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Targeted Reviews

Cannabis, cannabidiol, and epilepsy — From receptors to clinical response

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ABSTRACT

Recreational cannabis use in adults with epilepsy is widespread. The use of cannabis for medicinal purposes is also becoming more prevalent. For this purpose, various preparations of cannabis of varying strengths and content are being used. The recent changes in the legal environment have improved the availability of products with high cannabidiol (CBD) and low tetrahydrocannabinol (THC) concentrations. There is some anecdotal evidence of their potential efficacy, but the mechanisms of such action are not entirely clear. Some suspect an existence of synergy or "entourage effect" between CBD and THC. There is strong evidence that THC acts via the cannabinoid receptor CB_1. The mechanism of action of CBD is less clear but is likely polypharmacological. The scientific data support the role of the endocannabinoid system in seizure generation, maintenance, and control in animal models of epilepsy. There are clear data for the negative effects of cannabis on the developing and mature brain though these effects appear to be relatively mild in most cases. Further data from well-designed studies are needed regarding 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.

Key questions

1. What is the role of the endocannabinoid system in response to cannabis and its compounds?
2. Does the epidemiology of cannabis use support developing cannabis and its compounds for the treatment of epilepsy?
3. What are the cognitive, psychosocial, and behavioral effects of cannabis and its compounds?
4. What is the evidence for efficacy of cannabis and its compounds for the treatment of human epilepsy?

1. Introduction

Despite the recent interest, there is nothing new or revolutionary about proposing the use of cannabis or its derivatives for medicinal purposes. The oldest known written reports on cannabis use come from China (Chinese Emperor Fu Hsi, ca. 2900 BC, mentioned cannabis as a medicine that possessed *yin* and *yang*; there are also written records on cannabis from Chinese Emperor Shen Nung from 2737 BC [1,2]). The first definite scientific documentation of *Cannabis sativa* uses for medical and ritual purposes obtained through recent archeological discoveries in China comes from circa 2500 years BC [3]. Similar uses – medicinal, religious, and recreational – have been reported over the following millennia from Asia, Africa, Europe, and North/Central America [4]. Reports of cannabis use for the management of seizures came from modern neurologists including O'Shaughnessy and Gowers [5,6]. What is truly new is the hype that cannabis and its products have generated in the last few years and the numerous, mainly anecdotal, reports of its efficacy for seizure control in patients with various, mostly catastrophic, epilepsies [7].

The modern history of cannabis in the United States started in the 17th century with the decree by King James that forced all property owners in the colony to grow 100 plants of hemp for industrial/export purposes (the word hemp indicates industrial use, and the words cannabis and marijuana imply medicinal and recreational uses) [1]. Throughout the mid-to-late 19th century, cannabis growth, processing, distribution, and use were ubiquitous. During those times, cannabis was used mainly for medicinal purposes, with the US Dispensatory in 1854 listing cannabis compounds as possible remedies for neuralgia, depression, pain, muscle spasms, etc. At that time, the main supplier of "Piso's Cure for Consumption" was Hazeltine Corporation in Warren, PA. At the request of the federal government via the "Pure Food and Drug Act", the name of their product was changed to "Piso's Cure" and, later, to "Piso's Remedy" for coughs and colds. It was thought to be a remedy for all ages as indicated in Norman Rockwell's advertisement that stated "Good for young and old" with multiple suggested uses. From then until the early 20th century, the use of cannabis plant products was not regulated. The first restrictions were introduced in 1906 by the "Pure Food and Drug Act". Between 1893 and 1894, the "Indian Hemp Drugs Commission" contracted by the British government produced a detailed report on the growth, production, uses, and abuses of cannabis products. Many

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of the same issues were addressed by the Commission as are being resurrected in America as well as around the world today [8]. Despite opposition from the American Medical Association (AMA) in 1937, the US government made it illegal to possess or transfer cannabis. Recently, the political climate has changed, and many states have introduced various pieces of legislation ranging from limited approval of high-cannabidiol (CBD) products for medicinal purposes (e.g., Carly's Law in Alabama) to complete legalization of cannabis use in an attempt to circumvent the federal law (e.g., Colorado). The majority of the public is in support of some form of legalization of cannabis use with the "Ending Federal Marijuana Prohibition Act of 2013 (H.R. 499)" introduced recently. Thus, the question is, "are we going to see a resurrection of medical (and other) cannabis use in the US in the next decade"? Since the answer is most likely "yes", given the current growth in medicinal and recreational uses in Colorado after legalization [9], as physicians, we need to understand the medical aspects of cannabis use. Therefore, this targeted review poses four key questions:

1. What is the role of the endocannabinoid system in response to cannabis and its compounds?
2. Does the epidemiology of cannabis use support developing cannabis and its compounds for the treatment of epilepsy?
3. What are the cognitive, psychosocial, and behavioral effects of cannabis and its compounds?
4. What is the evidence for efficacy of cannabis and its compounds for the treatment of human epilepsy?

