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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

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Table 1
Percent seizure reduction attributed to the addition of artisanal cannabis: combined data from Washington and California.

% Seizure reduction	California	Washington	Combined	Percent of total
0	27	10	37	14%
1–25	29	12	29	15%
26–50	25	23	60	18%
51–75	45	0	45	17%
76–99	75	0	75	28%
100	24	2	26	10%
Total	225	47	272	

physical or occupational therapy. Adverse side effects included sedation, decreased appetite, and sleep disturbance.

Approximately 36% (81) of patients were able to wean off of one or more AEDs. Ten of the 24 patients with seizure freedom were able to completely wean all pharmaceuticals (4% of the entire cohort). Those patients that reported worsening of seizures returned to baseline seizure frequency after CBD treatment was discontinued. Cost of CBD treatment is a significant issue for the majority of these families and for many, CBD dose increases were prevented by the inability to pay for the product.

3.3. Cases

The following brief case reviews demonstrate common features in herbal cannabinoid treatment of epilepsy: the complex nature of artisanal cannabis preparations and variations from one batch to the next, the presumed efficacy of acidic cannabinoids, clinical responses at doses below 0.1 mg/kg/day, biphasic anticonvulsant/proconvulsant dose–response effects, and the use of THC to acutely treat GTCs.

3.3.1. Case #1

In a 4-year-old girl with Dravet syndrome (SCN1A mutation positive), concurrently treated with levetiracetam, potassium bromide, and CBD at 0.08 mg/kg/day, a 90% reduction in generalized tonic–clonic seizures and complete resolution of complex partial seizures was attributed to the subsequent addition of THCA at 0.02 mg/kg/day. In this case, increased doses of THCA reportedly resulted in exacerbation of myoclonic seizures, and increased doses of CBD reportedly resulted in frequent "shivers" that may have been partial seizures. The benefits of this ultra-low dose cannabinoid therapy lasted 8 months; the patient subsequently developed frequent breakthrough seizures that have been thus far refractory to other cannabinoid approaches but have responded to the addition of valproic acid.

3.3.2. Case #2

A 3-month-old girl with infantile spasms, eventually diagnosed with tuberous sclerosis complex and a de novo TSC2 mutation, had a complete clinical response to vigabatrin at 190 mg/kg/day at 10 months of age. After 4 months of seizure-freedom, the patient started a taper of vigabatrin and seizures returned with a new presentation of focal seizures. Returning to the previous vigabatrin dose was not effective and the patient continued to have an average of 6 seizures or seizure clusters daily. Levetiracetam was not effective and was eventually discontinued. Vigabatrin was tapered slightly and the cannabis trial began at 20 months with an artisanal blend containing an approximate ratio CBD:CBDA:THC:THCA:CBN of 1:1:1:2:1. At 0.2 mg/kg/day total cannabinoids, the mother reported more frequent seizure episodes with shorter duration and post-ictal phase. At 0.65 mg/kg/day of the original formula, seizure episodes had reportedly decreased to average 3 daily. The subsequent cannabis formula contained higher levels of acidic cannabinoids with an approximate ratio CBD:CBDA:THC:THCA:THCV of 0:7:1:6:1. She received ~0.4 mg/kg/day total cannabinoids for 8 months and experienced a decrease of dyscognitive seizures from several per day to an average once weekly, and a decrease of focal seizures from several per day to approximately one per month. The mother also reported shorter seizure duration, faster recovery, and the resolution of a loud screeching vocalization that had previously preceded the focal seizures, During that 8-month period the patient tapered and discontinued vigabatrin and continues to use artisanal cannabis as her only antiepileptic treatment.

3.3.3. Case #3

A 10-year-old boy with epilepsy onset at 2 months of age presented with photosensitive generalized tonic–clonic seizures 1–4 times daily despite treatment with lamotrigine and valproic acid. His seizures had previously not responded to carbamazepine, phenobarbital, zonisamide, and levetiracetam. After adding THCA 0.05 mg/kg/day, his parents noted an immediate reduction in seizure frequency. Increasing the dose of THCA to 2.2 mg/kg/day did not yield obvious additional benefit, but he remained at this higher dose. At follow-up after 3 months of treatment with THCA, his parents reported that seizure frequency had decreased 40%, and seizure duration also decreased, enabling the patient to discontinue the use of Diastat for seizure rescue. A subsequent formula containing higher levels of THC in a THCA:THC ratio of 4:1 produced a transient somnolent side effect and did not alter seizure frequency. Confounding factors in this case include the initiation of vitamin D3 2000 IU daily around the time of the beginning of the THCA trial [11].

