Hot Topics in Neuroscience

MEDICAL MARIJUANA FOR EPILEPSY?

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This ongoing column explores off-label or emerging treatment options, drug development trends, and theoretical concepts in the field of neuroscience.

ABSTRACT

Treatment-refractory epilepsy remains an important clinical problem. There is considerable recent interest by the public and physicians in using medical marijuana or its derivatives to treat seizures. The endocannabinoid system has a role in neuronal balance and ictal control. There is clinical evidence of success in diminishing seizure frequencies with cannabis derivatives, but also documentation about exacerbating epilepsy or of no discernible effect. There are lay indications and anecdotal reports of success in attenuating the severity of epilepsy, but without solid investigational corroboration. Marijuana remains largely illegal, and may induce adverse consequences. Clinical applications are not approved, thus are restricted and only recommended in selected treatment unresponsive cases, with appropriate monitoring.

KEY WORDS

Marijuana, medical marijuana, Charlotte's Web, endocannabinoid system, cannabidiol, epilepsy, convulsions, seizures, ictus, treatment unresponsive epilepsy, Dravet syndrome, Lennox-Gestaut, Doose syndrome

INTRODUCTION

Approximately three million people in the United States are diagnosed with epilepsy and over one third of them experience poorly controlled seizures.[1] Along with the recent legalization of marijuana products, there is now general interest in medical marijuana as an ictal therapy.

ENDOCANNABINOID SYSTEM/ MECHANISM OF ACTION

A neuronal balance between excitatory and inhibitory synaptic communication is required for normal brain function. An imbalance can result in ictal phenomena.[2] The brain's endocannabinoid system provides on-demand protection against convulsive activity, having a major role in regulating the central nervous system. Endocannabinoids, their receptors, synthetic and degradative enzymes, and uptake mechanisms make up the endocannabinoid system. Exogenous cannabinoids reportedly mimic endocannabinoid activity in reducing seizures and countering neurodegeneration. This has precipitated questions about employing marijuana to establish ictal control.[2] Cannabis-derived substances, such as medical marijuana, are exogenous cannabinoids undergoing clinical applications and research to determine whether they diminish seizure frequencies. Dronabinol, nabilone, and nabiximols are pharmaceutical derivatives of

cannabis under investigation, with the latter one rich in cannabidiol.[3]

There are two cannabinoid receptors: CB1 and CB2. The CB1 receptors are expressed predominantly at presynaptic sites in GABAergic neurons.[4,5] These receptors are present in high densities at neuronal terminals of the basal ganglia, cerebellum, hippocampus, neocortex, hypothalamus, and limbic cortex.[6] To a lesser extent, the CB1 receptors are located in periaqueductal gray, dorsal horns, and immune cells. The CB2 receptor is primarily focused towards the human immune system; when activated, they can affect inflammation and immunosuppression. CB2 presence is also documented in animal brain physiology.

How does CB1 receptor activity affect clinical seizures?[2] The agonistic activity of CB1 decreases cAMP by inhibition of adenyl cylase, induces potassium efflux by stimulating A type and G-protein coupled inward rectifying potassium channels; also, it decreases calcium influx by inhibiting voltage-dependent N and P/Q-type calcium channels. This diminishes neuronal hyperexcitability and may attenuate seizure frequency. It also ameliorates the spasticity and tremors of multiple sclerosis and Huntington's disease in animal models.[7]

Seizures affect the endocannabinoid system and the expression of CB1 protein in the animal hippocampus.[8] This increases the expression of CB1 receptors in the CA1 through CA3 regions of the hippocampus and is postulated to be the mechanism of action for epilepsy control.

Marijuana has two neuro-active components that influence the endocannabinoid system: the psychoactive, delta-9-tetrahydrocannabinol (THC) and the non-psychoactive cannabidiol (CBD).[9] The marijuana sold illegally contains a high THC concentration and little or no CBD; medical marijuana approved for clinical studies of subjects with epilepsy has more CBD and a low THC content. In animal models of epilepsy, both CBD and THC are reported to have anticonvulsant properties.[10]

THC acts via CB1 receptors; CBD acts synergistically with THC, but the mechanism of action is unclear. CBD has low affinity to CB1 and CB2 receptors; the anticonvulsant properties are explained via cannabinoid receptor-independent mechanisms.[11,12] These include the regulation of cytosolic calcium levels via mitochondrial Na^{+}/Ca^{++} exchanger, blocking low voltage (T-type) Ca^{++} channels inhibiting glycine activity, membrane hyperpolarization by agonistic activity on 5HT1A receptors, and increasing endogenous adenosine levels. Together, they decrease convulsive activity.

