eCBs degradation are fatty acid amide hydrolase (FAAH) for AEA [28], and monoacylglycerol lipase (MAGL) for 2-AG [32]. More recently, two additional hydrolases were also found to recognize AEA [29, 30] and 2-AG [33], and are reported in Tables 1 and 2, respectively. Moreover, accumulating data suggest that eCBs are also susceptible to oxidative metabolism by several fatty acid oxygenases [36].

**Table 2** Major biosynthetic and hydrolytic enzymes of 2-AG

| Name (abbreviation) | Amino acids (human) | References |
|---|---|---|
| Biosynthetic enzymes | | |
| Diacylglycerol lipase α (DAGLα) | 1042 | [29] |
| Diacylglycerol lipase β (DAGLβ) | 672 | [29] |
| Hydrolytic enzymes | | |
| Monoacylglycerol lipase (MAGL) | 579 | [30] |
| α/β-hydrolase domain 6 (ABHD6) | 337 | [31] |
| α/β-hydrolase domain 12 (ABHD12) | 404 | [31] |

*N.D.* not determined

## 3 Literature Search Strategy

We performed a systematic search in Medline and PubMed up to 31 August 2015. Randomized controlled trials were identified by searching Medline (PubMed), EMBASE, and Cochrane CENTRAL for the words "Cannabis," "Cannabinoids," "Endocannabinoids," and "randomized controlled trial" with different search strategies, setting the limits "humans" and "English."

The keywords used were cannabis, marijuana, marihuana, randomized, double-blind, simple blind, human. The reference lists of all the relevant articles was also analyzed to include all reports and reviews related to the subject.

The search included studies and data available in English and French. For each clinical study, the number of patients assessed, the type of study and comparisons made,

the products and the dosages used, and their efficacy and adverse effects were identified.

## 4 (Endo)Cannabinoids in Epilepsy

Epilepsy affects about 1 % of the world's population. It is estimated that 20–30 % of epileptics are not adequately controlled by conventional drugs.

Many studies have reported alterations of distinct components of ECS both in animal models of epilepsy and in human patients [37, 38]. Furthermore, ECS-targeting compounds have been shown to be effective against epilepsy (Table 3). In particular, in several cases ECS activation seems to prevent seizures and to reduce mortality, whereas pharmacological blockade of ECS exerts a proconvulsive action (Table 3) [39–49].

Cannabidiol (CBD) appears to be the most promising CB in animal studies. It has a powerful anticonvulsant activity and minimal neurotoxicity [50]. Several anecdotal reports suggest that cannabis has anticonvulsant properties and would be effective in treating partial epilepsies and generalized tonic-clonic seizures [51–54].

In 1975 CBD and four of its derivatives (CBD-aldehyde-diacetate, 6-oxo-CBD-diacetate, 6-hydroxy-CBD triacetate and 9-hydroxy-CBD-triacetate) were shown to: (i) protect mice against maximal electroshock convulsions, (ii) potentiate pentobarbital sleeping-time, and (iii) reduce spontaneous motor activity [55]. CBD was found to be an effective anticonvulsant with specific activity comparable to antiepileptic drugs. Hence, it was suggested as a drug for the treatment of children with pharmaco-resistant epilepsy [56, 57]. The application of the $CB_1R$ antagonists SR141716A or AM251 to "epileptic" neurons caused the development of continuous epileptiform activity, resembling electrographic status epilepticus. The induction of status epilepticus-like activity by $CB_1R$ antagonists was reversible, and could be overcome by maximal concentrations of $CB_1R$ agonists. Indeed, a highly selective $CB_1R$ agonist like arachidonyl-2'-chloroethylamide (ACEA) enhances the anticonvulsant action of valproate in a mouse model of maximal electroshock-induced seizure [58].

Importantly, the $CB_1R$ sublocation in the hippocampus and other brain regions can differ between presynaptic elements that originate from distinct cellular subtypes explaining some different (sometimes conflicting) effects (Table 3). In particular, in an animal model it was demonstrated that $CB_1R$ expression in hippocampal glutamatergic neurons (but not GABAergic) is necessary and sufficient to protect against kainic acid (KA)-induced seizures [59].To date, there are only sparse data to draw definitive conclusions on whether or not occasional or chronic marijuana use may influence seizure frequency [60]. In one case report, marijuana smoking was proposed to induce seizures [61]. In another study, patients suffering from secondary generalized epilepsy with temporal focus treated with CBD remained almost seizure-free; other patients demonstrated partial improvement in their clinical condition [62].

