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Efficacy of artisanal preparations of cannabidiol for the treatment of epilepsy: Practical experiences in a tertiary medical center

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ABSTRACT

Medically refractory epilepsy continues to be a challenge worldwide, and despite an increasing number of medical therapies, approximately 1 in 3 patients continues to have seizures. Cannabidiol (CBD), one of many constituents of the *Cannabis sativa* or marijuana plant, has received renewed interest in the treatment of epilepsy. While highly purified CBD awaits Food and Drug Administration (FDA) approval, artisanal formulations of CBD are readily available and are seeing increased use in our patient population. Although randomized controlled trials of CBD are ongoing and promising, data regarding artisanal formulations of CBD are minimal and largely anecdotal. Here, we report a retrospective study to define the efficacy of artisanal CBD preparations in children with epilepsy. Given the known interaction between CBD and clobazam, we also conducted a subgroup comparison to determine if clobazam use was related to any beneficial effects of CBD. Additionally, we compared response rates with CBD and with clobazam alone within an overlapping patient cohort. A pediatric cohort with epilepsy of 108 patients was identified through a medical record search for patients using CBD oil. The addition of CBD resulted in 39% of patients having a >50% reduction in seizures, with 10% becoming seizure-free. The responder rate for clobazam was similar. No patients achieved CBD monotherapy, although the weaning of other antiepileptic drugs (AEDs) became possible in 22% of patients. A comparable proportion had AED additions during CBD therapy. With concomitant use of clobazam, 44% of patients had a 50% reduction in seizures upon addition of CBD compared with 33% in the population not taking clobazam; this difference was not statistically significant. The most common reported side effect of CBD was sedation in less than 4% of patients, all of whom were also taking clobazam. Increased alertness and improved verbal interactions were reported in 14% of patients in the CBD group and 8% of patients in the CBD and clobazam group. Benefits were more marked in the CBD alone group, in contrast to the CBD and clobazam group, but this difference was not statistically significant. In summary, these findings support efficacy of artisanal CBD preparations in seizure reduction with few significant side effects. The response to CBD was independent of concurrent clobazam use, although clobazam may contribute to the sedation seen with concurrent CBD use.

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1. Introduction

Despite continued development of new medications for the treatment of epilepsy, nearly 1 in 3 patients remain drug-resistant [1,2]. While research into novel treatments of epilepsy is ongoing, we have not yet achieved the goal of "no seizures, no side effects."

In recent years, there has been a resurgence of interest in the use of medical marijuana, or more specifically, cannabidiol (CBD)-containing products in the treatment of medically refractory epilepsy. Greater than 400 distinct chemical entities can be found in *Cannabis s.*, including over 60 cannabinoid compounds [3]. As has been reviewed extensively by others, the pharmacology of individual cannabinoids is complex, with multiple pharmacologic targets independent of the cannabinoid 1 or cannabinoid 2 receptors [4]. As such, a treatment with multiple mechanisms of action may prove to be more effective than that of its constituents in isolation. *Cannabis*-derived products have been used medicinally since at least 2700 BCE by the Chinese and were part of the pharmacopeia in the United States into the 1930s [5].

Excitement regarding the efficacy of CBD in the treatment of epilepsy has grown in large part because of reports of almost miraculous successes by the lay media. While far from being a miracle cure, published

Abbreviations: AED(s), antiepileptic drug(s); CAE/JAE, childhood/juvenile absence epilepsy; CBD, cannabidiol; EME, early myoclonic epilepsy; ESES, electrical status epilepticus of sleep; LGS, Lennox–Gastaut syndrome; THC, tetrahydrocannabinol; TSC, Tuberous Sclerosis Complex; VNS, vagus nerve stimulator.

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data increasingly suggest that CBD may be efficacious for the treatment of epilepsy. However, concerns for bias remain. A notable study from Colorado, one of the first states to legalize CBD oil for epilepsy treatment, utilized surveys of patient caregivers. The responder rate was reported to be 22% in patients originally from Colorado compared with 47% in patients whose families had moved to the state in order to benefit from CBD oil, a difference which suggests a reporting bias [6]. However, recently published randomized controlled trials of a highly purified pharmaceutical-grade CBD demonstrated efficacy in both Lennox–Gastaut Syndrome (LGS) and Dravet Syndrome, lending support for efficacy in drug-resistant epilepsy [7,8].

