Understanding Cannabinoids and Epilepsy©

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Executive Summary
Can natural occurring cannabinoids (components of marijuana) treat epilepsy?

Dr. James Bradstreet, one of the most experienced and respected doctors in treating autism and associated disorders, addresses this important question. The short answer is: yes. What's known as "high ratio CBD/THC cannabis products" do have documented efficacy in cases of drug-resistant epilepsy. Surveys of parents using a 35:1 CBD/THC ratio to treat their children with catastrophic epilepsy reported an astonishing response rate of 84%. (These findings are also relevant to parents who are concerned about side effects of traditional seizure medications, even if their children's epilepsy is not drug-resistant.)

But it's a complex issue, and Dr. Bradstreet counsels parents to become educated about the biochemistry involved in the interaction between cannabis and the human body. He discusses variables that can affect response – both in the patient profile and in the form of delivery of the cannabis. He also elaborates on the various plant species that may be used, including subspecies as a result of hybridization.

Thank you Dr. Bradstreet for remaining on the forefront of treatment of seizures – one of the most challenging conditions that's so often associated with autism. We encourage our readers to become familiar with the basic concepts he describes below, and gain a greater understanding of how marijuana-derived chemicals may help reduce the frequency and severity of seizures in a child or adult.

Question: Do natural occurring cannabinoids treat epilepsy? On the surface that may seem straightforward and a simple yes or no answer, but the reality is a more complex answer.

To get to our answer let us first look at what nature has provided. Our understanding of biochemistry of the endocannabinoid system (eCS) has grown rapidly in the last decade. The eCS is the natural occurring, complex and vital regulatory apparatus intrinsic to all humans. It is a means for various fatty substances (ligands) to be recognized by all organs, but seeming most important to the central nervous system (CNS) and the immune system. This allows each of us to adjust our immune responses and behaviors to survive in response to the challenges posed by differing diets, infectious diseases and our gastrointestinal ecosystem (microbiome).

The complexity of being human comes with an average 1.5 million point mutations on our DNA referred to as single nucleotide polymorphisms (SNPs). Several of these SNPs influence the levels of critical neurotransmitters like dopamine and serotonin. There is also a complex interaction between the endogenous fatty acids produced to regulate our own eCS, and cannabis use with each person's combination of these SNPs (Ermis, et al. 2015). This eCS regulation is strongly influenced by the individual's microbiome [that complex ecosystem of bacteria and fungi living within our bodies] (Cani 2102).

Because of these critical variables, predicting a response to exogenous (from without your body) cannabinoid (marijuana) derived chemicals is challenging. Further complicating our estimate of response to medical marijuana versus special extracts and concentrates is the *entourage effect*. Simply,

the entourage effect was first proposed by Ben-Shabat and colleagues (1998) at Hebrew University in Jerusalem to explain the complex interactions of various fatty acids, some of which have no apparent direct effect on the eCS. Equally, studies of the cocktail of chemicals in marijuana taken together, as opposed to pharmacological extracts studied as isolates, have very different effects.

Here is an example. Tetrahydrocannabinol (THC) the psychoactive agent in marijuana, is the most powerful naturally-occurring activator of the receptor on neurons known as CBR1. THC is also well known to be neuroprotective at extremely low levels, while at somewhat higher levels which would be easily obtained with either medical marijuana or recreational use of cannabis plants it appears to be neurotoxic (Sarne, et al. 2011). However, cannabidiol (CBD), a very well-studied cannabinoid which does not attach itself to either CB1R or CB2R (the immunologically important receptor), protects neurons from THC induce toxicity (Russo 2011). The potential risk of THC is also linked to a person's vulnerability based on their various SNPs. Moreover, although not presently known, researchers suspect the THC-mediated effects are further tied to the composition of the diet and the metabolic effects of a person's microbiome.

Now we need a little background on marijuana plants. Cannabis has two major species: sativa and indica, and one less well-characterized species, ruderalis (a hardy plant - native of Russia). The C. indica species are commonly thought of as medicinal, while sativas are more associated with the psychotropic effects. Unfortunately, it is far more complex than that. Hybridization has created countless subspecies with significant variations in their individual cocktail of cannabinoid chemistry. Typically, species are characterized for the ratio of THC to CBD, and this is an important consideration. However, CBD purified extracts have inconsistent and inadequate anti-epileptic activity when investigated in isolation. Recently, cannabidivarin (CBDV), a lesser-known cannabinoid compound, enhanced the anti-seizure effects of CBD and again demonstrated the benefits of the entourage effect, since neither act via traditional cannabinoid receptors (Hill et al, 2013).

The present research is far from sufficient to define the "right" THC-CBD-CBDV ratio for treating epilepsy, especially in children where concerns abound. But for parents of children with drug-resistant epilepsy, there isn't time to wait on more rigorous science; they are diving into treatment with CBD-enriched decarboxylated oils and medical marijuana from local or regional dispensaries.

So what is driving this rush to cannabis products for children? Simply this – many times it works. Porter and Jacobson (2013) surveys parents using a CBD/THC ratio of 35:1 in children with catastrophic epilepsy and found a response rate of 84%. We don't know anything about the other entourage fatty acids present in the compound.

In summary, while caution needs to be the mandate, high ratio CBD/THC cannabis products do have documented efficacy in cases of drug-resistant epilepsy and clearly deserve our attention. Hopefully, we will learn more soon about the additional effects of CBDV and other entourage fatty acids.

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