



Testimony to Senate Drug Caucus
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June 24, 2015

First, let me express my sincere appreciation for your consideration of the topic of cannabidiol in the treatment of epilepsy. These patients are often some of the most marginalized in both society and healthcare and the investment of your time today is significant and appreciated.

Epilepsy is a disease that can have devastating consequences, including profound cognitive, behavioral, and psychiatric comorbidities, impacting long term outcomes and quality of life. We know, without a doubt, that intractable, medically refractory epilepsy with onset before three years of age is associated with lower IQ later in life. When we shift our focus to older children and adults with pharmaco-resistant epilepsy, we can add associated social stigma, cognitive and psychiatric disorders, physical injuries, and significantly increased mortality due to significantly increased rates of sudden, unexpected death, drowning, accident, and suicide.

Medically refractory epilepsy is not rare. In fact, of the 2.3 million patients living in the United States with epilepsy, more than 1 million of them live with uncontrolled seizures. Statistically speaking, if you fail two appropriate drugs, your chance of subsequent seizure freedom with current prescription medications falls to less than 10 per cent. As seizures steal away developmental milestones, the parents and families of children with intractable epilepsy watch (in some cases quickly) as their child morphs into a shadow of who they once were and struggle to cope with the concept of current therapies not working. These children are taking antiepileptic drugs that attempt to suppress seizures, but can also cause a widespread list of side effects, including: cognitive impairment, developmental delay, blindness, liver failure, bone marrow failure, electrolyte abnormalities, significant rash, and even death. In fact, you would struggle to find a medication list with more significant side effects other than chemotherapy. So there is a real thirst for novel therapies, even potentially risky ones, with the chance that they may get some of their child back. Not in 5 or 10 years, when permanent damage is done, but right now.

Although significant increases in anticonvulsant drug options have been made in the past 15 years, we still have a great need for novel therapy types. In recent years, anecdotal reports of profound success in using medical marijuana, made widespread through the popular media, has created the impression that cannabis derived products are perhaps the panacea for this problem. But medical

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marijuana is not the accurate term for our discussion today. Of the more than 80 cannabinoids found in the marijuana plant, two are of particular interest to most marijuana researchers. The first, Δ^9 -THC (Δ^9 -tetrahydrocannabinol) is the major psychoactive component of marijuana, causing most of the effects pursued during recreational use. The second, CBD (cannibidiol), is a nonpsychoactive compound that has come into focus in the past few years as a novel therapy for intractable epilepsy. In addition to potentially being anticonvulsant, there is also evidence to suggest that CBD has neuroprotective and anti-inflammatory effects. The exact mechanism(s) that CBD amplifies or impairs to create these effects is hypothesized, but is largely unknown, although there are well known endocannabinoid pathways that are well understood. Both Δ^9 -THC and CBD act on two cannabinoid receptors in the human body: CB1 and CB2. CB1 is a receptor in the brain, modulating the GABA (inhibitory) and glutamatergic (excitatory) neurons in the nervous system, potentially affecting seizures. The CB2 receptor, in contrast, exists in the human immune and hematologic (blood) systems and is somewhat less relevant for our discussion today.

Of significant concern to us in the epilepsy world is the fact that in animal models, CBD appears to be anticonvulsant while Δ^9 -THC appears to be proconvulsant in some species. In addition, early research is beginning to show that consistent dosing of CBD is important for maximum effectiveness, while anecdotal studies suggest that small amounts of Δ^9 -THC must be given in concert with CBD for it to work. Most industry (medical marijuana) reported data out of Colorado and California suggests a target ratio of 20:1 (CBD: Δ^9 -THC). But the risks of cannabis exposure to the developing brain must be considered. Recent studies suggest that early exposure to cannabis (before 15 years of age) increases risk of psychosis, lowers the long term IQ, and causes impairment of long-term executive function. (Incidentally, some other currently marketed anticonvulsants have similar data, to say nothing of the cognitive issues that come with seizing countless times per day.) Δ^9 -THC is far more potent than CBD, so while CBD is not psychoactive, only small amounts of Δ^9 -THC are needed to have some effect and cannabis itself has >80 cannabinoids and 300 other compounds. We have only discussed two. These compounds themselves may have other unknown effects and warrant their own safety evaluation.

Unfortunately, while popular culture, media reporting, and encouraging anecdotal reports suggest that CBD works well to treat epilepsy, we in the medical field are flying blindly. A total of four early clinical studies have been published on using CBD (or other cannabinoids) for epilepsy, all between 1978 and 1990. All were inadequately powered with only 9-15 patients per study. Their only conclusion was that adults could take 200-300mg/day of CBD and tolerate it without immediate effect. No significant long term data or epilepsy response could be derived from this.

Clinical (and Basic science) research is limited due to the Schedule I controlled substance nature of CBD as it is derived from the marijuana plant. As a way to slide around these federal restriction, many states have passed laws allowing the use of CBD or CBD containing compounds in the use of epilepsy, specifically in children. Many of these laws, including in my home state of Mississippi, are written with significant research and restrictive language, but they do not take into account the hows and whys of actually obtaining CBD (if it is even possible at all), much less the lack of clinical science behind it. These laws often create frustration between hopeful families and uncertain healthcare providers. This has also led to families uprooting and moving to states with existing widespread medical marijuana legislation intact, allowing them to find sources of CBD on their own, most typically outside of physician direction.