2. Key questions

2.1. What is the role of the endocannabinoid system in response to cannabis and its compounds?

The evidence for the importance of the endocannabinoid system (ECS) as a potential target for the development of new antiepileptic drugs comes from animal rather than human studies. Before we address the role of the ECS in response to cannabis for the management of epilepsy, we need to understand the overall role of the system. Endocannabinoid system research began with the discovery of cannabinoid receptor-1 (CB_1) in 1988 [10,11]. Since then, a system composed of cannabinoid receptors CB_1 and CB_2, their endogenous ligands N-arachidonoylethanolamine (anandamide; AEA) and 2-arachidonoylglycerol (2-AG), and various proteins that take part in their synthesis and removal has been described. Both CB_1 and CB_2 are metabotropic G-protein-coupled receptors. Their activation in response to excessive neuronal activity is dependent upon the "on-demand" synthesis of the AEA and 2-AG ligands [12,13]. The inactivation process of AEA and 2-AG is rapid, and it may include an intracellular facilitated transport mechanism, hydrolysis, or other currently unknown mechanism(s) [14]. The ECS is important for bioregulation as it takes part or is responsible for many processes such as inflammation, energy metabolism, immune regulation, memory, mood, and brain reward systems; overactivation of ECS may lead to obesity, type II diabetes, metabolic problems, and some forms of liver disease [15].

The cannabinoid receptors (CB_1 and CB_2) differ in their biological distribution and involvement. Cannabinoid type 1 receptors are predominantly located in the central (neocortex, hippocampus, basal ganglia, and cerebellum) and peripheral nervous systems with less pronounced expression in other tissues. By contrast, CB_2 receptors are located predominantly in the immune system with lesser density/representation in the central and peripheral nervous systems and in the gastrointestinal tract. The roles of these receptors are also divergent — CB_1 receptors are implicated in central food intake regulation, response to novelty and stress, addictive behavior, liver/gastrointestinal tract regulation, olfaction, and cardiovascular activity; the role of CB_2 receptors is less established, but overall, these receptors are thought to be mainly involved in immune regulation with lesser involvement in reward processing/addictive behavior and neurodegeneration.

Cannabis and its preparations such as marijuana smoke, kief, resin, oil, or tincture contain over 100 hydrocarbon compounds called "phytocannabinoids" [16]. The two most researched compounds are tetrahydrocannabinol (THC) and cannabidiol (CBD), with additional data available on several other cannabinoids including tetrahydrocannabivarin (THCV), cannabigerol, and cannabichromene [16,17].

Tetrahydrocannabinol and cannabidiol have been shown to be effective and have similar potency in the maximal electroshock model of epilepsy [18,19], but their mechanism of action was not elucidated until much later. A series of elegant experiments investigated the importance of ECS, THC, and CBD for the control of seizures in experimental models of epilepsy [20–22]. In the first set of experiments, these authors showed that both THC and CBD act as anticonvulsants in the maximal electroshock model of epilepsy and that the action of THC was mediated via the CB_1 receptor. The mechanism of action of CBD was different than that of THC and not elucidated in that study [22]. In the second set of experiments, the same authors solidified the role of the CB_1 receptor via testing the effects of AEA and AEA blockade in the same animal model of epilepsy and, again, showed strong anticonvulsant effect [21]. Finally, they showed, in the pilocarpine model of epilepsy (previously documented to resemble human focal-onset epilepsy), that THC and its analogue abolished seizures, while blocking the CB_1 receptor induced an epileptic condition similar to status epilepticus [20]. While these studies solidified the importance of the CB_1 receptor for the control of seizures, they also established that the antiepileptic mechanism of CBD is mediated via mechanism(s) different than the endocannabinoid system.

As indicated above, there is little doubt that CBD has antiepileptic properties. These properties have been studied in various animal models of epilepsy including the audiogenic [23], maximal electroshock [22,23], penicillin [24], pentylenetetrazole (PTZ) [25,26], pilocarpine [24], and transcorneal electroshock models [27] to show consistent antiepileptic effects. It is not clear how CBD exerts these properties. It has been proposed that CBD exerts its anticonvulsant effect via a polypharmacological profile and simultaneous modulation and/or prevention of neuronal hyperexcitability [24]. Multiple putative mechanisms of action of CBD have been discussed including effects on serotoninergic ($5HT_{1\alpha}$) receptors and NMDA receptors, regulation of Ca^{++} flow, enhancement of adenosine signaling, or interaction with GABA receptors (increased inhibition) [17,24,27–30]. These and other mechanisms of CBD's action may contribute to the synergistic or so-called "entourage" effects between CBD and THC and CBD's ability to reduce the psychoactive side effects of THC [16].

The current data not only support the role of the ECS in the generation and maintenance of seizures but also explain the positive effects of THC on seizure control in animal models of epilepsy. Further, the data support the notion that CBD is an effective and potentially potent anticonvulsant in animal models of epilepsy and that, through synergism with THC, it may exert direct and indirect effects on seizure control. Whether these or other effects will be observed in human epilepsy remains to be seen, but the results of animal studies appear to be in agreement with some of the anecdotal human data [28,31].

