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Cross-sectional and longitudinal evaluation of cannabidiol (CBD) product use and health among people with epilepsy

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ABSTRACT

Recent approval of Epidiolex® (pharmaceutical cannabidiol/CBD) for the treatment of Lennox Gastaut syndrome (LGS) and Dravet syndrome highlights a therapeutic efficacy of CBD in the treatment of epilepsy. However, a large number of patients with epilepsy elect to use alternative artisanal CBD products due to cost or access constraints. Despite widespread availability and variety of these artisanal CBD products, studies evaluating their safety or efficacy are rare, making conclusions about clinical utility uncertain. The purpose of the present study was to evaluate cross-sectional and longitudinal associations of artisanal CBD product use with quality of life, mental health, healthcare utilization, and epilepsy-specific outcomes within a large, observational cohort of people with epilepsy. Participants who reported using artisanal CBD products at baseline (Artisanal CBD Users; $n = 280$) and participants who used no cannabis-based products (Controls; $n = 138$) completed web-based assessments evaluating psychiatric symptoms, healthcare utilization, and epilepsy-specific factors. Follow-up surveys were collected in a subset of participants ($n = 190$) following baseline assessment for longitudinal comparison. Cross-sectionally, higher quality of life, lower psychiatric symptom severity, and improved sleep were observed among Artisanal CBD Users at baseline compared with Controls. Initiation of artisanal CBD product use was also related to improved health outcomes longitudinally. No group differences were observed for seizure control, but both groups included a high number of individuals with no past month seizures. Artisanal CBD Users reported significantly better epilepsy medication tolerability, use of fewer prescription medications overall, and reduced healthcare utilization compared with Controls. These findings are consistent with research indicating that practitioners recommending CBD in clinical care for epilepsy report integrating the use of CBD both as a means to improve patient quality of life as well as for seizure control.

1. Introduction

Cannabis and select chemicals found in the cannabis plant have received significant clinical attention as evidence accumulates suggesting potential utility for varied health conditions [1,2]. A number of recent studies demonstrated the safety and efficacy of cannabidiol (CBD) in the reduction of seizures for several specific epilepsy syndromes [3–5]. This led to the widespread regulatory approval of Epidiolex®, a pharmaceutical grade CBD product, for treatment of seizures associated with Dravet syndrome, Tuberous Sclerosis, and Lennox-Gastaut syndrome (LGS).

Pharmaceutical CBD is currently a restricted prescription medication, and insurance coverage is often limited to only those patients with the specific approved indications. As a result, a large number of patients with epilepsy elect to use alternative CBD products sold widely as dietary supplements by commercial vendors [6]. Other patients elect to use cannabinoid products that are less refined and include other phytocannabinoids and terpenoids found in cannabis, many of which contain THC in addition to or in lieu of varying concentrations of CBD [7]. Despite the widespread availability and variety of these alternative cannabinoid products – here

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referred to as artisanal CBD in contrast to pharmaceutical CBD – controlled studies evaluating their safety or efficacy are rare, making conclusions about the clinical utility of these products uncertain.

In addition to implications for seizure control, CBD products may prove valuable for their effects on psychosocial function and psychiatric health. It is well known that behavioral issues, especially psychiatric disorders, are overrepresented among people with epilepsy [8,9]. The overlap is so prominent that recent trends in epilepsy management include increased attention to cognitive and psychiatric comorbidities that are associated with seizure activity [10]. Accumulating evidence from laboratory experiments and observational studies suggest associations between CBD use and improved psychiatric health, sleep, and quality of life [e.g., [11,12–15]]. Thus, CBD-dominant cannabis products may produce anticonvulsant effects and attenuate psychiatric symptoms in a manner similar to other pharmaceuticals (e.g., divalproex sodium), but perhaps with a more favorable drug tolerability profile.

The purpose of the present analysis was to evaluate the cross-sectional and longitudinal associations of artisanal CBD product use with quality of life, mental health, healthcare utilization, and epilepsy-specific outcomes within a large, observational cohort of people with epilepsy. This study extends previously published studies by evaluating health outcomes in a large cohort of people with epilepsy using artisanal cannabinoid products compared with a control group, as well as a within-subject longitudinal evaluation of a subset of participants who initiated artisanal CBD product use during study participation.

2. Materials and methods

2.1. Study overview

Data were collected as a part of an observational cohort study conducted by Realm of Caring Foundation (Colorado Springs, CO, USA), a nonprofit organization dedicated to therapeutic cannabinoid research and education, in collaboration with researchers at the Johns Hopkins University School of Medicine (Baltimore, MD, USA). Potential participants were recruited using patient registries from Realm of Caring Foundation and social media posts. Registered patients (or their adult caregivers) who were already using a cannabinoid product, as well as those who were considering initiation of product use, were targeted for recruitment. All assessments were completed online using a survey platform hosted by Qualtrics (Provo, UT, USA). The study was approved by the Johns Hopkins University School of Medicine Institutional Review Board and informed consent was obtained.