In models of temporal lobe and partial seizures, CBD was therapeutic in reducing ictal frequencies. In the acute pilocarpine model of temporal lobe seizures, administration of CBD lowered the incidence of convulsions mediated by influence on the NMDA receptor.[11] In the penicillin model of partial seizures, CBD evidenced anticonvulsant effect through a GABA mediated mechanism.[12] Evidence regarding CBD-induced drug interactions is limited, but it inhibits CYP2C and CYP3A enzymes. It also induces CYP2B1/6 in animal models; enzyme induction varies widely in human studies.[13]

CLINICAL IMPLICATIONS

In the popular press, there are a plethora of uncontrolled clinical utilizations reporting medical marijuana as a treatment of epilepsy.[9] Many of these are anecdotal vignettes about children with refractory epilepsies, such as Dravet syndrome, Lennox-Gastaut, and Doose syndrome, etc. Most of them claim rather positive outcomes in decreasing seizure frequencies.

There has been a surge of interest in the "Charlotte's Web" form of marijuana.[14] The Charlotte's Web medical marijuana has very little THC, with greater than a minimum 30:1, CBD:THC ratio. The discussed person, Charlotte, had intractable Dravet syndrome epilepsy and her parents said that using this type of marijuana in their child attenuated her seizures; that led to the popularity of medical marijuana. It sparked interest in cannabinoids as a treatment for epilepsy, even despite the lack of scientifically proven evidence for safety or effectiveness. For legal access to it, her family moved to Colorado, heightening publicity, even though marijuana remains inconsistently legal elsewhere.

Marijuana was documented as protective against a first-onset seizure in men.[15] Cannabis had therapeutic benefit for both provoked and unprovoked seizures in men.[16] Smoking marijuana can precipitate an ictal event and be a proconvulsant.[5,17] In a clinical vignette, medical marijuana was administered for control of focal epilepsy in two adult subjects and that reportedly resulted in near complete seizure control.[18] Upon discontinuing marijuana, both patients experienced exacerbation of convulsions, documented on video-electroencephalography.

Anecdotal evidence in a survey revealed that 21 percent of patients with seizures in a tertiary epilepsy center admitted to utilizing

marijuana in the past year.[19] Among them, 24 percent believed it was beneficial. A pilot study of CBD versus placebo was conducted in eight normal volunteers and 15 patients with refractory generalized epilepsy.[20] In the first phase, the volunteers received CBD or placebo in double-blinded fashion for 30 days; the second phase included the subjects with epilepsy who were randomized double-blindedly to receive CBD or placebo for 135 days. Those with epilepsy continued their previous anticonvulsant medication. There were no adverse effects reported. Four subjects with epilepsy claimed to be almost seizure free, three experienced decreased frequency of partial seizures, and one remained unchanged. Among seven placebo-treated individuals, six of them did not improve and one claimed better seizure control.

Many conventional antiepileptic drugs are poorly tolerated by persons who experience adversities such as irritability, aggressive behavior, and/or insomnia. However, cannabidiol-enriched cannabis induces fewer such problems; yet, it still may provide benefits in mood, sleep, and alertness.[9] In a survey, some parents discontinued anticonvulsant medicine for their children after observing beneficial effects of cannabidiol, while still reporting improved and well-tolerated seizure control.[9]

However, marijuana abuse can be a concern. It is not universally legal. A 48-year-old man suffered seizures after consuming synthetic, purchased-online, cannabinoids.[21] Late-onset seizures were recorded in a 44-year-old individual who had a long history of smoking marijuana.[22] Recreational cannabis may exacerbate juvenile myoclonic epilepsy.[5] In an informal survey of 219 people with epilepsy who used cannabis, 90 percent of them did not notice any change in seizure frequency, seven percent reported better ictal control, and three percent experienced exacerbation of seizures.[5] There may be other adverse consequences which confound the decision to employ such agents in patients.

Despite positive reviews in the popular press, there is little support about the efficacy of medical marijuana by physician epilepsy specialists.[23] It remains as an unapproved therapy, without evidence-based support. Still awaited are well-designed investigations to establish the risk-to-benefit ratio, safety, and efficacy of medical marijuana for someone with epilepsy. General interest and anecdotal claims should be subservient to scientific scrutiny. Until then, great caution is advised for everyone considering its use and even greater concern by physicians who might recommend it to patients.

CONCLUSION

For those whose seizures remain uncontrolled without alternative conventional interventions available, medical marijuana has received anecdotal support, but only on an empirical basis. Any clinical trial is appropriate only in selected refractory cases and only when strictly monitored by a physician. Being illegal in many jurisdictions remains a concern.

There is a dearth of controlled scientific investigations reported on cannabidiol as an epilepsy control medication. Reportedly, there is no evidence for interactions between CBD and approved anticonvulsant drugs.[13] The varied legal status of marijuana, unregulated THC:CBD fraction preparations, lack of controlled double-blind studies, and unapproved indications for medical marijuana compromises understanding, research, and clinical applications. This makes prescribing such products by a physician complicated for medical and ethical reasons. An additional concern has to do with potential risk that marijuana might induce adverse consequences on the developing brain of children and adolescents.[24–26] At the current state of scientific understanding, the rationale for using medical marijuana in patients with epilepsy would be only when everything else has failed and the persons concerned are well-informed about the implications of its use.

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