

REVIEW ARTICLE

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Cannabinoids in the Treatment of Epilepsy

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DESPITE THE AVAILABILITY OF MORE THAN 20 DIFFERENT ANTISEIZURE drugs and the provision of appropriate medical therapy, 30% of people with epilepsy continue to have seizures.^{1,2} The approval of many new anti-seizure drugs during the past two decades, including several with novel mechanisms of action, has not substantially reduced the proportion of patients with medically refractory disease.¹ The safety and side-effect profile of antiseizure drugs has improved, but side effects related to the central nervous system are common and affect quality of life.³ Patients need new treatments that control seizures and have fewer side effects. This treatment gap has led patients and families to seek alternative treatments. Cannabis-based treatment for epilepsy has recently received prominent attention in the lay press⁴ and in social media, with reports of dramatic improvements in seizure control in children with severe epilepsy. In response, many states have legalized cannabis for the treatment of epilepsy (and other medical conditions) in children and adults (for a list of medical marijuana laws according to state, see www.ncsl.org/research/health/state-medical-marijuana-laws.aspx).

Cannabis has been used medicinally for millennia and was used in the treatment of epilepsy as early as 1800 B.C.E. in Sumeria.⁵ Victorian-era neurologists used Indian hemp to treat epilepsy and reported dramatic success.^{5,6} The use of cannabis therapy for the treatment of epilepsy diminished with the introduction of phenobarbital (1912) and phenytoin (1937) and the passage of the Marijuana Tax Act (1937). The discovery of an endogenous cannabinoid-signaling system in the 1990s⁷ rekindled interest in therapies derived from constituents of cannabis for nervous system disorders such as epilepsy (see ClinicalTrials.gov numbers, NCT02091375, NCT02224690, NCT02324673, NCT02318537, and NCT02318563). This review addresses the current preclinical and clinical data that suggest that compounds found in cannabis have efficacy against seizures. The pharmacokinetic properties of cannabinoids and related safety and regulatory issues that may affect clinical use are also discussed, as are the distinct challenges of conducting rigorous clinical trials of these compounds.

More than 545 distinct compounds have been isolated from cannabis species; the most abundant are the cannabinoids, a family of molecules that have a 21-carbon terpenophenolic skeleton and includes numerous metabolites.⁸ The best studied of these cannabinoids (termed “phytocannabinoids” if derived from the plant) are Δ^9 -tetrahydrocannabinol (Δ^9 -THC) and cannabidiol and their metabolites. (See Fig. 1 for the structure of Δ^9 -THC, cannabidiol, and one other cannabinoid, cannabidivarin, as well as their targets in the central nervous system, and their actions.) Most of the psychoactive effects of cannabis are mediated by Δ^9 -THC. Many of the noncannabinoid molecules in cannabis plants may have biologic activity. This review focuses on cannabinoids, since other cannabis-derived compounds have been less well studied.

Cannabinoid	Structure	Central Nervous System Targets	Actions
Δ^9 -Tetrahydrocannabinol		CB ₁ R CB ₂ R (microglia) TRPA1 TRPV2 TRPM8 $\alpha_7\beta$ GlyR 5-HT _{3A} R PPAR- γ GPR18 GPR55	Partial agonist Partial agonist Agonist Agonist Antagonist Enhancer Antagonist Activator Agonist Agonist
Cannabidiol		CB ₁ R CB ₂ R (microglia) GPR55 TPRA1 TRPV1-3 TRPV4 TRPM8 5-HT _{1A} R 5-HT _{3A} R α_3 GlyR PPAR- γ Ca _v 3 ion channel Adenosine reuptake	Antagonist Antagonist Antagonist Agonist Agonist Agonist Antagonist Enhancer Antagonist Enhancer Activator Inhibitor Inhibitor
Cannabidivarin		TRPA1 TRPM8 TRPV4 TRPV1-3 DAGL- α	Agonist Antagonist Agonist Agonist Inhibitor

Figure 1. Selected Pharmacologic Features of Cannabinoids Showing Antiseizure Effects in Preclinical Models.

The exact targets that mediate the antiseizure effects of cannabinoids are unknown. Several cannabinoids are known to bind to multiple targets in the central nervous system and exert effects at nanomolar or low micromolar concentrations. These targets include transient receptor potential cation channel, subfamily V, members 1, 2, and 3 (TRPV1-3), glycine receptor α (α_3 GlyR), peroxisome proliferator-activated receptor gamma (PPAR- γ), calcium-gated ion channel (Ca_v3 ion channel), and diacylglycerol lipase α (DAGL- α). There are conflicting results from multiple studies on the effects of Δ^9 -tetrahydrocannabinol on G-protein-coupled receptor (GPR) 55. CB₁R and CB₂R denote cannabinoid receptor types 1 and 2, 5-HT the serotonin receptors 5-hydroxytryptophan type 1A and 3A, TRPA transient receptor potential cation channel, subfamily A, and TRPM transient receptor potential cation channel, subfamily M. Adapted from Cascio and Pertwee⁹ and Pertwee and Cascio.¹⁰

CONTROL OF NEURONAL EXCITABILITY

The major cannabinoid receptor in the central nervous system is cannabinoid receptor 1 (CB₁R), a presynaptic, G-protein-coupled receptor that activates voltage-gated calcium channels and enhances potassium-channel conduction in presynaptic terminals. The cloning of CB₁R, the confirmation that Δ^9 -THC binds CB₁R, and the discovery of two endogenous ligands — 2-arachidonoylglycerol (2-AG) and anandamide — that bind CB₁R⁷ has stimulated investigations intend-

ed to elucidate the role of the endocannabinoids both in normal brain function and in disease states. CB₁R is activated by the activity-dependent synthesis of 2-AG and is involved in the retrograde control of synaptic transmission. Anandamide can also affect excitability in neuronal networks by activating the transient receptor potential (TRP) cation channel, subfamily V, member 1.¹¹ As modulators of neuronal excitability, endogenous cannabinoids are well poised to affect the initiation, propagation, and spread of seizures.