In May of 2015, as part of an amendment to TN state law 39-17-402, the State of Tennessee made legal the possession of CBD oil containing less than 0.9% tetrahydrocannabinol (THC) for the treatment of epilepsy. This local legalization has led to a rapid increase in both patient inquiries regarding CBD oil and in the use of CBD-containing products by patients, with and without prior consultation with their physicians. Given the lack of high quality double-blind randomized controlled trials for artisanal CBD preparations, studies which are unlikely to occur, we sought to determine the efficacy of artisanal CBD preparations in our cohort of patients with epilepsy. The hypothesis was that patients with drug-resistant epilepsy would see a reduction in both seizure frequency and in either number or overall dose of standard antiepileptic medications with the addition of CBD-containing products. In addition, given the reported interaction with clobazam, a subgroup analysis was performed comparing response rate of those also taking clobazam with those who were not. Lastly, given the limitations of a retrospective study, we investigated the efficacy of clobazam alone in a similar patient cohort to support the data collection methodology.

In this retrospective study, we report that artisanal CBD is helpful in the treatment of medically refractory seizures.

2. Material and methods

Data were collected in a retrospective manner utilizing the Synthetic Derivative at Vanderbilt University Medical Center from January 2006 through December of 2016. Patients using CBD oil were identified using a keyword search for the terms: “cannabis”, “cannabinoid”, “cannabidiol”, and “CBD oil”. Upon extraction, patient information was deidentified and saved for group analysis upon completion of data collection. The study was approved upon review by the Vanderbilt University Institutional Review Board, IRB#161821.

From within the CBD-searched cohort, a subgroup of patients who use clobazam in addition to CBD as an epilepsy treatment were identified to determine if an interaction between CBD and clobazam contributed to efficacy or side effects (Fig. 1). As validation of the data collection methodology, we identified patients from within the CBD-searched cohort who used clobazam prior to addition of CBD or clobazam alone. This allowed us to assess the clobazam responder rate in a similar cohort of patients. Baseline seizure frequency was determined from the documented seizure frequency most proximal to the introduction of the new agent with responses and side effects derived from clinical documentation in the months following addition of the treatment, often documented in the next clinic visit.

Documented response to CBD or clobazam was organized into 7 categories: seizure-free, >75% seizure reduction, >50% but <75% seizure reduction, <50% seizure reduction or subjective improvement, transient response (better initially, followed by no response/worsening), no benefit, and worsening of seizures. Responders were defined as patients with >50% reduction in seizure frequency. We excluded 6 and 12 patients from the CBD and clobazam groups, respectively, because of inadequate documentation of seizure frequency, treatment response, or to being lost to follow-up.

Numeric results were compared using Student’s *t*-test. Categorical data were compared using *z*-test and with logistic regression analysis. Data are presented as mean ± standard deviation (STD) or as number (%).

3. Results

To determine the efficacy of artisanal CBD-containing products in the treatment of medically refractory epilepsy, we utilized the Vanderbilt Synthetic Derivative to identify a total of 329 charts where CBD was documented out of 3,652,459. We identified 210 patients, who were

