Epilepsy & Behavior 97 (2019) 105–110

Contents lists available at ScienceDirect

Epilepsy & Behavior

journal homepage: www.elsevier.com/locate/yebeh

Cognitive functioning following long-term cannabidiol use in adults with treatment-resistant epilepsy

Roy C. Martin [a,*], Tyler E. Gaston [a,d], Matthew Thompson [b], Steve B. Ampah [c], Gary Cutter [c], E. Martina Bebin [a], Jerzy P. Szaflarski [a]

[a] University of Alabama at Birmingham, Department of Neurology, Birmingham, AL, USA
[b] Children's Hospital of Alabama, Birmingham, AL, USA
[c] University of Alabama at Birmingham, Department of Biostatistics, Birmingham, AL, USA
[d] Birmingham VA Medical Center, Birmingham, AL, USA

ARTICLE INFO

Article history:
Received 17 November 2018
Revised 22 April 2019
Accepted 24 April 2019
Available online xxxx

Keywords:
Cannabidiol (CBD)
Treatment resistant epilepsy (TRE)
NIH Toolbox Cognition Battery (NIHTB-CB)
Chalfont Seizure Severity Scale (CSSS)

ABSTRACT

Cognitive dysfunction is a common comorbidity in adults with treatment-resistant epilepsy (TRE). Recently, cannabidiol (CBD) has demonstrated efficacy in epilepsy treatment. However, our understanding of CBD's cognitive effects in epilepsy is limited. We examined long-term cognitive effects of CBD in adults with TRE as part of an ongoing prospective, open-label safety study. Twenty-seven adults with TRE (mean age: 34[standard deviation (SD) 14], female 52%) enrolled in the UAB CBD program completed standardized cognitive testing (NIH Toolbox Cognition Battery (NIHTB-CB)) at pre-CBD administration baseline and at one-year follow-up. Participants were receiving stable CBD dose at the time of one-year testing (mean = 36.5 mg/kg/day). The NIHTB-CB consisted of two global composite scales (Fluid and Crystallized) and seven individual tests measuring aspects of working memory, episodic memory, executive function, processing speed, and language. All participants had recorded Chalfont Seizure Severity Scale (CSSS) scores at each visit. Statistical analyses included t-test, Pearson correlation coefficient, and multivariate one-way ANOVA. At baseline, cognitive test performance was below average for both global composite scales (Fluid: 71 [±18] range: 46–117) and Crystallized (76 [±15] range: 59–112)]. Longitudinal analysis revealed no significant group change across the two global composite scales. Of the seven individual cognitive tests, none changed significantly over time. No correlation was found between the cognitive change scores and CBD dose (all P's ≥; 0.2). Change in cognitive test performance was not associated change in seizure severity rating. These findings are encouraging and indicate that long-term administration of pharmaceutical grade CBD is overall cognitively well-tolerated in adults with TRE.

1. Introduction

The use of *cannabis* derivative compounds within the context of clinical trial therapeutic interventions has become increasingly common in recent years [1]. Of particular interest has been the study of cannabidiol (CBD) as a relatively nonpsychoactive *cannabis*-derived compound compared with the more well-known and studied compound Δ^9-tetrahydrocannabidiol (Δ^9—THC) [2]. This trend extends to treatment trials in epilepsy with a growing number of studies providing information on CBDs safety and efficacy [3–5]. Two large open-label trials and a few smaller trials have shown promise towards meaningful seizure reduction, as well as positive safety profiles in children and adults with treatment-resistant epilepsy (TRE) [3,6,7]. One recent study found favorable self and/or family reported cognitive and behavioral outcomes in a small group of children and adults with TRE and tuberous sclerosis [8].

To date, side effect profiles reported in epilepsy CBD studies describe fairly common occurrence of CBD-related symptoms including somnolence, diarrhea, and fatigue [3], as well as potential interactions with antiseizure drugs (ASDs) [9] which may be a factor in the reported side effect profiles. Anecdotal reports of patients using artisanal *cannabis* products described improvements in mood, sleep, and alertness [10]. The use of CBD as a potentially preferred choice of cannabinoid-based ASD as related to cognitive effects comes from several studies demonstrating the overall neutral impact from CBD in contrast to the commonly found negative psychoactive impact upon cognitive processing with THC [11,12]. When using CBD-only preparations, primarily neutral cognitive effects have been reported, in contrast to more common occurrence of negative cognitive effects from the use of isolated Δ^9-THC content [11]. Furthermore, a few studies have shown that CBD may serve as a protective effect from the negative cognitive effects of Δ^9-THC [12] if used in a pretreatment format or as add-on to the THC. In

* Corresponding author at: University of Alabama at Birmingham, Department of Neurology, 1720 6th Avenue South, 650 Sparks Building, Birmingham, AL 35294, USA.
E-mail address: rmartin@uabmc.edu (R.C. Martin).

https://doi.org/10.1016/j.yebeh.2019.04.044
1525-5050/

one functional Magnetic Resonance Imaging (fMRI) study investigating cognitive test performance in healthy volunteers, CBD did not differentially affect test performance as compared to either groups receiving placebo or Δ^9-THC [13]. However, this study and others have found interesting differential brain activation patterns between CBD and THC across various experimental cognitive tasks such as motor response inhibition, and emotional processing and across various brain regions [14]. For example, administration of THC to healthy young adults resulted in attenuation of bilateral parahippocampal gyrus activation during an fMRI-based go-no go task, but CBD-augmented activation to that area [13].

