The Relationship Between Epilepsy and Cannabis

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Abstract

Epilepsy is a disorder in which several recurrent seizures occur and, despite the fact that there are over twenty anti-seizure drugs available, more than 30% of individuals with epilepsy continue to have seizures. Many researchers have turned to cannabis, specifically the constituent cannabidiol (CBD), as they search for new solutions to this treatment-resistant form of epilepsy. The purpose of this paper is to provide an assessment of the relationship between cannabis and epilepsy. This paper reviews a total of seven studies, including one case study, and one meta-analysis. A considerable amount of controversy surrounds this topic, as cannabis is illegal, both medicinally and recreationally, in many parts of the world, and many researchers are undecided as to whether its legalization would be beneficial or not. In spite of this disagreement, most researchers believe that cannabis, specifically CBD, has positive health benefits and reduces seizures in epilepsy. Future analysis requires high quality and reliable studies which can continue to further our understanding of the relationship between cannabis and epilepsy.

Keywords: marijuana, epilepsy, seizures, cannabidiol

There is a complex relationship between cannabis and epilepsy. To understand this relationship, I first define two important terms: cannabis and epilepsy. It is important to distinguish between epilepsy, the neurological disorder, and epileptic seizures, symptoms of the disorder, due to abnormal excessive or synchronous neuronal activity in the brain (Beghi et al., 2005). Epileptic seizures have different classifications with distinct symptoms, and therefore consist of many different treatments. Epilepsy can be defined as a disorder with several types of recurrent seizures that are often correlated with a disruption of consciousness (Kolb & Whishaw, 2009). Epilepsy is the most common chronic neurological disorder, affecting nearly 50 million people around the world (De Boer, 2002). The second term that must be defined, cannabis, is a psychoactive plant that grows naturally, with many chemical elements present in a variety of different levels and mixtures, some of which are psychoactive (Gordon & Devinsky, 2001). As of 2014, cannabis was the most commonly used illegal drug in the United States, with about 12% of the population over the age of 11 having used the drug recreationally within the past year (Volkow, Baylor, Compton, & Weiss, 2014). As research for epileptic treatment continues, and as medicinal cannabis progresses toward legalization throughout the world, this relationship between cannabis and epilepsy becomes increasingly important. Most of this research has found that cannabis, specifically the constituent cannabidiol (CBD), has positive health benefits and reduces seizures in epilepsy. This paper begins by exploring epilepsy and the recognized classifications, the diagnosis of the disorder, and a few of the available treatments. Next, it will look at several studies on the treatment of epilepsy involving cannabis, including a case study on Charlotte Figi. Finally, it will review some of the controversies surrounding cannabis and epilepsy treatment, then suggest future directions for research.

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Epilepsy, as defined earlier, is a disorder in which individuals experience recurrent seizures and disturbances in consciousness (Kolb & Whishaw, 2009). Epileptic seizures are relatively common, affecting about 5% of people, while recurring seizures are comparatively uncommon, affecting only about 0.5% of people (Kolb & Whishaw, 2009). Seizures that occur spontaneously, and without a disease of the central nervous system (CNS), are termed idiopathic, while seizures that are accompanied by a specific change in, or damage to, the CNS are called symptomatic (Kolb & Whishaw, 2009). These seizures can then be categorized even further into focal, generalized, akinetic, and myoclonic (Kolb & Whishaw, 2009). Focal seizures begin in one location and extend adjacently in the body and brain (Kolb & Whishaw, 2009). Complex seizures, a form of focal seizures, are often associated with three indicators: experiences that warn the individual of an attack, automatisms, and postural changes (Kolb & Whishaw, 2009). Generalized seizures are dissimilar from focal seizures in that they happen bilaterally in the brain and not in one location (Kolb & Whishaw, 2009). Akinetic and myoclonic seizures are primarily seen in children and involve a sudden collapse, or sudden spasms, of the body (Kolb & Whishaw, 2009). The symptoms of epilepsy vary immensely, although, there are three underlying symptoms that are found in most people with epilepsy: an aura or perceptual disturbance occurring before the seizure, loss of consciousness, and a motor component that ranges from mild to excessive movement (Kolb & Whishaw, 2009).

An electroencephalogram (EEG) is frequently used to diagnose epilepsy because it is convenient and moderately inexpensive (Smith, 2005). However, EEG is not a perfect diagnostic tool, as around 10% of patients with epilepsy do not qualify as epileptic patients when diagnosed using an EEG (Smith, 2005). Moreover, an abnormal EEG does not, in itself, reveal that an individual has a seizure disorder, as some estimate about 20% of healthy individuals show abnormal EEG patterns (Kolb & Whishaw, 2009; Smith, 2005).