2.2. Participants

Participants (n = 1783) who were enrolled in the parent study between April 2016 and July 2020 were considered for this analysis. We identified all participants who self-reported a current primary or secondary diagnosis of epilepsy by a doctor (n = 426 epilepsy cohort). An additional 6 participants who reported using pharmaceutical CBD and 2 participants who reported use of specific products that could be verified as a THC-dominant cannabis-based product were removed, resulting in a final sample size of 418 in the epilepsy cohort. Of these, 71 were adult patients who used an artisanal CBD product for medicinal purposes and 209 were adult caregivers of children or dependent adults who used an artisanal CBD product for medicinal purposes (Artisanal CBD Users; n = 280). A control group consisted of 29 adult patients who were considering, but had not yet initiated artisanal CBD product use, and 109 adult caregivers who were considering artisanal CBD product use for a dependent child or adult patient (Controls; n = 138). Note that a subset of these participants were included in a larger analysis of health outcomes within the parent study [15]. That prior analysis analyzed data over a shorter time period (i.e., April 2016 to February 2018) and did not evaluate outcomes specific to the cohort of people with epilepsy or examine epilepsy-specific measures.

2.3. Procedures and measures

Participants completed a web-based survey that measured several health content areas. Participants were either adults (18 years or older) who were capable of self-reporting all information on their own behalf or were the caregivers of children or dependent adult patients, in which case the caregiver completed study assessments based on observations of or interactions with the dependent patient under their care. Following completion of a baseline assessment, participants were prompted via e-mail to complete follow-up assessments at 3-month intervals. Approximately half of participants completed at least one follow-up assessment (n = 190 participants in the longitudinal cohort; 45.5% of the baseline sample). Participants that recorded any follow-up assessment completed an average of 2.6 follow-ups (median = 2) that occurred an average of 14 months after baseline assessment.

The survey included validated assessments of past month quality of life [World Health Organization Quality of Life assessment; WHOQOL-BREF; [16]], pain [Numeric Pain Rating Scale; NPRS; [17]], anxiety and depression [Hospital Anxiety and Depression Scale; HADS; [18]], and sleep [Pittsburgh Sleep Quality Index [PSQI] for adults, [19], and abbreviated Children's Sleep Habits Questionnaire [CSHQ] for children, [20]]. Pain is not typically considered a symptom of epilepsy and therefore was included in our analyses as a negative control (i.e., measure not expected to change in this population by product use). The WHOQOL-BREF contained measures of quality of life, health satisfaction, and subscales comprised of Physical Health, Psychological Health, Social Health, and Environment (i.e., safety and security, home and physical environment satisfaction, finance) domains. Caregiver burden was assessed using the Zarit Burden Interview Brief version [21], which includes subscales evaluating Role Strain (i.e., stress due to role conflict or overload) and Personal Strain (i.e., personal stress from the experience of caretaking). Higher scores on the WHOQOL-BREF measures are considered a positive health outcome, whereas lower scores on all other measures are considered a positive health outcome. Healthcare utilization variables included current prescription medication use, over-the-counter (OTC) medication use, and past-month outpatient healthcare visits, emergency department visits, hospital admissions, and sick days from work/school. All cannabinoid product(s) used as well as daily dose of CBD and other cannabinoids were recorded, to the extent possible. Free-text questions were included to index experienced adverse effects (“How has therapeutic use of cannabis/cannabinoids harmed or caused problems for the participant?”) and reasons for artisanal CBD product discontinuation (“Why did the participant stop medical use of cannabis/cannabinoid therapy?”). Participants were entered into a monthly raffle to win one of twenty $50 gift cards each time they completed a survey.

Participants could opt-in to an epilepsy-specific breakout assessment after completing the baseline survey (n = 194 participants from the baseline cohort opted-in). This epilepsy-specific breakout contained measures specific to epilepsy function, including epilepsy medication side effects collected using the Liverpool Adverse Events Profile (Supplemental Materials) [22] and information about the frequency of generalized and non-generalized seizures. These breakout surveys were not completed at the same time as the baseline assessment; therefore, we used information about CBD product use collected in the epilepsy-specific breakout

to categorize each participant as an Artisanal CBD User or Control for those data.

2.4. Data analysis

Sample demographics and characteristics were first compared between Artisanal CBD Users and Controls using independent samples *t*-tests (continuous) or Fisher's exact test (dichotomous). Baseline health outcomes were then compared between groups using independent samples *t*-tests and effect sizes were summarized as Cohen's *d*. Additional comparisons using available clinical cutoff criteria were made using logistic regression and effect sizes summarized as odds ratios. Secondary analyses evaluated the relation between product dosing (CBD raw and weight-adjusted daily oral dose) and clinical outcomes using linear or logistic regression.

Data on epilepsy medication side effects were available for a subset of participants who completed the breakout assessment. Comparisons of total scores and individual items by artisanal CBD use status were made using independent samples *t*-tests. Additional analyses controlled for concomitant anticonvulsive medication use (dichotomous yes/no).

Finally, longitudinal data from available participants were analyzed using linear mixed effect models. Primary models tested whether the impact of time (baseline versus follow-up) differed between Controls who (1) initiated cannabis use during follow-up ($N = 27$) or (2) did not initiate cannabis use at any time point ($N = 20$). Significant interactions were followed up by tests for change within each group. Secondary analyses were conducted with Artisanal CBD Users at baseline who sustained artisanal CBD use at all follow-up assessments ($N = 128$). Models were only tested for continuous variables given concerns about the small sample size and precision of estimates for conducting generalized linear models with either dichotomous or count variables.

All analyses were conducted using *R* Statistical analysis software with two-tailed tests and a type I error rate of 0.05.