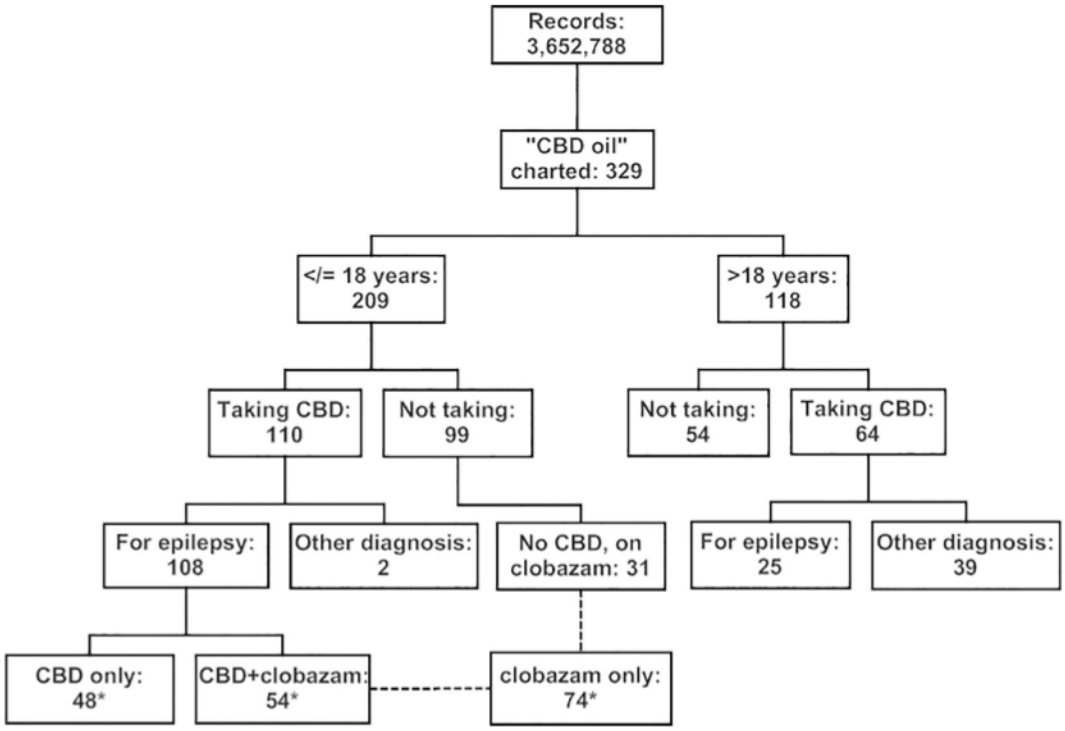

Fig. 1. Patient selection flow diagram. *Notes final number in group following exclusion for inadequate data.

Table 1
Reasons documented for taking CBD.

Reason for taking CBD	Age ≤18 N(%)	Age >19 N(%)
Epilepsy	108 (98.1)	25 (39.1)
Pain		13 (20.3)
Neoplasm		4 (6.3)
Mood/anxiety/depression	2 (1.8)	4 (6.3)
Unclear		4 (6.3)
Nonepileptic		3 (4.7)
Crohn's disease		2 (3.1)
Fibromyalgia		2 (3.1)
Dystonia		1 (1.6)
Toxic myopathy		1 (1.6)
Migraine		1 (1.6)
CP		1 (1.6)
MS		1 (1.6)
Tourette syndrome		1 (1.6)
Nausea		1 (1.6)

age 18 years and below, 110 of which were taking CBD oil. Of these, 108 patients were documented as taking CBD oil for epilepsy, which constituted the pediatric study cohort, and 2 for nonepilepsy reasons (Table 1). In the vast majority of the remaining patients, CBD use for epilepsy was discussed and documented in the medical record, but the patient had not yet started treatment. When documented, reasons for not taking CBD oil included the following: patient planned to but had yet to start, excessive cost, patient was not medically refractory, and concern for medication interactions. Two patients from this group were moving or had recently moved to Colorado specifically for CBD therapy.

In the adult cohort, age 19 years and above, 118 patients were identified, of whom 64 were actively taking CBD-containing products. In contrast to the pediatric cohort where over 98% of children were taking CBD for epilepsy, only 39% of adults were taking CBD for epilepsy (Table 1). Pain was the second most common reason for use and reported in 20% of adults, followed by a broad range of indications, predominantly neurologic and psychiatric in nature. Given the relatively low proportion of adults using CBD for epilepsy specifically, our subsequent analysis focuses only on the pediatric cohort.

We hypothesized that a clobazam cohort, obtained from patients who had either discussed CBD or who were on clobazam prior to starting CBD, would serve as an appropriate comparison group based on our observations that CBD was predominately used in patients with drug-resistant pediatric epilepsy, many of whom were also on clobazam. Indeed, significant differences between groups were minimal (Table 2). Together, structural and genetic etiologies accounted for 70% of the epilepsy overall. Greater than 58% of patients in both cohorts had abnormal magnetic resonance imaging (MRI), although a significantly higher number of charts in the CBD + clobazam cohort lacked documented MRI or reports when compared with the clobazam cohort. Over 93% of electroencephalogram (EEG)s were abnormal across all groups, with 20% consistent with an epileptic encephalopathy in the clobazam group and 17% and 31% in the CBD and CBD + clobazam groups, respectively. Focal seizures were the most common seizure type in all groups, occurring in greater than 28% of patients. Multiple seizure types were seen in greater than 17% of patients in all groups. Tonic seizures were reported more frequently in the clobazam group than in the CBD groups, likely due in part to a significantly greater representation of LGS in both the clobazam and CBD + clobazam groups versus the CBD group. Average age of epilepsy onset, 3 years, in the CBD group was significantly older than average age of onset in both the CBD and clobazam and clobazam alone groups. The clobazam cohort tended to have a greater incidence of treatment with a vagus nerve stimulator (VNS), while exposure to diet therapy was not significantly different between groups. The ketogenic diet was by far the most frequently used diet therapy. Cannabidiol + clobazam and clobazam groups both demonstrated greater numbers of patients with prior epilepsy surgery in comparison with none in the CBD group.

