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The current status of artisanal cannabis for the treatment of epilepsy in the United States

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ABSTRACT

The widespread patient use of artisanal cannabis preparations has preceded quality validation of cannabis use for epilepsy. Neurologists and cannabinoid specialists are increasingly in a position to monitor and guide the use of herbal cannabis in epilepsy patients. We report the retrospective data on efficacy and adverse effects of artisanal cannabis in Patients with medically refractory epilepsy with mixed etiologies in Washington State, California, and Maine. Clinical considerations, including potential risks and benefits, challenges related to artisanal preparations, and cannabinoid dosing, are discussed.

Results: Of 272 combined patients from Washington State and California, 37 (14%) found cannabis ineffective at reducing seizures, 29 (15%) experienced a 1–25% reduction in seizures, 60 (18%) experienced a 26–50% reduction in seizures, 45 (17%) experienced a 51–75% reduction in seizures, 75 (28%) experienced a 76–99% reduction in seizures, and 26 (10%) experienced a complete clinical response. Overall, adverse effects were mild and infrequent, and beneficial side effects such as increased alertness were reported. The majority of patients used cannabidiol (CBD)-enriched artisanal formulas, some with the addition of delta-9-tetrahydrocannabinol (THC) and tetrahydrocannabinolic acid (THCA). Four case reports are included that illustrate clinical responses at doses <0.1 mg/kg/day, biphasic dose–response effects, the use of THCA for seizure prevention, the use of THC for seizure rescue, and the synergy of cannabinoids and terpenoids in artisanal preparations.

This article is part of a Special Issue entitled "Cannabinoids and Epilepsy".

1. Introduction

An estimated 1.2 million Americans currently use medical cannabis with the recommendation of a medical provider in compliance with 24 state-regulated medical cannabis programs, an average of 0.8% of the population in those states [1]. Most medical cannabis states include seizure disorders in their qualifying list of conditions. The media coverage of cannabis use in epilepsy and heterogeneous state-level classification of medical cannabis use has clouded the usual requirement for rigorous scientific investigation and clinical trial pathway of the US Food and Drug Administration (FDA) for drug approval. Furthermore, obstacles such as lack of suitable pure materials, federal government classification, and emotional feelings about cannabis by researchers, clinicians, and medical administrators have produced the current situation where the widespread use of cannabis by patients has preceded quality validation of cannabis use for epilepsy. This "cart before the horse" situation has created the need for the medical community to respond to cannabis use in the clinical setting [2].

Nearly one-third of patients with epilepsy have symptoms that are refractory to treatment [3]. Although over 20 new seizure medications have been developed over the past several decades, the percentage of patients with medically intractable seizures has not changed dramatically [4]. Against this background, the media attention to anecdotal results with cannabis products in case reports and small uncontrolled studies has created demands for expanded access of herbal cannabis preparations [5–8]. Recently, one open-label interventional trial of purified cannabidiol (CBD) was published [9]. This study evaluated 214 patients with medically intractable seizures. Of these, 20% had a severe genetic epileptic encephalopathy, Dravet syndrome, and another 19% the Lennox–Gastaut syndrome. In the Dravet syndrome group ($n = 32$), there was a 50% reduction in motor seizures with one patient seizure free. In the patients with Lennox-Gastaut syndrome there was a mean reduction of 37% in motor seizures. Over the 12-week treatment phase of the study, there was an overall 30% reduction in seizures.

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2. Methods

We conducted a retrospective chart review of clinical records from patients with epilepsy seen at a children's hospital in Washington State and a private cannabinoid medicine practice in California. Four case reports were described from a private cannabinoid medicine practice in Maine. Details of patient responses to treatment were primarily derived from parental reports.

3. Results

3.1. Washington

In the state of Washington, the dilemma of federal and state law still exists. Washington is a "legal" state since the passing of Washington Initiative 502 (I-502) in 2012. This bill allows adult 21 years or older to possess small amounts of cannabis products and provides for a license system for producers, processors, and retailers. But under Federal law, cannabis and its products remain Schedule I drugs and thus physicians cannot legally prescribe any cannabis product. Under Washington state law, a physician can issue an "authorization" card that allows a patient to purchase cannabis products from state licensed retailers. There is no regulatory state control on the quality, purity, or reproducibility of the products dispensed.

The lack of oversight by regulatory agencies of cannabis products has created a quagmire of patient use of cannabidiol for seizure control. We are able to validate the product our patients are taking by serum analysis of drug levels. Although strongly requested to keep seizure diaries, most of this author's (RPS) patients do not. Seizure frequency figures are mostly by parental recall. Most of the patients consume CBD, 9-delta-tetrahydrocannabinol (THC), and/or most recently 9-delta-tetrahydrocannabinolic acid (THCA). Most obtain their product from local growers or they grow and process the final product themselves. Some families obtain hemp-based CBD products from out-of-state retailers. A few families rely on the producer to validate concentration of CBD, THC, and/or THCA while others have second party companies note these concentrations of the extract. However, once patients start taking the products, we can validate serum levels using a CLIA-certified laboratory.