3. Results

3.1. Sample characteristics and artisanal CBD product use

Participants were predominantly Caucasian (74%) with a roughly even split by gender (55% female) (Table 1). Participants were, on average, 21 years old (51% under 18 years old) and the majority (90%) had no history of non-medicinal ("recreational") cannabis use. Consistent with the nature of the analyzed sample, the majority of participants reported epilepsy as their primary medical condition (93%). The other 7% reported epilepsy secondary to cancer, autoimmune conditions, neuropsychiatric conditions, chronic pain, insomnia/sleep disorders, or other conditions. Artisanal CBD Users did not significantly differ from Controls on demographic variables, with the exception that they were more likely to report lifetime non-medicinal cannabis use, OR = 2.76, $p = .02$. The majority of participants using an artisanal CBD product reported using it as an adjunctive medication ($n = 126$; 45%). The remaining reported use as a last resort (after all other options failed; $n = 82$, 29%), secondary treatment (use after initial treatment failed; $n = 44$, 16%), as a first line treatment ($n = 17$, 6%), or were unsure ($n = 11$; 4%).

Most participants within the Artisanal CBD User group ($n = 217$ of 280) indicated use of a specific product that could be verified as a CBD-dominant cannabis-based product. Sixty-three participants indicated use of a cannabis-based product at baseline but did not provide specific product details. Health-related outcomes from this group did not differ from those using known products, and effect sizes for analyses of health-related outcomes were similar when comparisons included this group versus excluded them. Therefore, for purpose of analysis, it is assumed that these participants were using an artisanal CBD product. A subset of Artisanal CBD Users reported also using known THC-dominant products ($n = 25$), products containing high concentrations of both CBD and THC ($n = 9$), or products in which the primary chemical constituent was a minor cannabinoid such as CBG, CBN, THC-A, CBD-A, or THC-V ($n = 7$). Product information necessary to calculate daily dose for CBD was available from 110 participants. The median absolute CBD dose was 50.0 mg/day (IQR = 23.4–150.0 mg/day) with a weight-adjusted dose of 1.4 mg/kg/day (IQR = 0.5–2.8 mg/kg/day).

3.2. Seizure control and epilepsy medication adverse effects

Fig. 1 contains box-plots of past-month generalized and non-generalized seizure types as reported in the epilepsy-specific survey. Although Artisanal CBD Users who completed the supplemental epilepsy-focused survey ($n = 138$) reported qualitatively fewer seizures than Controls ($N = 56$), group differences for past-month generalized ($p = .87$) or other, ($p = .34$) seizure types were

Table 1
Participant demographics by Artisanal CBD product use.

	Controls ($N = 138$)	Artisanal CBD Users ($N = 280$)	*p*	Effect Size[a]
Demographics				
Age in years (mean [sd])	19.6 (15.0)	22.3 (16.3)	0.10	0.17
Under 18	56.5%	48.0%	0.12	0.71
Female	56.5%	55.0%	0.83	0.94
White	75.9%	72.4%	0.47	0.83
Patient with autism	14.5%	14.6%	0.99	1.01
Non-Medicinal Cannabis Use				
Lifetime	5.1%	12.9%	0.02	2.76
Past year	3.6%	7.1%	0.19	2.04
Past month	2.2%	5.0%	0.20	2.36
Primary Medical Condition				
Cancer	1.4%	0.7%	0.92	
Autoimmune	0.7%	0.7%		
Neurological	93.5%	92.9%		
Neuropsychiatric	3.6%	3.9%		
Behavioral	0.0%	0.0%		
Chronic pain	0.7%	0.7%		
Insomnia/sleep disorder	0.0%	0.4%		
Other	0.0%	0.7%		

[a] Effect sizes summarized as Cohen's *d* for age and odd's ratios otherwise.

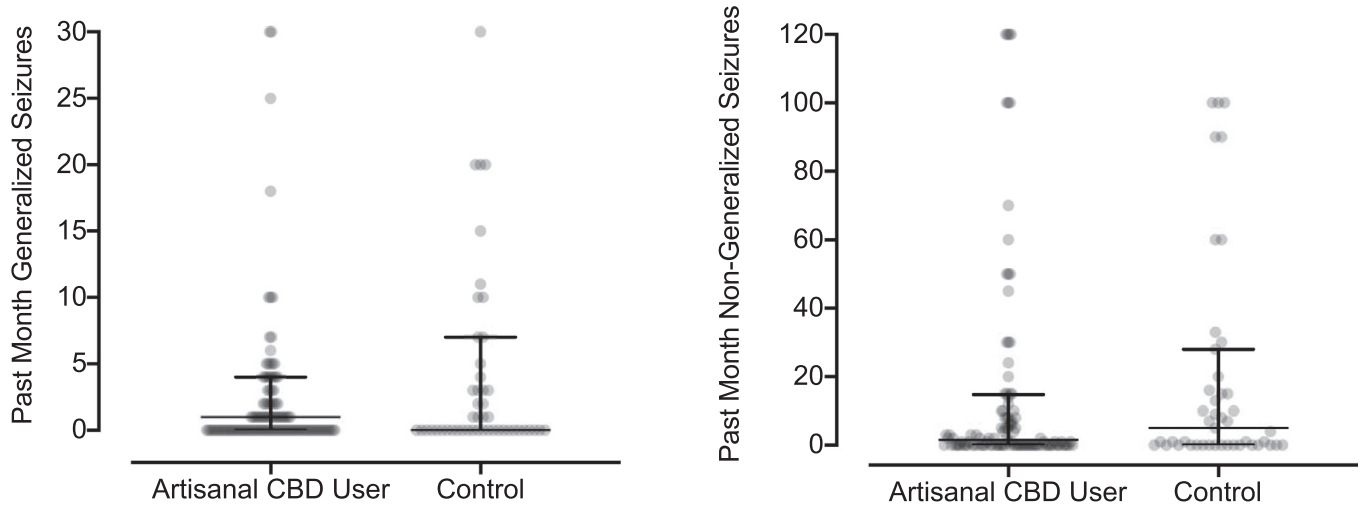

Fig. 1. Seizure Control by Artisanal CBD product use. Plotted are individual participant data and median/interquartile range plots of past-month generalized (left panel) and non-generalized (right panel) seizures by artisanal CBD product use. Lines demarcate 25th–75th percentile and median. *Y*-axes are plotted to each group's 90th percentile. Artisanal refers to non-pharmaceutical (i.e., non-Epidiolex®) use.

