Cannabis sativa has been used for centuries to treat a variety of ailments including rheumatism, pain and convulsions. In the US, cannabis has been available over the counter until 1941 and used to treat epilepsy among other maladies; this use declined with the introduction of phenobarbital and phenytoin and the Marijuana Tax Act of 1937. More recently, cannabinoid-based therapies have been approved for conditions like chronic pain, painful HIV-associated sensory neuropathy, chemotherapy-induced nausea and vomiting, and spasms. Interest has grown over the past several years in the use of cannabinoids, particularly cannabidiol, for use in the treatment of epilepsy, stimulated by case reports and anecdotal reports of efficacy in the management of refractory epilepsies such as Dravet’s Syndrome and Lennox Gasteau syndrome. This article will review the evidence to support the use of cannabidiol in epilepsy and evaluate the available safety and efficacy data.

CANNABINOIDS
Over 500 compounds have been isolated from cannabis species, approximately 70 of which are cannabinoids, a molecule with 21-carbon terpenophenolic skeleton. In addition to the cannabinoids, potentially neuro-active substances like terpenes, hydrocarbons, ketones, aldehydes, and small hydrophobic compounds capable of crossing the blood-brain barrier constitute the remainder.

The many cannabinoids and their metabolites generate a complex and often contradictory picture of their effects on seizure control. The two major and best studied neuro-active components are Δ9-THC (Tetra hydro Cannabinol) and cannabidiol (CBD). Δ9-THC is known to be psychoactive and CBD is thought to be essentially non-psychoactive. These compounds exist in different amounts in each species. For example, of the two common species of cannabis, Cannabis sativa usually has a higher Δ9-THC:CBD ratio as compared to Cannabis indica. As a result, it is possible that any anti-epileptic effects observed are mitigated by one or a combination of the many compounds found in cannabis.

ENDOCANNABINOID SYSTEM
The endocannabinoid system was discovered in 1990 with the identification of the Cannabinoid Receptor type 1 (CB1R) which is a G-protein coupled receptor that activates voltage-gated calcium channels and enhances potassium channel conductance in the presynaptic terminals. CB1R are mostly found in the central nervous system. More specifically, CB1R receptors are found in the brain stem, limbic system, and neocortical areas that modulate seizure activity. The receptor density is the highest in the substantia nigra pars reticulata, corpus striatum, cerebellum, hippocampus and dentate gyrus. Cannabinoids also influence thalamocortical projections, which could alter seizure threshold by increasing synchronicity. Δ9-THC has a high affinity for CB1R receptors. The endogenous ligands for the CB1R are anandamide and 2-arachidonylglyceol (2-AG). These endocannabinoids are produced on demand during excessive neuronal excitation and are thought to be a part of the natural dampening feedback loop.

The endocannabinoid system, on which cannabis acts, is strongly affected by seizures, and the up regulation of CB1R activity causes anti-seizure effects. But when Δ9-THC was used in animal models it induced seizures. The second type of endocannabinoid receptor, Cannabinoid Receptor...
Type 2 (CB2R), is located mostly in the immune and hematopoietic cells but can become up regulated in the other tissues. Cannabidiol is the most common non-psychotic cannabinoid, which has shown to have anti-seizure effects. Like THC it also exerts an agonistic effect on the CB1R receptors but at high doses it has an indirect antagonistic effect on the CB1R resulting in the anticonvulsant properties. Conversely, some believe that CBD does not act on cannabinoid receptors but on other non-endocannabinoid signaling systems and is a multi-target drug. Both cannabidiol and Δ9-THC may also have anti-inflammatory and anti-oxidant properties. The combination of the anti-seizure effects, antioxidant properties, and lack of psychotropic effects leads to the thought that there is significant potential for use of this in humans.