In one available controlled study [63], the role of cannabinoids in the treatment of epilepsy remains speculative. CBD presents an interesting therapeutic potential, but additional research on its anticonvulsant properties, whether alone or in association with the standard drugs, is deemed necessary.

**Table 3** Effect of endocannabinoid system-targeting compounds on animal models of epilepsy

| Target | Compound | Seizure | References |
|---|---|---|---|
| $CB_1$ agonist | WIN55,212-2 | ↓ | [37–40] |
| | | ↑ | [41] |
| | 2-AG | ↓ | [42] |
| | Methanandamide | ↓ | [42] |
| $CB_1$ antagonist/agonist inverse | Rimonabant | ↑ | [38, 39, 41] |
| | AM251 | ↑ | [40, 43] |
| | | NE | [44] |
| FAAH inhibitor | URB597 | ↓ | [44] |
| | AM374 | ↓ | [45] |
| Uptake inhibitor | AM404 | ↓ | [44] |
| | UCM707 | ↓ | [46] |
| Mix FAAH/MAGL inhibitor | AM6701 | ↓ | [47] |

*2-AG* 2-arachidonoylglycerol, *CB* cannabinoid, *FAAH* fatty acid amide hydrolase, *MAGL* monoacylglycerol lipase, *NE* no effect

### 4.1 Cannabis as a Treatment for Epilepsy: Efficacy and Safety

Several studies [61, 64–66] suggest that cannabis has anticonvulsant properties, and would be effective in treating partial epilepsies and generalized tonic-clonic seizures, still known as "grand mal." They are based on the fact that in individuals who smoke marijuana to treat their epilepsy, cessation of cannabis use precipitates the re-emergence of convulsive seizures, while resuming consumption of this psychotropic drug controls epilepsy (the data are reported in Table 4). However, current data are insufficient to provide support for the efficacy of CBs for reducing seizure frequency [67].

A daily dose of 200–300 mg of CBD may be safe (5–20 mg/kg/day), although the number of patients treated at this dose is small and, except for one study (CBD 100 mg was given for 6 months) [68], the treatment lasted only for a short period of time [63, 69].

No significant data are reported on electroencephalogram (EEG) changes during the use of cannabis.

**Table 4** Pertinent data from the main studies in epileptic patients

| Reference | Type of study | Patients number (C/A) | Epilepsy | Response to cannabis | Components/dosage | Therapy duration | Adverse effects |
|---|---|---|---|---|---|---|---|
| Davis and Ramsey [64] | Ob | 5, C | UN | 3/5 pt SF | THC/UN dose | 7 weeks | UN |
| Keeler and Reifler [61] | CR | 1, A | GTC | SF | UN | 6 months | UN |
| Consroe et al. [51] | CR | 1, A | UE | SF | UN | UN | UN |
| Feeney [65] | CS | 72, A | UN | 13/72 pt partial improvement | UN | UN | UN |
| Mechoulam and Carlini [66] | CT | 9, A | UE-T | Group I (4 pt treated with CBD) vs group II (5 pt)<br>Group I: 2/4 SF, 1/4 partial improvement, 1/4 no improvement<br>Group II: no improvement | Group I: 200 mg CBD daily<br>Group II: placebo | 3 months | No toxic effects |
| Cunha et al. [62] | CT | 15, A | T | Group I (7 pt treated with CBD) vs Group II (8 pt as controls)<br>Group I: 4/7 pt SF<br>Group II: 1/8 pt SF | Group I: 200–300 mg of CBD daily<br>Group II: placebo | 3–18 weeks | UN |
| Ames [56] | CT | 12, A | UE | Group I vs group placebo. No significant differences | Group I: 300 (for the first week)—200 mg (for the next 3 weeks) of CBD daily<br>Group II: placebo | 4 weeks | UN |
| Trembly and Sherman [68] | RT | 12, A | UE | UN | 100 mg for 3 times/day of CBD | 6 months | UN |
| Ng et al. [80] | Case-control study | 308, A | UN | UN | UN | UN | UN |
| Gordon et al. [60] | Descriptive study | 215, A | UN | 17/215 pt SFR | UN | UN | UN |
| Lorenz [81] | Ob | 4, C | UN | 2/4 pt SFR | THC, UN dose | UN | UN |
| Gross [82] | CS | 28, A | UN | 15/28 pt SFR | UN | UN | UN |
| Mortati [83] | CR | 1, A | UN | SFR | UN | UN | UN |

