EPILEPSY CURRENTS

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Cannabidiol: Promise and Pitfalls

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Over the past few years, increasing public and political pressure has supported legalization of medical marijuana. One of the main thrusts in this effort has related to the treatment of refractory epilepsy—especially in children with Dravet syndrome—using cannabidiol (CBD). Despite initiatives in numerous states to at least legalize possession of CBD oil for treating epilepsy, little published evidence is available to prove or disprove the efficacy and safety of CBD in patients with epilepsy. This review highlights some of the basic science theory behind the use of CBD, summarizes published data on clinical use of CBD for epilepsy, and highlights issues related to the use of currently available CBD products.

Cannabidiol is the major nonpsychoactive component of *Cannabis sativa*. Over the centuries, a number of medicinal preparations derived from *C. sativa* have been employed for a variety of disorders, including gout, rheumatism, malaria, pain, and fever. These preparations were widely employed as analgesics by Western medical practitioners in the 19th century (1). More recently, there is clinical evidence suggesting efficacy in HIV-associated neuropathic pain, as well as spasms associated with multiple sclerosis (1).

Basic Pharmacological Mechanisms

Cannabidiol pharmacological effects are mediated through G protein coupled receptors, cannabinoid type I (CB_1) and cannabinoid type II (CB_2), which are highly expressed in the hippocampus and other parts of the central nervous system (2). When activated, CB_1 receptors inhibit synaptic transmission through action on voltage-gated calcium and potassium channels, which are known to modulate epileptiform and seizure activity (3). CB_2 receptors are primarily expressed in the immune system and have limited expression in the central nervous system. The effects of CBD are CB_2 receptor independent (3).

Studies have demonstrated that CBD has a low affinity for the CB_1 receptors, but even at low concentrations, CBD decreases G-protein activity (3). CB_1 receptors are expressed on many glutamatergic synapses that have been implicated in seizure threshold modulation. CBD may act at CB_1 receptors to inhibit glutamate release (4). Studies have shown changes in the expression of CB_1 receptors during epileptogenesis and after recurrent seizures (5). CB_1 receptor expression is upregulated at GABAergic synapses and shown to be downregulated at glutamatergic synapses in epilepsy, contributing to lowering seizure thresholds.

Other targets for CBD include transient receptor potential (TRP) channels that are involved with the modulation of intracellular calcium (1, 6). Cannabinoids are highly lipophilic, allowing access to intracellular sites of action, resulting in increases in calcium in a variety of cell types including hippocampal neurons. CBD actions on calcium homeostasis may provide a basis for CBD neuroprotective properties.

Evidence in Animal Models

When administered alone, CBD is an effective anticonvulsant in maximal electrical shock (MES), magnesium-free, 4-aminopyridine, and audiogenic models (7, 8). Co-administration with AEDs leads to various effects; anticonvulsant effects of CBD are enhanced with phenytoin or phenobarbital but decreased with chlordiazepoxide, clonazepam, trimethadione, and ethosuximide. In a recent study using an acute pilocarpine model, although CBD administration reduced the number of animals displaying seizure activity, CBD did not appear to have any significant effect on the number of seizures per animal (7).

Clinical Evidence in Epilepsy

While animal experimental data clearly suggest a potential benefit, supportive clinical data are quite sparse. In a case-

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control study of 308 cases of new onset seizures, Brust and colleagues found that marijuana use was significantly less prevalent among men who had unprovoked seizures compared to case controls (9). This difference was not significant in women. The authors suggest a potential protective effect against seizures with marijuana use; however, this should be considered speculative.

A survey of patients seen in a tertiary epilepsy center found that 21% of patients admitted to using marijuana in the last year, and 24% of patients believed marijuana to be effective for their seizures (10). While interesting, this anecdotal observation does not rise to the level of evidence needed to evaluate a potential new therapeutic modality.