not statistically significant. A floor effect may have contributed to this outcome because 49% of participants reported no past-month generalized seizures and 41% reported no past-month non-generalized seizure types.

Artisanal CBD Users reported lower epilepsy medication-related adverse effects than Controls, $t_{192} = 3.42$, $p < .001$, $d = 0.54$ (Fig. 2), as well as a lower odds of meeting threshold adverse event scores than Controls, OR = 0.49, $p < .05$. Significant group differences on the severity of individual items from the Liverpool Adverse Events Profile were observed for Anger, Concentration, Dizzy, Hair Loss, Memory, Restlessness, Sleep, Sleepiness, Tiredness, Unsteadiness, and Vision (all *p*-values <0.05). Controlling for the use of concomitant seizure medication did not change the significance or direction of the group differences on epilepsy medication-related adverse effects scores, $b = -6.14$, $p < .01$, and people using concomitant seizure medications also reported greater side-effect scores, $b = 5.05$, $p < .05$.

3.3. Baseline comparisons

3.3.1. Quality of life, pain, mood, and sleep

Compared with Controls, Artisanal CBD Users had greater health satisfaction, $t_{254} = 3.00$, $p < .01$, $d = 0.40$, scores on the WHOQOL-BREF. Ratings of Quality of Life were qualitatively higher among Artisanal CBD Users compared with Controls, but the difference was not statistically significant, $t_{260} = 1.94$, $p = .053$, $d = 0.26$. Scores on the composite Psychological Health domain of the WHOQOL-BREF were also higher for Artisanal CBD Users compared with Controls, $t_{254} = 2.18$, $p < .05$, $d = 0.29$, whereas scores on the Physical Health, $t_{253} = 1.54$, $p = .13$, $d = 0.21$, Social Relationships, $t_{243} = 0.80$, $p = .43$, $d = 0.11$, and Environment, $t_{259} = 0.20$, $p = .84$, $d = -0.03$, domains did not significantly differ.

Overall, pain scores in this cohort were low in both groups (Recent Average Pain Mean: Artisanal CBD Users = 2.5, Control = 2.7). Consistent with these low scores, and because chronic pain is not typically a symptom of epilepsy, Artisanal CBD Users did not differ from Controls on pain measures, including recent average pain, $t_{332} = 0.73$, $p = .47$, $d = 0.09$, or recent worst pain, $t_{331} = 0.49$, $p = .62$, $d = 0.06$.

Artisanal CBD Users endorsed lower anxiety, $t_{307} = 3.18$, $p < .01$, $d = 0.38$, and depression, $t_{308} = 2.14$, $p < .05$, $d = 0.26$, scores on the HADS compared with Controls (Fig. 3). Current CBD product use was associated with a lower odds of meeting clinical threshold anxiety scores (composite score 8+; Zigmond and Snaith), OR = 0.49, $p < .01$, but the odds of meeting clinical threshold depression scores (composite score 8+; Zigmond and Snaith) were not significantly different between groups, OR = 0.79, $p = .35$.

Sleep scores were lower (indicating better sleep) for adult Artisanal CBD Users compared with adult Controls on the PSQI, $t_{129} = 2.20$, $p < .05$, $d = 0.42$. Sleep ratings on the child sleep measure (CSHQ) were not significantly different between groups, $t_{158} = 1.94$, $p = .054$, $d = 0.32$, but sleep scores were qualitatively better for Artisanal CBD Users compared with Controls.

3.3.2. Caregiver burden

Caregivers of patients currently using artisanal CBD products reported significantly lower scores on the Role Strain subscale of the Zarit Burden Interview compared with caregivers of Controls, $t_{289} = 2.44$, $p < .05$, $d = 0.30$. There were no differences on the composite score for Personal Strain, $t_{289} = 0.32$, $p = .75$, $d = 0.04$, or for total score, $t_{289} = 0.97$, $p = .33$, $d = 0.12$, of the Zarit Burden Interview.

3.3.3. Concomitant medication and healthcare utilization

Fig. 4 shows concomitant medication use and healthcare utilization between groups. Artisanal CBD Users had a lower odds of reporting prescription medication use compared to controls, OR = 0.16, $p < .01$. Evaluation of specific concomitant medication types found that this difference was attributable to lower rates of anticonvulsant medication use in the Artisanal CBD Users (78.5%) compared to Controls (95.6%), OR = 0.17, $p < .001$. Artisanal CBD Users and Controls did not significantly differ on rates of prescription medication use for psychiatric health (Artisanal CBD User = 12.8%, Control = 16.2%, $p = .36$), behavioral disruptions (Artisanal CBD User = 1.5%, Control = 2.9%, $p = .45$), sleep (Artisanal CBD User = 3.4%, Control = 5.9%, $p = .30$), pain (Artisanal CBD User = 3.0%, Control = 5.9%, $p = .18$), or other indications (Artisanal CBD User = 18.9%, Control = 18.4%, $p = .99$). Of note, although Artisanal CBD Users had a lower odds of using prescription medications than Controls, high rates of prescription medication use were still observed with 88% of Artisanal CBD Users reporting use of both cannabinoid products and prescription medications.