*C* children, *A* adult, *CT* controlled trial, *CR* case report, *Ob* observational study, *RT* randomized trial, *CS* cross-sectional study, *UN* unknown, *GTC* generalized tonic-clonic, *UE* uncontrolled epilepsy, *T* temporal, *pt* patients, *SF* seizure-free, *SFR* seizure frequency reduction, *CBD* cannabidiol, *THC* $\Delta^9$-tetrahydrocannabinol

Furthermore, drug–drug interactions (e.g., CBD and clobazam) [70] should be considered; in fact, drug metabolism via the cytochrome P450 system has emerged as an important factor involved in several drug interactions that can result in drug toxicities, reduced pharmacological effects, and adverse drug reactions. In this respect, a recent studies have indicated that CBD is a potent inhibitor of two P450 isozymes (CYP 2C19 and CYP 3A4,13) [71, 72].

### 4.2 Adverse Effects and Toxicity

Clinical presentations following the use of synthetic CBs have included agitation, anxiety, emesis, hallucinations, psychosis, tachycardia, and unresponsiveness. Convulsions have only rarely been associated with marijuana exposures. The absence of anticonvulsant phytocannabinoids in spice products could potentially be one of multiple unknown mechanisms contributing to convulsions [67, 73, 74].

### 4.3 Cannabinoid Use in Children

Safety and tolerability data for CBD-enriched cannabis use among children are not available. Objective measurements of a standardized preparation of pure CBD are needed to determine whether it is safe, well tolerated, and efficacious at controlling seizures in this pediatric population with difficult-to-treat seizures.

Severe childhood epilepsies are characterized by frequent seizures, neurodevelopmental delays, and impaired quality of life. In these treatment-resistant epilepsies, families often seek alternative treatments. A recent survey [75] explored the use of CDB-enriched cannabis in children with treatment-resistant epilepsy. The survey was presented to parents belonging to a Facebook group dedicated to sharing information about the use of CBD-enriched cannabis to treat their child's seizures. Nineteen responses met the following inclusion criteria for the study: a diagnosis of epilepsy and current use of CBD-enriched cannabis. Thirteen children had Dravet syndrome, four had Doose syndrome, and one each had Lennox-Gastaut syndrome and idiopathic epilepsy. The average number of antiepileptic drugs tried before using CBD-enriched cannabis was 12. Sixteen (84 %) of the 19 parents reported a reduction in their child's seizure frequency while taking CBD-enriched cannabis. Of these, two (11 %) reported complete seizure freedom, eight (42 %) reported a >80 % reduction in seizure frequency, and six (32 %) reported a 25–60 % seizure reduction. Other beneficial effects included increased alertness, better mood, and improved sleep. Side effects included drowsiness and fatigue. This survey shows that parents are using cannabidiol-enriched cannabis as a treatment for their children with treatment-resistant epilepsy [75]. Currently, a drug based on CBD (Epidiolex©), produced by GW Pharmaceuticals, has commenced the second of two phase III clinical trials for the treatment of Lennox-Gastaut syndrome, a rare and severe form of childhood-onset epilepsy. During 2014, Epidiolex has received Orphan Drug Designation from the FDA for treatment of LGS. At the American Epilepsy Society Annual Meeting (6 December 2015), seven posters relating to the physician-sponsored Expanded Access Program for Epidiolex were presented; the information presented included data about 261 patients enrolled in this expanded access program, representing a twofold increase in patient numbers over the previous disclosure in April 2015 [76]. Promising sign of efficacy have been reported, with a median reduction in total seizures of 45 % across all patients after 12 weeks treatment, and maintenance of clinical effect at 36 weeks; 47 % of patients experienced a ≥50 % reduction in seizures after 12 weeks' treatment; Epidiolex was well tolerated—only 4 % of patients withdrew due to side effects [77].