In an effort to provide additional outcome data for the growing CBD epilepsy literature, the current study presents results of one-year cognitive outcome in a group of adults participating in the University of Alabama at Birmingham (UAB) CBD open-label compassionate-use study [4]. Other than the reporting of CNS symptom adverse events, prior CBD epilepsy studies have not systematically examined cognitive function outcome via formal neurocognitive assessment methods.

The present study assessed cognitive function by the use of a standardized and validated computer-based battery of tests (i.e., NIH Toolbox Cognition Battery (NIHTB-CB)), as part of a comprehensive battery measurement of physiologic, mood/Quality of Life (QOL), and adaptive behavior [4]. Based upon prior literature investigating CBD and cognition as well as relatively neutral side effect profile, we hypothesized that compared to a pre-CBD baseline cognitive testing, no statistically significant changes would be evident at one-year follow-up testing for patients on steady-state CBD dose.

2. Methods

2.1. Participants

Study participants were part of the open-label compassionate use UAB CBD program approved by the State of Alabama legislative act "Carly's Law". The overall goal of this study was to assess the safety and tolerability of CBD in adults and children with TRE. Only the adult participants (ages ;≥ 19 years old) recruited for the program were included for the present study. Detailed study design and description are provided in recent publications [4,9]. All study participants and/or their legal representatives signed informed consent approved by UAB Institutional Review Board. The study received approval from the U.S. Food and Drug Administration (FDA) and registered with www.clinicaltrials.gov under the number (NCT02700412).

In summary, each participant underwent a comprehensive admission screening process before inclusion to the study [9] that included medical records review by a study approval committee, as well as extensive inclusion/exclusion criteria list review. Inclusion criteria included having a defined TRE defined as failure to respond to four or more ASDs including ;≥1 trials of two concurrent ASDs. Exclusion criteria included the use of medical marijuana or CBD-based product within 30 days of study enrollment and history of substance abuse or addiction (all inclusion and exclusion criteria are available at www.uab.edu/cbd).

At initial study visit, participants completed comprehensive physical, neurological, and laboratory testing [9]. Participants received a pharmaceutical formulation of highly purified CBD derived from *Cannabis sativa* L. plant in oral solution (100 mg/ml; Epidiolex® in the U.S.; GW Research Ltd., Cambridge, United Kingdom) [15] with start dose at 5 mg/kg/day divided between morning and evening doses. Participants were instructed to take CBD at usual time of their ASD administration. CBD was gradually titrated upwards in 5 mg/kg/day increments over the course of follow-up study visits (every two weeks) until reaching a tolerable and treatment effective dose. The maximum CBD dose was 50 mg/kg/day. Seizure severity was assessed via standardized questionnaire (Chalfont Seizures Severity Scale; CSSS) [16].

For the purpose of this study, baseline cognitive testing was completed prior to initiating the CBD medication and then again at approximately 48 weeks after baseline. Only participants receiving stable dose CBD at the one-year study visit were included in the study analyses.

2.2. Cognitive test battery

Cognitive performance assessed by using the NIH Toolbox Cognition Battery (NIHTB-CB); Version 2.0; www.Healthmeasures.net/nih-toobox). The NIH Toolbox is a multidimensional set of measures that researchers can use to assess cognitive, sensory, motor, and emotional function across the ages 3–85. The measures have been normed and validated in a broad sample of the U.S. population [17,18]. The cognitive measures selected for use in this study were seven individual tasks that assess aspects of attention/working memory, executive function, episodic memory, and language. Two global composite scores (Crystallized and Fluid) were also calculated. Good test–retest reliability reported on these measures with minimal change in the Crystallized measures and modest change for Fluid measures (i.e., approximately one scale score unit improvement) [17].

2.2.1. Tests comprising the Fluid Composite score

(1) Dimensional Change Card Sort (DCCS) Test measures aspects of cognitive flexibility/set-shifting by having participants select stimulus choice per two-target matching category (i.e., color or shape). Dimensional Change Card Sort score derived from combination of selection accuracy and reaction time. (2) Flanker Inhibitory Control and Attention Test requires participant to select a specific choice within an array of distracting visual stimuli (i.e., directional arrows) and assesses inhibitory responding. Flanker score based on combination of accuracy and reaction time. (3) Picture Sequence Memory Test requires participants to recall in sequence pictured stimuli from common contextual theme (i.e., scenes from a park). Memory score based on placement accuracy of stimuli. (4) Pattern Comparison Processing Speed Test is a measure assessing speed of processing by having participants make speeded dichotomous choice of same/different between two visually-presented objects. Correct responses within 90 s represent total score. (5) List Sorting Working Memory Test assesses visual working memory by having participants recall and sequence dual modality (auditory/visual) presented sets of simple common animals and/or foods. Total correct responses for one-item and two-item trials.