3.3.4. Case #4

An 11-year-old girl with a complex genetic epilepsy including de novo DEPDC5, maternally inherited SCN5A, and paternally inherited RNASEH2B mutations had an onset of seizures at 10 months following a vaccination. She initially presented with GTCs every 3–5 days and 4–20 myoclonic seizures per day. At the time she was treated with primidone and acetazolamide, and had previously experienced seizure exacerbations with oxcarbazepine, lamotrigine, rufinamide, valproic acid, and levetiracetam. Her seizures had not responded to the Ketogenic Diet and had partially responded to a vagus nerve stimulator. Low dose CBD at 0.05 mg/kg/day reportedly improved cognition, but higher doses of CBD caused an increase in myoclonic seizures. Tetrahydrocannabinol at 1 mg/kg/day reportedly produced a 4-day seizure-free episode, followed by a recurrence of seizures. At 2 mg/kg/day, THCA resulted in a reported overall 90% seizure reduction and improved tolerance to temperature fluctuations. This patient also was able to abort GTCs, which usually required recue medication, using oromucosal or rectal THC 10 mg given at seizure onset and repeated after 1 min if needed, which was demonstrated in the inpatient setting via EEG monitoring [12]. At one point, a new formula of THCA at the same dosage resulted in notably decreased efficacy. A terpenoid analysis of the previous formula demonstrated the presence of high levels of alpha-linalool, absent in the less effective formula. Returning to a THCA formula based on the linalool-dominant chemovar improved her response. At 13 years old, after nearly 2 years of significant developmental progress (e.g. coloring within lines, zipping a jacket, increased vocabulary, steady gait, ability to run) and seizure reduction using cannabinoid monotherapy (except for the addition of phenobarbital during acute illnesses), the efficacy of all treatments began to diminish, and a few months later the patient died of SUDEP.

4. Discussion

4.1. Clinical considerations in the use of artisanal cannabis preparations

Clinicians in a position to guide epilepsy patients in the use of medical cannabis must carefully consider potential risks and benefits of this experimental treatment. Potential benefits of artisanal cannabis preparations in the treatment of epilepsy are difficult to quantify due to the lack of controlled trials. Translating experimental preclinical data and human clinical trials using purified and standardized cannabinoid preparations to the clinical decision-making scenarios that arise with the use of artisanal cannabis has many challenges. The emerging data on patient

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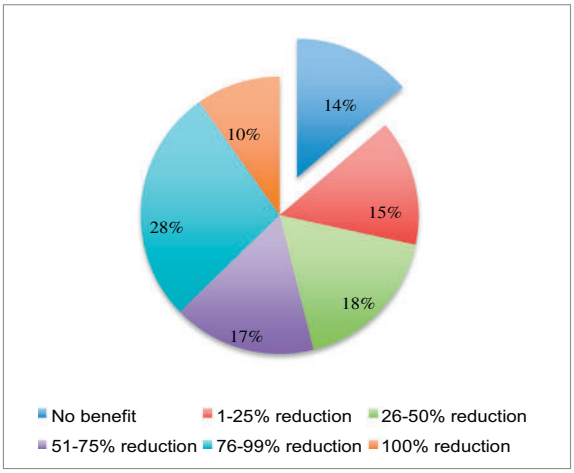

Fig. 1. Percent of cohort and overall seizure reduction, combined data from Washington and California.

response to artisanal cannabis is promising, though limited. In our uncontrolled observational data of 272 patients, some degree of seizure reduction was reported in 86% of cases (Fig. 1).

Most patients who consider cannabis products as medically-supervised treatment for epilepsy have seizures that have failed to improve with multiple AEDs, and most have experienced the morbidity associated with side effects of the medications. The likelihood of treatment success with additional AEDs after the first agent fails diminishes significantly. In an evaluation of 525 patients, 14% of those who seizures failed to respond to the first AED became seizure-free when treatment was changed to another drug, but only 3% became seizure-free while taking two drugs [3]. For these patients with refractory seizures with low likelihood of clinical response to a subsequent AED, and considerable morbidity and mortality associated with continued seizures, the risk/benefit considerations of the clinician shift significantly away from data on potential benefits of cannabis treatment toward a comparison of adverse effects.