2.2. Does the epidemiology of cannabis use support developing cannabis and its compounds for the treatment of epilepsy?

According to the World Health Organization, approximately 2.5% (147 million) of the adult population worldwide uses cannabis for recreational or other reasons [32]. When used for medicinal purposes, cannabis is considered a complementary and alternative medicine (CAM) as it is not a mainstream or conventional therapy [33]. Approximately 40% of adults with epilepsy use or have used CAMs either because of lack of efficacy of the standard therapies, because of their side effects, or for other reasons. While the majority of CAMs are nonpharmacological (e.g., meditation, relaxation techniques, or stress

management), the use of botanicals is of particular concern [33]. One of the botanicals used by patients with epilepsy is cannabis or, more recently, its other preparations including oil. Since its use is widespread in patients with epilepsy, it is of interest whether epidemiologic studies can provide insight into the effects of cannabis on seizure threshold in individuals who do not have epilepsy but use cannabis and in patients with seizures who use cannabis for recreational purposes. Some recent publications provide insights for such uses.

In a recent informal interview of >215 patients with active epilepsy who have used recreational cannabis intermittently or regularly, the investigators determined that more than 90% of them failed to appreciate any benefit of cannabis for seizure control [5]. Only 7% believed that their seizures were better, and the rest felt that their seizures were worse with the use of cannabis. These authors also reported anecdotally that generalized epilepsies, especially juvenile myoclonic epilepsy, may get worse with the recreational use of cannabis [5]. This is in agreement with the single-case study that reported worsening of epilepsy in a patient with generalized seizures after use of cannabis [34] and a report of negative effects of cannabis products on an EEG in a patient with otherwise controlled genetic generalized epilepsy [35]. In a 1976 study, 29% of patients with epilepsy reported self-medication with cannabis for the treatment of epilepsy — of those, one reported that cannabis caused seizures, and only one indicated improvement with cannabis use [36]. In a more recent Canadian study, 28/165 patients with epilepsy were active users of cannabis [37]. Of the cannabis users, 68% reported improvements in seizure severity and 54% in seizure frequency. Further, in this study, the use of cannabis was associated with a longer duration of epilepsy and an increased seizure frequency. This likely reflects the notion that patients with more frequent and difficult to control medical conditions are more likely to resort to CAMs in order to improve their health [38]. Even more recently, Hamerle et al. reported on 310 patients with epilepsy, of whom 63 (20.3%) reported cannabis use after the diagnosis of epilepsy was made [39]. Of these 63 patients, 53 reported no effect of cannabis use on seizure frequency, 7 reported an increase in seizure frequency, and 3 reported improvement.

Finally, one of the early epidemiologic case–control studies of illicit drug use in the US in patients with new-onset seizures included cannabis [40]. While the prevalence of cannabis use in patients with new-onset seizures was lower than that in controls, these differences were not significant. With careful analyses, these authors were able to show that cannabis use in men (but not in women) was protective against new-onset unprovoked seizures and protective against new-onset provoked seizures when used within 90 days of seizure presentation; this effect was only present in sole cannabis users. This protective effect was not observed in multidrug users, such as those combining heroin with cannabis [40].

In summary, there is some evidence that cannabis may be protecting patients from new-onset seizures and that it may help with seizure control in patients with already established epilepsies, but, overall, the epidemiological data in support of this notion are relatively weak and, sometimes, contradictory. Further evidence from well-designed retrospective and prospective studies investigating various cannabis preparations, strengths, and compositions (THC/CBD proportion) is needed.

2.3. What are the cognitive, psychosocial, and behavioral effects of cannabis and its compounds?

The cognitive, psychosocial, and behavioral side effects of cannabis use (smoking or other uses) are usually mild and transient. Further, the effects of THC and CBD are opposite, with THC being the psychoactive compound and CBD being void of such properties and possibly able to offset some of the psychoactive effects of THC [41–43]. These effects may be dependent on dose and/or THC/CBD content [42–44]. The effects of cannabis use, similar to other drugs, may be divided into acute/subacute and chronic [45] as well as withdrawal, with the understanding that the occurrence of such effects is dependent, in part, on the THC/CBD content, the mode of intake (smoking, oral intake), and the age of initiation of use. Some of these effects are unlikely to be present in pharmaceutical preparations of cannabis that contain small amounts of THC and high CBD content and are grossly devoid of various contaminants.

2.3.1. Acute and subacute effects

The effects of inhaled cannabis smoke are perceptible within seconds to minutes, while the effects of cannabis preparations taken orally are usually delayed for minutes to hours. Because of its high lipid solubility, the peak concentration of THC is reached within days of single use and, with the half-life of ~7 days, its elimination takes up to 30 days; the distribution of THC in tissues follows different phases, with a rapid peak in the blood and then in the brain and a peak in fat tissue delayed by 5–7 days [41]. Overall, cannabis used for recreational purposes may cause several psychoactive as well as constitutional symptoms. The psychoactive symptoms include relaxation, euphoria ("high"), anxiety, jocularity, and increased sociability. More severe side effects of cannabis use may include depersonalization, changes in perception of time, and decreased memory functions and abstract thinking. Other cognitive impairments and physical symptoms of sympathetic instability include conjunctival injection, hypotension or hypertension, tachycardia, and appetite changes; psychomotor performance is typically affected with effects similar to those of alcohol [15]. With increasing doses, confusion, visual and/or auditory hallucinations, and paranoia may appear. Finally, cannabis has been reported as the potential etiology or precipitating factor in reversible cerebral vasoconstriction syndrome [46]. One case compilation reported 58 cannabis-related ischemic and one hemorrhagic stroke in patients within 30 min of cannabis use [47]. These data suggest the possibility of cannabis causing ischemic changes in the brain via a vasospastic mechanism.