Baseline seizure frequency averaged 89/month with a range from 0 to 675 seizures/month in the CBD group, 372/month with a range of 0.33 to 4680/month in the CBD and clobazam group, and 437/month with a range from 0.25 to 10,800 seizures/month in the clobazam group (Supplemental Fig. 1). Following addition of CBD or clobazam, 33% of the CBD group, 44% of the CBD + clobazam group, and 38% of the clobazam group had a >50% reduction in seizure frequency. No seizures were reported at follow-up in 14% of the CBD group, 9% of CBD + clobazam group, and in 11% of the clobazam group (Fig. 2). A small or subjective improvement was reported in an additional 13% of patients upon addition of CBD. No change in seizure frequency was reported in 33% of CBD, 37% of CBD and clobazam, and 26% of clobazam patients. Sixteen percent of patients had increased seizures following addition of clobazam, significantly higher than 4% in the CBD + clobazam group, but was not significantly different than the 6% seen in the CBD group. Cannabidiol was added despite seizure freedom at the time of addition in 10% of the CBD group.

Examination of responder rate by electroclinical syndrome was complicated by a small N in many groups. In LGS, the most commonly noted syndrome in all cohorts, responder rate was 58% with CBD, 52% with CBD and clobazam, and 40% with clobazam alone. In patients who could not be classified into a clearly defined electroclinical syndrome, responder rate was 31% for CBD and 40% for both CBD and clobazam and clobazam alone.

Alternative markers of efficacy may include the ability to wean medications or other epilepsy therapies or may be suggested by whether the patient is still taking the medication. Duration of treatment may also be a marker of efficacy under the assumption that if a medication is working, it will be continued. On average, patients had been treated with greater than 5 antiepileptic drugs (AEDs) prior to addition of CBD or clobazam. Following addition of CBD or clobazam, no patients were able to wean all other medications resulting in CBD or clobazam monotherapy. Medication reduction was seen in 21% of CBD, 26% CBD + clobazam patients, and 18% of clobazam patients following addition of CBD or clobazam (Fig. 2). Increased doses or addition of other AEDs were seen in 15% of CBD, in 17% of CBD and clobazam patients, and 7% of clobazam patients, values which were not statistically different. Overall, 19–33% of patients in all groups had AED reductions and additions during treatment, reflecting the fluid nature of epilepsy management.

Duration of treatment was significantly longer in the clobazam group with an average of 2.5 years vs 1.1 and 1.3 years in the CBD and CBD + clobazam groups, respectively (Table 3). As duration of therapy may be confounded by the time the treatment became available, we also investigated the rate of continuation. On average, 71% of patients were still taking CBD with a rate of continuation not significantly different from 77% in the clobazam cohort. The most common reason for stopping CBD was no benefit, whereas side effects were the most common reason for stopping clobazam. Sedation was the most common side effect and was significantly more frequent in the clobazam group, reported in 36% of patients in the group versus 7% of patients in the CBD and clobazam group and 0% of patients in the CBD group.

Treatment changes made at the time of addition of CBD or clobazam could confound interpretation of treatment response and were also investigated. While significantly more treatment changes were made at the time of clobazam initiation compared with CBD initiation, a nearly equal number of treatments were added as were removed (Table 3).

Cannabidiol has anecdotally been reported to have myriad benefits in addition to improving seizure control [9]. Increased alertness, improved verbal communication, better social interaction, and better mood were the most commonly reported beneficial side effects (Table 3). Increased alertness and improved verbal skills were reported more frequently with CBD than with CBD and clobazam, although this was not significantly different. Improved alertness was also reported with the addition of clobazam.

Artisanal CBD is available from multiple companies as evident from the use of 10 different CBD products in our cohort (Fig. 3). The origin

Table 2
Demographics of pediatric epilepsy treatment groups.