## 5 Conclusions

Cannabis use is prevalent in patients with epilepsy, and various preparations of cannabis are currently in use. With the legalization of cannabis in some US states, there has been an increase in availability of high-CBD/low-THC products for the treatment of epilepsies with poorly controlled seizures including catastrophic childhood epilepsies. There is some anecdotal evidence of the potential efficacy of cannabis in treating epilepsy. Based on this evidence, there has been an increase in patients with epilepsy, their caregivers, growers, and legislators asking for cannabis to be legalized in its various forms. As these efforts continue and the availability of cannabis preparations grows, the professional epilepsy community is at a crossroads: as there is an increasing push to legalize "medical marijuana," there is also increased concern about its efficacy, the relative potency of various preparations, availability of medication-grade preparations, dosing, and potential short- and long-term side effects including adverse effects on prenatal and childhood development [78].

No conclusive statements can be made at present on the efficacy of CBs or eCBs-oriented drugs as a treatment for epilepsy. Further data from well-designed studies are needed to clearly assess short- and long-term efficacy and side effects of CBD or high-CBD/low-THC products for the treatment of seizures and epilepsy in children and adults [79].

In summary, the present analysis of the available literature suggests that data are still insufficient to support the efficacy of cannabis as adjunctive treatment for refractory, partial, or generalized epilepsy.

