

## Practical Issues in Medical Cannabis Use: A Mother and Scientist Weighs in on the Issues Facing Medical Cannabis Use and the Future of Research

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The political and health controversies surrounding medical cannabis have exploded over the last three years. This has been due in large part to the discovery that it may benefit children with severe treatment-resistant epilepsy—a debilitating brain disease with no effective treatment.

My son has a severe form of epilepsy. Three years ago another parent told me that cannabis was alleviating the severity of his child's seizures. I searched the Pubmed database and found a reasonable number of studies<sup>1-3</sup> supporting anti-seizure effects of one specific cannabinoid, Cannabidiol (CBD). CBD is a non-psychoactive cannabinoid; that is, it does not induce a "high." Though there were no definitive data on dose, side effects, or efficacy, there was enough promise in the studies I reviewed to encourage me toward further investigation into whether CBD might lessen the frequency and severity of my son's seizures. Uncontrolled epilepsy in children is a cruel disease that can lead to significant cognitive, motor, and behavioral delays. Neither the patient nor the caretaker knows when the next seizure will strike or how much damage it will cause. In fact, sudden unexplained death in epilepsy (SUDEP) is responsible for 34% of all sudden deaths in children.<sup>4</sup> The percentage of patients with epilepsy who have untreatable seizures has remained the same (at about 30% to 35%) since the approval of phenytoin in 1953, despite the development of 40 second- and third-generation anti-seizure drugs over the last 60 years. I believe that any therapy with the potential to reduce seizure frequency or severity in this difficult-to-treat and constantly suffering population must be explored.

I searched medical cannabis dispensaries in San Francisco, where I

live, for CBD. As the parent of a child with a serious brain disease, I suddenly found myself consulting "bud-tenders" who had no medical training for advice on how to transform raw cannabis, which contains hundreds of cannabinoids and terpenes, into an appropriate medication for my son. I was not alone. In every state in which medical cannabis was legal, other parents were doing the same thing. I decided to survey these parents to find out how they were solving what seemed to me an insurmountable problem. How were they deciding what to give their children? How did they calculate dosage? How did they administer the cannabis? The results of this survey were published in late 2013 in *Epilepsy and Behavior*.<sup>5</sup> My motivation for publishing the results of the survey was not to establish proof of efficacy. Indeed, establishing efficacy is impossible with a survey, and the reasons for this are clearly explained in the paper. Instead, my goal was to focus the attention of the medical community—both clinicians and researchers—on the experience of these parents in order to prompt further research into the safety, tolerability, and efficacy of specific cannabinoids in the treatment of epilepsy.

The survey results were astonishing. Parents reported incredible benefits to their children. Their willingness to experiment with preparations of cannabinoids obtained from unknown sources without medical guidance was disturbing, yet understandable, given the severity of this disease. It attests to the desperation a parent feels in the face of watching one's child slowly deteriorate. Importantly, however, it also attests to the lack of support these families received from their physicians and the researchers in the community. Support might

have come in the form of following the child medically, with routine blood work to document effects on organ function, dangerous drug-drug interactions, and serious adverse events. Documentation of data from a large enough number of patients over the past two years could have provided some insight that would inform future treatment of pediatric epilepsy patients with cannabinoids. For these data to be meaningful, however, the chemical content of the cannabis that the children are ingesting must be defined. There is enormous variability in the cannabinoid content of artisanal preparations of medical cannabis. Trying to decipher the effects of an undefined preparation is tantamount to trying to decipher the effects of a handful of drugs taken together, without knowing which drugs they are or in what amount they are given. To collect interpretable data, cannabinoid content of the preparations being administered must be known.

For many frustrating months I attempted to find a reliable and safe source of CBD. I could not. Available samples were only provided in small artisanal batches and were not reproducible. They were often inaccurately labeled. What bud-tenders were calling CBD was always a mixture of many components of the plant, including the psychoactive cannabinoid, tetrahydrocannabinol (THC). The preparations also contained contaminants such as heavy metals, solvents, and pesticides—facts we discovered when we tested these preparations at medical cannabis testing facilities.

At the end of that discouraging search, we desperately wanted a preparation that met Food and Drug Administration (FDA) requirements for safety, would be supplied reliably,

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and could be administered in a clinical setting with oversight by our pediatric epileptologist. Together with another family, we approached the only pharma company we could find working in the cannabinoid field, GW Pharma, which is based in the United Kingdom. We asked if they would be willing to produce a pure CBD medication for our children that met FDA standards for safety. To our amazement, they agreed and found an FDA mechanism by which our physician could administer CBD legally through our hospital's pharmacy. The FDA's Expanded Access (or Compassionate Use) Program was established to allow patients access to potentially beneficial investigational drugs in the case of "a disease or condition associated with morbidity that has substantial impact on day-to-day functioning of the patient" and for which there are no effective treatment options.<sup>6</sup> Obtaining the investigational drug via this mechanism required an enormous amount of work. First, our physician had to get FDA and institutional approval of the protocol. Second, DEA approval for importing and storing a schedule 1 substance was required. Six months of applications and permits later, permission by all parties was granted. The speed with which we were granted permission is a testament to GW Pharma and their hard work and commitment to our children. Word spread fast, and they were soon asked to open additional Expanded Access programs at dozens of hospitals and clinics for hundreds of children. After evaluating the safety, tolerability, and potential efficacy of CBD in pediatric patients with severe treatment-resistant epilepsy through essentially an open-label trial (i.e. data

gathered via the Expanded Access programs), GW Pharma decided to continue its clinical investigation with formal Phase 2 and 3 FDA trials. Results from the first Phase 3 trial are expected later this year.<sup>7</sup>

Unfortunately, most of the 200,000 pediatric patients with treatment-resistant epilepsy in the United States have not had access to GW's pure CBD, Epidiolex, over the past two years. Consequently, distressed parents have continued to test artisanal preparations. Some say THC is also needed for full benefits. Some say it's a specific strain that is most useful. Despite two years of the use of artisanal cannabinoid preparations, we still lack information on how to treat pediatric epilepsy with medical cannabis. We do not have analyses of the chemical composition of these preparations nor any documentation of basic safety and tolerability issues. Have there been any serious adverse events? What dose is most appropriate? Are there drug-drug interactions to be aware of? These remain unanswered questions for any physician who would like to recommend medical cannabis to improve his/her patient's quality of life. This is relevant not just for epilepsy patients but also for patients suffering from a host of other ailments who entrust medical cannabis to improve their disease and disease-related symptoms and overall quality of life.

How should we proceed with a scientifically valid exploration of the benefits and risks of medical cannabis for all of these patients? For the benefit of patients who are eager for guidance by their physicians and for the physicians who are eager for information to provide that guidance, I would argue for the unrestricted gathering of methodologically sound clinical data. This type of

observational study would provide important information about whether the investigational drug is beneficial—and for whom.

While clinical research is complicated in the case of medical cannabis by patients' access to non-FDA-approved forms of the drug under investigation, the potential still exists to create valid methodologically sound research protocols that would provide meaningful and interpretable data. This research must begin, however, with a critical step: defining the drug under investigation. Whether patients are ingesting capsules or oils or vaporizing raw flowers, accurate documentation of the chemical components of the preparations and the dose administered is essential. Prospective open-label trials as well as randomized placebo-controlled trials can contribute to this knowledge base. Together, these data can guide informed treatment with a variety of defined medically appropriate cannabinoid preparations in a number of diseases. I hope that two years from now, how to treat seizures with cannabinoids will no longer be a mystery. We will have actual data.

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