When considering the risks of herbal cannabis products in the treatment of epilepsy, the clinician must distinguish the adverse effects of therapeutic use in specific patient populations from the more thoroughly studied risks of illicit cannabis/THC product consumption. Few data are available that evaluates the adverse effects of herbal cannabis preparations in patients with seizures, and adverse effects may vary widely from one preparation to the next. A recent report from Israel on 74 patients with intractable epilepsy using CBD-enriched medical cannabis, age 1–18 years, described the following adverse effects: seizure exacerbation in 18%, somnolence/fatigue in 22%, and gastrointestinal symptoms in 7% of subjects [13]. A parent survey of 19 children with epilepsy age 2–16 years using CBD-enriched cannabis preparations described drowsiness in 37%, fatigue in 16%, and appetite decrease in 5% of subjects [14]. Assessment of adverse effects can be challenging in children, especially those with developmental delay and impairments in communication. In a Canadian case series of 18 adults with epilepsy using herbal THC-dominant cannabis, 2 (11%) reported adverse effects [15]. Quality studies using high concentrations of THC in this population have not been performed.

One of the authors (DRS) has infrequently observed pro-convulsant effects associated with a variety of cannabis preparations, including THC-dominant, CBD-dominant, and THCA-dominant formulas, in certain patients. In a recent Canadian study that included 108 adults with epilepsy who reported cannabis use, 5 patients (5%) reported possible seizure precipitation related to cannabis use, while improvement in seizures was perceived by 84% [16]. As demonstrated in the above cases, some patients that experience exacerbations related to one cannabinoid may respond favorably to another cannabinoid.

Other, non-medical, risks must also be considered in the decision to trial artisanal cannabis preparations. Availability of a consistent supply of the medication is frequently interrupted due to horticultural, manufacturing, and economic factors. Current market prices for artisanal cannabis preparations observed in Maine, California, and online range from 5 to 50 cents per milligram. Higher dosing ranges are financially unfeasible for many patients unless they grow and produce their own medicine, a complex process that presents many potential interruptions in treatment. Sudden loss of access to cannabinoids may result in rebound seizures. Hospital admissions present challenges, and patients or their guardians often must choose between interrupting cannabis treatment and violating hospital policies that forbid self-administration of medications, especially those with Schedule I status. In one of the sites (RPS), the hospital has families sign a waiver and allows them to administer home dosing of product, but does not provide storage. The potential for disruption of medical treatment or family structure related to child protective services and other legal agencies, even when the patient and medical provider operate within state laws, must also be carefully considered on a case-by-case basis [17].

Overall, the safety profile of quality-controlled herbal cannabis preparations is likely equal or superior to most AEDs. A 2008 review of the adverse effects of medical cannabinoids in clinical trials found no increase in serious adverse effects in the cannabis groups compared to controls [18]. A more recent review found serious adverse effects to be more common in the cannabis group compared to controls (summary odds ratio 1.41, 95% CI 1.04–1.92) [19]. Herbal cannabis has remarkably low toxicity, even at high doses, and no lethal dose of cannabis has been described. Conversely, the morbidity of AEDs are the most common impediment to achieving full effective dosing due to multiple types of toxicity ranging from tiredness to memory problems and even death [20,21].

In patients with refractory epilepsy that have a low likelihood of responding to a subsequent AED, a trial of artisanal cannabis formulas may be indicated. The cannabinoids' novel mechanisms of action are an attractive consideration for possible seizure control. By considering the observations and recommendations described in this paper, clinicians can further reduce the potential for harm in patients using cannabis as an anticonvulsant.

4.2. Challenges in clinical cannabinoid medicine

The clinical application of artisanal cannabis preparations in epilepsy patients is fraught with challenges, as is the interpretation of observational data. The patient population that considers herbal cannabis as a treatment for epilepsy is heterogeneous in etiology, currently predominantly pediatric, and has seizures that are usually refractory to multiple conventional treatments. Polypharmacy is common, and while potential pharmacokinetic interactions have been identified [22], less is known about drug–drug pharmacodynamic interactions. The cannabinoids may reduce seizures via numerous mechanisms of action that warrant further investigation, including THC's reduction of glutamate excitotoxicity via the CB1 receptor [23], CBD's modulation of numerous non-cannabinoid receptors [24], and several proposed targets of THCA [25]. Objective measurement of treatment response can be challenging, and subjective reports of the efficacy of artisanal cannabis can be strongly influenced by the placebo effect, especially in patients that have invested significant resources into securing access to these formulas [26]. This is especially true outside the formal methodology of a clinical trial.