As excessive electrical activity in the neurons cause seizures, epilepsy treatment often involves anticonvulsant drugs that reduce the levels of such electrical activity (Kolb & Whishaw, 2009). Anticonvulsant drugs can be classified according to their effects on sustained high frequency repetitive firing (SRF) of action potentials and on the modification of postsynaptic gamma-aminobutyric acid (GABA) responses (Macdonald & Mclean 1986). These anticonvulsant drugs often reduce seizures; however, they also produce other side effects. The most common side effects are cognitive defects, which include psychomotor slowing, reduced attentiveness, and memory deficiency (Loring & Meador, 2001). As mentioned earlier, roughly 30% of people with epilepsy continue to have seizures, suggesting that there is room for improvement surrounding epileptic treatment (Friedman & Devinsky, 2015). This treatment-resistant form of epilepsy is characterized by persistent seizures, despite treatment with adequate doses of two appropriate antiepileptic drugs (Krauss & Sperling, 2012). In an effort to reduce the number of people with treatment-resistant epilepsy, researchers are looking for new medications, such as cannabis.

As mentioned earlier, cannabis, is a naturally-growing, psychoactive plant, with many chemical elements that are present in a variety of different levels and mixtures (Gordon & Devinsky, 2001). The main cannabinoid components of cannabis are delta-9-tetrahydrocannabinol (THC), which is involved in changing brain functions and altering behaviour, and cannabidiol (CBD), which is the primary non-intoxicating constituent (Gordon & Devinsky, 2001). An important note is that heating these cannabinoids results in their decarboxylation, which produces components with psychoactive effects. Evidence suggests that the mechanism of action of THC involves the cannabinoid receptor (CB1), while that of CBD, the focus of epilepsy treatment, is considerably less well understood (Szaflarski & Benin, 2014). THC induces antagonistic effects on the CB1 receptors. These receptors are associated with cognition, memory, reward, anxiety, pain sensation, motor coordination, and endocrine function, responsible for THC's mental and behavioural effects (Sharma, 2012). As of October 2018, the only countries that have completely legalized recreational cannabis use are Canada and Uruguay, although several countries have adopted a decriminalization policy (Habibi & Hoffman, 2018). Several countries have legalized medicinal cannabis, including Australia, Canada, Chile, Colombia, Germany, Greece, Israel, Italy, the Netherlands, Peru, Poland, and the United Kingdom (Habibi & Hoffman, 2018). Many other countries have legalized cannabis for the treatment of epilepsy, which has resulted in improved availability of products with high CBD and low THC concentrations (Szaflarski & Benin, 2014). It is important to note that most studies using cannabis for epilepsy treatment are concerned with CBD rather than THC. Cannabis use has been associated with substantial adverse effects, including the interference with cognitive and motor functioning (Volkow et al, 2014). Cannabis can be addictive, and repeated use during adolescence has been shown to have the greatest impact (Volkow et al, 2014). Cannabis addiction is defined in the Diagnostic and Statistical Manual of Mental Disorders (DSM-V) as a problematic pattern of use leading to clinically significant impairment or distress as manifested by at least two of a variety of symptoms in a 12 month

period (American Psychiatric Association, 2013). According to a review done by Volkow et al. (2014), approximately 9% of people who experiment with cannabis will become addicted.

A study, done by Wallace, Blair, Falenski, Martin, and DeLorenzo (2003), used male rats to induce epileptic seizures by injecting a substance known as pilocarpine. The researchers then monitored the seizures using EEGs and measured the hippocampal levels of the endocannabinoid Arachidonoylglycerol (2-AG), an endogenous agonist of the CB1 receptor and the primary endogenous ligand for the CB2 receptor. The results indicated that the epileptic rats exhibited altered activity of the cannabinoid (CB1) receptor. When the researchers administered SR141716A (a drug that inhibits the CB1 receptor) to the rats, they found that it increased seizure frequency and duration. The epileptic rats showed increased activity of the hippocampal CB1 receptors, as well as an increase in 2-AG levels in the hippocampus. This evidence suggests that cannabinoids play a significant role in the treatment of epilepsy. Wallace et al. (2003) demonstrated that the activation of the CB1 receptor by cannabinoid drugs can alter the frequency and duration of epileptic seizures, suggesting that cannabinoid treatment is more effective than some of the previously used anticonvulsants in epileptic rats.