CANNABIDIOL IN EPILEPSY
A Cochrane review reported recently examined available data for cannabidiol in epilepsy which consisted of four trials evaluating only responder rate and safety of Δ9-THC, cannabidiol, or other cannabinoids, and owing to the paucity of data concluded that there “is insufficient body of evidence to recommend using marijuana to treat epilepsy.” However, studies are currently underway to evaluate this potential. Since 2013, several epilepsy centers have been collecting data on children and young adults with severe epilepsy to better understand the potential application of cannabidiol as part of a study authorized by the FDA. The study includes patients taking a purified extract of cannabis containing cannabidiol (99 percent) and less than 0.1 percent of Δ9-THC called Epidiolex (GW Pharmaceuticals). According to preliminary safety and dosing data, in which cannabidiol was given to 137 patients over at least 12 weeks of treatment, cannabidiol therapy resulted in a median seizure reduction of 54 percent.

Following this encouraging early data, GW Pharmaceuticals proceeded with randomized controlled trials for use of Epidiolex in Dravet’s Syndrome and Lennox-Gastaut Syndrome (LGS). The company shared results from a recent Phase 3 trial in the treatment of LGS showing that Epidiolex achieved a significant reduction in the monthly frequency of drop seizures when added as an adjunct to patients’ current treatment over a 14-week period compared with placebo. On average, patients were taking approximately three AEDs, having previously tried and failed an average of six other AEDs. During the treatment period, patients taking Epidiolex achieved a median reduction in monthly drop seizures of 44 percent compared with a reduction of 22 percent in patients receiving placebo, according to the company.

Top-line results from a second Phase 3 trial assessing Epidiolex in three treatment arms (20mg/kg/day, 10mg/kg/day, and placebo) in patients with LGS are expected to be reported later this year.

SIDE EFFECTS
In addition to discussing studies underway to evaluate efficacy, it is important to take a closer look at the side effect profile of cannabinoids. Short-term side effects of cannabis include impairment of memory, judgment, and motor performance. They may also cause cardiovascular and autonomic effects like tachycardia, hypotension, dry mouth and conjunctival injection. Other side effects include dizziness and dysphoria, while long-term side effects may include addiction, cognitive impairment, decreased motivation, and increased risk of psychotic disorders. Infrequently, cannabis may also cause hallucinations, ataxia, tremulousness, and subjective muscle weakness. It is also worth noting that higher levels of Δ9-THC cause psychosis and increased risk for motor vehicle accidents. Δ9-THC may also have irreversible effects on the endocannabinoid system of children and young adults, which may lead to cognitive and behavioral changes.

Imaging studies of the brain in patients with long term cannabis use showed impaired connectivity between the prefrontal cortex and precuneus and decreased volume in the hippocampi and amygdalae. Long-term use in childhood is associated with lower than expected IQ-scores. It is unclear whether the effects are solely mediated via Δ9-THC or whether the long-term exposure to cannabidiol and cannabidivarin also have the same deleterious effects. In addition, the risk of neuro-developmental impairment from cannabis use should be weighed against the potential benefits for not controlling the seizures.

In clinical trials, serious side effects have been been associated with long-term or short-term administration of cannabidiol in healthy volunteers and patients with multiple disease conditions. Side effects include somnolence (21 percent), diarrhea (17 percent), fatigue (17 percent), and

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decreased appetite (16 percent). Both cannabidiol and Δ9-THC inhibit the CYP2C isoenzyme at low concentrations and CYP3A4 at higher concentrations. By inhibiting the Cytochrome P-450 enzymes, they can increase the toxicity of the other anti-epileptic drugs also metabolized by the P450 system such as carbamazepine, phenytoin and clobazam.

**CONCLUSION**

The current human data is inconclusive that either cannabidiol or Δ9-THC may be effective in the treatment of some patients with epilepsy. Further study is warranted but will require regulatory laws against marijuana to be relaxed. We currently need more double-blinded, placebo-controlled trials to determine the safety, efficacy, and benefits of cannabinoids. While the future may be unclear, continuing studies will hopefully reveal whether cannabinoids have a place in epilepsy care.

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