Preliminary studies have identified defects in

the endocannabinoid system in persons with epilepsy. In one study, patients with newly diagnosed temporal-lobe epilepsy had significantly lower levels of anandamide in cerebrospinal fluid than healthy controls.¹² In another study, tissue resected from patients undergoing surgery for epilepsy had lower levels of CB₁R messenger RNA, particularly in the glutamatergic terminals in the dentate gyrus, than did specimens obtained post mortem from persons without epilepsy. There was also reduced expression of diacylglycerol lipase α (DAGL- α), the enzyme responsible for the “on-demand” synthesis of 2-AG in postsynaptic neurons.¹³ These studies support the suggestion that the endocannabinoid system plays a role in the inhibition of seizures in humans with epilepsy.

The endocannabinoid system is strongly activated by seizures, and the upregulation of CB₁R activity has antiseizure effects. In mice, hippocampal anandamide levels rise after seizures induced by the intraperitoneal injection of kainic acid.¹⁴ In cultures of neurons from the hippocampus, CB₁R antagonists induce prolonged, seizurelike discharges,¹⁵ whereas CB₁R agonists eliminate these discharges.¹⁶ Conditional knockout mice that lack pyramidal-cell CB₁R in their forebrain have more severe and prolonged seizures than wild-type mice in response to kainic acid^{14,17}; in contrast, viral-vector-mediated overexpression of CB₁R in hippocampal pyramidal cells is protective.¹⁸ Reducing the metabolic degradation of endocannabinoids ameliorates experimentally induced seizures.¹⁹

PRECLINICAL EVIDENCE OF ANTISEIZURE EFFECTS

The activation of CB₁R receptors with the use of Δ^9 -THC or synthetic agonists in experimentally induced seizures has been studied in various animal models (see Hill et al. for a summary²⁰). In most studies, CB₁R agonists reduced seizures, but in others no effect was observed, and in four studies CB₁R activation was associated with convulsant effects at some doses. CB₁R antagonists reduced the threshold for seizure in some studies in animals,²¹ a finding that further supports the possibility that CB₁R activation has anticonvulsant effects.

Other plant cannabinoids have also been studied in animal models of seizures and epi-

lepsy. Cannabidiol, the most abundant nonpsychoactive cannabinoid, has shown antiseizure effects in several *in vivo* and *in vitro* models of epilepsy.²² Unlike Δ^9 -THC, cannabidiol does not exert its main neural effects through the activation of CB₁R. At high levels, cannabidiol may function as an indirect CB₁R antagonist.²³ Cannabidiol alters neuronal excitability by other means. These include binding to members of the TRP family of cation channels at low levels,²⁴ which antagonizes the G-protein-coupled receptor 55, leading to decreased presynaptic release of glutamate²⁵; activating 5-hydroxytryptophan 1A receptors²⁶; and inhibiting adenosine reuptake through multiple mechanisms.²⁷ In addition, cannabidiol may exert antioxidant and anti-inflammatory effects.²⁸ Cannabidiol's lack of psychoactive effects and the preclinical evidence of antiseizure effects has generated interest in its potential as an antiseizure drug in humans.

Cannabidivarin, the propyl variant of cannabidiol, has also shown antiseizure effects in both *in vitro* and *in vivo* models.²⁹ Like cannabidiol, cannabidivarin has antiseizure effects that are independent of the endocannabinoid system and may function by means of its influence on TRP channels or by lowering 2-AG synthesis through the inhibition of DAGL- α .³⁰ Little is known about the antiseizure effects of other phytocannabinoids. Cannabinol and Δ^9 -THCV, the propyl variant of Δ^9 -THC, have been shown to have anticonvulsant effects in a few small studies.²⁰

EVIDENCE OF ANTISEIZURE EFFECTS IN HUMANS

Despite the preclinical data and anecdotal reports on the efficacy of cannabis in the treatment of epilepsy that include reports from epileptologists,³¹⁻³⁴ a recent Cochrane review concluded that “no reliable conclusions can be drawn at present regarding the efficacy of cannabinoids as a treatment for epilepsy”³⁵ owing to the lack of adequate data from randomized, controlled trials of Δ^9 -THC, cannabidiol, or any other cannabinoid (Table 1). This assessment was confirmed in a recent systematic review by the American Academy of Neurology.⁴⁷

Limited epidemiologic evidence supports the view that cannabinoids have antiseizure properties in humans. In a case-control study of illicit drug use and new-onset seizures in Harlem,

New York, men who used cannabis within 90 days before hospital admission were at a significantly lower risk for presenting with new-onset seizures than men who did not use cannabis (odds ratio, 0.36; 95% confidence interval, 0.18 to 0.74).⁴⁸

Several patient and caregiver surveys have examined the effects of cannabis in epilepsy. In one survey, 28 of 136 patients in an epilepsy center that provided tertiary care reported cannabis use. Most of these patients associated use with a reduction in seizure frequency and severity.⁴⁵ A 2013 survey of caregivers of 19 children with severe epilepsy who were receiving cannabidiol-enriched cannabis extracts indicated that 2 of the children had become seizure-free and 8 others had a reduction in the frequency of seizures of 80% after taking the extract.⁴² In a 2015 survey of 75 parents whose children were treated with oral cannabis extracts in Colorado, the parents reported that one third of the children had a reduction in seizures of more than 50%.³⁴ However, electroencephalograms were obtained for 8 of these children before and after the administration of cannabis, and none showed improvement in background activity.