**Compliance with Ethical Standards**

**Financial disclosure** The authors have no financial relationships to disclose with regard to this article.

**Conflict of interest** AV, MC, MM and FF have no conflicts of interest.

## References


1. Ben Amar M, Léonard L. Chapter 16: Cannabis. In: Léonard L, Ben Amar M, editors. Les Psychotropes: Pharmacologie et Toxicomanie. Montreal: Les Presses de l'Université de Montréal; 2002. p. 571–627.
2. O'Shaugnessy WB. On the preparations of the Indian hemp, or gunjah (*Cannabis indica*): their effects on the animal system in health, and their utility in the treatment of tetanus and other convulsive diseases. Transactions of Medical and Physical Society of Bengal, 1838–1840. p. 421–461.
3. Robson P. Therapeutic aspects of cannabis and CBss. BrJ Psychiatry. 2001;178:107–15.
4. Carter GT, Weijdt P, Kyashna-Tocha M, Abrams DI. Medicinal cannabis: rational guidelines for dosing. Drugs. 2004;75:464–70.
5. Fankhauser M. Chapter 4: history of cannabis in Western medicine. In: Grotenhermen F, Russo R, editors. Cannabis and CBss: pharmacology, toxicology and therapeutic potential. New York: The Haworth Integrative Healing Press; 2002. p. 37–51.
6. Ben Amar M. Cannabinoids in medicine: a review of their therapeutic potential. J Ethnopharmacol. 2006;105:1–25.
7. Mirken B. Marijuana on the state. Lancet. 2004;364:842.
8. Hoey J. Marijuana: federal smoke clears a little. CMAJ. 2001;164:1397.
9. Health Canada. Medical Use of Marihuana. Stakeholder Statistics. Ottawa: Office of Cannabis Medical Access, Health Canada; 2005. p. 2.
10. Gorter RW, Butorac M, Pulido Cobian E, van der Sluis W. Medical use of cannabis in the Netherlands. Neurology. 2005;64:917–9.
11. Health Canada CIHR. Medical Marihuana Research Program. Ottawa: Health Canada and Canadian Institutes of Health Research; 1999. p. 7.
12. Health Canada [website]. Medical use of marijuana. Ottawa: Health Canada; 2015. Available from: http://www.hc-sc.gc.ca/dhp-mps/marihuana/index-eng.php. Accessed 10 July 2015.
13. Collège des médecins du Québec. Guidelines concerning the prescription of dried cannabis for medical purposes. Montreal: Collège des médecins du Québec; 2014. Available from: http://www.cmq.org/en/MedecinsMembres/DossierMembreFormulaires/~/media/Files/Cannabis/Guidelinesprescription-cannabis.pdf?111402. Accessed 10 July 2015.
14. Izzo AA, Borrelli F, Capasso R, Di Marzo V, Mechoulam R. Non-psychotropic plant cannabinoids: new therapeutic opportunities from an ancient herb. Trends Pharmacol Sci. 2009;30:515–27.
15. McKim WA. Drugs and behavior. An introduction to behavioral pharmacology, 4th ed. Upper Saddle River: Prentice-Hall; 2000. p. 400.
16. Pertwee RG, Howlett AC, Abood ME, Alexander SP, Di Marzo V, Elphick MR, Greasley PJ, Hansen HS, Kunos G, Mackie K, Mechoulam R, Ross RA. International Union of Basic and Clinical Pharmacology. LXXIX. Cannabinoid receptors and their ligands: beyond CB1 and CB2. Pharmacol Rev. 2010;62:588–631.
17. Fezza F, Bari M, Florio R, Talamonti E, Feole M, Maccarrone M. Endocannabinoids, related compounds and their metabolic routes. Molecules. 2014;19:17078–106.
18. Viscomi MT, Oddi S, Latini L, Pasquariello N, Florenzano F, Bernardi G, Molinari M, Maccarrone M. Selective CB2 receptor agonism protects central neurons from remote axotomy-induced apoptosis through the PI3K/Akt pathway. J Neurosci. 2009;29:4564–70.
19. Ross RA. Allosterism and cannabinoid CB(1) receptors: the shape of things to come. Trends Pharmacol Sci. 2007;28:567–72.
20. Galve-Roperh I, Rueda D, Gómez del Pulgar T, Velasco G, Guzmán M. Mechanism of extracellular signal-regulated kinase activation by the CB(1) cannabinoid receptor. Mol Pharmacol. 2002;62:1385–92.
21. Sánchez C, de Ceballos ML, Gomez del Pulgar T, Rueda D, Corbacho C, Velasco G, Galve-Roperh I, Huffman JW, Ramón y Cajal S, Guzmán M. Inhibition of glioma growth in vivo by selective activation of the CB(2) cannabinoid receptor. Cancer Res. 2001;61:5784–89.
22. Schmid HHO, Schmid PC, Natarajan V. *N*-Acylated glycerophospholipids and their derivatives. Prog Lipid Res. 1990;29:1–43.
23. Jin XH, Uyama T, Wang J, Okamoto Y, Tonai T, Ueda N. cDNA cloning and characterization of human and mouse Ca(2+)-independent phosphatidylethanolamine *N*-acyltransferases. Biochim Biophys Acta. 2009;1791:32–8.
24. Okamoto Y, Morishita J, Tsuboi K, Tonai T, Ueda N. Molecular characterization of a phospholipase D generating anandamide and its congeners. J Biol Chem. 2004;279:5298–305.
25. Simon GM, Cravatt BF. Endocannabinoid biosynthesis proceeding through glycerophospho-*N*-acyl ethanolamine and a role for alpha/beta-hydrolase 4 in this pathway. J Biol Chem. 2006;281:26465–72.
26. Liu J, Wang L, Harvey-White J, Osei-Hyiaman D, Razdan R, Gong Q, Chan AC, Zhou Z, Huang BX, Kim HY, Kunos G. A biosynthetic pathway for anandamide. Proc Natl Acad Sci. 2006;103:13345–50.
27. Simon GM, Cravatt BF. Anandamide biosynthesis catalyzed by the phosphodiesterase GDE1 and detection of glycerophospho-*N*-acyl ethanolamine precursors in mouse brain. J Biol Chem. 2008;283:9341–9.
28. Cravatt BF, Giang DK, Mayfield SP, Boger DL, Lerner RA, Gilula NB. Molecular characterization of an enzyme that degrades neuromodulatory fatty-acid amides. Nature. 1996;384:83–7.
29. Wei BQ, Mikkelsen TS, McKinney MK, Lander ES, Cravatt BF. A second fatty acid amide hydrolase with variable distribution among placental mammals. J Biol Chem. 2006;281:36569–78.
30. Tsuboi K, Sun YX, Okamoto Y, Araki N, Tonai T, Ueda N. Molecular characterization of *N*-acylethanolamine-hydrolyzing acid amidase, a novel member of the choloylglycine hydrolase family with structural and functional similarity to acid ceramidase. J Biol Chem. 2005;280:11082–92.
31. Bisogno T, Howell F, Williams G, Minassi A, Cascio MG, Ligresti A, Matias I, Schiano-Moriello A, Paul P, Williams EJ, Gangadharan U, Hobbs C, Di Marzo V, Doherty P. Cloning of the first sn1-DAG lipases points to the spatial and temporal regulation of endocannabinoid signaling in the brain. J Cell Biol. 2003;163:463–8.
32. Dinh TP, Carpenter D, Leslie FM, Freund TF, Katona I, Sensi SL, Kathuria S, Piomelli D. Brain monoglyceride lipase participating in endocannabinoid inactivation. Proc Natl Acad Sci. 2002;99:10819–24.
33. Navia-Paldanius D, Savinainen JR, Laitinen JT. Biochemical and pharmacological characterization of human α/β-hydrolase domain containing 6 (ABHD6) and 12 (ABHD12). J Lipid Res. 2012;53:2413–24.
34. Ueda N, Tsuboi K, Uyama T. Metabolism of endocannabinoids and related *N*-acylethanolamines: canonical and alternative pathways. FEBS J. 2013;280:1874–94.