Gloss and Vickrey conducted a Cochrane systematic review of the use of CBD in the treatment of epilepsy (11). Their methodology included only those trials that were randomized and controlled and excluded case series, case reports, and expert opinion. They were able to identify only 4 randomized controlled studies reported in the literature, and they included a letter to the editor and an abstract. The total number of subjects enrolled in these studies was 48 (11–14). While only four studies and a letter to the editor were in the actual analysis, the authors included a complete reference listing of all articles reviewed for inclusion.

These reports suffered from a number of design flaws, including incomplete baseline quantification of baseline seizure frequency, indeterminate time periods for outcome determination and, in some cases, inadequate (or missing) statistical analysis—in general, a lack of sufficient detail to adequately evaluate and interpret the findings. Limitations aside, several studies did report that administration of adjunctive CBD did not result in meaningful changes in seizure frequency (11–13).

Cunha et al. reported a 2-phase pilot study of CBD versus placebo in normal volunteers and patients with refractory secondarily generalized epilepsy (14). In the first phase, 8 normal volunteers received CBD or placebo in a doubled-blind fashion, at a dose of 3 mg/kg for 30 days. The second phase was also double-blinded in 15 patients with epilepsy receiving 200 to 300 mg daily of CBD or placebo for 135 days. Patients continued baseline AED. All subjects tolerated CBD well, with no serious adverse events. Four of the epilepsy patients receiving CBD were "almost free of convulsive crisis" for the duration of the study. Three other patients receiving CBD had a partial reduction in seizures, and 1 subject had no response. Of the 7 patients receiving placebo, seizure frequency was unchanged in 6, and 1 had clear improvement in seizure control.

Using rigorous review methodology, Gloss and Vickery conclude that based on the low quality of the reports available, there is insufficient data available to draw any conclusions regarding the efficacy and or long-term safety of CBD in treating epilepsy (11). From the data available, it does appear that daily doses of 200 to 300 mg were safe in this small group of patients for a short period of time (14).

Tolerability and Drug Interactions

CBD is well tolerated in humans with doses up to 600 mg not resulting in psychotic symptoms (15). In the few small placebo-controlled studies performed, no significant CNS effects were noted. Oral CBD undergoes extensive first-pass metabolism via CYP3A4, with a bioavailability of 6%. Following single doses in humans, the half-life of CBD when taken orally is about 1 to 2 days.[1] In vitro studies have shown that CBD is a potent inhibitor of multiple CYP isozymes, including CYP 2C and CYP3A (16, 17). Whether these in vitro observations are relevant at plasma concentrations likely to be seen in patients is unclear. In addition, given its metabolism via CYP3A4, clinical trials of CBD in patients receiving enzyme-inducing AEDs, such as carbamazepine or phenytoin, will require detailed pharmacokinetic studies.

A number of difficulties exist in evaluating published data on CBD or marijuana use for epilepsy. The extremely limited published studies were small, poorly described, and not well designed. Contributing to the difficulty of interpreting published studies, CBD products are not produced under the guidance of good manufacturing practices (GMP) and are not subject to regulations governing labeling, purity, and reliability. In other words, currently, there is no guarantee of consistency between products, or even differing lots produced by the same manufacturer. Without independent testing (e.g. USP certification) of CBD products for content and purity, as well as bioavailability testing of specific products, uncertainty surrounds the use of available CBD products in routine clinical settings.

Conclusions

At this time, there does seem to be a growing body of basic pharmacologic data suggesting there may be a role for CBD, especially in the treatment of refractory epilepsy. However, given the lack of well-controlled trials, we must also ask if we are getting ahead of ourselves. Clearly, this is an emotionally and politically charged issue. If this were any other uninvestigated pharmaceutical compound, would we feel as compelled to make the agent widely available before statistically valid class 1 evidence was available for review? Until data from well-designed clinical trials are available and reliable, and standardized CBD products that are produced using GMP are available, caution must be exercised in any consideration of using CBD for the treatment of epilepsy. In the meantime, based upon promising preliminary data, further clinical research should be wholeheartedly pursued.

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