Case reports support the antiseizure effects of cannabis in patients with epilepsy^{6,32-34,49} and show exacerbation of seizures after abrupt discontinuation.⁵⁰ However, in a survey conducted in Germany among adults with epilepsy who used cannabis, the substance had no apparent effect on seizure control,⁴⁶ and some case reports have shown an exacerbation of seizures among patients who used cannabis^{43,51} or a synthetic cannabinoid.⁵²

Few prospective therapeutic trials have been performed that involve the isolated use of cannabinoids to treat epilepsy. A study conducted in 1949 indicated that two of five institutionalized children with refractory epilepsy achieved seizure control after receiving treatment with a Δ^9 -THC analogue.³⁶ To our knowledge, only four placebo-controlled studies of the use of cannabinoids for the treatment of epilepsy have been performed (reviewed in Gloss and Vickrey³⁵). All the studies were considerably underpowered and had methodologic problems, including the lack of blinding. Two studies showed a reduction in the number of seizures in patients treated with cannabidiol, whereas the other two studies showed no effect.

Since 2013, a consortium of 10 epilepsy centers has been collecting prospective data on children and young adults with severe epilepsy who are receiving Epidiolex, a purified cannabis extract containing 99% cannabidiol and less than 0.10% Δ^9 -THC (GW Pharmaceuticals), through an expanded-access program authorized by the Food and Drug Administration (FDA). A preliminary report from this open-label study, initiated by investigators to assess the safety and dosing of cannabidiol, noted that among 137 patients who had received at least 12 weeks of treatment, the median reduction in the number of seizures was 54%.⁴¹ Randomized clinical trials of Epidiolex are now being conducted for the treatment of two forms of severe, childhood-onset epilepsy: Dravet's syndrome (a severe myoclonic epilepsy of infancy) (NCT02091375) and the Lennox-Gastaut syndrome (a childhood-onset, treatment-resistant epilepsy characterized by multiple types of seizures and developmental delay) (NCT02224690). Although some of the anecdotal evidence described above suggests that cannabidiol-rich treatments may ameliorate seizures in patients with these disorders, no evidence suggests that the antiseizure effects of cannabidiol are limited to the treatment of these conditions. The clinical development of synthetic forms of cannabidiol is also in progress (NCT02318563). Table 1 summarizes the current clinical evidence for the use of cannabinoid-containing compounds in the treatment of epilepsy.

SAFETY IN HUMANS

Much of the available data regarding the safety and side-effect profile of cannabinoids, especially with long-term use, come from studies examining the effects of recreational use.^{53,54} The short-term side effects of cannabis use may include impairment of memory, judgment, and motor performance. High levels of Δ^9 -THC are associated with psychosis and an increased risk of motor-vehicle accidents. With long-term use there is a risk of addiction, which occurs in approximately 9% of long-term users. Other effects of long-term use include cognitive impairment, decreased motivation, and an increased risk of psychotic disorders.

Cannabis-based treatment with Δ^9 -THC may have irreversible effects on brain development.

Table 1. Clinical Trials, Case Series, and Case Reports on Cannabinoids in the Treatment of Epilepsy.

Compound and Study Type	Dose*	No. of Participants	Results	Reference
Isolated oral cannabinoids				
THC isomers				
Case series of institutionalized children with intellectual disability and epilepsy treated for 3–7 wk		5	One patient was seizure-free and one patient nearly seizure-free	Davis and Ramsey ³⁶
Cannabidiol				
Prospective, placebo-controlled, 3-mo trial involving adults with treatment-resistant epilepsy	200 mg/day	Treatment: 4 Placebo: 5	Two patients in the cannabidiol group were seizure-free and one showed partial improvement No report of baseline seizure measurement	Mechoulam and Carlini ³⁷
Prospective, placebo-controlled trial involving teenagers and adults with treatment-resistant convulsive seizures (at least 1 per wk) in which participants had 8–18 wk of exposure	200–300 mg/day	Treatment: 8 Placebo: 7	Four patients in cannabidiol group and 1 in placebo group were seizure-free; somnolence was a reported side effect Clinicians were not masked to group assignment; one patient switched groups for unknown reasons	Cunha et al. ³⁸
Prospective, placebo-controlled, 3-wk trial involving institutionalized adults with intellectual disability and epilepsy	200–300 mg/day	Treatment: 6 Placebo: 6	No significant difference between groups Somnolence was a reported side effect	Ames and Cridland ³⁹
Prospective randomized, double-blind placebo-controlled, 6-mo crossover study involving adults with treatment-resistant epilepsy	300 mg/day	12	No significant difference between cannabidiol and placebo Somnolence was a reported side effect	Tremblay and Sherman ⁴⁰
Purified oral cannabidiol extract				
Prospective, open-label, 12-wk trial involving children and young adults with severe, childhood-onset epilepsy		137	Median reduction in weekly rate of convulsive seizures of 54% Somnolence and diarrhea were the most common side effects	Devinsky et al. ⁴¹
Oral cannabis extracts				
Cannabis indica extract				
Case report of a 40-yr-old man with focal epilepsy who was resistant to bromides	32 mg/day	1	Seizure-free for 6 mo followed by recurrence when cannabis extract was discontinued; seizure control resumed with resumption of cannabis several months later	Gowers ⁶
Cannabidiol-Δ^9-THC-containing extracts of varying composition				
Survey among participants in a Facebook group for parents of children with severe epilepsies	Cannabidiol: Up to 28 mg/kg body weight/day Δ^9 -THC: Up to 0.8 mg/kg body weight/day	19	Improvement with cannabidiol- Δ^9 -THC reported by 16 patients (84%); 2 patients (11%) became seizure-free	Porter and Jacobson ⁴²