Currently, there are approximately 47 patients taking artisanal or hemp-based CBD and/or other related products in our clinic population. There are 20 males and 27 females with age ranges from 2 to 18 years. Patients have seizures that are intractable to medications, with an approximate average number of antiepileptic drugs (AEDs) of 2.5 agents per patient [3]. Families discussed the possibility of starting CBD before initiating treatment. Once started, the patient returned to clinic and was subsequently followed for seizure control, serum levels, and possible side effects. Patients were accrued consecutively as they identified themselves as initiating CBD.

A total of 10 patients (21%) stopped taking CBD due to ineffectiveness. Two of these patients had Dravet syndrome (SCN1A mutation positive) [10], one had 15q11 duplication syndrome, two had not benefited from temporal lobe resection, three had hypoxic ischemic encephalopathy, and two had a non-specific epileptic encephalopathy. Cannabidiol levels ranged from 0.56 to 36.2 ng/mL.

The remaining 37 continue taking CBD and have reported reduced seizure frequency. There are two patients who have become seizure-free. The first patient is 7-year-old who had generalized seizures described as myoclonic with absence and EEG demonstrating 3-Hz spike-and-wave complexes. She is also currently on the Modified Atkins diet (30 mg of carbohydrates). Her last CBD level was 9.5 ng/mL. Tetrahydrocannabinol levels were not detected. The second patient is a 5-year-old young boy who had a traumatic delivery at birth and hypoxic ischemic encephalopathy. He has tonic generalized seizures and myoclonic seizures of his upper extremities. He is currently on 3 seizure medications in addition to the CBD extract. His CBD level is 1.8 ng/mL and delta-9-THC level is 0.8 ng/mL.

Four patients with Dravet syndrome, all with pathological SCN1A mutations, had seizure frequency reduction [10]. It is difficult to estimate the reduction of seizures as frequency was estimated by parent recall. By parental estimate, generalized motor seizures have decreased by approximately 20%–30% in each. The myoclonic seizures, photic induced myoclonic seizures, and staring episodes did not change in frequency. One of the patients was on the Ketogenic Diet and medications of valproic acid and clobazam. One patient was just on the Ketogenic Diet. The third patient was taking topiramate and clobazam. The fourth patient was only taking valproic acid. The CBD serum levels were variable as were the THC levels. Patients had CBD and THC levels of: 22 and 26 ng/mL, 15 and 13 ng/mL, and 4 and 6 ng/mL, respectively. The fourth patient had a CBD level of 10 ng/mL without THC levels detected.

The other 33 patients had assorted etiologies of medically intractable seizures, ranging from hypoxic ischemic events at delivery, multiregional cortical dysplasia, and unknown causes with normal MRI scans of the brain. Parental recall placed seizure reduction from 20% up to 40%. There did not seem to be a particular seizure type that is most altered by CBD or the combination of CBD + THC. Some patients have added THCA to the combination of cannabis products. By parental recall, no changes in seizure frequency with additional THC or THCA dosing were identified. Levels of CBD varied from 9 to 80 ng/mL. The THC levels varied from undetectable to 28 ng/mL. Most of the THC was added to "enhance" CBD effect on seizures. But, there was no clear benefit noted in terms of seizure frequency changes. We have not been able to reliably obtain serum THCA levels commercially.

Side effects reported were minimal. We followed liver transaminase levels, and even with very high CBD dosing, elevated levels were not seen. The most common side effects reported were somnolence (~20%), decreased appetite (~15%), and fatigue (~15%). Increased upper respiratory infections were reported in one patient.

3.2. California

In a Los Angeles-based medical cannabis practice, 225 patients with intractable seizures, ranging in age from 2 years to 46 years, have been followed for at least three months and up to 30 months of treatment with CBD-rich whole plant extract, accrued consecutively. The average number of AEDs tried prior to CBD treatment was 10. The average number of AEDs that patients were taking at initiation of CBD treatment was 3, with clobazam, valproic acid, and levetiracetam as the most common. Patients took CBD-rich whole plant cannabis extract in either olive oil or coconut/MCT oil, either sublingually or ingested. All patients used products laboratory-tested for cannabinoid potency. The CBD:THC ratios in the oils used by this cohort ranged from 27:1 to 15:1. Dosing ranged from 1 mg CBD/kg/day up to 9 mg CBD/kg/day.

Patient diagnoses include the following: Dravet syndrome (12 patients), Lennox–Gastaut syndrome (15 patients), Rett syndrome (2 patients), Angelman syndrome (2 patients), other genetic syndromes (22 patients), congenital brain malformation (11 patients), birth trauma/anoxia (7 patients), metabolic syndromes (6 patients), and tuberous sclerosis complex (2 patients); the majority of the rest of the patients had epilepsy of unknown etiology.

Ten patients (4%) reported worsening of seizures and 17 patients (8%) reported no effects of CBD treatment. Twenty-nine (13%) reported no change in the number of seizures but decreased severity and/or duration of seizures. Overall, 75% reported reduction of seizure frequency: 25 (11%) reported 25–50% reduction, 45 (20%) reported 50–75% reduction, 75 (33%) reported 75–99% reduction, and 24 (11%) reported seizure freedom (Table 1).

Parents reported beneficial side effects of increased alertness, improved mood ("happier"), better sleep, increased appetite, less use of rescue medicine, and less hospital/emergency department (ED) visits. Parents also reported improved stamina when participating in