2.2.2. Tests comprising the Crystallized Composite score

(1) The Oral Reading Recognition Test has participants read computer presented words of varying pronunciation difficulty. (2) The Picture Vocabulary Test is a measure of receptive vocabulary in which participants hear a word and then asked to select one out of four pictures that best corresponds to that word.

2.3. Data analyses

We first compared demographic and clinical characteristics of our study participant sample by dividing into two groups. The first group consisted of all participants having completed both baseline and one-year cognitive testing (n = 27) and were taking CBD at the time of their one-year testing session. The second group consisted of the remaining study participants (n = 53). We used Wilcoxon's test, Pearson's chi-square test, and Fisher's exact test where appropriate.

We assessed whether baseline test scores differed between participants who completed the one-year follow-up cognitive testing and those who completed testing at baseline only (n = 13). Bonferroni correction [0.05/10 (7 individual test scores, 3 composite scores) = 0.0005 P-value] was used given the multiple comparisons. In addition, results from a sensitivity analysis that used multivariate one-way ANOVA (MANOVA) were also reported given the caveat of lost data.

To determine whether there were significant changes in cognition following the one-year CBD exposure, we employed the paired t-test to determine changes in cognitive test scores at one-year relative to baseline test scores (n = 27) and included Bonferroni correction for multiple comparisons. The t-test with correction for multiple comparisons was chosen over the MANOVA since participants would be deleted from the analysis if they were missing even one (or more) test scores out of the seven core cognitive tests. However, we included results from the MANOVA as a sensitivity analysis.

To determine whether changes in cognition were associated with one-year CBD exposure, we used the Pearson's linear correlation test as a preliminary analysis to assess the strength of the relationship between changes in cognition measures and individual CBD dose at one-year. We also examined the same association by adjusting for baseline cognitive test performance through multiple regression analysis.

To assess whether a reduction in seizures improved cognitive test performances, the previous analysis was repeated with the seizure severity measure instead of the CBD dose variable.

All analysis performed using R statistical software version 3.2.3.

3. Results

3.1. Participants and baseline characteristics

As of the cutoff date (3/12/19) for data analysis, the study had 80 enrolled participants [mean age = 33 ± 14 years, female = 44 (55%), White (91%)]. Of those 80 participants, 27 had completed both baseline and one-year cognitive testing and were taking CBD at time of the one-year visit.

Table 1 presents the baseline demographic and clinical characteristics of study participants having completed baseline and one-year cognitive testing (N = 27) and the remaining study sample (N = 53). The two groups did not differ across age, proportion female/male, or race (i.e., majority both groups White). Both groups were taking similar number of Antiepileptic drugs (AEDs) (i.e., combined groups mean = 3), similar number of previously tried AEDs (i.e., mean = 9), history of epilepsy surgery (yes – 48%), and seizure severity scores.

Of note, there was 1 participant with exceptionally high seizure severity score of 315 at baseline and 21 at year 1. A sensitivity analysis that excluded this participant from the analysis did not yield appreciable changes in the conclusions drawn, so this participant remained in all analyses.

3.2. Cognitive function and seizure severity (at baseline and one-year)

3.2.1. Baseline results

Table 2 presents cognitive test performances between our group of participants with both baseline and one-year testing as compared with those participants with baseline only cognitive testing. No statistically significant changes between group differences were found for the NIHTB Cognitive Composite scores or any of the seven individual tests (all P's > 0.20). A sensitivity analysis that used MANOVA ($F(9, 12) = 0.54$, $P = 0.83$) also produced similar nonsignificant baseline cognitive functioning.

For the study participants completing both baseline and one-year cognitive testing (N = 27), group-level performances on the DCCS, Flanker Test, Oral Reading, and Picture Vocabulary Test were within psychometric normal limits (i.e., standard score between 80 and 115) at baseline while all other cognitive measures were below that performance level (Table 2). Across the individual tests at baseline, there was wide performance heterogeneity with 47% of individual test scores above a standard score of 80, while the remaining 53% below that level. Of the 96 individual test scores below 80 standard score, 36 (38%) were below standard score of 62.

We noted that sample size varied across the individual subtests (Table 2), as well as the composites scores due to reasons of occasional technical issues (e.g., Wi-Fi disconnection during a test) or participant issues (i.e., inattention to task, fatigue, or visual complaints). However, the total number of missing subtest data points was small. Only seven missing score data points (4%) for the baseline test scores (i.e., 189 total scores = 27 subjects × 7 individual subtests) and only six missing score data points (3%) for the one-year test scores.

3.2.2. One-year cognitive outcome

No statistically significant score changes were found across the seven individual cognitive tests or the Composite scores (i.e., Fluid and Crystallized; Table 3) after correcting for multiple comparisons (i.e., Bonferroni). A nonsignificant CBD effect on cognitive function was also observed with a sensitivity analysis that used a MANOVA ($F(9, 10) = 2.49$, $P = 0.09$).