2.3.2. Chronic effects

After long-standing chronic use of cannabis, even when abstinence is achieved, persistent symptoms of use may be observed [2,48]. These include the risks of subtle attention and memory impairment. There also is dependence characterized by the inability to abstain from cannabis use. There are several potential physical chronic effects related to smoking cannabis similar to tobacco use that comprise chronic bronchitis/emphysema, neoplastic changes including oral and lung cancer, and cardiovascular effects [2]. An example of tangible chronic results of cannabis use is the negative effect on axons and their connectivity [49]. Further, one functional MRI (fMRI) study that compared teenagers who were or were not exposed to cannabis during prenatal development showed that as the amount of prenatal cannabis exposure increased, there were significant changes in the levels of brain activity in multiple regions, suggesting that prenatal cannabis exposure alters neural functioning during visuospatial working memory processing in young adulthood [50]. Another fMRI study provided additional evidence for the negative effects of chronic cannabis use on the brain and showed altered participation of frontal and limbic systems in emotion processing when compared with healthy controls [51]. Finally, chronic immunosuppression, endocrine, and reproductive effects have also been observed [2,41].

2.3.3. Age-related effects on cognition

There is growing evidence that recreational cannabis use has short- and long-term effects on the developing and mature brain [52]. A study that compared the effects of prenatal tobacco with cannabis exposure on cognitive performance in adolescents showed that prenatal cigarette exposure was associated with lowered IQ, poorer impulse control, and poorer performance on visuoperceptual tests; prenatal cannabis exposure negatively impacted the use of these skills in problem-solving situations requiring visual integration, analytical skills, and sustained attention [53]. An fMRI study mentioned previously [50] indicated that prenatal exposure to cannabis is associated with altered neural networks for visuospatial memory. Another study assessed the IQ in

adolescents before, during, and after cannabis use to show that current use was significantly correlated in a dose-related fashion with a decline in IQ over the ages studied with IQ decreasing by 4.1 points in current heavy users compared with gains in IQ points for light current users, former users, and nonusers [54]. A recent MRI study showed negative effects on diffusion tensor imaging measures that were dependent on the age at which cannabis use commenced [49]. The negative effects of cannabis exposure and use on prenatal and early postnatal development are likely observed because of the importance of the ECS for the development of the central nervous system and the effects that cannabis products exert on the system [55].

2.3.4. Withdrawal

Withdrawal from cannabis is observed frequently, and the symptoms of withdrawal may be similar to those of acute alcohol withdrawal including tremulousness, insomnia, gastrointestinal problems, and delirium. In a study of 469 adult cannabis smokers who had made an attempt to quit while not in a controlled environment, ~42% experienced withdrawal symptoms [56]. The number of the withdrawal symptoms was associated with the frequency of cannabis use; the withdrawal symptoms included craving for cannabis products, sleep disturbances, changes in appetite, verbal/physical aggression, moodiness, and various physical symptoms. Again, these symptoms are unlikely to be present in the users of pharmaceutical preparations of cannabis with high CBD and low THC content.

Finally, only one study addressed the combined side effects of high CBD and low THC preparation of cannabis [57]. In a press release, GW Pharma provided safety data on 62 patients who received Epidiolex as part of their compassionate use study (>97% CBD; <3% THC) [57]. The most frequent side effects reported were somnolence, fatigue, diarrhea, and changes in appetite, with ~80% of patients reporting at least one side effect. None of the patients withdrew from the study because of the side effects. Serious adverse events occurred in 7 patients including one death due to SUDEP. None of these serious adverse events were deemed related to the treatment with CBD/THC combination by the investigators.

2.4. What is the evidence for efficacy of cannabis and its compounds for the treatment of human epilepsy?

Substantial progress has been made in our understanding of the effects of cannabinoids on various animal models of epilepsy [15,28]. There are also many anecdotal (single case) reports of cannabis efficacy for the treatment of epilepsy including the highly publicized case of Charlotte Figi [6,58,59], but what is the available body of evidence for the use of cannabinoids for the treatment of human epilepsy?

Let us start with some more anecdotal evidence (Table 1). In one study, five institutionalized children with grand mal epilepsy were treated with isomeric homologues of THC and showed some response to either of the two analogues [62]. While these authors suggested the need for further trials of these compounds, it is unclear whether such attempts have been made. Recently, a study reported on the use of cannabinoids in children with treatment-refractory epilepsy [65]. In this study, the authors surveyed an internet-based (Facebook) group of approximately 150 parents of children with various types of medication-resistant epilepsy including Dravet and Lennox–Gastaut syndromes. Nineteen of the parents responded by providing diagnostic and treatment data. The dosage of cannabidiol (CBD) was 1–28 mg/kg/day with a small percentage of tetrahydrocannabinol (THC) intermixed; in most cases, the THC content was less than 10%. Three of the children became seizure-free, while another 10 had 80% or more improvement in seizure control. These changes were associated with a mixture of positive (better mood, increased alertness, better sleep, and decreased self-stimulation) and negative (drowsiness, fatigue, and decreased appetite) side effects.