Maa and Figi (2014) conducted a case study on Charlotte Figi, a young girl with Dravet syndrome. This syndrome is characterized by severe epilepsy, caused by a gene mutation. Charlotte Figi began developing frequent myoclonic seizures when she was 90 days old. Her condition continued to worsen even after several different anticonvulsants, including levetiracetam, oxcarbazepine, valproate, and valium, were prescribed to her. By the time she was 5 years old, she had significant cognitive defects, including psychomotor slowing, inability to eat or drink, as well as up to 50 generalized seizures per day. Charlotte's mother, Paige Figi, contacted two brothers from Colorado., known as the Stanley brothers, who developed a strain of cannabis specifically for Charlotte, later titled "Charlotte's Web" (CW), which has a low dose of THC and a high dose of CBD. Roughly two years after Charlotte started the treatment with CW, she regained the ability to eat, drink, walk, and talk on her own. Her seizures reduced from about 300 per week to about 2-3 nocturnal seizures a month. Maa proposes that the earlier studies', that cannabis was a proconvulsant, might have been due to the mode of administration. For example, when cannabis is smoked, heat might alter some of its anti-epileptic properties. Maa emphasizes the importance of the extracting method for CBD, as the conditions and solvents used play a critical role in maintaining the strains' anti-epileptic properties. This case must be looked at critically and objectively, as one person is not a representative of the population, and the reliability and validity of any case study remains in doubt.

A study, done by Gross, Hamm, Ashworth, and Quigley (2004), attempted to determine the frequency of cannabis use in people with epilepsy, as well as these participants' beliefs. The researchers surveyed 136 participants over the telephone. The results, though fairly inconclusive, showed that the epileptic patients used cannabis slightly more than the general population. It was also found that participants with more severe and frequent seizures consumed cannabis. Gross et al. (2004) proposed two possible solutions. These participants may have sought out cannabis after their conventional anticonvulsant medications failed, or cannabis, itself, might have caused the increased seizure frequency and severity. Another interesting statistic was that only 41% of the surveyed participants had heard of cannabis use for the management of epilepsy. This study suggests that, although many beneficial effects have been reported for single patients and animals, much more research is required before any conclusions regarding the effectiveness of cannabis, as a treatment for epilepsy, can be made.

A study done by Devinsky et al. (2016) attempted to establish the safety, tolerability and effectiveness of CBD with the treatment-resistant form of epilepsy. In their experiment, they studied 214 patients, 1-30 years of age, with severe treatment-resistant epilepsy that was contracted when they were young. These patients were given an oral cannabidiol dosage between 2–50 mg/kg per day for 12 weeks. The median reduction of monthly seizures was 36.5%, suggesting that CBD may reduce the frequency of seizures. Five participants reported zero seizures during the 12-week period. It is worth noting that 20% of participants experienced serious adverse events, including 19% who experienced diarrhea and reduced appetite. These findings are hard to interpret, as no control group was present, and nocturnal seizures were not recorded, which necessitates further research. This study shows some promising results regarding the safety, tolerability and the reduction of seizures using the cannabis constituent, CBD.

In a study by Press, Knupp, and Chapman (2015), they attempted to establish a relationship between oral cannabis extracts (OCEs) and epilepsy. The researchers conducted a retrospective study of 75 young patients with a variety of epileptic syndromes. While there was little to no difference when comparing the strains of the cannabis, it is worth noting that none of the participants reported significant improvement when they received THC alone. When 30 participants were evaluated, before and after their treatments, only 10% had improved EEG readings.

57% of the parents of these patients reported some improvement, with 33% reported having a significant (more than 50%) reduction in seizures. Some of these improvements include an increase in alertness, improved language and motor skills, and better sleep. On the other hand, 44% of patients reported adverse effects. Some of these effects included the worsening of seizures, fatigue, and gastrointestinal symptoms; however, most of these participants described that these adverse effects were mild and the benefits outweighed the harm. Press et al. (2015) concluded that although many adverse effects arose in the analysis of this retrospective study, some families did report significant improvement with cannabis treatment. Once again, more studies are needed to evaluate the effectiveness and safety of OCE treatment for epilepsy.