	CBD N(%)/mean ± SD	CBD + clobazam N(%)/mean ± SD	Clobazam N(%)/mean ± SD
Sex			
Female	23 (47.9)	24 (44.4)	34 (45.9)
Male	25 (52.1)	30 (55.6)	40 (54.1)
Total	48	54	74
Current age (years)	10.4 (1.1 to 18)	7.8 (1.4 to 16)	8.5 (1.4 to 18)
Race/ethnicity			
White	45 (93.8)	50 (92.7)	63 (85.1)
Black	2 (4.2)	2 (3.7)	6 (8.1)
Hispanic	2 (4.2)	–	2 (2.7)
Arabic	–	1 (1.9)	1 (1.4)
Unknown	1 (2.1)	1 (1.9)	–
Etiology			
Structural	22 (45.8)	22 (40.7)	32 (43.2)
Genetic	16 (33.3)	17 (31.5)	23 (31.1)
Infectious	1 (2.1)	–	4 (5.4)
Metabolic	3 (6.3)	5 (9.3)	1 (1.4)
Immune	–	–	–
Unknown	6 (12.5)	10 (18.5)	13 (17.6)
Age epilepsy onset (years)	3 ± 3.9	1.2 ± 1.5**	1.5 ± 1.8*
MRI findings			
Normal	12 (25.0)	12 (22.2)	21 (28.4)
Abnormal	32 (66.7)	31 (57.4)	48 (64.9)
Unknown	4 (8.3)	11 (20.4)***	4 (5.4)***
Seizure types			
Multiple	4 (8.3)*	14 (25.9)*	14 (18.9)
Focal	13 (27.1)	13 (24.1)	12 (16.2)
Focal with bihemispheric spread	10 (20.8)	7 (13.0)	9 (12.2)
Epileptic spasms	5 (10.4)	7 (13.0)	8 (10.8)
Myoclonic–atonic	2 (4.2)	1 (1.9)	3 (4.1)
Absence	5 (10.4)	2 (3.7)	6 (8.1)
GTC	7 (14.6)	3 (5.6)	6 (8.1)
Tonic	2 (4.2)	2 (3.7)	10 (13.5)
Myoclonic	–	2 (3.7)	5 (6.8)
EEG findings			
Normal	3 (6.3)	2 (3.7)	3 (4.1)
Focal discharges	25 (52.1)	25 (46.3)	35 (47.3)
Generalized discharges	12 (25.0)	10 (18.5)	22 (29.7)
Epileptic encephalopathy	8 (16.7)	16 (29.6)	14 (18.9)
Electroclinical epilepsy syndrome			
Lennox–Gastaut syndrome	12 (25.0)	27 (50.0)*	40 (54.1)**
Early myoclonic encephalopathy	–	2 (3.7)	1 (1.4)
West syndrome	–	1 (1.9)	–
Childhood absence epilepsy	3 (6.3)	1 (1.9)	2 (2.7)
Juvenile absence epilepsy	1 (2.1)	–	1 (1.4)
Juvenile myoclonic epilepsy	1 (2.1)	–	–
Epileptic encephalopathy w/ CSWS	–	1 (1.9)	1 (1.4)
Epilepsy w/ myoclonic–atonic seizures	1 (2.1)	3 (5.6)	3 (4.1)
Epilepsy w/ eyelid myoclonia (Jeavons)	1 (2.1)	–	1 (1.4)
Childhood epilepsy with centrotemporal spikes	1 (2.1)	–	–
Childhood occipital epilepsy	1 (2.1)	–	–
Dravet	–	4 (7.4)	4 (5.4)
GEFS +	1 (2.1)	–	-
Epilepsy with GTC alone	–	–	1 (1.4)
Unclassified	26 (54.2)	15 (27.8)	20 (27.0)
Age CBD start (years)	8.8 ± 4.8	5.9 ± 4.0	7.2 ± 3.8
Total AED exposure	4.5 ± 2.7	6.5 ± 2.3***	6.1 ± 2.1
VNS	4 (8.3)	7 (12.7)	16 (21.3)
Diet therapy			
History of diet therapy	9 (18.8)	19 (35.2)	30 (40.5)
Currently on diet therapy	4 (8.3)	10 (18.5)	9 (12.2)
Diet used ketogenic	11 (84.6)	25 (86.2)	35 (89.7)
MAD	2 (15.4)	3 (10.3)	3 (7.7)
LGI	0	1 (3.4)	1 (2.6)
Epilepsy surgery	0	6 (11.1)*	9 (12.2)*

"–" indicates value not reported.
* $p < 0.05$ by Student's *t*-test or by *z*-test.
** $p < 0.01$ by Student's *t*-test or by *z*-test.
*** $p < 0.0001$ by Student's *t*-test or by *z*-test.