Patients face significant challenges in accessing cannabis preparations that are standardized, consistent, and quality-controlled. While most medical cannabis states have seen the emergence of third party laboratories that allow consumers to analyze purchased and homemade cannabis products [27], and industry standards are emerging to guide such laboratories [28], inaccurate product labeling is pervasive in this new and often-unregulated industry. A 2015 study of edible cannabis products available in Seattle, San Francisco, and Los Angeles found that of 75 products examined, 17% were accurately labeled for

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cannabinoid content, 23% were inaccurate with higher than labeled concentrations, and 60% contained lower than labeled concentrations [29]. At the Seattle site, there were 3 patients who had essentially no CBD level detected but >10 ng/mL of THC. The label of the extract indicated a 17:1 ratio of CBD:THC (RPS unpublished data). Many patients purchase and use purportedly CBD-dominant "hemp" formulas that are sold online and shipped across state and international borders. Patients are led to believe that such products are legal, even in states without medical cannabis laws, despite the fact that CBD remains classified as Schedule 1 [30]. In 2015 and again in 2016, the FDA published analytic results of several commercial CBD products and issued warning letters to their manufacturers. Many products were underlabeled for CBD content, contained no CBD, or contained significant amounts of THC [31,32].

Potency testing of artisanal cannabis products may enable patients to make dosing adjustments and achieve consistent and accurate dosing of the active constituents from one batch to the next. The content of physiologically active minor phytoconstituents, such as terpenoid compounds and acidic cannabinoids, may still vary widely based on horticultural factors and processing techniques. Most cannabis formulators use ethanol, butane, or supercritical CO_2 as extraction solvents, and then dilute the extract using low-viscosity oil such as medium chain triglyceride or olive oil. Extraction methods that involve heat and/or high pressure likely fail to retain volatile terpenoid compounds, such as alpha-linalool, which has been shown to possess anticonvulsant properties in preclinical models [33]. Varying content of these minor constituents may affect clinical response [34]. Artisanal cannabis products may also be contaminated with neurotoxic substances such as mycotoxins, organic solvents, pesticides, and heavy metals [35,36], and patients who use laboratory testing for cannabinoid potencies may not have access to analytics on potential contaminants.

4.3. Cannabis dosing in epilepsy

Cannabinoids have a wide safe and effective dosing range in clinical practice. While clinical trials of Epidiolex have evaluated a dosing range of 2–50 mg/kg/day, one of the authors (DRS) has observed anticonvulsant effects in patients at doses as low as 0.02 mg cannabinoids/kg/day, confirmed by on-site analysis of the cannabis preparation using high performance liquid chromatography. While clinical responses in this low dosage range may be surprising, ultra-low doses of cannabinoids have been shown to be physiologically active in preclinical models: a single application of 0.002 mg/kg THC to mice induced long-lasting activation of protective signaling molecules in the brain, including the transcription factor CREB and the trophic factor BDNF (brain derived neurotrophin) [37]. Other preclinical studies have reported that intraperitoneal injection of 0.002 mg/kg THC reduced damage and preserved cardiac function when administered to mice 2 h before myocardial infarction [38], and also reduced apoptotic, oxidative, and inflammatory injury in mice with hepatic ischemia/reperfusion [39].

The extraordinarily wide dosing range of cannabis is complicated by non-linear dose response relationships. Biphasic dose–response trends have been frequently described in cannabinoid literature; THC and anxiety in both rodents and humans [40], THC + CBD and analgesia in humans [41], THC and locomotor activity in rodents [42], synthetic CB1 agonists and novelty seeking in rodents [43], and other behavioral outcomes have all demonstrated biphasic dose–response trends. Cerebral metabolism in rodents has also demonstrated a biphasic dose–response relationship: very low doses of THC increased cerebral metabolism, measured by 2-deoxyglucose uptake, while higher doses of THC decreased cerebral metabolism. Limbic regions, particularly the hippocampus, were more sensitive to THC, suggesting a selective regional action of the drug at lower doses [44]. Based on these findings, further research is needed to elucidate potential biphasic dose–response trends in the anticonvulsant activity of THC and other modulators of the endocannabinoid system, and such trends should not be unexpected in clinical practice. Cannabidiol, however, may be less likely than THC to exhibit biphasic dose–response effects because its anticonvulsant properties are likely via CB1-independent mechanisms of action [24]. Clinicians are cautioned to avoid making the simple assumption that higher doses of cannabinoids will yield stronger therapeutic effects. If previous clinical improvements begin to diminish, especially after a dosage increase, clinicians may consider dosage reduction as a potential strategy to improve efficacy.

