Medical Marijuana in Epilepsy

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What is medical marijuana?

Medical marijuana is the use of extracts from the cannabis plant for treatment of medical conditions. Use of cannabis to treat various conditions such as nausea, anorexia (decreased appetite), glaucoma, pain, muscle spasticity, asthma, depression, and anxiety has been known for about 5000 years. Marijuana has pain-relieving properties and its use is now approved in a number of states in the US for pain management. Marijuana has been a particularly interesting candidate for epilepsy treatment. Cannabis-based treatment (medical marijuana) for epilepsy has been the focus of a number of debates in the lay press and in social media following reports of dramatic improvements in seizure control in children with severe epilepsy. Several states have legalized cannabis for the treatment of epilepsy (and other medical conditions) in children and adults. This article reviews for families the information available regarding marijuana use in treatment of epilepsy.

The availability of more than 20 seizure medications may not change the outcome for 30% of epilepsy patients who continue to have seizures despite adequate medical therapy. These patients, who are "medically refractory" to treatment with medications, are further evaluated for other forms of therapy such as vagal nerve stimulators (a surgical implant), ketogenic diet and/or other surgical options. Patients and families often seek newer modalities of treatment that may offer better seizure control with fewer side effects.

History of marijuana in treatment of epilepsy

There is evidence that cannabis was used in the treatment of epilepsy as early as 1800 b.c. in Sumeria. Even in the Victorian era, neurologists used Indian hemp to treat epilepsy. Use of cannabis for the treatment of epilepsy diminished with the introduction of the anti-seizure medications phenobarbital and phenytoin in 1912 and 1937 respectively. The Marijuana Tax Act law was also passed in 1937, which essentially terminated all research related to medical use of marijuana.

It was discovered in the 1970s that "cannabis" like substances are produced in the normal human brain. These function as neurotransmitters chemicals that allow communications between nerve cells through "receptors". This is called the "endogenous cannabinoid-signaling system". There is evidence from multiple studies that patients with different kinds of epilepsy may have lower levels of endogenous (produced within the brain) cannabinoids and that this system plays a role in the inhibition of seizures in patients with epilepsy.

More than 545 distinct compounds have been isolated from cannabis plant species. The most abundant are the cannabinoids; the best studied of these cannabinoids are Δ9 -tetrahydrocannabinol (Δ9 -THC) and cannabidiol (CBD) and their metabolites. The anti-seizure effect of plant-derived cannabinoids such as cannabidiol and cannabidivarin, another variant of cannabidiol, has been studied in animal models of seizures and epilepsy.

Current medical evidence

A guideline statement created from both Cochrane and American Academy of Neurology review of this topic concludes that no reliable conclusions could be drawn at present regarding the efficacy of cannabinoids as a treatment for epilepsy. This is largely due to lack of adequate data from clinical trials. There are four small clinical studies reported to date; two demonstrated benefit while the other two showed no benefit to use of cannabidiol in seizure frequency.

On the other hand, several patient and caregiver surveys have reported reduction in seizure frequency and severity with cannabis use. A 2015 survey of 75 parents whose children were treated with oral cannabis extracts in Colorado reported that one third of the children had a reduction in seizures of more than 50%.
However, there was no change in the EEG studies obtained before and after the administration of cannabis.

Since 2013, an expanded-access program (which is an open label program following individuals with epilepsy treated with cannabinoids, and is not a clinical trial) has been authorized by the Food and Drug Administration (FDA). This program is collecting data from a consortium of 10 epilepsy centers on children and young adults with severe epilepsy who are receiving Epidiolex, a purified cannabis extract containing 99% cannabidiol. Preliminary findings among 137 patients who had received at least 12 weeks of treatment show a median reduction in the number of seizures of 54%.

Clinical Trials

Randomized clinical trials using a purified 98% oil-based CBD extract (Epidiolex) as add-on treatment are now ongoing for the treatment of two forms of severe, childhood onset epilepsy: Dravet's syndrome (a severe myoclonic epilepsy of infancy) and the Lennox–Gastaut syndrome (a childhood-onset, treatment-resistant epilepsy characterized by multiple types of seizures and developmental delay).

Initial reports at 3 months of treatment demonstrate 32% median reduction of seizures.

Adverse Effects

The short-term side effects of cannabis use include impairment of memory, judgment, and motor performance. Knowledge from recreational use of cannabinoids provides information about the long-term side effects. With long-term use in addition to risk of addiction there may be irreversible cognitive impairment, decreased motivation, and an increased risk of psychotic disorders. Long-term use of cannabis in childhood may have effects on brain development and may be associated with lower-than-expected IQ scores.
When taken during pregnancy, children of recreational users have not shown an increased risk of congenital abnormalities, but difficulties with attention, impulse control, and executive function have been reported.

Other reported adverse effects are 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.

Issues Relevant to Use in Epilepsy Treatment

The perception among many patients and caregivers is that sufficient evidence of safety and efficacy of cannabis in treatment of epilepsy already exists. According to some studies, based on the current evidence, about 20 % of epilepsy patients are actively using cannabis for treatment of their seizures often without their physician's prescription or advice. In addition to seizure reduction, parents also reported other beneficial effects including increased alertness, better mood, and improved sleep. These reports are subject to bias given that they solely represent self-assessment, rather than data from clinical trials.

This is compounded by the common belief that nature's products are safe and by conversion of anecdotes into facts, especially when highlighted by the media. Failure to appreciate the difference between research and treatment and a desire to control one's care can also affect patient and caregiver perception of experimental therapies. For example, in Colorado, parents who had moved their family to the state to receive cannabinoid therapy reported response to therapy twice as high as that by parents who were already residing in the state (47% vs. 22%).

On the other hand, only a minority of neurologists reported that there was sufficient data to support the efficacy and safety of cannabinoids in epilepsy. About half of them would recommend its use in severe cases of medically refractory seizures. It is possible that the discrepancy between medical specialists and the general public is triggered by the slow progress in science.

Conclusion and Recommendations

Extensive preclinical data support that two cannabinoids, THC and CBD, with better data for CBD, possess anti-seizure properties. Solid clinical data in patients with epilepsy, however, remain lacking. Despite available circumstantial and anecdotal data, good quality placebo-controlled blinded studies are necessary before a conclusive statement can be made. It is not known at this time whether cannabis is more effective in children than adults, if a particular epilepsy type is more responsive to cannabinoids, or whether purified forms of cannabis are safe for the developing brain. Not enough data is currently available to safely and confidently recommend marijuana as an effective therapy for epilepsy. Patients and families are encouraged to participate in clinical trials. Consideration should be given for isolated use in a patient who has failed conventional therapy and is not a candidate for clinical trial. All patients and families should discuss any natural or experimental therapies they are using with their health care professionals.

References

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