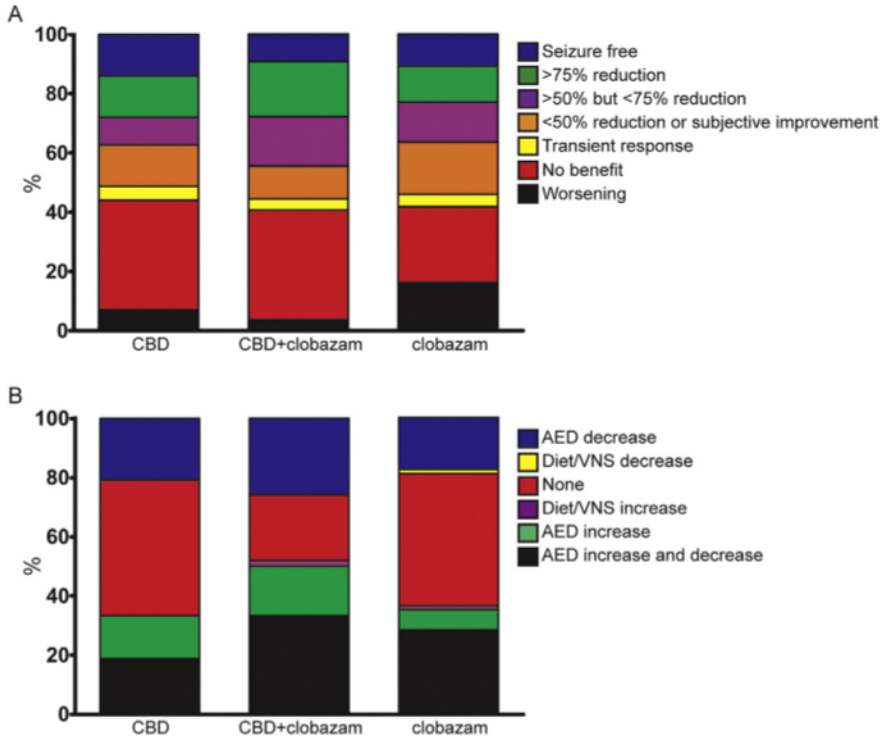

Fig. 2. Seizure response and treatment modifications following treatment with CBD or clobazam. Change in seizure frequency following addition of CBD or clobazam (A). Adjustments to AED and other epilepsy therapies following addition of CBD or clobazam (B). Cannabidiol and CBD + clobazam groups compared with the clobazam group and one another using a *z*-test.

of CBD was not documented in 26% of patients. Dosing in milligrams/kilogram (mg/kg) could be determined in most cases, with the average CBD dose of 2.9 mg/kg/day in the CBD group and 5.8 mg/kg/day in the CBD and clobazam group. Doses ranged widely, from 0.018 to 50 mg/kg/day. In approximately 10% of total CBD patients, only the volume of oil per dose was documented, with the dose unknown or undocumented in 6.3% of the CBD group and 20% of the CBD + clobazam group (Table 3). Average daily clobazam dose was 1.5 ± 1.4 mg/kg/day.

4. Discussion

Given the surge of interest and use of artisanal CBD-containing products by patients for the adjunctive or primary treatment of epilepsy, we set out to determine the efficacy of such products within a pediatric population with epilepsy. Consistent with other studies, our retrospective study suggests that artisanal CBD is helpful in the treatment of medically refractory epilepsy [10] with benefits that cannot be credited to interaction with clobazam and increased levels of its active metabolite. These data add additional support for the use of artisanal CBD in the treatment of drug-resistant epilepsy as in our patient population. As has recently been reported, outside of seizure control, CBD use was also associated with increased alertness, improved verbal communication, better social interactions, and better mood, suggesting additional benefits to use of CBD [9].

Prior to the recent randomized controlled trials for pharmaceutical grade CBD, much of the data supporting the efficacy of artisanal CBD have been in the form of parent-based surveys, with notable concern for reporting bias [6,11]. Although some of these studies were designed primarily to detail the real-world practice patterns of patients and their families, the data have also been used to make the arguments for efficacy and safety.

As with any retrospective study, our results may be confounded by reporting bias, inconsistent follow-up intervals, and incomplete documentation. Patients were being actively treated for drug-resistant epilepsy, thus, additional interventions were added and removed at the time CBD was started and throughout the treatment process, potentially confounding efficacy results and limiting our ability to draw long-term conclusions regarding efficacy. We cannot exclude that results of efficacy for CBD-containing products include some degree of parental bias or placebo effect. Indeed, even with severe epileptic encephalopathies such as LGS, the placebo responder rate can range from 10 to 30% [12]. Our inclusion of clobazam as a comparator and our finding of a similar response rate in the clobazam and CBD groups suggest that artisanal CBD can be of comparable benefit. Although we cannot exclude potential bias owing to patient belief in a higher likelihood of effect of CBD over clobazam given the retrospective nature of this study, we do feel that these data are, nonetheless, accurate representations of a population of patients that have drug-resistant pediatric epilepsy. As blood CBD levels were not recorded in our patients, we cannot verify the contents of the artisanal products used. However, the 10% seizure-free rate and 33% responder rates presented here are quite similar with the results from prior studies of artisanal CBD preparations in patients from Colorado [6], Washington State, and California, providing further support for efficacy of artisanal CBD products [13].

Additional confounds arise from variability in artisanal CBD preparations and incomplete and/or subjective bias in reporting of seizure frequency, response to intervention, and side effects. Continued emphasis on adoption of the American Academy of Neurology (AAN) practice parameters will benefit future retrospective studies greatly [14].