There was a small group level decline found for the DCCS task (;P = 0.02). However, outlier's did not drive the overall change, as we found change in both positive and negative directions. The mean change for the group was −4.96 standard score units (see Table 3). The change

Table 1
Baseline characteristics of participants with one-year cognitive data compared with remaining participants.

	One-year cognitive Testing (n = 27)	Remaining Study participants (n = 53)	Test statistic
Age at enrollment (Yrs)	22 30 45 (34 ± 14)	23 26 34 (32 ± 14)	$F_{1,78} = 0.2$, $P = 0.6$[1]
Gender			
Female	52% (14)	57% (30)	$X^2 = 0.2$, $P = 0.7$[2]
Male	48% (13)	43% (23)	
Race			
American Indian/Alaska Native	4% (1)	0% (0)	$X^2 = 2.0$, $P = 0.4$[2]
African-American	7% (2)	8% (4)	
White	89% (24)	92% (49)	
Age at seizures onset	4.5 8.0 19.0 (11.9 ± 10.1)	0.5 2.9 9.2 (7.7 ± 12.3)	$F_{1,77} = 9.0$, $P = .005$[1]
Number of AEDs at enrollment	3.0 3.0 4.0 (3.3 ± 0.9)	2.0 3.0 4.0 (3.0 ± 0.9)	$F_{1,77} = 1.0$, $P = 0.3$[1]
Number of AEDs tried	7.0 9.0 13.0 (10 ± 4)	7.0 8.0 11.0 (9 ± 4)	$F_{1,77} = 0.2$, $P = 0.7$[1]
History epilepsy surgery*			
No	70% (19)	42% (22)	$X^2 = 6.0$, $P = 0.05$[2]
Yes	30% (8)	58% (30)	
CSSS	57 67 97 (85 ± 59)	42 83 122 (83 ± 48)	$F_{1,78} = 0.03$, $P = 0.9$[1]
1-year reduction in seizure severity (CSSS)	−80 −55 −18 (−63 ± 60)	−83 −49 −11 (−49 ± 60)	$F_{1,78} = 0.04$, $P = 0.5$[1]

a b c represent the lower quartile a, the median b, and the upper quartile c for continuous variables. X ± s represents Mean ± 1 SD. Numbers after the percents are frequencies. CSSS = Chalfont Seizure Severity Scale. *Information unavailable for one participant.

Table 2
Cognitive characteristics of participants with one-year cognitive data compared with baseline only participants.

	N	One-year participants	Baseline only	Test statistic
		Testing (at baseline)	Participants	
		(n = 27)	(n = 13)	
Total composite	31	51 66 80 (70 ± 19)	57 62 73 (66 ± 15)	$F_{1,29} = 0.06$, $P = 0.8$[1]
Fluid Composite	32	60 72 80 (71 ± 18)	50 64 83 (66 ± 17)	$F_{1,30} = 0.1$, $P = 0.7$[1]
Crystallized	36	66 70 82 (76 ± 15)	70 77 86 (80 ± 14)	$F_{1,34} = 2.0$, $P = 0.2$[1]
Card sort	37	78 82 94 (85 ± 15)	78 83 90 (84 ± 9)	$F_{1,35} = 0.07$, $P = 0.8$[1]
Flanker	35	79 89 98 (87 ± 17)	78 82 86 (83 ± 13)	$F_{1,33} = 0.8$, $P = 0.4$[1]
List sort	35	61 75 92 (76 ± 18)	72 82 96 (82 ± 19)	$F_{1,33} = 1.0$, $P = 0.3$[1]
Oral Reading	39	68 77 90 (80 ± 15)	70 80 85 (80 ± 13)	$F_{1,37} = 0.01$, $P = 0.9$[1]
Pattern comparison	40	54 58 78 (67 ± 23)	46 53 68 (62 ± 22)	$F_{1,38} = 2.0$, $P = 0.2$[1]
Picture sequencing	35	64 76 81 (74 ± 13)	66 76 86 (78 ± 19)	$F_{1,33} = 0.9$, $P = 0.3$[1]
Picture vocabulary	38	68 75 94 (81 ± 16)	72 90 94 (86 ± 15)	$F_{1,36} = 0.5$, $P = 0.5$[1]
CSSS	40	57 67 97 (85 ± 59)	72 94 139 (103 ± 56)	$F_{1,38} = 2.0$, $P = 0.2$[1]
Change in CSSS at one year	40	−80 −55 −18 (−63 ± 60)	−119 −73 −26 (−80 ± 64)	$F_{1,38} = 0.6$, $P = 0.5$[1]

a b c represent the lower quartile a, the median b, and the upper quartile c for continuous variables. X ± s represents Mean ± 1 SD. Numbers after the percents are frequencies. CSSS = Chalfont Seizure Severity Scale. *Information unavailable for one participant.

score range went from a 20-point improvement to a 22-point decline. Six patients showed change declines of 10 or more standard score units, while five patients showed either no score change or improvement. We also noted mild improvement for the Picture Vocabulary Test ($P = 0.03$) with mean group change upwards of 4.85 standard score units. Of our 27 study participants with one-year cognitive data, a statistically significant reduction in seizure severity was observed (Table 3).