35. Ueda N, Tsuboi K, Uyama T. *N*-Acylethanolamine metabolism with special reference to *N*-acylethanolamine-hydrolyzing acid amidase (NAAA). Prog Lipid Res. 2010;49:299–315.
36. Rouzer CA, Marnett LJ. Endocannabinoid oxygenation by cyclooxygenases, lipoxygenases, and cytochromes P450: cross-talk between the eicosanoid and endocannabinoid signaling pathways. Chem Rev. 2011;111:5899–921.
37. Romigi A, Bari M, Placidi F, Marciani MG, Malaponti M, Torelli F, Izzi F, Prosperetti C, Zannino S, Corte F, Chiaramonte C, Maccarrone M. Cerebrospinal fluid levels of the endocannabinoid anandamide are reduced in patients with untreated newly diagnosed temporal lobe epilepsy. Epilepsia. 2010;51:768–72.
38. Soltesz I, Alger BE, Kano M, Lee SH, Lovinger DM, Ohno-Shosaku T, Watanabe M. Weeding out bad waves: towards selective cannabinoid circuit control in epilepsy. Nat Rev Neurosci. 2015;16:264–77.
39. Wallace MJ, Blair RE, Falenski KW, Martin BR, De Lorenzo RJ. The endogenous cannabinoid system regulates seizure frequency and duration in a model of temporal lobe epilepsy. J Pharmacol Exp Ther. 2003;307:129–37.
40. Fezza F, Marrone MC, Avvisati R, Di Tommaso M, Lanuti M, Rapino C, Mercuri NB, Maccarrone M, Marinelli S. Distinct modulation of the endocannabinoid system upon kainic acid-induced in vivo seizures and in vitro epileptiform bursting. Mol Cell Neurosci. 2014;62:1–9.
41. Citraro R, Russo E, Ngomba RT, Nicoletti F, Scicchitano F, Whalley BJ, Calignano A, De Sarro G. CB1 agonists, locally applied to the cortico-thalamic circuit of rats with genetic absence epilepsy, reduce epileptic manifestations. Epilepsy Res. 2013; 106:74–82.
42. Rizzo V, Ferraro G, Carletti F, Lonobile G, Cannizzaro C, Sardo P. Evidences of cannabinoids-induced modulation of paroxysmal events in an experimental model of partial epilepsy in the rat. Neurosci Lett. 2009;462:135–9.
43. Clement AB, Hawkins EG, Lichtman AH, Cravatt BF. Increased seizure susceptibility and proconvulsant activity of anandamide in mice lacking fatty acid amide hydrolase. J Neurosci. 2003;23:3916–23.
44. Deshpande LS, Blair RE, Ziobro JM, Sombati S, Martin BR, DeLorenzo RJ. Endocannabinoids block status epilepticus in cultured hippocampal neurons. Eur J Pharmacol. 2007;558:52–9.
45. Carletti F, Gambino G, Rizzo V, Ferraro G, Sardo P. Cannabinoid and nitric oxide signaling interplay in the modulation of hippocampal hyperexcitability: study on electrophysiological and behavioral models of temporal lobe epilepsy in the rat. Neuroscience. 2015;303:149–59.
46. Shubina L, Aliev R, Kitchigina V. Attenuation of kainic acid-induced status epilepticus by inhibition of endocannabinoid transport and degradation in guinea pigs. Epilepsy Res. 2015; 111:33–44.
47. Karanian DA, Karim SL, Wood JT, Williams JS, Lin S, Makriyannis A, Bahr BA. Endocannabinoid enhancement protects against kainic acid-induced seizures and associated brain damage. J Pharmacol Exp Ther. 2007;322:1059–66.
48. Marsicano G, Goodenough S, Monory K, Hermann H, Eder M, Cannich A, Azad SC, Cascio MG, Gutiérrez SO, van der Stelt M, López-Rodriguez ML, Casanova E, Schütz G, Zieglgänsberger W, Di Marzo V, Behl C. Lutz B CB1 cannabinoid receptors and on-demand defense against excitotoxicity. Science. 2003;302: 84–8.
49. Naidoo V, Karanian DA, Vadivel SK, Locklear JR, Wood JT, Nasr M, Quizon PM, Graves EE, Shukla V, Makriyannis A, Bahr BA. Equipotent inhibition of fatty acid amide hydrolase and monoacylglycerol lipase—dual targets of the endocannabinoid system to protect against seizure pathology. Neurotherapeutics. 2012;9:801–13.