Several previous studies (Table 1), some of them randomized and blinded, provided data on a total of 105 patients (some of these patients received placebo). Ames and Cridland reported in a "letter to the editor" that they randomized 12 institutionalized patients with poorly controlled epilepsy to receive CBD 100 mg twice daily or placebo [60]. They planned a cross-over study, but they ran out of supply of CBD and were not able to complete the research. They did not observe any differences between treatment groups. Cunha et al. conducted a two-phase study [61]. In phase I, healthy volunteers received 3 mg/kg/day of CBD for 30 days and were compared with healthy controls who received identical-appearing capsules; no differences between groups in adverse events were observed. In phase II, 15 adults with focal-onset epilepsies were randomized to 200–300 mg/day of CBD or placebo. Of the patients who received CBD, 7/8 reported improvement in seizures (none were seizure-free); of the patients who received placebo, 7 remained unchanged (one crossed over to the treatment group after one month) and one patient who received placebo reported improvement [61]. Trembly and Sherman conducted a double-blind, cross-over, placebo-controlled trial in 12 adults with incompletely controlled epilepsy [66]. While the published abstract indicated that there were no differences between placebo and active treatment (CBD 100 mg three times per day) in standard laboratory work or neuropsychological/mood testing, a later book chapter reported on the lack of efficacy for seizure management

Table 1
Compilation of efficacy data from studies of CBD or THC that included more than one patient. A total of 105 children and adults were reported (some received placebo) with 42/69 (61%) treated with CBD and/or THC reported as improved.

Author (reference)	Number of participants	Age of participants	Diagnosis	Preparation	Dosage	Response
Ames and Cridland [60]	12[a]	Adults	Epilepsy and MR	CBD capsules	Up to 600 mg/day	–
Cunha et al. [61]	15[b]	Adults	Focal-onset epilepsy	CBD capsules	~1.5 mg/kg/day	4/8 CBD and 1/8 placebo improved
Davis and Ramsey [62]	5	Children	Epilepsy and MR	THC isomers	Up to 4 mg/day	2/5 improved and 1/5 worsened
GW Pharma [57]	27	Children and adults	Epilepsy	CBD (Epidiolex)	–	13/27 improved 50% or more
Lorenz [63]	6[c]	Children	Epilepsy and MR	THC	Up to 0.12 mg/kg/day	4/6 improved
Mechoulam and Carlini [64]	9[d]	Adults	Temporal lobe epilepsy	CBD	200 mg/day	3/4 CBD and 0/5 placebo improved
Porter and Jacobson [65]	19[e]	Children	Catastrophic epilepsies	CBD/THC	CBD up to 28 mg/kg/day THC up to 0.8 mg/kg/day	16/19 improved
Trembly and Sherman [66]	12[f]	Adults	Epilepsy	CBD	300 mg/day	–

MR — mental retardation.
– Not reported or not available.
[a] Six received placebo, and six received CBD (randomized and blinded study).
[b] Seven in the CBD group and eight in the placebo group; one from the placebo group transitioned after 1 month to the treatment group (total treated = 8).
[c] Case series of 8 children but only 6 with seizures/epilepsy.
[d] Four patients received CBD, and five patients received placebo (randomized and blinded study).
[e] Facebook-based group of parents who reported on their children.
[f] Blinded cross-over study.

[31,66]. Mechoulam and Carlini treated 4 patients with CBD (200 mg daily) and 5 patients with placebo and showed that 3/4 of patients treated with CBD improved while none of the patients who received placebo improved [64]. Finally, the data provided in a press release by GW Pharma [46] provide some evidence for efficacy of the low-THC/high-CBD product. Of the 27 patients (Table 1) enrolled in the study, 48% reported at least 50% seizure reduction, and 15% were seizure-free at the end of 12 weeks of treatment. There are numerous difficulties with the available data as the written reports provide very limited information on how the studies were conducted, how patients were randomized, how groups were compared, what were the doses of other concomitant antiepileptic drugs (AEDs), etc. Thus, given the quality of the available data, no reliable conclusions can be drawn from the available studies.

Nevertheless, the available studies provide some important safety data as very few of the included subjects, whether in the internet study by Porter and Jacobson or in the other studies presented above, suffered from severe adverse events. One of the reasons for this may be the fact that the majority of the studies used low-dose CBD (e.g., 200–600 mg/day; Table 1). In addition, since improvements were noted in some of the above studies (42/69; 61% patients treated with cannabis preparations who had outcome data available), further development of cannabis for the treatment of poorly controlled epilepsy may be warranted. Thus, trials of cannabis-derived products for the treatment of poorly controlled seizures in patients with Dravet syndrome (NCT02091375; NCT02091206) are being initiated (www.clinicaltrials.gov; accessed: 8/14/14), and studies of other epilepsies are being developed.