Compound and Study Type	Dose*	No. of Participants	Results	Reference
Oral cannabis extract, with high ratio of cannabidiol to Δ^9 -THC				
Case report of 5-yr-old girl with Dravet's syndrome		1	Reduction of >90% in frequency of generalized tonic-clonic seizures, which allowed for reduction of other drugs taken for epilepsy	Maa and Figi ³³
Oral cannabis extracts				
Retrospective case series of children with refractory epilepsy at a center in Colorado		75	Reduction of >50% in frequency of seizures in 25 patients (33%)	Press et al. ³⁴
Smoked cannabis				
Cannabis				
Case report of 20-yr-old man with refractory tonic-clonic seizures whose seizures were well-controlled		1	Seizures were exacerbated after smoking marijuana	Keeler and Reiffle ⁴³
Case report of 24-yr-old man with refractory generalized epilepsy		1	Nearly seizure-free after daily cannabis use	Consroe et al. ⁴⁴
Case report of 29-yr-old man with refractory focal epilepsy		1	Suppression of complex partial seizures with cannabis use and exacerbation of seizures on withdrawal	Ellison et al. ³¹
Case report of 45-yr-old man with cerebral palsy and refractory focal epilepsy		1	Reduction of >90% in nocturnal seizures and tonic-clonic seizures	Mortati et al. ³²
Survey of active users at center for patients with tertiary epilepsy		28	Reduction in severity of seizures reported by 19 patients (68%); 15 patients (54%) reported reduction in frequency of seizures	Gross et al. ⁴⁵
Survey of cannabis users seen at center for patients with tertiary epilepsy		Active users: 13 Former users: 297	Reduction in frequency of seizures reported by 2 active users (15%); increase in frequency and severity of seizures reported by 7 former users (0.2%)	Harmerle et al. ⁴⁶

* Data on dosage has been provided when available.

The endocannabinoid system undergoes development in childhood and adolescence; long-term exposure to endocannabinoids, especially Δ^9 -THC, may lead to cognitive and behavioral changes. Imaging studies of the brain reveal altered structure and function in long-term adult users, including impaired connectivity of the prefrontal cortices and precuneus⁵⁴ and decreased volume in the hippocampi and amygdalae.⁵⁵ Long-term use of cannabis in childhood may be associated with lower-than-expected IQ scores⁵⁶ (although socioeconomic status may be a confounding factor; see Rogeberg⁵⁷). It is unknown whether adverse effects on the brain are mediated solely by psychoactive cannabinoids, such as Δ^9 -THC, or whether long-term exposure to cannabidiol and cannabidivarin also have deleterious effects. Until more data become available, the neurodevelopmental risks of cannabinoid-based therapies should be weighed against the potential benefits for seizure control, since seizures also affect brain development. Notably, scientific data on the potential long-term developmental effects of FDA-approved antiseizure drugs are also limited.

Many antiseizure drugs are associated with teratogenicity and neurodevelopmental impairments in children who are exposed in utero. Little is known about the effects of fetal exposure to cannabinoids. Studies of children born to parents who are recreational cannabis users have not shown an increased risk of congenital abnormalities, but difficulties with attention, impulse control, and executive function have been reported.⁵⁸ However, potential confounding factors, such as socioeconomic status and coexisting maternal psychiatric illness, limit the extent to which these findings can be interpreted.

Data regarding the outcomes of short-term and long-term exposure to cannabinoids in recreational users are often confounded by the factors that drive a person to use cannabis. More valid data regarding the safety of short-term use comes from randomized clinical trials of cannabinoid-containing medications, including purified cannabis extracts (Cannador, Society for Clinical Research, Germany; 2:1 ratio of Δ^9 -THC and cannabidiol),⁵⁹ nabixomols (Sativex, GW Pharmaceuticals, 1:1 ratio of Δ^9 -THC and cannabidiol),⁶⁰ and the synthetic Δ^9 -THC analogues dronabinol (Marinol, Unimed Pharmaceuticals),⁶¹ and nabilone (Cesamet, Valeant Pharmaceuticals).⁶² These trials involved the systematic collection of

data on safety. In a pooled analysis that included 1619 patients in short-term placebo-controlled studies who received cannabinoids for the treatment of pain and tremor and for spasticity related to multiple sclerosis, 6.9% withdrew because of adverse effects, as compared with 2.2% who withdrew in the placebo groups.⁴⁷ Adverse effects that occurred in more than one study included nausea, weakness, mood changes, psychosis, hallucinations, suicidal ideation, dizziness or lightheadedness, fatigue, and feeling of intoxication. No deaths from overdose were reported in association with cannabinoid-containing medications. In small studies of cannabidiol use in healthy volunteers and in patients with multiple disease conditions, serious side effects have been associated with either long-term or short-term administration of doses of up to 1500 mg daily.⁶³ In the preliminary results of an open-label study of the use of cannabidiol oral solution for severe, refractory, childhood-onset epilepsy, the most common side effects were somnolence (occurring in 21% of the participants), diarrhea (17%), fatigue (17%), and decreased appetite (16%). Increased frequency or severity of seizures, weight loss, diarrhea, pneumonia, and abnormal results on tests of liver function were less common, occurring in 1 to 7% of patients.⁴¹

Long-term recreational use of cannabis is associated with a risk of dependence.⁵⁴ Little is known regarding the potential for the abuse of cannabinoid-based treatments when they are administered in a clinical setting. A single-dose, double-blind, crossover study involving 23 recreational cannabis users showed higher scores on scales of drug preference for dronabinol and high-dose nabiximols but not for low-dose nabiximols,⁶⁴ which suggests that there may be a potential for abuse associated with cannabinoid-based therapies, at least when the compounds used contain Δ^9 -THC or its analogues. Few data are available on the effects of other cannabinoids, although the relative absence of psychoactive effects reported for cannabidiol and cannabidivarin suggests that the potential for abuse of these compounds is low.