Variability represents a key challenge and concern for the use of artisanal products for medical treatment of epilepsy, given the lack of both regulation and verification of such products. This has previously been demonstrated in a study of commercially available edible marijuana products where THC content was shown to be mislabeled in 83% of samples tested [15]. Cannabidiol content, when labeled, was mislabeled in 100% of samples tested [15]. In contrast to the clobazam group, in which doses were easily discerned in all patients, exact doses could not be determined in over 25% of patients taking CBD, due to either a lack of dose documentation overall or report of volumes administered only. Cannabidiol was obtained through 10 different vendors with source of CBD not documented in over 30% of patients. Even for patients

Table 3
Duration of therapy and reasons for discontinuation of CBD or clobazam.

	CBD N(%)/mean ± SD	CBD + clobazam N(%)/mean ± SD	Clobazam N(%)/mean ± SD
Confounds at treatment start			
Treatment added	1 (2.1)	5 (9.3)	11 (14.9)*
Treatment removed	2 (4.2)	4 (7.4)	12 (16.2)*
None	39 (81.3)	43 (79.6)	48 (64.9)*
Treatments added and removed	5 (10.4)	2 (3.7)	3 (4.1)
Still taking	34 (70.8)	36 (65.5)	57 (77.0)
Duration treatment (years)	1.1 ± 0.8	1.3 ± 1.0	2.5 ± 1.9***
Reason stopped			
No benefit	9 (18.8)	5 (9.3)	4 (5.4)
Cost	2 (4.2)	3 (5.6)	0 (0.0)
Side effects	0 (0.0)	4 (7.4)	13 (17.6)**
Unknown	3 (6.3)	1 (1.9)	0 (0.0)
Deceased	0 (0.0)	2 (3.7)	2 (2.7)
Negative side effects			
Shaking	–	1 (1.9)	–
Sedation	–	4 (7.4)	27 (36.5)**
Rash	–	1 (1.9)	–
Increased seizures	1 (2.1)	2 (3.7)	–
Retching/reflux	–	1 (1.9)	–
Dizziness/unsteadiness	1 (2.1)	–	1 (1.4)
Nausea	1 (2.1)	–	–
Drooling	–	–	1 (1.4)
Transient fever	–	–	1 (1.4)
Worsened behavior/aggression	–	–	2 (2.7)
Loss head control	–	–	1 (1.4)
Positive side effects			
Alert	9 (18.8)	5 (9.3)	5 (6.8)
Better mood	2 (4.2)	2 (3.7)	–
More verbal	5 (10.4)	3 (5.6)	1 (1.4)
Better social interaction	3 (6.3)	2 (3.7)	–
Development/cognition	–	3 (5.6)	1 (1.4)
Focus	1 (2.1)	1 (1.9)	–
Decreased hyperactivity	1 (2.1)	–	–
Decreased aggression	2 (4.2)	–	–
Anxious/stereotypies	1 (2.1)	1 (1.9)	–
Tremor	–	1 (1.9)	1 (1.4)
Motor function	2 (4.2)	–	–
Spasticity	1 (2.1)	–	1 (1.4)
Tone	–	–	1 (1.4)
Sleep	–	1 (1.9)	–
Appetite	–	1 (1.9)	–
gi/gu	–	2 (3.7)	–
CBD dose (mg/kg)	3.0 ± 2.9	5.6 ± 5.3	–
Unknown	3 (6.3)	11 (20.4)	0
Liquid dose only	5 (10.4)	5 (9.3)	0

"–" indicates value not reported.
* $p < 0.05$ by Student's *t*-test or by *z*-test.
** $p < 0.01$ by Student's *t*-test or by *z*-test.
*** $p < 0.0001$ by Student's *t*-test or by *z*-test.

whose exact dose was documented, this may or may not be accurate or consistent because of limited regulation of artisanal products. A review of consumer-facing marketing and shopping websites for different vendors revealed a wide range of concentrations, pricing, and also dosing advice provided by these companies (Table 4). A common theme with many of the consumer-facing sites was lack of transparency regarding the exact manufacturing process for the CBD. Several companies purport to extract CBD from locally or, at times, internationally grown *Cannabis* according to good manufacturing practice (GMP) guidelines with third party certificates of analysis (COA) available, while others appear to use purified CBD isolates from unidentified wholesale manufacturers. Several companies are USA distributors for international manufacturers. The absence of regulation creates the potential for significant batch-to-batch variability in CBD concentration, wide variations in non-CBD cannabinoid content, and potential product impurities. This variability within and between artisanal products not