3. Summary

Cannabis use is prevalent in patients with epilepsy, and various preparations of cannabis are currently in use. With the legalization of cannabis in some states in the U.S., there is increased availability of high-CBD/low-THC products for the treatment of epilepsies associated with poorly controlled seizures including catastrophic epilepsies of childhood. There is some anecdotal evidence of the potential efficacy of cannabis in treating epilepsy. Based on this evidence, there has been an increased effort on the part of patients with epilepsy, their caregivers, growers, and legislators to legalize various forms of cannabis. As these efforts continue and the availability of cannabis preparations grows, the professional epilepsy community is at the crossroads — as there is increasing push to legalize "medical marijuana", there is also increased concern about its efficacy, the relative efficacy of various preparations, the availability of medication-grade preparations, the dosing, as well as the potential short- and long-term side effects including the negative effects on prenatal and childhood development. While we are cognizant of these effects, it is incumbent upon us to design and conduct studies that will address these issues. Such efforts are underway under the leadership of industry and major academic centers. If cannabis as a treatment for epilepsy fulfills its promise, will we, in the future, prescribe "it" for epilepsy treatment? Only well-designed studies can answer this question.

Disclosure

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Key questions (answered)

1. **What is the role of the endocannabinoid system in response to cannabis and its compounds?**

   There is substantial evidence in support of THC as a substrate for cannabinoid receptors and the mediation of its effect via ECS. The mechanism of action of CBD is less clear and unlikely directly mediated via the cannabinoid receptors. There is potential synergy ("entourage effect") between THC and CBD, and it is clear that some of the negative effects of THC may be offset or eliminated by CBD, further supporting the notion of different mechanisms of action of these compounds.
2. **Does the epidemiology of cannabis use support developing cannabis and its compounds for the treatment of epilepsy?**

   Some data are indicating that cannabis may be protecting patients from new-onset seizures and that it may help with seizure control in patients with already established epilepsies, but, overall, the epidemiological data in support of this notion are relatively weak and, sometimes, contradictory.
3. **What are the cognitive, psychosocial, and behavioral effects of cannabis and its compounds?**

   The evidence for negative and variable effects of cannabis products on cognition is irrefutable. Dose-related and age-of-use-initiation-related effects have been observed. It is not clear whether similar effects will be observed with preparations that have high CBD/low THC content, but this appears to be unlikely as CBD may be able to offset the negative psychosocial and cognitive effects of THC.
4. **What is the evidence for efficacy of cannabis and its compounds for the treatment of human epilepsy?**

   To summarize, the evidence is weak at best (Table 1). There is a lack of well-designed, controlled, longitudinal and double-blind studies. Currently, such studies are being developed, proposed, or conducted.

References

[1] Deitch R. Hemp — American history revisited. NYC: Alegora Publishing; 2003.
[2] Gold M. Marijuana. NYC: Plenum Publishing Corporation; 1989.
[3] Jiang HE, Li X, Zhao YX, Ferguson DK, Hueber F, Bera S, et al. A new insight into *Cannabis sativa* (Cannabaceae) utilization from 2500-year-old Yanghai Tombs, Xinjiang, China. J Ethnopharmacol 2006;108(3):414–22.
[4] Cohen S. In: Petersen R, editor. Therapeutic aspects. , Marihuana research findings: 1996 Rockville, Maryland: NIDA; 1977. p. 194–214.
[5] Gordon E, Devinsky O. Alcohol and marijuana: effects on epilepsy and use by patients with epilepsy. Epilepsia 2001;42(10):1266–72.
[6] O'Shaughnessy W. On the preparations of Indian hemp, or gunjah. Provincial Med J 1843;123:363–9.
[7] Mathern G, Nehlig A, Sperling M. Cannabidiol and medical marijuana for the treatment of epilepsy. Epilepsia 2014;55(6):781–2.
[8] Kaplan J. Marijuana (Report of Indian Hemp Commission 1893–1894). Silver Spring, Maryland: Thos. Jefferson Publishing Company; 1969.
[9] Annas GJ. Medical marijuana, physicians, and state law. N Engl J Med 2014;371:983–5.
[10] Johnson M, Devane W, Howlett A, Melvin L, Milne G. Structural studies leading to the discovery of a cannabinoid binding site. NIDA Res Monogr 1988;90:129–35.
[11] Devane WA, Dysarz III FA, Johnson MR, Melvin LS, Howlett AC. Determination and characterization of a cannabinoid receptor in rat brain. Mol Pharmacol 1988;34(5):605–13.
[12] Hofmann ME, Frazier CJ. Marijuana, endocannabinoids, and epilepsy: potential and challenges for improved therapeutic intervention. Exp Neurol 2013;244:43–50.
[13] Lutz B. On-demand activation of the endocannabinoid system in the control of neuronal excitability and epileptiform seizures. Biochem Pharmacol 2004;68(9):1691–8.