Artisanal CBD Users also had a lower odds of having past-month emergency department visits OR = 0.57, $p < .05$, and reporting past-

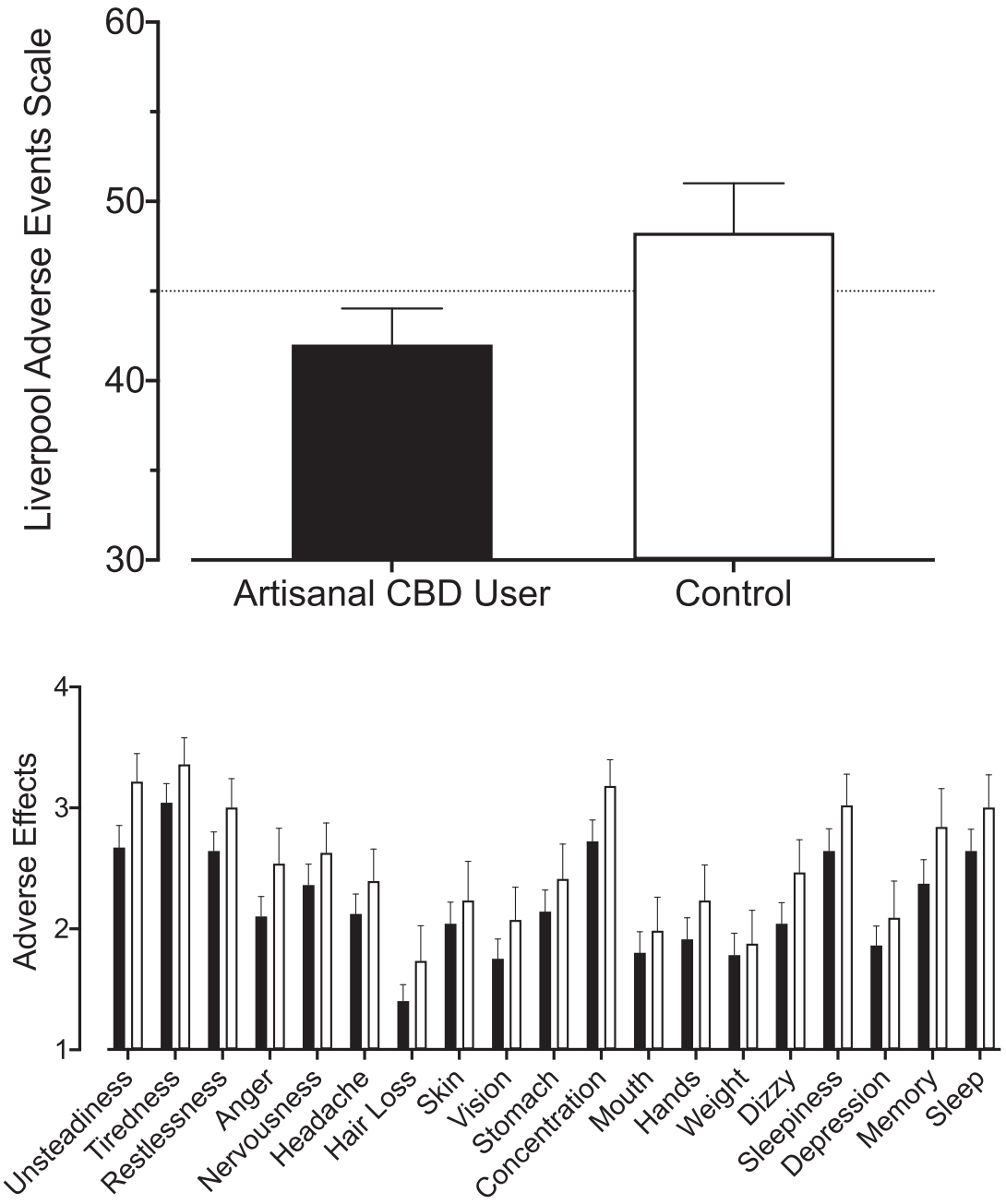

Fig. 2. Epilepsy medication adverse effects. Plotted are group mean scores on the Liverpool Adverse Events Profile on total scores (top panel) and individual items (bottom panel). Controls (white bars) and participants using an artisanal CBD product (black bars) are plotted. Error bars are standard error of the mean. A clinical cutoff of greater than 45 is also presented in the top panel in the dotted line). Artisanal refers to non-pharmaceutical (i.e., non-Epidiolex®) use. Individual items available in the Supplemental Materials.

month sick days from school/work, OR = 0.60, $p < .05$, compared with Controls. There were no significant differences between groups on the odds of OTC medication use, OR = 0.77, $p = .23$, having a past-month outpatient medical visit, OR = 0.69, $p = .10$, or a past-month hospital admission, OR = 0.64, $p = .18$.