3.3. One-year change in cognitive function and association with stable CBD dosage at one year

Pearson correlation analysis revealed no statistically significant association between changes in cognitive test performance and CBD dose (at one year) across the three cognitive composite scores and the seven individual cognitive tests (all P values > 0.2). No statistically significant effects found across any of the cognitive measures or composites after adjusting for baseline cognitive test performance (all P values > 0.22).

Table 3
Change in cognitive function and seizure severity.

Outcome	Visit			P-value
	Baseline	Year 1 ± 2 months	Change	
Total composite	67.8 (18.7)	68.3 (17.7)	0.47 ± 6.9	0.77
Range	[47, 110]	[47, 109]	[−13, 16]	
N	19	19		
Fluid	69.7 (19.4)	69.1 (20.0)	−0.68 ± 8.2	0.72
Range	[46, 117]	[46, 110]	[−13, 20]	
N	19	19		
Crystallized	74.8 (15.0)	76.9 (15.2)	2.12 ± 7.3	0.16
Range	[59, 112]	[60, 108]	[−9, 21]	
N	25	25		
Card sort	84.7 (14.6)	79.7 (14.4)	−4.96 ± 9.8	0.02
Range	[56, 116]	[46, 101]	[−22, 20]	
N	26	26		
Flanker	87.5 (16.3)	85.3 (16.6)	−2.21 ± 12.3	0.39
Range	[53, 121]	[55, 117]	[−24, 25]	
N	24	24		
List sorting	75.8 (17.6)	75.6 (20.3)	−0.28 ± 11.0	0.9
Range	[46, 104]	[46, 114]	[−23, 27]	
N	25	25		
Pattern Comparison	66.4 (23.2)	69.7 (25.7)	3.31 ± 12.3	0.18
Range	[46, 140]	[46, 136]	[−17, 32]	
N	26	26		
Picture sequencing	73.0 (13.0)	74.6 (13.6)	1.52 (8.0)	0.37
Range	[52, 108]	[52, 109]	[−18, 14]	
N	23	23		
Oral Reading	79.4 (14.8)	77.4 (15.6)	−2.0 ± 5.8	0.08
Range	[60, 114]	[58, 107]	[−13, 14]	
N	26	26		
Picture vocabulary	81.0 (16.7)	85.9 (15.5)	4.85 ± 10.6	0.03
Range	[59, 118]	[61, 118]	[−14, 28]	
N	26	26		
CSSS	84.7 (59.4)	21.6 (23.0)	−63.1 ± 60	<0.0001
Range	[16, 315]	[0, 99]	[−289, −6]	
N	27	27		

3.4. One-year change in cognitive function and association with change in seizure severity

Pearson correlation analysis revealed no statistically significant association between changes in cognitive test performance and seizure severity change (all P values > 0.27). No statistically significant effects found across any of the cognitive measures or composites after adjusting for baseline cognitive test performance (all P values > 0.17).

4. Discussion

There exists a growing body of encouraging evidence from randomized controlled trials (RCTs) and open-label investigations for the safety and efficacy of CBD as adjunctive treatment for persons with epilepsy [19]. Improvements in seizure frequency have been reported in both adults and pediatric groups [4]. With those findings in mind, the present prospective, open-label study examined long-term cognitive outcomes for a group of adults with TRE who were taking therapeutic doses of CBD over the course of one year. To our knowledge, this is one of the first studies [20] to investigate with standardized neurocognitive measures the potential cognitive impact of long-term stable CBD dose in persons with TRE. The CBD administered was pharmaceutical grade and well-characterized in terms of dosage and measurement of adverse events [4].

Our primary finding was that the addition of CBD to TRE participants' medication regimen did not appreciably affect global cognitive function as measured via standardized cognitive measures (i.e., NIH TCB). Neither the NIHTB-CB Fluid Composite score nor the Crystallized Composite score changed statistically from baseline to one-year. We also found no statistically determined performance change across any of the seven individual cognitive tasks. The only exception to these findings was for a very modest group level difference between baseline and one-year performance on the DCCS task. This task assessed set-shifting ability via a card-sorting format and represented an aspect of executive function [17]. The direction of performance change was negative as the group displayed lower scores at one-year compared to baseline assessment of approximately one-third standard deviation unit (Table 2).

Reasons for the performance change on the DCCS task as opposed to the other cognitive measures is not currently clear. Whether this particular test has properties that are sensitive to CBD effects is unclear. The DCCS task measures aspects of executive functioning described the

form of flexibility/set-shifting [17,21]. Whether CBD specifically affected this cognitive function remains open to discussion. The other NIHTB-CB executive measure (i.e., Flanker task) showed a similar slight downward pattern of change as the DCCS task (see Table 2) but not reaching statistical significance possibly because of larger standard deviation within the group. At the same time, both tests have previously demonstrated positive correlation with each other in a normative healthy adult group [22] and involve processing speed/reaction time selection demands. Prior studies utilizing fMRI measurement in other groups (e.g., healthy volunteers) have demonstrated that CBD modifies several regional brain areas including frontostriatal resting-state connectivity [23] that have involvement with executive tasks of the type from the NIHTB-CB, as well as brain areas involved with various cognitive operations (e.g., verbal memory, response inhibition) [13]. However, while interesting to speculate on these findings in relation to our present cognitive data, further work is needed with persons with TRE and functional connectivity associations.