In addition, the overall lack of regulation of this product in these states and in the medical cannabis industry raises significant concerns about what these children are actually taking. As most families are getting their product directly from a dispensary or from a grower, there is very little control over what ratio of CBD/ Δ^9 -THC is being administered, to say nothing of lack of consistent dosing. CBD and Δ^9 -THC do not come from the same plant and are refined differently. Ratios of each can be variable depending on plant clone, weather, and soil. There has even been description of variation of compound in the same greenhouse. And this is not a hypothetical concern: in February of 2015, the FDA issued warning letters to firms about 18 different products that advertised as CBD containing compounds but did not actually contain adequate CBD to claim as such. Seven of these contained no CBD, and two of the ones that did, including the only product with more than 1 percent CBD, were marketed for pet usage in dogs and cats.

We also struggle to contest with placebo effect and anecdotal reporting bias, found in epilepsy therapies in general, but especially in this product. There is even an unusual side to studying this therapy in that some families view cannabinoids as “natural” or “artisanal” and this selection bias creates potentially spurious reporting results. As an example of this, the University of Colorado group reported on 75 children with refractory epilepsy taking “oral cannabis extract” for their epilepsy. The response rate (parental reporting) overall was similar to the typical placebo response rate in several recent studies, but families that have moved to Colorado for the therapy were three times more likely to report a >50 percent reduction in seizure frequency, despite similar epilepsy substrates and age groups. In another evaluation of Colorado children, 47 percent of these patients had some adverse effect, 21 percent of these being new or worsened seizures and of these fifty-eight children there was one death.

With this background, it is easy to understand the dramatic outcry that has come from the caregivers of epileptic children for increased access to medical marijuana, specifically cannabidiol, as well as the healthcare provider need for expanded research before declaring it efficacious or safe. There is a substantial difference between anecdotal successes in popular media and clinical observation that deserves evaluation. Relative to that, in the past two years, the Epilepsy Foundation, American Epilepsy Society, American Medical Association, and CURE have all released position statements with language supporting the rights of Americans with epilepsy to have “access to physician directed care, including medical marijuana.” This is coupled with calls for the DEA to “end restrictions that limit clinical trials and research into medical marijuana for epilepsy,” and CBD’s DEA schedule I ranking be “reviewed” as a barrier to research. These statements are especially complicated in light of variable access to therapy based on geography and state laws. In all statements, the gold standard of well-designed clinical research studies are recommended. No organization is calling for the widespread legalization of marijuana (medical or recreational), but rather the specific evaluation of marijuana, especially cannabidiol in the safe treatment of epilepsy.

With all of this in mind, we at the University of Mississippi Medical Center have partnered with our parent institution, the University of Mississippi, to start a study on consistently grown, harvested, and refined CBD from a natural source. There is a synthetic CBD (Epidiolex) currently being studied in the U.S., but researchers are unable to get significant quantities of stable and reliable CBD from a natural source. The University of Mississippi has historically had the only Federally monitored marijuana farm in the United States for 47 years and they are truly world experts in this product. We hope to complete the process of getting group IND, NIDA and DEA approval, both for the production and use in humans, with a separate DEA schedule I clearance for me as a healthcare provider. Our study will start small, but we currently have a waiting list of about sixty-five children waiting for the trial (and that is only the tip of a very large iceberg). At present NIDA has funded one kilogram of product (with an option to extend to thirty kilograms if funding becomes available). The reported average dose for an adult is 200-300 mg two times daily. With this amount we can do approximately one month of study on fifty patients. This is not nearly enough time to learn anything beyond entry level information.

We will initially be targeting only those older children who are pharmacologically resistant with associated profound developmental delays, but plan to move quickly to incorporate younger children into the study once we have determined palatability, dosing, and safety. Our study will be compassionate use only, and we will use pre product disease and post product disease (as measured by familial reporting and electroencephalography) as our baseline. In addition, we will be monitoring the effect of the CBD on the electrolytes, liver functions, bone marrow, and metabolism

of the patient's existing anticonvulsants. There is significant information to be mined from this project, information only available with controlled stable product given in a research setting.

Long term, however, large double blind placebo studies, with analysis of CBD and CBD/ Δ^9 -THC combinations are required. Many families report that small amounts of Δ^9 -THC are required for maximum therapy and this is a question for which we have no answer, although Epidiolex should help to narrow that field, especially when compared with our data. Expanded studies are also needed to compare epilepsy syndrome efficacy and safety. The best anecdotal stories show an impressive response in Dravet syndrome and infantile spasms, two catastrophic epilepsies. But epilepsy medications are not one size fits all, and some therapies make one epilepsy better while exacerbating another. To achieve significant research numbers, this will have to be done in several sites, again raising an issue with quality controlled product distribution.

In summary, unfortunately, we in the medical world just do not know enough about CBD, or its use in medical refractory epilepsy. But we do know that it shows promise and deserves study. We want to use any potential therapy we can to fight for these patients. And we do feel an urgency due to our patients' severity of disease and the fact that this therapy is being used by children located in pockets in our country, without significant medical oversight. But we desperately need objective and unbiased data on the safety and efficacy of this product before we can endorse it or safely make recommendations about it. Our currently existing research set-up is not meeting this mandate. We would welcome any changes to the Federal government's restrictions on CBD as a research compound for the study of epilepsy. This week's discussed removal of the Public Health Service review is a step in the right direction. We need consistent access to stable product, fast track processing or redefinition of FDA/DEA credentialing for research and increased funding and scientifically constant product from the NIH/NIDA. Our patients need and deserve it.

Thank you for your time and consideration.

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