3.3.4. Cannabinoid dose effects

CBD dosing (raw and weight-based) was not significantly related to quality of life, pain, mood, sleep, or caregiver burden results with the exception that higher CBD mg/kg doses were associated with higher WHOQOL Environmental domain Quality of Life scores ($p < .05$). Dosing was also not associated with healthcare utilization outcomes with the exception that higher CBD doses (both raw and weight adjusted), were associated with lower odds of a past-month outpatient visit ($p < .05$).

3.3.5. Adverse effects of CBD use

Among the 280 baseline Artisanal CBD Users, the majority did not report an adverse effect in free text responses ($N = 222$; 79%). The remaining reported experiencing side effects such as somnolence ($N = 30$; 11%), high or prohibitive product cost ($N = 12$; 4%), worsening of epilepsy symptoms ($N = 10$; 4%), concerns about or barriers related to legality ($N = 8$; 3%), and concerns about or experienced drug-drug interactions ($N = 3$, 1%).

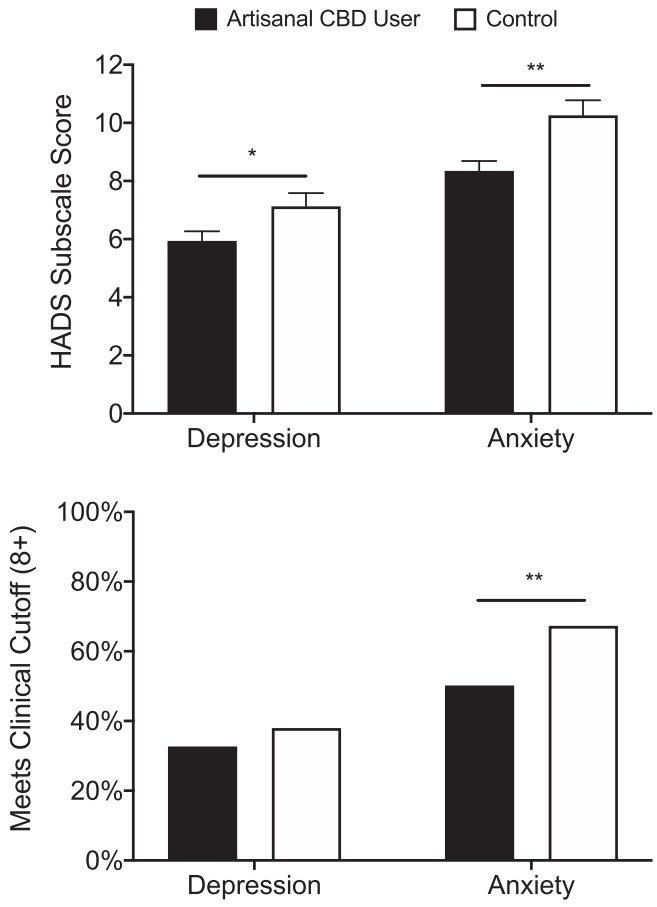

Fig. 3. Anxiety and depression symptoms by Artisanal CBD product use. Plotted are mean scores (top) or percentage of participants meeting clinical cutoffs for those using an artisanal CBD product (black bars) or not using an artisanal CBD product (white bars) at the baseline assessment. Error bars are standard error of the mean. Artisanal refers to non-pharmaceutical (i.e., non-Epidiolex®) use. * $p < .05$; ** $p < .01$.

3.4. Longitudinal comparisons for control initiators

Follow-up assessments were completed by 190 participants (139 baseline Artisanal CBD Users and 51 Controls). Among baseline Controls, 27 reported using artisanal CBD products in all follow-ups completed, 20 sustained no artisanal CBD product use for all follow-up assessments, and 4 reported both using and not using artisanal CBD products in separate follow-up assessments. Among baseline Artisanal CBD Users with follow-up data, 128 reported using artisanal CBD products in all follow-ups completed, 4 reported not using artisanal CBD products in all follow-ups completed, and 7 reported both using and not using artisanal CBD products at separate follow-up assessments. Among participants that reported a reason for discontinuation, 4 reported cost constraints, 3 reported perceived drug–drug interactions, 1 reported worsening of epilepsy symptoms, 1 reported concerns about legality, 1 reported side effects, and 1 reported another rationale (i.e., switched to a different adjunctive medication during an anticonvulsant taper).

Controls that initiated artisanal CBD use during the follow-up period did not differ on quality of life, pain, mood, sleep, or caregiver burden measures at baseline compared with those who did not initiate (all $p > .22$). Among participants that initiated artisanal CBD product use, 4 also reported using THC-dominant products and 2 also reported using products high in both THC and CBD concentrations.

A significant time by use interaction was observed for Quality of Life, Physical Health, and Psychological Health domains of the WHOQOL-BREF and the anxiety and depression subscales of the HADS, all $ps < 0.05$. Follow-up tests indicated significant increases in Quality of Life, $b = 0.75$, $p = .005$, Physical Health, $b = 2.73$, $p < .001$, and Psychological Health, $b = 2.41$, $p = .002$, among participants who initiated artisanal CBD use, but no significant changes among baseline Controls who did not initiate use. Similarly, anxiety scores, $b = -2.62$, $p = .008$, and depression scores, $b = -3.87$, $p < .001$ on the HADS decreased among participants who initiated artisanal CBD use but did not significantly change among those who did not initiate use. Group by time interactions were not significant for health satisfaction, pain, sleep, or caregiver burden measures, all $ps > 0.05$.