We also found that CBD dosage at time of one-year assessment, as well as seizure severity ratings (CSSS) at one-year, were not statistically associated with change in cognitive test performance. In a prior study from our UAB CBD program [4] CSSS ratings declined substantially within the initial 12-week period and remained stable over the course of the remaining study weeks. It appears from our current findings that seizure severity reduction is not an important factor affecting cognitive functioning in our sample. Our study is in general agreement with prior studies investigating the effects of CBD on cognitive function in TRE [8] and other populations including healthy volunteers, cannabis users, neurological patients, and schizophrenia (see comprehensive review from Osborne [12]). Prior nonepilepsy studies, although mostly acute single-dose studies, have shown that CBD exhibits primarily null effects to measures assessing aspects of working memory [24], reaction time [25], verbal memory [13], and general mental status [26] and, in some instances, it has attenuated the negative cognitive effects of THC [12]. For example, one study [27] utilizing a 6-week, randomized, placebo-controlled design found that stable antipsychotic-treated adults with schizophrenia receiving CBD did not demonstrate appreciable changes from baseline to the endpoint on a comprehensive cognitive test battery [28] (i.e., standardized tests of processing speed, verbal fluency, attention/vigilance, memory, working memory, and reasoning/problem-solving) as compared to the placebo group. Additionally, side effect profiles were similar although sedation more noted in the CBD group. In another study [13], healthy volunteers receiving acute orally administered 600 mg/day CBD dose showed no performance differences compared to a placebo group on fMRI measures of verbal memory, fearful face recognition, and response inhibition. In one recent epilepsy study, cognitive and behavioral benefits were reported by means of self/parent report for children and adults with tuberous sclerosis and TRE having taken CBD (max dose 50 mg/kg/day) over a one-year period. This group of mostly children/adolescents (14 of the 18 patients) with majority having developmental delays, the reports were for improvement in aspects of cognitive function (e.g., verbal communication, alertness). Both our current findings and those from the Hess et al. [8] study are encouraging and serve as basis for additional future investigation with larger patient samples.

It was noteworthy that the current cognitive assessment approach represented testing across a breadth of cognitive domains and that as a treatment group our sample did not demonstrate appreciable cognitive change over time with the addition of the adjunctive CBD treatment. NIH Toolbox Cognition Battery measures assessing aspects of executive functioning, language, working memory, and memory were similar performance across the two time points.

As a group, cognitive functioning was below average and remained in that range over the course of the one-year interval. The level of cognitive test performances for this group with TRE is not unexpected since these were persons with very intractable and with severe epilepsy. While a few of the study participants had average-to-above average cognitive testing performance, the majority of participants were performing below average ranges. At baseline assessment, 47% of participants had composite scores within psychometrically defined normal ranges (i.e., above standard score of 80). This was true for both tasks considered more susceptible to medical treatments (i.e., Fluid tests), as well as those considered more resilient to neurological injury or medical treatment (i.e., Crystallized tests).

This study had several limitations that include previously mentioned issues involved with any prospective, open-label study [4] (e.g., treatment expectation bias, flexible dosing schedule). We acknowledge study limitations that include substantial proportion of study participants not completing cognitive testing at the one-year interval, as well as those not able to complete testing at baseline visit. Those participants not completing cognitive testing at baseline presented with significant cognitive and in some instances motoric disabilities (i.e., developmental disabilities) that prevented their ability to complete the computerized tests. This suggests that for cognitive testing in this group of severely disabled patients, reliance upon caregiver interview questionnaires will be needed (see Hess et al. [8]). The omission of those not tested and those who decided to leave the study may have enriched the cohort for responders, thus weakening the correlations of the changes on cognitive functions and clinical severity. However, the improvements in the clinical outcomes (i.e., seizure frequency) were similar to those reported by others using Epidiolex. Nevertheless, there is a need for investigating cognitive performance in randomized placebo-controlled trials that includes persons with higher Intellectual Quotient (IQ) levels. Of additional note, several test scores within our participant sample were clearly approaching floor levels (i.e., standard scores < 61). Approximately, 20% of test scores fell below that standard score level.

Another issue involves the lack of comparison of non-CBD group with TRE that would help provide gauge for measuring any practice/retest effects. Even though our CBD group did not show substantial change over the retest interval, there exists possibility that our group may have not shown possible practice effect. This question remains open as our data collected was within context of a large open-label safety/efficacy study and not intended as comparison project. Future study would be needed to answer this question.