50. Mechoulam R. Chapter 1: the pharmacohistory of *Cannabis sativa*. In: Mechoulan R, editor. CBss as therapeutic agents. Boca Raton: CRC Press; 1986. p. 1–19.
51. Consroe P, Wood JC, Buchsbaum H. Anticonvulsant nature of marihuana smoking. JAMA. 1975;234:306–7.
52. Ellison JM, Gelwan E, Ogletree J. Complex partial seizure symptoms affected by marijuana abuse. J Clin Psychiatry. 1990;51:439–40.
53. Grinspoon L, Bakalar JB. Marihuana. The Forbidden Medicine. New Haven: Yale University Press; 1997. p. 296.
54. Gurley RJ, Aranow R, Katz M. Medicinal marijuana: a comprehensive review. J Psychoactive Drugs. 1998;30:137–47.
55. Carlini EA, Mechoulam R, Lander N. Anticonvulsant activity of four oxygenated cannabidiol derivatives. Res Commun Chem Pathol Pharmacol. 1975;12:1–15.
56. Ames FR, Cridland S. Anticonvulsant effect of cannabidiol. S Afr Med J. 1985;69:14.
57. Cortesi M, Fusar-Poli P. Potential therapeutical effects of cannabidiol in children with pharmacoresistant epilepsy. Med Hypotheses. 2007;68:920–1.
58. Luszczki JJ, Czuczwar P, Cioczek-Czuczwar A, Czuczwar SJ. Arachidonyl- 2′-chloroethylamide, a highly selective CBs CB1 receptor agonist, enhances the anticonvulsant action of valproate in the mouse maximal electroshock- induced seizure model. Eur J Pharmacol. 2006;547:65–74.
59. Monory K, Massa F, Egertová M, Eder M, Blaudzun H, Westenbroek R, Kelsch W, Jacob W, Marsch R, Ekker M, Long J, Rubenstein JL, Goebbels S, Nave KA, During M, Klugmann M, Wölfel B, Dodt HU, Zieglgänsberger W, Wotjak CT, Mackie K, Elphick MR, Marsicano G, Lutz B. The endocannabinoid system controls key epileptogenic circuits in the hippocampus. Neuron. 2006;51:455–66.
60. Gordon E, Devinsky O. Alcohol and marijuana: effects on epilepsy and use by patients with epilepsy. Epilepsia. 2001;42: 1266–72.
61. Keeler MH, Reifler CB. Grand mal convulsions subsequent to marijuana use. Case report. Dis Nerv Syst. 1967;28:474–5.
62. Cunha JM, Carlini EA, Pereira AE, et al. Chronic administration of cannabidiol to healthy volunteers 2 and epileptic patients. Pharmacology. 1980;21:175–85.
63. Gloss D, Vickrey B. Cannabinoids for epilepsy. Cochrane Database Syst Rev. 2014;3:CD009270.
64. Davis JP, Ramsey HH. Anti-epileptic action of marijuana active substances. Fed Proc. 1949;8:167.
65. Feeney DM. Marihuana use among epileptics. JAMA. 1976;235:1105.
66. Mechoulam R, Carlini EA. Toward drugs derived from cannabis. Naturwissenschaften. 1978;65:174–9.
67. Koppel BS, Brust JC, Fife T, Bronstein J, Youssof S, Gronseth G, Gloss D. Systematic review: efficacy and safety of medical marijuana in selected neurologic disorders: report of the Guideline Development Subcommittee of the American Academy of Neurology. Neurology. 2014;82:1556–63.
68. Trembly B, Sherman M. Double-blind clinical study of cannabidiol as a secondary anticonvulsant. In: Marijuana '90 International Conference on Cannabis and Cannabinoids; 1990 July 8–11, section 2. Kolympari: International Association for CBs Medicines; 1990. p. 5.
69. Dos Santos RG, Hallak JE, Leite JP, Zuardi AW, Crippa JA. Phytocannabinoids and epilepsy. J Clin Pharm Ther. 2015;40: 135–43.
70. Geffrey AL, Pollack SF, Bruno PL, Thiele EA. Drug-drug interaction between clobazam and cannabidiol in children with refractory epilepsy. Epilepsia. 2015;56:1246–51.
71. Yamaori S, Ebisawa J, Okushima Y, et al. Potent inhibition of human cytochrome P450 3A isoforms by cannabidiol: role of

