



AMERICAN EPILEPSY SOCIETY

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December 30, 2015

Speaker Galen Hadley and the Nebraska Legislature
Room 2103
Nebraska State Capitol
P.O. Box 94604
Lincoln, NE 68509

Dear Speaker Hadley,

On behalf of the American Epilepsy Society I am writing today to speak against Nebraska LB 643 and to share the position of our organization and highlight some of the experience of our members in other states, especially those in Colorado who have seen the most epilepsy CBD cases in the U.S. We applaud your existing measured approach and for giving this issue thoughtful consideration.

The American Epilepsy Society is the leading U.S. organization of clinical and research professionals specializing in the diagnosis and treatment of people with epilepsy, with more than 3,800 members engaged in all aspects of epilepsy. For nearly 85 years, the members of the American Epilepsy Society have led nearly every medical and scientific advance in epilepsy. Each year, the American Epilepsy Society hosts a scientific meeting on epilepsy more than 1,500 scientific studies are presented, making this the world's largest and most respected epilepsy meeting. This year's meeting in Philadelphia attracted over 5000 attendees from around the world.

Epilepsy is the most common and potentially devastating neurological disease that affects people across the lifespan. In America, one in 26 people will be diagnosed with epilepsy at some time in the course of their life - more will experience an isolated seizure. Epilepsy is associated with significant morbidity and mortality and carries an increased risk of many co-morbidities including depression, cognitive dysfunction, and autism. Today between 2.2 and 3 million Americans, including almost 400,000 children, live with epilepsy, with one third living with treatment-resistant seizures that do not respond to current medications. The large number of treatment resistant cases emphasizes the urgency of bringing forth new treatments for epilepsy, but those treatments must be proven safe and effective in order to be truly helpful to people with epilepsy.

Despite the pressure of anecdotal evidence prevalent in the popular press and social media, for the past two years the American Epilepsy Society has been opposed to the expanded use of medical marijuana and its derivative, cannabidiol or CBD, in the treatment of children with severe epilepsy. At this time there is no evidence from controlled trials that strongly supports the use of marijuana for treatment of epilepsy. Our position is informed by the lack of available research and supported by the position statements from the American Academy of Neurology, the American Academy of Pediatrics, and the American Medical Association. Additionally, a 2014 survey of practitioners published in the journal *Epilepsy Currents* found that the

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majority of epilepsy practitioners agreed with and supported the American Epilepsy Society position. (A copy of the society's position is attached). The American Epilepsy Society has consistently advised states against acting on anecdotal evidence alone and has called for more research. The need for more research is a consistent theme from nearly every medical society in the U.S. To help advance research, the American Epilepsy Society has requested that the Federal Drug Enforcement Agency reschedule marijuana to ease access for clinical studies.

AES has also been supportive of the compassionate use program of GW Pharmaceuticals, where a purified and uniform preparation of cannabidiol (CBD) called Epidiolex is being administered under the guidance and close monitoring of an appropriate medical professional.

The lead investigator for this clinical trial, AES member Dr. Orrin Devinsky, released promising results of the phase 2 study during the annual meeting of the American Epilepsy Society. While Dr. Devinsky called the findings promising, he cautioned that "these results are from an uncontrolled study. Further study is needed before results can be confirmed. Randomized controlled studies are now underway to help us better understand the effectiveness of the drug."

This next phase is called a phase III placebo controlled study, and AES supports this critical step to help our whole community better understand the potential role of CBD in treatment of epilepsy. It is also important to note that in these studies Epidiolex was added to current AED treatment regimes.

It is very important to note that the CBD oil Epidiolex used in the clinical trials is a vastly different substance than the artisanal cannabis products that are being considered for use in Nebraska, and that have been used in states where the product is legal like Colorado. In states like Colorado where medical marijuana and its derivatives are legal the content of these products is not regulated for purity or uniformity. Pharmacy-grade products like Epidiolex have followed Good Manufacturing Processes, meaning that the CBD content is measured by rigorous standards, that it is carefully monitored for additives or contaminants and that even the equipment used for manufacturing meets rigorous standards. None of this is true for the artisanal products.

A study by a team from Children's Hospital Colorado that was presented during the AES Annual Meeting in December 2014 has recently been published in the April issue of the journal *Epilepsy & Behavior*. This study found that artisanal "high CBD" oils resulted in no significant reduction in seizures in the majority of patients and in those for whom the parents reported improvements, these improvements were not associated with improvement in electroencephalograms (EEGs), the gold standard monitoring test for people with epilepsy.