Some safety concerns have been raised with regard to the pharmacokinetic interactions of cannabinoids in patients with epilepsy who are long-term users. Cannabinoids can inhibit cytochrome P-450 (CYP) enzymes. Both Δ^9 -THC and cannabidiol inhibit the CYP2C family of isozymes

at low micromolar concentrations and CYP3A4 at higher concentrations.⁶⁵ These enzymes help to metabolize many antiseizure drugs,⁶⁶ and inhibition can potentiate drug toxicity and efficacy. Both cannabidiol and Δ^9 -THC are metabolized through the P-450 system, especially through CYP2C9 and CYP3A4.⁶⁵ These isozymes are induced by commonly prescribed antiseizure drugs, such as carbamazepine, topiramate, and phenytoin, and are inhibited by others, such as valproate,⁶⁶ and the potential for drug–drug interactions between antiseizure drugs and cannabinoids is bidirectional. Preliminary evidence suggests that cannabidiol can raise the serum levels of the N-desmethyl metabolite of clobazam, which can have antiseizure and sedative effects.⁶⁷

As is the case with any medication, accidental ingestion of cannabis by children is a concern, and with cannabis preparations, the concern is particularly great because these preparations are not packaged in childproof containers and because some are made in formulations that may be appealing to children (gummies, brownies, or other edible forms).⁶⁸ Finally, there are safety concerns related to the preparation of cannabis for medicinal use. Although many states have approved the use of “medical” marijuana, patients or caregivers often process the plant for therapeutic use. Reliance on recipes pulled from the Internet that use butane or high-proof alcohols to extract cannabinoids from plant material has resulted in more than 30 home explosions in a 5-month period in Colorado.⁶⁹

ISSUES RELEVANT TO USE IN EPILEPSY TREATMENT

The delay between initial reports of the antiseizure efficacy of cannabinoids in preclinical models in the 1970s and the recent start of clinical studies reflects, in part, the classification of cannabis and any product derived from it as a Schedule I drug by the Drug Enforcement Agency. Schedule I drugs are defined as having no currently accepted medical use and a high potential for abuse.⁷⁰ Synthetic cannabinoids, since they are not derived from the cannabis plant, are sometimes subject to less restrictive scheduling if clinical evidence supports medical usefulness. For instance, the synthetic Δ^9 -THC isomer dronabinol is a Schedule III medication and is often prescribed for the treatment of

chronic nausea and vomiting in patients with the autoimmune deficiency syndrome. The rationale for the discrepancy between restrictions governing naturally occurring cannabinoids and synthesized cannabinoids is not clear. Cannabis-based drugs such as nabiximols (cannabidiol and Δ^9 -THC) have been approved by regulatory bodies in more than 20 countries on the basis of the results of clinical trials that have established efficacy and a favorable safety profile, including a low potential for abuse.⁷¹ The Schedule I category limits the availability of pure cannabidiol, Δ^9 -THC, and other cannabinoids derived from cannabis while placing a high regulatory burden on investigators who want to study these agents in cell cultures, animal models, or patients. This burden includes the need to purchase and find space for expensive and heavy safes, add locks and security systems to the laboratory or clinic, and complete a long and complex process to apply for and then pass multiple inspections in order to possess these compounds. Paradoxically, as more state legislatures give the lay community access to diverse strains and preparations of cannabis and federal policy continues to limit the access of scientific and clinical investigators to compounds such as cannabidiol, a dissociation is created between an exponential rise in use and a slow rise in scientific knowledge.

PERCEIVED THERAPEUTIC BENEFIT

Another obstacle to scientific inquiry into cannabinoids for the treatment of epilepsy is the perception among many patients and caregivers that sufficient evidence of their safety and efficacy already exists.⁷² The gap between patient beliefs and available scientific evidence highlights a set of factors that confound cannabinoid research and therapy, including the naturalistic fallacy (the belief that nature’s products are safe), the conversion of anecdotes and strong beliefs into facts, failure to appreciate the difference between research and treatment,⁷³ and a desire to control one’s care, including access to therapies of perceived benefit.⁷⁴ In one study of children with epilepsy in Colorado, the rate of response to therapy reported by parents who had moved their family to the state to receive cannabinoid therapy was more than twice as high as that reported by parents who were already residing in the state (47% vs. 22%).³⁴ This finding

suggests that the stronger the belief that the drug will be beneficial and the greater the sacrifice involved to obtain the drug, the greater the reported response. In the future, randomized, controlled studies of cannabinoids will have to contend with large placebo effects that may actually prevent researchers from demonstrating the efficacy of cannabinoids over placebo.