Artisanal CBD Users that sustained use during all follow-up assessments showed increased Health Satisfaction, $b = 0.40$, $p < .001$ and Environment, $b = 0.45$, $p = .02$, scores on the WHOQOL-BREF at follow-up as well as a modest decrease in anxiety scores, $b = -0.78$, $p = .03$, on the HADS. In addition, caregivers of CBD Users that sustained use during the follow-up period reported significant decreases in the Caregiver Burden total score, $b = -1.14$, $p = .045$ and Role Strain subscale, $b = -0.59$, $p = .009$, at follow-up. No significant changes were observed at follow-up on ratings of pain, depression, or sleep (all $ps > 0.05$ in this group).

4. Discussion

This large, observational cohort study evaluated differences in a variety of health outcomes – psychiatric symptoms, healthcare utilization, and epilepsy-specific factors – based on artisanal CBD product use among people with epilepsy. No group differences were observed in seizure control based on self-reported number of past month seizures. Generally, higher quality of life, lower psychiatric symptom scores and improved sleep were observed among people using an artisanal CBD product based on both cross-sectional and longitudinal comparisons. Artisanal CBD Users reported significantly better epilepsy medication tolerability, a lower odds of prescription medication use and traditional anticonvulsant use, and reduced healthcare utilization compared with Controls. These findings are consistent with research indicating that practitioners recommending CBD in clinical care for epilepsy report integrating the use of CBD both as a means to improve patient quality of life as well as for seizure reduction [23].

Seizure control did not differ based on artisanal CBD product use in this study. This may be related to a number of factors, including those that could not be controlled in the observational setting. Participants reported using a median CBD dose of 1.4 mg/kg/day, which is well below the dose commonly used with pharmaceutical products (e.g., 10 mg/kg/day is the current recommend maintenance dose for pharmaceutical CBD). It is possible that the lower dose is due to the effects (either related to efficacy or tolerability) of THC or other cannabinoids and/or terpenes found in "full-spectrum" or "broad spectrum" artisanal CBD products compared with pharmaceutical CBD, or that most patients in this cohort were concurrently using other seizure control medications. Differences in dosing could also mean that a shorter effective half-life was observed due to either the lower dose and/or more infrequent dosing [24]. Moreover, the relatively low daily doses used by this cohort, and the narrow range of doses reported may explain why dose effects were generally not observed in this study. Future work using artisanal CBD products is needed with more stringent experimental control over dosing frequency, amount, and chemotype to evaluate these explanations and their impact on seizure control outcomes.

Important to note is that Artisanal CBD Users also had a lower odds of reporting traditional anticonvulsant use than Controls (78.5% versus 95.6%). The possible benefits of CBD for seizure con-

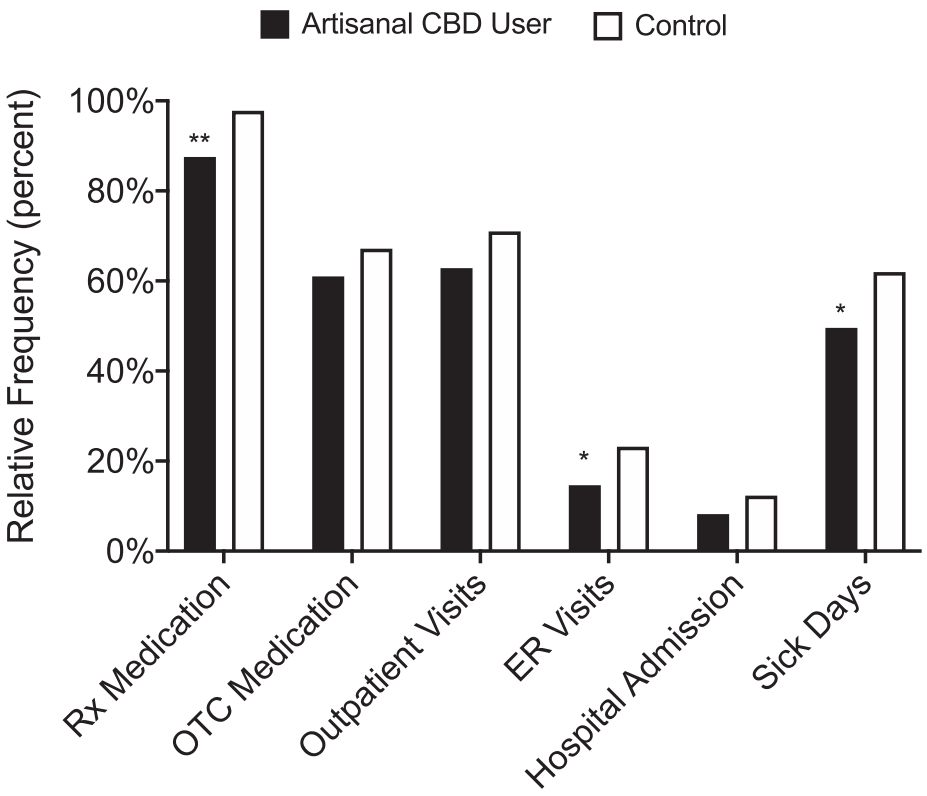

Fig. 4. Healthcare utilization by Artisanal CBD product use. Plotted are the percentage of participants reporting use of prescription medications, over-the-counter medications, or the specified event in the past month or those using an artisanal CBD product (black bars) or not using an artisanal CBD product (white bars) in the baseline assessment. Artisanal refers to non-pharmaceutical (i.e., non-Epidiolex®) use. * $p < .05$; ** $p < .01$.

trol and psychiatric health thus should be considered in the context of potential risks associated with monotherapy compared to current standards of care for CBD as an adjunctive medication [for two case reports on sudden death risk see [25]]. Factors such as stigma or lack of provider knowledge about medicinal cannabis may lead to reduced patient-provider communication about cannabis use. Lack of communication can heighten potential risks when treatment course is undertaken as entirely patient-directed rather guided by patient–provider interactions. These findings therefore further emphasize the need for controlled research to determine optimal methods for artisanal CBD product use in the treatment of epilepsy to determine CBD product types, doses, and concomitant use of other medications that maximize possible clinical benefit while minimizing potential risks.