Gloss and Vickrey (2014) conducted a meta-analysis of 26 studies attempting to assess the efficacy and safety of the use of cannabinoids for epilepsy treatment. Their inclusion criteria included any randomized controlled trial, involving participants with any form of epilepsy and the use of any type of cannabis. Of the 26 studies that were assessed, 22 were removed, as many were only case studies. The four studies that remained provided no reliable conclusions concerning the efficacy, or safety, of the use of cannabinoids. However, Gloss and Vickrey (2014) concluded that there were no significant side effects of the cannabinoids, with the exception of mild drowsiness in one study. This meta-analysis has low power and the evidence is far from conclusive. First, the meta-analysis only incorporated four studies, and all of the studies were conducted before 1990. Second, all four of the studies were assessed to be low quality and to be at a high risk for bias. Finally, the sample sizes were extremely low for each of the four studies, as the highest had only 15 participants. It is important to note that the evidence found by Gloss and Vickrey (2014) is inconclusive, as the factors mentioned above suggest that cannabis and epilepsy is still in the early stages of research. This analysis calls for continued research involving cannabinoids and epilepsy that include better designed, and higher quality studies.

The most recent study done by Devinsky et al. (2018), investigated a promising new strain of highly purified CBD, marketed under the trade name Epidiolex, and its effectiveness in patients with severe childhood-onset epilepsy. The researchers included 55 participants, with four different types of intractable genetic epilepsy, and tested Epidiolex for both efficacy and safety. The median monthly convulsive seizure frequency was determined prior to the Epidiolex treatment at 59.4 per month, as well as 12 and 48 weeks post-treatment. The frequency of the seizures was reduced to 22.5 per month and 23.3 per

month, respectively. This decrease in convulsive seizure frequency (51.4%) was significant; however, there was no significant difference in seizure percent change between weeks 12 and 48. Side effects of Epidiolex were generally mild, with the most common adverse effects being diarrhea, somnolence, and fatigue. It is important to recognize some of the limitations of this study. Since the study was open-label, this highly publicized drug comes with copious amounts of positive anecdotal evidence, suggesting the possibility of a placebo effect. Another limitation of this study was that the dosage of other antiepileptic drugs was not strictly controlled, although the participants were instructed to keep the dosages as consistent as possible. This study shows some encouraging results regarding the effectiveness of Epidiolex in reducing seizures, warranting additional quality controlled experimental trials.

The findings in the above studies are critical in our understanding of how cannabis affects patients with epilepsy. However, more research must be conducted before a concrete conclusion can be formulated. An important limitation in the previous literature is the fact that in most countries, cannabis is illegal. An interesting finding in the study done by Press et al. (2015), was that families that moved to Colorado (a state where cannabis can be prescribed for epilepsy) were three times as likely to report significant reduction in seizures. They hypothesized that this may be due to the placebo effect, and a bias due to a strong desire for the medications to work (Press et al., 2015). These researchers support the need for controlled, blind trials that would help diminish the possibility of confounding factors, such as the placebo effect (Press et al., 2015). Volkow et al. (2014) hypothesized that as cannabis becomes legalized, its use will increase, and so will the number of people that will experience negative health effects. In contrast, there are many benefits to the legalization of cannabis that may outweigh the harm (Wodak, 2002). These benefits may include the relief of pain and nausea for cancer and HIV/AIDS patients, tax revenue, control of crime, and decreased costs of the criminal justice system (Wodak, 2002). Canada has recently legalized recreational cannabis, and it will be interesting to see how this effects the research on epilepsy treatment.

Cannabis, specifically the cannabinoid component of CBD, has shown some evidence of positive health benefits and an efficacy in the reduction of seizures in epilepsy. Cannabinoid treatment has been shown to be more effective than some anticonvulsants in rats. The case-study of Charlotte Figi also provides evidence for the positive effects of CBD treatment, although the reliability and validity of any case study must be met with skepticism. Some families in the Press et al. (2015) study

reported significant improvement with cannabis treatment. The most recent study done by Devinsky et al. (2018) also shows promising results regarding the safety, tolerability and the reduction of seizures using the highly purified strain of CBD, Epidiolex. An underlying attitude for all of the literature discussed is that more studies are needed to evaluate the effectiveness and safety of cannabis treatment and epilepsy. An important limitation that must be recognized is that these studies are not consistent. One study using smoked cannabis may have vastly different effects than a study using purified cannabidiol, therefore making them difficult to compare. Further evidence will ensure a greater understanding of the relationship between cannabis and epilepsy. This paper calls for continued research regarding cannabinoids, specifically CBD, and their effectiveness in the treatment of epilepsy, with better designed and higher quality studies.

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