The currently planned randomized clinical trials of cannabidiol will target primarily children with severe epilepsy. Placebo response rates are high among children and adolescents with a wide variety of conditions, including pain-related disorders (e.g., migraines and gastrointestinal disorders), medical disorders (e.g., asthma), and psychiatric disorders (e.g., anxiety, major depression, obsessive-compulsive disorder, and attention-deficit disorder).⁷⁵ The issue of high response rates to placebos in studies of children is especially relevant to epilepsy and emphasizes the importance of placebo-controlled trials. A meta-analysis showed that among patients with treatment-resistant focal epilepsy, children had more improvement with placebo than did adults (19.9% vs. 9.9%), although there was no significant difference in the response to active treatment.⁷⁶ Children with intellectual disability and severe epilepsy are especially prone to elevated response rates to placebo. For instance, in a clinical trial of clobazam in children with the Lennox–Gastaut syndrome (mean age, 12.4 years), the response rate (defined as a decline of more than 50% in the number of drop seizures [brief seizures associated with a sudden increase or decrease in muscle tone, often causing a fall if the person is standing]) in the placebo group was 31.6%, a rate similar to that in the group receiving clobazam. However, the average weekly frequency of seizures was significantly lower in the clobazam group.⁷⁷

CONCLUSIONS AND FUTURE DIRECTIONS

Preclinical and preliminary data from studies in humans suggest that cannabidiol and Δ^9 -THC may be effective in the treatment of some patients with epilepsy. However, current data from studies in humans are extremely limited, and no conclusions can be drawn. Relaxation of the regulatory status of cannabis-derived drugs, especially those containing a high proportion of nonpsychoactive cannabinoids, for which the potential for abuse is low, could help to accelerate scientific study. Despite the power of anecdote and the approval of medical cannabis by many state legislatures, only double-blind, placebo-controlled, randomized clinical trials in which consistent preparations of one or more cannabinoids are used can provide reliable information on safety and efficacy. The use of medical cannabis for the treatment of epilepsy could go the way of vitamin and nutritional supplements, for which the science never caught up to the hype and was drowned out by unverified claims, sensational testimonials, and clever marketing. If randomized clinical trials show that specific cannabinoids are unsafe or ineffective, those preparations should not be available. If studies show that specific cannabinoids are safe and effective, those preparations should be approved and made readily available.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

REFERENCES

1. Brodie MJ, Barry SJ, Bamagous GA, Norrie JD, Kwan P. Patterns of treatment response in newly diagnosed epilepsy. *Neurology* 2012;78:1548-54.
2. Kwan P, Brodie MJ. Early identification of refractory epilepsy. *N Engl J Med* 2000;342:314-9.
3. Perucca P, Gilliam FG. Adverse effects of antiepileptic drugs. *Lancet Neurol* 2012; 11:792-802.
4. Gupta S. Weed. In: Gupta S, ed. CNN, 2013 (see video promotion for program at <http://www.cnn.com/videos/bestoftv/2013/08/05/gupta-weed-promo.cnn>).
5. Schultes RE. Man and marihuana. *Nat Hist* 1973;82:59.
6. Gowers WR. *Epilepsy and other chronic convulsive disorders*. London: Churchill, 1881.
7. Devane WA, Hanus L, Breuer A, et al. Isolation and structure of a brain constituent that binds to the cannabinoid receptor. *Science* 1992;258:1946-9.
8. ElSohly M, Gul W. Constituents of cannabis sativa. In: Pertwee R, ed. *Handbook of cannabis*. Oxford, United Kingdom: Oxford University Press, 2014:3-22.
9. Cascio MG, Pertwee RG. Known pharmacological actions of nine nonpsychotropic phytocannabinoids. In: Pertwee RG, ed. *Handbook of cannabis*. Oxford, United Kingdom: Oxford University Press, 2014:137.
10. Pertwee RG, Cascio MG. Known pharmacological actions of delta-9-tetrahydrocannabinol and of four other chem-