The improvement in symptomatic depression and anxiety is a notable finding and is consistent with recent open-label clinical trials demonstrating improvements in quality of life following pharmaceutical CBD treatment in patients with epilepsy [26,27]. Psychiatric comorbidity has become a prominent emphasis in recent years as the interest in providing comprehensive neuropsychiatric care in epilepsy has increased. The current study suggests that comorbid psychiatric symptoms may improve with cannabinoids through mechanism(s) that may relate to direct effects of CBD and/or amelioration of unwanted side effects from concomitant antiepileptic medication. Rationales for use by study participants in this study were consistent with these possible pathways insofar as some participants reported using CBD products alone for seizure control, some reported using CBD products as an adjunct to prescription medications to improve inadequate seizure control, and others reported using as an adjunct to prescription medications to reduce adverse effects of those medications. These data are broadly consistent with existing reports across epilepsy types, including severe forms, where quality of life improves if depression symptoms improve, even if discrete seizure control does not appreciably change [26].

In contrast to other patient populations in the parent study, all those with epilepsy reported using a CBD product, although some reported additional use of cannabis products with other cannabinoid composition. This is consistent with data showing that patients with epilepsy tend to self-select CBD-dominant products when seeking medicinal cannabis from commercial sources with the intention of treating epilepsy [6]. This tendency is relevant considering the cost and regulatory barriers in obtaining access to pharmaceutical grade CBD extract, and suggests that patients with epilepsy are using artisanal products of a similar chemotype. Important to also note is that a subset of participants experienced adverse effects from artisanal CBD products, some of which motivated discontinuation of use. These adverse experiences included medical effects such as off-target side effects and drug–drug interactions as well as included prohibitive costs and legal concerns. These findings emphasize the need for further investigation of these potentially adverse experiences to predict who might experience them and with which products.

This study is broadly limited by the use of an observational cohort that is limited to self-report data. These limitations mean that we are not able to directly verify epilepsy characteristics and did not have control over factors like CBD dose or frequency of administration. These limitations are partly offset by the strengths of the observational approach. Specifically, observational research methods in large, real-world samples allow for evaluation of CBD product use in an individual's natural environment and avoid generalization limitations related to ability to participate in

clinical trial research (e.g., due to time or accessibility constraints). Future work is needed in more controlled contexts to extend this research. For example, ecological momentary assessment (EMA) designs could evaluate the effect of specific products on seizure control or mood improvement under a more proximal time course (e.g., day-to-day, within-day). These kinds of studies could help determine if mood or sleep improvement is dependent upon improvements in seizure control or occur independently of changes in seizure frequency or strength.

This study is also limited by the convenience sample design (e.g., people registered with the Realm of Caring Foundation), which may not generalize to the broader population of patients with epilepsy. Of note, the nature of the sample means that there is a possible referral bias and related increases in expectation for clinical benefit. We also did not collect information about cognitive performance and future studies would benefit from cognitive-behavioral assessments to index changes in conjunction with (or independent from) psychological health. As noted in prior analyses in the parent cohort [15], relatively high rates of missing data were observed for the longitudinal component likely due to the modest incentives used. Effect sizes also ranged in size with some small (e.g., WHOQOL-BREF; $d = 0.27$), and others medium (Liverpool Adverse Effect Profile; $d = 0.53$) by standard convention. The effects of concomitant anticonvulsant usage cannot be discounted and may provide synergistic effects that allowed lower dosages of CBD products. Notably, no impacts were observed for pain (a symptom not tied to epilepsy) demonstrating that these effects cannot be solely attributed to a positive report bias. Because it is not known how these findings translate to broader clinical samples, we recommend replication under more controlled conditions with larger and more consistent dosing schedules.

These findings broadly highlight real-world evidence for the possible utility of artisanal CBD products in a diverse and heterogenous population of patients with epilepsy. Although the lack of a placebo control group precludes determination of efficacy, the consistent observation of clinically meaningful differences between groups at baseline and with Controls who initiated artisanal CBD product use over time suggests that use of these products can improve health and quality of life for people with epilepsy. This evidence of artisanal CBD use, with broadly positive clinical effects, emphasizes the need for controlled trials in more directed patient populations with a range of non-pharmaceutical CBD products already used in the commercial market. These data emphasize a potential utility of these products that must be considered as an integral component of clinical care for epilepsy as well as for psychiatric symptoms, either comorbid with or independent to the condition.

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Declarations of Interest

RV has received financial compensation as a consultant or advisory board member from Canopy Growth Corporation, MyMD Pharmaceuticals, WebMD, and Syqe Medical Ltd. MBM is an employee of Canopy Growth Corporation and past non-executive director at AusCann Group Holdings Ltd. JAS has received research funding from Lundbeck (institution only), and receives royalties from Springer.

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Appendix A. Supplementary data

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