phenolic hydroxyl groups in the resorcinol moiety. Life Sci. 2011;88:730–6.
72. Jiang R, Yamaori S, Okamoto Y, et al. Cannabidiol is a potent inhibitor of the catalytic activity of cytochrome P450 2C19. Drug Metab Pharmacokinet. 2013;28:332–8.
73. Macleod J, Oakes R, Copello A, Crome I, Egger M, Hickman M, Oppenkowski T, Stokes-Lampard H, Davey Smith G. Psychological and social sequelae of cannabis and other illicit drug use by young people: a systematic review of longitudinal, general population studies. Lancet. 2004;363:1579–88.
74. Arseneault L, Cannon M, Poulton R, Murray R, Caspi A, Moffitt TE. Cannabis use in adolescence and risk for adult psychosis: longitudinal prospective study. BMJ. 2002;325:1212–3.
75. Porter BE, Jacobson C. Report of a parent survey of cannabidiol-enriched cannabis use in pediatric treatment-resistant epilepsy. Epilepsy Behav. 2013;29:574–7.
76. Friedman D, Devinsky O. Cannabinoids in the treatment of epilepsy. N Engl J Med. 2015;10(373):1048–58.
77. Devinsky O, et al. Epidiolex (Cannabidiol) in treatment resistant epilepsy, American Epilepsy Society Annual Meeting, Poster, December 7, 2015.
78. Lorentzos MS, Webster R. Cannabinoids for paediatric epilepsy: weeding out the issues. J Paediatr Child Health. 2015;51:476–7.
79. Szaflarski JP, Bebin EM. Cannabis, cannabidiol, and epilepsy–from receptors to clinical response. Epilepsy Behav. 2014;41:277–82.
80. Ng SKC, Brust JCM, Hauser WA, Susser M. Illicit drug use and the risk of new-onset seizures. Am J Epidemiol. 1990;132:47–57.
81. Lorenz R. Experiences with THC-treatment in children and adolescents. In: IACM 2nd Conference on CBss in Medicine. Koeln: International Association for Cannabis as Medicine; 2003. p. 6.
82. Gross DW, Hamm J, Ashowrth NL, Quigley D. Marijuana use and epilepsy. Neurology. 2004;62:2095–7.
83. Mortati K, Dworetzky B, Devinsky O. Marijuana: an effective treatment in partial epilepsy? A case report and review of the literature. Rev Neurol Dis. 2007;4:103–6.