At the same time, we did note a substantial range of cognitive test performances suggesting a potentially representative sampling of the cognitive levels seen in epilepsy clinics treating patients with TRE. Study participants' standard scores ranged from severely impaired to high average psychometric ranges. As noted above, we found null associations between CBD dose at one-year and cognitive performance after controlling for baseline performance levels. While certainly with limitations, as highlighted above, our present findings are encouraging in addition to the reports of clinical efficacy of CBD as adjunctive treatment for TRE. Further work utilizing randomized, placebo-controlled designs and larger samples will validate these promising early efforts.

Acknowledgment

This study supported in part by funds from the State of Alabama ("Carly's Law"), the UAB Epilepsy Center, and GW Research Ltd., Cambridge, UK (in-Kind donation of Epidiolex®). The study was presented in part at the 71st Annual Meeting of the American Epilepsy Society in Washington, D.C. (December 1–5, 2017).

Disclosures

RCM: Funding: NIH, NSF. Editorial board member for Epilepsy Currents

TG: salary support from the State of Alabama ("Carly's Law"), consulting fee from Greenwich Biosciences, Inc.

MT: none.

SA: none.

GC: **Data and Safety Monitoring Boards:** AMO Pharmaceuticals, Biolinerx, Horizon Pharmaceuticals, Hisun Pharmaceuticals, Merck, Merck/Pfizer, Opko Biologics, Neurim, Novartis, Ophazyme, Sanofi-Aventis, Reata Pharmaceuticals, Receptos/Celgene, Teva pharmaceuticals, NHLBI (Protocol Review Committee), NICHD (OPRU oversight committee). **Consulting or Advisory Boards:** Atara Biotherapeutics, Axon, Biogen, Argenix, Brainstorm Cell Therapeutics, Charleston Labs Inc., Click Therapeutics, Genzyme, Genentech, GW Pharma, Klein-Buendel Incorporated, Medimmune, Medday, Novartis, Roche, Scifluor, Somahlution, Teva pharmaceuticals, TG Therapeutics, UT Houston. Dr. Cutter is employed by the University of Alabama at Birmingham and President of Pythagoras, Inc. a private consulting company located in Birmingham AL.

MB: salary support from the State of Alabama ("Carly's Law"), consulting fee from Greenwich Biosciences, Inc. and salary support from GW Research Ltd., Cambridge.

JPS: Funding: NIH, NSF, Shor Foundation for Epilepsy Research, EFA, Department of Defense, UCB Biosciences, NeuroPace Inc., FDA, AES, SAGE Therapeutics Inc., Greenwich Biosciences Inc., Serina Therapeutics Inc., and Eisai, Inc. Consulting/Advisory Boards: SAGE Therapeutics Inc., Greenwich Biosciences Inc., NeuroPace, Inc., Upsher-Smith Laboratories, Inc., Medical Association of the State of AL, Serina Therapeutics Inc., LivaNova Inc., Lundbeck, and Elite Medical Experts LLC. Editorial board member for Epilepsy & Behavior, Journal of Epileptology (associate editor), Journal of Medical Science, Epilepsy Currents (contributing editor), and Folia Medica Copernicana.

We confirm that we have read the journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