- ical constituents of cannabis that activate cannabinoid receptors. In: Pertwee RG, ed. *Handbook of cannabis*. Oxford, United Kingdom: Oxford University Press, 2014: 115.
11. Castillo PE, Younts TJ, Chávez AE, Hashimoto-dani Y. Endocannabinoid signaling and synaptic function. *Neuron* 2012;76:70-81.
12. Romigi A, Bari M, Placidi F, et al. Cerebrospinal fluid levels of the endocannabinoid anandamide are reduced in patients with untreated newly diagnosed temporal lobe epilepsy. *Epilepsia* 2010;51:768-72.
13. Ludányi A, Eross L, Czirják S, et al. Downregulation of the CB1 cannabinoid receptor and related molecular elements of the endocannabinoid system in epileptic human hippocampus. *J Neurosci* 2008;28:2976-90.
14. Marsicano G, Goodenough S, Monory K, et al. CB1 cannabinoid receptors and on-demand defense against excitotoxicity. *Science* 2003;302:84-8.
15. Deshpande LS, Sombati S, Blair RE, Carter DS, Martin BR, DeLorenzo RJ. Cannabinoid CB1 receptor antagonists cause status epilepticus-like activity in the hippocampal neuronal culture model of acquired epilepsy. *Neurosci Lett* 2007;411:11-6.
16. 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.
17. Monory K, Massa F, Egertová M, et al. The endocannabinoid system controls key epileptogenic circuits in the hippocampus. *Neuron* 2006;51:455-66.
18. Guggenhuber S, Monory K, Lutz B, Klugmann M. AAV vector-mediated overexpression of CB1 cannabinoid receptor in pyramidal neurons of the hippocampus protects against seizure-induced excitotoxicity. *PLoS One* 2010;5(12):e15707.
19. Karanian DA, Karim SL, Wood JT, et al. Endocannabinoid enhancement protects against kainic acid-induced seizures and associated brain damage. *J Pharmacol Exp Ther* 2007;322:1059-66.
20. Hill AJ, Hill TDM, Whalley BJ. The development of cannabinoid based therapies for epilepsy. In: Murillo-Rodríguez E, Onaivi ES, Darmani NA, Wagner E, eds. *Endocannabinoids: molecular, pharmacological, behavioral and clinical features*. Sharjah, United Arab Emirates: Bentham Science, 2013:164-204.
21. 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;307:129-37.
22. Devinsky O, Cilio MR, Cross H, et al. Cannabidiol: pharmacology and potential therapeutic role in epilepsy and other neuropsychiatric disorders. *Epilepsia* 2014;55:791-802.
23. Pertwee RG. The diverse CB1 and CB2 receptor pharmacology of three plant cannabinoids: delta9-tetrahydrocannabinol, cannabidiol and delta9-tetrahydrocannabinol. *Br J Pharmacol* 2008;153:199-215.
24. De Petrocellis L, Ligresti A, Moriello AS, et al. Effects of cannabinoids and cannabinoid-enriched Cannabis extracts on TRP channels and endocannabinoid metabolic enzymes. *Br J Pharmacol* 2011;163:1479-94.
25. Syntayev S, Jensen TP, Ross RA, Ruskov DA. Cannabinoid- and lysophosphatidylinositol-sensitive receptor GPR55 boosts neurotransmitter release at central synapses. *Proc Natl Acad Sci U S A* 2013;110:5193-8.
26. Campos AC, Ferreira FR, Guimarães FS. Cannabidiol blocks long-lasting behavioral consequences of predator threat stress: possible involvement of 5HT1A receptors. *J Psychiatr Res* 2012;46:1501-10.
27. Carrier EJ, Auchampach JA, Hillard CJ. Inhibition of an equilibrative nucleoside transporter by cannabidiol: a mechanism of cannabinoid immunosuppression. *Proc Natl Acad Sci U S A* 2006;103:7895-900.
28. Hampson AJ, Grimaldi M, Axelrod J, Wink D. Cannabidiol and (-)Delta9-tetrahydrocannabinol are neuroprotective antioxidants. *Proc Natl Acad Sci U S A* 1998;95:8268-73.
29. Hill TD, Cascio MG, Romano B, et al. Cannabidiol-rich cannabis extracts are anticonvulsant in mouse and rat via a CB1 receptor-independent mechanism. *Br J Pharmacol* 2013;170:679-92.
30. Iannotti FA, Hill CL, Leo A, et al. Non-psychoactive plant cannabinoids, cannabidiol (CBDV) and cannabidiol (CBD), activate and desensitize transient receptor potential vanilloid 1 (TRPV1) channels in vitro: potential for the treatment of neuronal hyperexcitability. *ACS Chem Neurosci* 2014;5:1131-41.
31. Ellison JM, Gelwan E, Ogletree J. Complex partial seizure symptoms affected by marijuana abuse. *J Clin Psychiatry* 1990;51:439-40.
32. Mortati K, Dworetzky B, Devinsky O. Marijuana: an effective antiepileptic treatment in partial epilepsy? A case report and review of the literature. *Rev Neurol Dis* 2007;4:103-6.
33. Maa E, Figi P. The case for medical marijuana in epilepsy. *Epilepsia* 2014;55:783-6.
34. Press CA, Knupp KG, Chapman KE. Parental reporting of response to oral cannabis extracts for treatment of refractory epilepsy. *Epilepsy Behav* 2015;45:49-52.
35. Gloss D, Vickrey B. Cannabinoids for epilepsy. *Cochrane Database Syst Rev* 2014;3:CD009270.
36. Davis JP, Ramsey HH. Anti-epileptic action of marijuana-active substances. *Fed Proc, Am Soc Exp Biol* 1949;8:284.
37. Mechoulam R, Carlini EA. Toward drugs derived from cannabis. *Naturwissenschaften* 1978;65:174-9.
38. Cunha JM, Carlini EA, Pereira AE, et al. Chronic administration of cannabidiol to healthy volunteers and epileptic patients. *Pharmacology* 1980;21:175-85.
39. Ames FR, Cridland S. Anticonvulsant effect of cannabidiol. *S Afr Med J* 1986;69:14.
40. Tremblay B, Sherman M. Double-blind clinical study of cannabidiol as a secondary anticonvulsant. Presented at the Marijuana '90 International Conference on Cannabis and Cannabinoids, Kolympari, Crete, July 8-11, 1990. abstract.
41. Devinsky O, Sullivan J, Friedman D, et al. Epidiolex (cannabidiol) in treatment resistant epilepsy. Presented at the annual meeting of the American Academy of Neurology, Washington, DC, April 18-25, 2015. abstract.
42. 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.
43. Keeler MH, Reifler CB. Grand mal convulsions subsequent to marijuana use: case report. *Dis Nerv Syst* 1967;28:474-5.
44. Consroe PF, Wood GC, Buchsbaum H. Anticonvulsant nature of marijuana smoking. *JAMA* 1975;234:306-7.
45. Gross DW, Hamm J, Ashworth NL, Quigley D. Marijuana use and epilepsy: prevalence in patients of a tertiary care epilepsy center. *Neurology* 2004;62:2095-7.
46. Hamerle M, Ghaeni L, Kowski A, Weissinger F, Holtkamp M. Cannabis and other illicit drug use in epilepsy patients. *Eur J Neurol* 2014;21:167-70.
47. Koppel BS, Brust JC, Fife T, et al. 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.
48. Brust JC, Ng SK, Hauser AW, Susser M. Marijuana use and the risk of new onset seizures. *Trans Am Clin Climatol Assoc* 1992;103:176-81.
49. Gordon E, Devinsky O. Alcohol and marijuana: effects on epilepsy and use by patients with epilepsy. *Epilepsia* 2001;42:1266-72.
50. Hegde M, Santos-Sanchez C, Hess CP, Kabir AA, Garcia PA. Seizure exacerbation in two patients with focal epilepsy following marijuana cessation. *Epilepsy Behav* 2012;25:563-6.
51. Feeney DM. Marijuana use among epileptics. *JAMA* 1976;235:1105.
52. Tofighi B, Lee JD. Internet highs — seizures after consumption of synthetic cannabinoids purchased online. *J Addict Med* 2012;6:240-1.