[14] De Petrocellis L, Cascio MG, Di Marzo V. The endocannabinoid system: a general view and latest additions. Br J Pharmacol 2004;141(5):765–74.
[15] Robson PJ. Therapeutic potential of cannabinoid medicines. Drug Test Anal 2014; 6(1–2):24–30.
[16] Russo EB. Taming THC: potential cannabis synergy and phytocannabinoid–terpenoid entourage effects. Br J Pharmacol 2011;163(7):1344–64.
[17] Pertwee RG. The diverse CB1 and CB2 receptor pharmacology of three plant cannabinoids: delta9-tetrahydrocannabinol, cannabidiol and delta9-tetrahydrocannabivarin. Br J Pharmacol 2008;153(2):199–215.
[18] Karler R, Cely W, Turkanis SA. The anticonvulsant activity of cannabidiol and cannabinol. Life Sci 1973;13(11):1527–31.
[19] Karler R, Cely W, Turkanis SA. Anticonvulsant properties of delta 9-tetrahydrocannabinol and other cannabinoids. Life Sci 1974;15(5):931–47.
[20] Wallace MJ, Blair RE, Falenski KW, Martin BR, DeLorenzo RJ. The endogenous cannabinoid system regulates seizure frequency and duration in a model of temporal lobe epilepsy. J Pharmacol Exp Ther 2003;307(1):129–37.
[21] Wallace MJ, Martin BR, DeLorenzo RJ. Evidence for a physiological role of endocannabinoids in the modulation of seizure threshold and severity. Eur J Pharmacol 2002;452(3):295–301.
[22] Wallace MJ, Wiley JL, Martin BR, DeLorenzo RJ. Assessment of the role of CB1 receptors in cannabinoid anticonvulsant effects. Eur J Pharmacol 2001;428(1):51–7.
[23] Consroe P, Wolkin A. Cannabidiol — antiepileptic drug comparisons and interactions in experimentally induced seizures in rats. J Pharmacol Exp Ther 1977;201(1): 26–32.
[24] Jones NA, Glyn SE, Akiyama S, Hill TD, Hill AJ, Weston SE, et al. Cannabidiol exerts anti-convulsant effects in animal models of temporal lobe and partial seizures. Seizure 2012;21(5):344–52.
[25] Jones NA, Hill AJ, Smith I, Bevan SA, Williams CM, Whalley BJ, et al. Cannabidiol displays antiepileptiform and antiseizure properties in vitro and in vivo. J Pharmacol Exp Ther 2010;332(2):569–77.
[26] Shirazi-zand Z, Ahmad-Molaei L, Motamedi F, Naderi N. The role of potassium BK channels in anticonvulsant effect of cannabidiol in pentylenetetrazole and maximal electroshock models of seizure in mice. Epilepsy Behav 2013;28(1):1–7.
[27] Consroe P, Benedito MA, Leite JR, Carlini EA, Mechoulam R. Effects of cannabidiol on behavioral seizures caused by convulsant drugs or current in mice. Eur J Pharmacol 1982;83(3–4):293–8.
[28] Devinsky O, Cilio MR, Cross H, Fernandez-Ruiz J, French J, Hill C, et al. Cannabidiol: pharmacology and potential therapeutic role in epilepsy and other neuropsychiatric disorders. Epilepsia 2014;55(6):791–802.
[29] Mechoulam R, Peters M, Murillo-Rodriguez E, Hanus LO. Cannabidiol — recent advances. Chem Biodivers 2007;4(8):1678–92.
[30] Ryan D, Drysdale AJ, Lafourcade C, Pertwee RG, Platt B. Cannabidiol targets mitochondria to regulate intracellular Ca^{2+} levels. J Neurosci 2009;29(7):2053–63.
[31] Gloss D, Vickrey B. Cannabinoids for epilepsy. Cochrane Database Syst Rev 2014;3: CD009270.
[32] Gloss D. Management of substance abuse. Cannabis: World Health Organization; 2014 [cited 2014 August 13].
[33] Sirven JI, Drazkowski JF, Zimmerman RS, Bortz JJ, Shulman DL, Macleish M. Complementary/alternative medicine for epilepsy in Arizona. Neurology 2003; 61(4):576–7.
[34] Keeler MH, Reifler CB. Grand mal convulsions subsequent to marijuana use. Case report. Dis Nerv Syst 1967;28(7 Pt 1):474–5.
[35] Perez-Reyes M, Wingfield M. Letter: cannabidiol and electroencephalographic epileptic activity. JAMA 1974;230(12):1635.
[36] Feeney DM. The marijuana window: a theory of cannabis use. Behav Biol 1976; 18(4):455–71.
[37] Gross DW, Hamm J, Ashworth NL, Quigley D. Marijuana use and epilepsy: prevalence in patients of a tertiary care epilepsy center. Neurology 2004;62(11):2095–7.
[38] Eisenberg DM, Kessler RC, Foster C, Norlock FE, Calkins DR, Delbanco TL. Unconventional medicine in the United States. Prevalence, costs, and patterns of use. N Engl J Med 1993;328(4):246–52.
[39] Hamerle M, Ghaeni L, Kowski A, Weissinger F, Holtkamp M. Cannabis and other illicit drug use in epilepsy patients. Eur J Neurol 2014;21(1):167–70.
[40] Ng SK, Brust JC, Hauser WA, Susser M. Illicit drug use and the risk of new-onset seizures. Am J Epidemiol 1990;132(1):47–57.