References

[1] Grotenhermen F, Muller-Vahl K. Medicinal uses of marijuana and cannabinoids. J Crit Rev Plant Sci 2016;35(5–6):378–405.
[2] Rosenberg EC, Tsien RW, Whalley BJ, Devinsky O. Cannabinoids and epilepsy. Neurotherapeutics 2015;12:747–68.
[3] Devinsky O, Friedman D, Thiele E, Laux L, Sullivan J, Miller I, et al. Cannabidiol in patients with treatment-resistent epilepsy: an open-label interventional trial. Lancet Neurol 2016;15:270–8.
[4] Szaflarski JP, Bebin EM, Cutter G, DeWolfe J, Dure LS, Gaston TE, et al. Cannabidiol improves frequency and severity of seizures and reduces adverse events in an open-label add-on prospective study. Behavior;Epilepsy Behav 2018;87:131–6.
[5] Stockings E, Zagic D, Campbell G, Weier M, Hall WD, Nielsen S, et al. Evidence for cannabis and cannabinoids for epilepsy: a systematic review of controlled and observational evidence. J Neurol Neurosurg Psychiatry 2018;89:741–53.
[6] Devinsky O, Cross JH, Laux L, Marsh E, Miller I, Nabbout R, et al. Trial of cannabidiol for drug-resistent seizures in the Dravet syndrome. N Engl J Med 2017;376(21):2011–20.
[7] Szaflarski JP, Bebin EM, Comi AM, Patel AD, Joshi C, Checketts D, et al. Long-term safety and treatment effects of cannabidiol in children and adults with treatment-resistant epilepsies: expanded access program results. Epilepsia 2018;59(5):1540–8.
[8] Hess EJ, Moody KA, Geffrey AL, Pollack SF, Skirvin LA, Bruno PL, et al. Cannabidiol as a new treatment for drug-resistant epilepsy in tuberous sclerosis complex. Epilepsia 2016;57(10):1617–24.
[9] Gaston TE, Bebin EM, Cutter GR, Liu Y, Szaflarski JP, Program ftUC. Interactions between cannabidiol and commonly used antiepileptic drugs. Epilepsia 2017;58(9):1586–92.
[10] Porter BE, Jordon C. Report of a parent survey of cannabidiol-enriched cannabis use in pediatric treatment resistant epilepsy. Behavior;Epilepsy Behav 2013;29(3):574–7.
[11] Scott JC, Slomiak ST, Jones JD, Rosen AFG, Moore TM, Gur RC. Association of cannabis with cognitive functioning in adolescents and young adults: a systematic review and meta-analysis. JAMA Psychiat 2018;75(6):585–95.
[12] Osborne AL, Solowij N, Weston-Green K. A systematic review of the effect of cannabidiol on cognitive function: relevance to schizophrenia. Neurosci Biobehav Rev 2017;72:310–24.
[13] Bhattacharyya S, Morrison PD, Fusar-Poli P, Martin-Santos r, Borgwardt S, Winton-Brown T, et al. Opposite effects of delta-9-tetrahydrocannabinol and cannabidiol on human brain function and psychopathology. Neuropsychopharmacology 2010;35(3):764–74.
[14] Allendorfer JB, Szaflarski JP. Neuroimaging studies towards understanding the central effects of pharmacological cannabis products on patients with epilepsy. Behavior;Epilepsy Behav 2017;70(part B):349–54.
[15] Gardner F. Now Epidiolex (FDA approves IND studies of CBD). Available from http://www.g2pharm.com/uploads/oshaughnessyarticle-comesnowepidiolex.pdf2013.
[16] J.S. D, Sander JW. The Chalfont Seizure Severity Scale. Journal of Neurology Neurosurg Psychiatry 1991;54(10):873–6.
[17] Weintraub S, Dikmen SS, Heaton RK, Tulsky DS, Zelazo PD, Slotkin J, et al. The cognition battery of the NIH toolbox for assessment of neurological and behavioral function: validation in an adult sample. J Int Neuropsychol Soc 2014;20(6):567–78.
[18] Heaton RK, Akshoomoff N, Tulsky DS, Mungas D, Weintraub S, Dikmen SS, et al. Reliability and validity of composite scores from the NIH Toolbox Cognition Battery in adults. J Int Neuropsychol Soc 2014;20(6):588–98.
[19] Gaston TE, Szaflarski JP. Cannabis for the treatment of epilepsy: an update. Curr Neurol Neurosci Rep 2018;18(11):73.
[20] Bortnik K, Trobliger R, Boreale K, Zeng R, Lancman M, Segal E. Impact of treatment with epidiolex (cannabidiol) on the cognitive functioning of pediatric patients with treatment-resistent epilepsy. Annual Meeting of the American Epilepsy Society; New Orleans, LA2018; 2018.
[21] Mungas D, Heaton R, Tulsky D, Zelazo PD, Slotkin J, Blitz D, et al. Factor structure, convergent validity, and discriminant validity of the NIH Toolbox Cognitive Health Battery (NIHTB-CHB) in adults. J Int Neuropsychol Soc 2014;20:1–9.
[22] Zelazo PD, Anderson JE, Richler J, Wallner-Allen K, Beaumont JL, Conway KP, et al. NIH Toolbox Cognition Battery (CB): validation of executive function measures in adults. J Int Neuropsychol Soc 2014;20(6):620–9.
[23] Grimm O, Loffler M, Kamping S, Hartmann A, Rohleder C, Leweke M, et al. Probing the endocannabinoid system in healthy volunteers: Cannabidiol alters fronto-striatal resting-state connectivity. Eur Neuropsychopharmacol 2018;28:841–9.
[24] Schoedel KA, Chen N, Hilliard A, White L, Stott C, Russo E, et al. A randomized, double-blind, placebo-controlled, crossover study to evaluate the subjective abuse potential and cognitive effects of nabiximols oromucosal spray in subjects with a history of recreational cannabis use. Hum Psychopharmacol Clin Exp 2011;26:224–36.
[25] Roser P, Juckel G, Rentzsch J, Nadulski T, Gallianat J, Stadelmann AM. Effects of acute oral tetrahydrocannabinol and standardized cannabis extract on the auditory P300 event-related potential in healthy volunteers. Eur Neuropsychopharmacol 2008;18:569–77.
[26] Wade DT, Robson P, House H, Makela P, Aram J. A preliminary controlled study to determine whether whole-plant cannabis extracts can improve intractable neurogenic symptoms. Clin Rehabil 2003;17(1):21–9.
[27] Boggs DL, Surti T, Gupta A, Gupta S, Niciu M, Pittman B, et al. The effects of cannabidiol (CBD) on cognition and symptoms in outpatients with chronic schizophrenia a randomized placebo controlled trial. Psychopharmacology 2018;235:1923–32.
[28] Green MF, Nuechterlein KH. The MATRICS initiative: developing a consensus cognitive battery for clinical trials. Schizophr Res 2004;72(1):1–3.