4.4. Acidic cannabinoids

In *Cannabis sativa*, the phytocannabinoids are synthesized in glandular trichomes of the leaves and flowers, and first appear in their acidic forms, (e.g. THCA, cannabidiolic acid (CBDA)). The acidic cannabinoids gradually decarboxylate to their neutral counterparts (e.g. THC and CBD) due to heat, auto-oxidation, and light. While most common extraction and delivery methods of cannabis employ heat sufficient to convert most cannabinoids into their neutral form [45], decarboxylation is often incomplete and trace amounts of acidic cannabinoids can be found in the bodily fluids of cannabis consumers [46]. Certain delivery methods that have a long history of therapeutic use, such as cannabis tea, maintain the predominantly acidic state of cannabinoids [47]. Most research into the clinical effects of cannabinoids to date have focused on the neutral forms, but new interest is emerging to investigate the distinct physiologic effects of acidic cannabinoids [25]. 9-Delta-tetrahydrocannabinolic acid is becoming a popular treatment approach for patients with epilepsy in legal states, and is sometimes more readily available and/or affordable than CBD.

9-Delta-tetrahydrocannabinolic acid does not produce psychoactive effects in animals at relatively high doses [48], and psychoactivity has not been observed in humans. Though most THCA-dominant preparations will contain at least trace amounts of THC, THCA does not convert into THC in vivo. Accidental exposure of artisanal THCA formulations to heat would likely trigger partial conversion to THC. In 1979, Karler and Turkanis reported THCA's anticonvulsant activity in the maximal electroshock seizure model in mice at 200 mg/kg. More recently, THCA and CBDA have been shown to convey antiemetic responses in rodents at surprising low doses, 0.05 mg/kg [49] and 0.0005 mg/kg [50], respectively. There is conflicting evidence on the ability of THCA to bind the CB1 receptor, and THCA may have lower CNS penetration than THC due to the polar carboxylic residue. Potential immunomodulatory, anti-inflammatory, and neuroprotective effects have been suggested by in vitro experiments [25]. The low-heat extraction and processing methods needed to produce THCA formulations are likely to retain higher levels of other physiologically active phytoconstituents, such as the volatile terpenoids. Based on the early preclinical evidence of THCA's anticonvulsant effects, and recent anecdotal evidence of efficacy in patients with epilepsy, further investigation is warranted.

5. Limitations

The observational data presented in this paper have several limitations, including the lack of a control group, reliance upon parental report for seizure frequency and other characteristics, a heterogeneous patient population, changes in concurrent treatments, and the variables inherent in artisanal botanical medicines. Without a placebo group we are unable to determine the effect from bias, which may be heightened by traditional and social media coverage that focuses on the benefits of artisanal cannabis, and by the significant investment of resources made by patients and/or their families to secure access to artisanal preparations.

6. Conclusion

Despite the inherent challenges in the clinical use of artisanal cannabis preparations, patients with refractory epilepsy may benefit from such treatments. In the combined data from practices in Washington and

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California, 86% of patients experienced some clinical benefit, and 10% experienced a complete clinical response. Adverse effects were mild, though 4% of patients experienced an exacerbation of seizures in response to cannabis, and beneficial side effects such as improved cognition were reported. While most patients used CBD-dominant formulas, some patients received THC and/or THCA in addition to CBD, and some patients who did not respond well to CBD benefited from preparations dominant in THC and/or THCA. Cannabinoids appear to have a broad safe and effective dosing range in patients with epilepsy; some patients respond at ultra-low doses, and non-linear dose–response relationships have been observed. Effective total cannabinoid doses ranged from 0.05 to 9 mg/kg/day, and effective serum levels of CBD ranged from 1.8 to 80 ng/mL. To avoid issues related to the variability of artisanal preparations, clinicians can measure serum cannabinoids levels, and patients or their families should be advised not to rely on product labels, but to test every batch of medicine for cannabinoid potencies and potential contaminants at analytic laboratories using industry-standard methods [28]. Clinicians can navigate the cannabinoid dosing nuances by providing patients with individualized, methodical titration instructions.

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Conflicts of interests

RPS is a site investigator for clinical trials funded by GW Pharmaceuticals. He has also received financial support from GW Pharmaceuticals for development of educational materials. DRS is a co-owner and medical director of a private integrative medicine practice, co-owner of a cannabis analytic laboratory, and co-owner of a medical cannabis patient education website.

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