Additionally, in 13% of cases reviewed seizures worsened with use of cannabis and in some patients there were significant adverse events. These are not the stories that you have likely heard in your public hearings or have read in popular press, but they are the reality of AES members who are practitioners at Children's Hospital Colorado who have cared for the largest number of cases of children with epilepsy treated with cannabis in the U.S.

Unlike the product used in the GW Pharmaceutical study, the families and children moving to Colorado are receiving unregulated, highly variable artisanal preparations of cannabis oil prescribed, in most cases, by physicians with no training in pediatrics, neurology or epilepsy. As a result, the epilepsy specialists in Colorado have been at the bedside of children having severe dystonic reactions and other movement disorders, developmental regression, intractable vomiting and worsening seizures that can be so severe they have to put the child into a coma to get the seizures to stop.

Because these products are unregulated, it is impossible to know if these dangerous adverse reactions are due to the CBD or because of contaminants found in these artisanal preparations. The Colorado team has also seen families who have gone into significant debt, paying hundreds of dollars a month for oils that do not appear to work for the vast majority. For all these reasons not a single pediatric neurologist in Colorado recommends the use of artisanal cannabis preparations. Possibly of most concern is that some families are now opting out of proven treatments, such as surgery or the ketogenic diet, or newer antiseizure medications because they have put all their hope in CBD oils.

The well intentioned law makers who have enacted laws in many states have done so without the benefit of robust scientific evidence. However, this has created an uneasy situation where the laws are ahead of the science because we do not understand how and why various treatments work and for whom they are effective. Research also helps us understand the correct dose, side effects, and potential interactions with other medications. At present, the epilepsy community does not know if marijuana is a safe and effective treatment nor do we know the long-term effects that marijuana will have on learning, memory and behavior, especially in infants and young children. This knowledge gap is of particular concern because both clinical data in adolescents and adults and laboratory data in animals demonstrate that there are potential negative effects of marijuana on these critical brain functions.

The American Epilepsy Society is sympathetic to the desperation parents of children with severe, treatment-resistant epilepsy, and understands the need for compassionate use of promising new therapies in appropriate and controlled circumstances. We are however opposed to the use of artisanal preparations of unregulated compounds of cannabis that contain unverified content and are produced by people with no experience in pharmaceutical production. That is what is currently happening in Colorado and may soon be happening in multiple states across the county as they legalize the use of medical marijuana products.

The artisanal products currently provided in Colorado do not meet the FDA definition of expanded or compassionate use. The FDA requires compassionate use therapies to meet the same criteria as an investigational new drug which require standard purity, content and content uniformity testing of the product and adherence to good manufacturing processes. None of these criteria are met in the products being given to people with epilepsy in Colorado and we are seeing the distressing results noted above. And yet, these and other similar products are being considered for use in several states.

It is also worth noting that in late February 2015, the FDA issued several warning letters to firms that claim their products contain CBD. The FDA has tested those products and, in some of them, did not detect any CBD as claimed on the label. Because there is no standard for these products, the market is increasingly flooded with a wide variety of products. Should Nebraska approve access to these preparations it will bear the burden of monitoring for quality and controlling for the continuity of supply. This requires a level of new administrative oversight and the associated budget impact.

Currently, the previously mentioned pharmaceutical grade marijuana extract of purified cannabidiol (Epidiolex from GW Pharmaceuticals) is being rigorously tested in several types of epilepsy. These FDA authorized trials are ongoing at dozens of US epilepsy centers; many have already completed or at least finished enrollment. None of the results of these controlled trials have been published as of December 2015, but it is likely that we will have scientifically rigorous data to evaluate during 2016. In addition, because the trials enrolled so quickly it is possible that an FDA approved product could be on the market sometime in 2017. Once an FDA approved product is on the market and available to people with epilepsy throughout the US, there is much less urgency for individual states to pass complex legislation about regulation and distribution of medical marijuana.

In sum, there simply is no clinical, controlled research to support the adoption of new CBD legislation for epilepsy such as your state is considering. The anecdotal results of a few families in Colorado, shared in the media, should not be the basis for law making. The rush by states to pass CBD legislation has created an unusual situation where people with epilepsy and their families are demanding access to a highly variable homegrown substance that may or may not be beneficial and the medical and scientific community lacks the necessary efficacy and safety data to make good treatment decisions regarding cannabis for people with epilepsy, especially in children.

Sincerely,

A handwritten signature in black ink that reads "Michael D. Privitera MD". The signature is fluid and cursive, with the letters "MD" written in a smaller, more distinct font at the end.

Michael D. Privitera, MD
President
American Epilepsy Society
Director, Epilepsy Center
University of Cincinnati Neuroscience Institute

cc: Patrick D. O'Donnell, Clerk
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