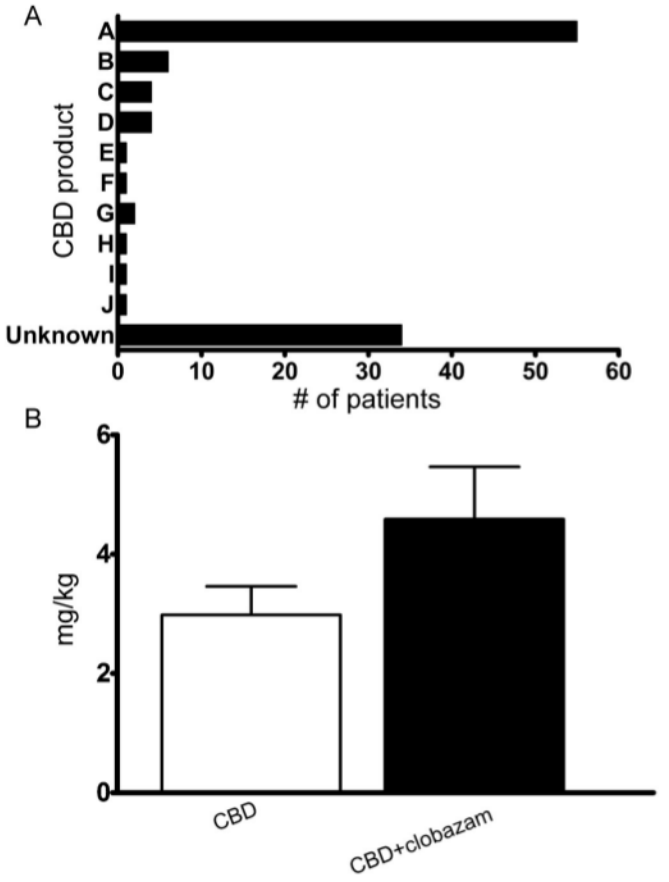

Fig. 3. Variability in CBD products and dosing. Multiple CBD-containing products were reportedly used in the treatment of epilepsy, with the majority from 1 vendor (A). Cannabidiol product used was not documented in over 1 in 3 patients. Average daily CBD dose (B) was not significantly different in CBD and CBD + clobazam groups. Data represent mean ± SEM, compared with Student's *t*-test.

only complicates the interpretation of seizure-response rates but also, more importantly, places patients at risk for inconsistent seizure control.

These concerns are amplified when considered in the context of studies evaluating generic formulations of seizure medications which suggest that the 80 to 125% range of bioequivalence may be too broad [16] and that transition to generic medications may increase seizure incidence and medical resource utilization [17]. While some feel that the concern regarding variability in generics is overstated [18], others recommend against switching between different generic formulations in patients who have achieved good seizure control [19]. Thus, issues with bottle to bottle, batch to batch, and strain to strain consistency for a plant-based product used to treat severe epilepsy remain of great concern.

Table 4
Variability in artisanal CBD concentration, cost, and recommended dose.

Originating state of artisanal product	CBD concentration range of oil based products (mg/ml)	Price range (US$/mg CBD)	Manufacturer recommended dose (mg)
Arizona	8–33	0.20–0.28	8–33
California	3–150	0.07–0.30	1–78
Colorado	7–54	0.07–0.19	7–54
New Jersey	50–250	0.08–0.14	7–250
Tennessee	47–60	0.07–0.11	1.5–30
Washington	1.6–10	0.13–0.31	1.6–10

Despite an extensive history of cannabis use as a medication in China back to 2700 BCE, in India in 1000 BCE, and in the US through the early 20th century, the medical use of cannabis was stunted in the US following criminalization in the 30s [5]. Its use remains restricted because of its status as a Schedule 1-controlled substance at the federal level, in spite of pressure from states which have allowed legalization for both medical and recreational use. Medical providers are tasked with using the best evidence available in making treatment decisions, a process which may put them at odds with family members who also want the best for their loved ones and may favor expediency and hope over evidence-based practice.

Given the inconsistency of the lay-information and the known drug–drug interactions, in order to appropriately advise patients on artisanal CBD use and side effect profile, it is critical for medical providers who treat epilepsy to actively inquire into its use as an adjunctive treatment. Taking a proactive approach is particularly relevant considering that treatments patients consider to be herbal/natural remedies may be underreported on medication lists [20]. While pharmaceutical grade CBD may ultimately be FDA approved, the use of artisanal products will very likely continue to expand because of biases against pharmaceutical products and artisanal product marketing which fosters the belief that unpurified *Cannabis* extract will have additional health benefits over pure CBD alone. Artisanal CBD will very likely have continued use in patients with epilepsy. Medical providers cannot ignore its usage and need to work with patients and their families to find the most appropriate treatment for their epilepsy.

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Conflict of interest

None.

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