[41] Ashton CH. Pharmacology and effects of cannabis: a brief review. Br J Psychiatry 2001;178:101–6.
[42] Morgan CJ, Freeman TP, Schafer GL, Curran HV. Cannabidiol attenuates the appetitive effects of delta 9-tetrahydrocannabinol in humans smoking their chosen cannabis. Neuropsychopharmacology 2010;35(9):1879–85.
[43] Morgan CJ, Schafer G, Freeman TP, Curran HV. Impact of cannabidiol on the acute memory and psychotomimetic effects of smoked cannabis: naturalistic study: naturalistic study [corrected]. Br J Psychiatry 2010;197(4):285–90.
[44] Bolla KI, Brown K, Eldreth D, Tate K, Cadet JL. Dose-related neurocognitive effects of marijuana use. Neurology 2002;59(9):1337–43.
[45] Nutt D, King LA, Saulsbury W, Blakemore C. Development of a rational scale to assess the harm of drugs of potential misuse. Lancet 2007;369(9566):1047–53.
[46] Ducros A, Boukobza M, Porcher R, Sarov M, Valade D, Bousser MG. The clinical and radiological spectrum of reversible cerebral vasoconstriction syndrome. A prospective series of 67 patients. Brain 2007;130(Pt 12):3091–101.
[47] Wolff V, Armspach JP, Lauer V, Rouyer O, Bataillard M, Marescaux C, et al. Cannabis-related stroke: myth or reality? Stroke 2013;44(2):558–63.
[48] Hall W, Solowij N. Adverse effects of cannabis. Lancet 1998;352(9140):1611–6.
[49] Zalesky A, Solowij N, Yucel M, Lubman DI, Takagi M, Harding IH, et al. Effect of long-term cannabis use on axonal fibre connectivity. Brain 2012;135(Pt 7):2245–55.
[50] Smith AM, Fried PA, Hogan MJ, Cameron I. Effects of prenatal marijuana on visuospatial working memory: an fMRI study in young adults. Neurotoxicol Teratol 2006; 28(2):286–95.
[51] Gruber SA, Rogowska J, Yurgelun-Todd DA. Altered affective response in marijuana smokers: an fMRI study. Drug Alcohol Depend 2009;105(1–2):139–53.
[52] Batalla A, Bhattacharyya S, Yucel M, Fusar-Poli P, Crippa JA, Nogue S, et al. Structural and functional imaging studies in chronic cannabis users: a systematic review of adolescent and adult findings. PLoS One 2013;8(2):e55821.
[53] Fried PA. Adolescents prenatally exposed to marijuana: examination of facets of complex behaviors and comparisons with the influence of in utero cigarettes. J Clin Pharmacol 2002;42(11 Suppl):97S–102S.
[54] Fried P, Watkinson B, James D, Gray R. Current and former marijuana use: preliminary findings of a longitudinal study of effects on IQ in young adults. CMAJ 2002; 166(7):887–91.
[55] Harkany T, Guzman M, Galve-Roperh I, Berghuis P, Devi LA, Mackie K. The emerging functions of endocannabinoid signaling during CNS development. Trends Pharmacol Sci 2007;28(2):83–92.
[56] Levin KH, Copersino ML, Heishman SJ, Liu F, Kelly DL, Boggs DL, et al. Cannabis withdrawal symptoms in non-treatment-seeking adult cannabis smokers. Drug Alcohol Depend 2010;111(1–2):120–7.
[57] GW Pharmaceuticals announces physician reports of Epidiolex(R) treatment effect in children and young adults with treatment-resistant epilepsy from Physician-Led Expanded Access Treatment Program [press release] http://ir.gwpharm.com/releasedetail.cfm?ReleaseID=855006; 2014.
[58] Consroe PF, Wood GC, Buchsbaum H. Anticonvulsant nature of marihuana smoking. JAMA 1975;234(3):306–7.
[59] Maa E, Figi P. The case for medical marijuana in epilepsy. Epilepsia 2014;55(6): 783–6.
[60] Ames FR, Cridland S. Anticonvulsant effect of cannabidiol. S Afr Med J 1986;69(1): 14.
[61] Cunha JM, Carlini EA, Pereira AE, Ramos OL, Pimentel C, Gagliardi R, et al. Chronic administration of cannabidiol to healthy volunteers and epileptic patients. Pharmacology 1980;21(3):175–85.
[62] Davis J, Ramsey H, editors. Anti-epileptic action of marijuana-active substances, Federation of American Society for Experimental Biology; 1949.
[63] Lorenz R. On the application of cannabis in paediatrics and epileptology. Neuro Endocrinol Lett 2004;25(1–2):40–4.
[64] Mechoulam R, Carlini EA. Toward drugs derived from cannabis. Naturwissenschaften 1978;65(4):174–9.
[65] Porter BE, Jacobson C. Report of a parent survey of cannabidiol-enriched cannabis use in pediatric treatment-resistant epilepsy. Epilepsy Behav 2013;29(3):574–7.
[66] Trembly B, Sherman M, editors. Double blind clinical study of cannabidiol as a secondary anticonvulsant. Marijuana '90 International Conference on Cannabis and Cannabinoids, Kolympari, Crete: International Association of Cannabinoid Medicines; 1990.