53. Hall W, Solowij N. Adverse effects of cannabis. *Lancet* 1998;352:1611-6.
54. Volkow ND, Baler RD, Compton WM, Weiss SR. Adverse health effects of marijuana use. *N Engl J Med* 2014;370:2219-27.
55. Lorenzetti V, Solowij N, Whittle S, et al. Gross morphological brain changes with chronic, heavy cannabis use. *Br J Psychiatry* 2015;206:77-8.
56. Meier MH, Caspi A, Ambler A, et al. Persistent cannabis users show neuropsychological decline from childhood to midlife. *Proc Natl Acad Sci U S A* 2012;109:E2657-E2664.
57. Rogeberg O. Correlations between cannabis use and IQ change in the Dunedin cohort are consistent with confounding from socioeconomic status. *Proc Natl Acad Sci U S A* 2013;110:4251-4.
58. Behnke M, Smith VC. Prenatal substance abuse: short- and long-term effects on the exposed fetus. *Pediatrics* 2013;131(3):e1009-e1024.
59. Zajicek JP, Sanders HP, Wright DE, et al. Cannabinoids in multiple sclerosis (CAMS) study: safety and efficacy data for 12 months follow up. *J Neurol Neurosurg Psychiatry* 2005;76:1664-9.
60. Collin C, Davies P, Mutiboko IK, et al. Randomized controlled trial of cannabis-based medicine in spasticity caused by multiple sclerosis. *Eur J Neurol* 2007;14(3):290-6.
61. Jatoti A, Windschitl HE, Loprinzi CL, et al. Dronabinol versus megestrol acetate versus combination therapy for cancer-associated anorexia: a North Central Cancer Treatment Group study. *J Clin Oncol* 2002;20(2):567-73.
62. Chan HS, Correia JA, MacLeod SM. Nabilone versus prochlorperazine for control of cancer chemotherapy-induced emesis in children: a double-blind, crossover trial. *Pediatrics* 1987;79:946-52.
63. Bergamaschi MM, Queiroz RHC, Zuardi AW, Crippa JAS. Safety and side effects of cannabidiol, a Cannabis sativa constituent. *Curr Drug Saf* 2011;6:237-49.
64. Schoedel KA, Chen N, Hilliard A, et al. A randomized, double-blind, placebo-controlled, crossover study to evaluate the subjective abuse potential and cognitive effects of nabiximols oromucosal spray in subjects with a history of recreational cannabis use. *Hum Psychopharmacol* 2011;26:224-36.
65. Stout SM, Cimino NM. Exogenous cannabinoids as substrates, inhibitors, and inducers of human drug metabolizing enzymes: a systematic review. *Drug Metab Rev* 2014;46:86-95.
66. Patsalos PN, Perucca E. Clinically important drug interactions in epilepsy: general features and interactions between antiepileptic drugs. *Lancet Neurol* 2003;2:347-56.
67. Friedman D, Cilio MR, Tilton N, et al. The effect of epidiolex (cannabidiol) on serum levels of concomitant anti-epileptic drugs in children and young adults with treatment-resistant epilepsy in an expanded access program. Presented at the annual meeting of the American Epilepsy Society, Seattle, December 5-9, 2014. abstract.
68. Wang GS, Roosevelt G, Heard K. Pediatric marijuana exposures in a medical marijuana state. *JAMA Pediatr* 2013;167:630-3.
69. Healy J. Odd byproduct of legal marijuana: homes that blow up. *New York Times*. January 18, 2015:A1 (http://www.nytimes.com/2015/01/18/us/odd-byproduct-of-legal-marijuana-homes-blow-up.html?_r=0).
70. Drug Enforcement Agency. Drug scheduling: drug schedules (<http://www.dea.gov/druginfo/ds.shtml>).
71. Robson P. Abuse potential and psychoactive effects of δ -9-tetrahydrocannabinol and cannabidiol oromucosal spray (Sativex), a new cannabinoid medicine. *Expert Opin Drug Saf* 2011;10:675-85.
72. Mathern GW, Beninsig L, Nehlig A. Fewer specialists support using medical marijuana and CBD in treating epilepsy patients compared with other medical professionals and patients: result of Epilepsia's survey. *Epilepsia* 2015;56:1-6.
73. Henderson GE, Churchill LR, Davis AM, et al. Clinical trials and medical care: defining the therapeutic misconception. *PLoS Med* 2007;4(11):e324.
74. Devinsky O. Medical marijuana survey and epilepsy. *Epilepsia* 2015;56:7-8.
75. Weimer K, Gulewitsch MD, Schlarb AA, Schwille-Kiuntke J, Klosterhalfen S, Enck P. Placebo effects in children: a review. *Pediatr Res* 2013;74:96-102.
76. Rheims S, Cucherat M, Arzimanoglou A, Ryvlin P. Greater response to placebo in children than in adults: a systematic review and meta-analysis in drug-resistant partial epilepsy. *PLoS Med* 2008;5(8):e166.
77. Ng YT, Conry JA, Drummond R, Stolle J, Weinberg MA. Randomized, phase III study results of clobazam in Lennox-Gastaut syndrome. *Neurology* 2011;77:1473-81.

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