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ORIGINAL INVESTIGATION

The effects of cannabidiol (CBD) on cognition and symptoms in outpatients with chronic schizophrenia a randomized placebo controlled trial

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Abstract

Rationale Preliminary evidence suggests that cannabidiol (CBD) may be effective in the treatment of neurodegenerative disorders; however, CBD has never been evaluated for the treatment of cognitive impairments associated with schizophrenia (CIAS).

Objective This study compared the cognitive, symptomatic, and side effects of CBD versus placebo in a clinical trial.

Methods This study was a 6-week, randomized, placebo-controlled, parallel group, fixed-dose study of oral CBD (600 mg/day) or placebo augmentation in 36 stable antipsychotic-treated patients diagnosed with chronic schizophrenia. All subjects completed the MATRICS Consensus Cognitive Battery (MCCB) at baseline and at end of 6 weeks of treatment. Psychotic symptoms were assessed using the Positive and Negative Syndrome Scale (PANSS) at baseline and biweekly.

Results There was no main effect of time or drug on MCCB Composite score, but a significant drug × time effect was observed ($p = 0.02$). Post hoc analyses revealed that only placebo-treated subjects improved over time ($p = 0.03$). There was a significant decrease in PANSS Total scores over time ($p < 0.0001$) but there was no significant drug × time interaction ($p = 0.18$). Side effects were similar between CBD and placebo, with the one exception being sedation, which was more prevalent in the CBD group.

Conclusions At the dose studied, CBD augmentation was not associated with an improvement in MCCB or PANSS scores in stable antipsychotic-treated outpatients with schizophrenia. Overall, CBD was well tolerated with no worsening of mood, suicidality, or movement side effects.

Trial registration https://clinicaltrials.gov/ct2/show/NCT00588731

Keywords Cannabidiol · CBD · Cannabinoids · Schizophrenia · Psychosis · Cognition · Memory · Attention

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Introduction

Schizophrenia is associated with cognitive deficits in learning, recall, attention, working memory, and executive function (Heinrichs and Zakzanis 1998; Keefe et al. 2006). The cognitive impairments associated with schizophrenia (CIAS) are independent of phase of illness, are not simply the result of the symptoms or the treatments and are thought to represent a core feature of the illness that persist even after other symptoms have been effectively treated (Riley et al. 2000). CIAS are more strongly predictive of functional outcome than any other symptom measure, including psychotic symptoms (Hughes et al. 2003). Most patients (~70%) appear to have moderate to severe cognitive impairments (Heinrichs and

Zakzanis 1998; Keefe et al. 2005). Since existing antipsychotic drugs, all of which block dopamine (D2) receptors, have limited efficacy for CIAS (Buchanan et al. 2007), there is a need to develop treatments for CIAS that target other non-dopaminergic neurotransmitter systems. Several novel approaches have or are being tested for CIAS including pharmacological approaches targeting the glutamatergic system, cholinergic system including specific nicotinic receptors and non-pharmacological cognitive retraining (CRT) (Boggs et al. 2014; Bradley et al. 2010; D'Souza and Markou 2012; O'Donnell et al. 2010; Radek et al. 2010).

One potential target for improving CIAS is the endocannabinoid system that has been implicated in schizophrenia and in cognition (Leweke et al. 1999; Riedel and Davies 2005). The endocannabinoid system is comprised of two G-coupled receptors referred to as the cannabinoid 1 receptor (CB1R) and the cannabinoid 2 receptor (CB2R). While both are present in the brain and periphery, the former is primarily localized in the brain and the latter in the periphery (Devane et al. 1988; Schatz et al. 1997). The primary endocannabinoid ligands are anandamide (AEA) and 2-arachidonoylglycerol (2-AG), and the primary catabolic enzymes for these ligands are fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase (MAGL), respectively (Mechoulam and Parker 2013). CB1Rs are highly prevalent in areas associated with cognition including the hippocampus, cerebral cortex, basal ganglia, and cerebellum (Eggan and Lewis 2007). Studies in animals and humans have demonstrated that both synthetic and phytocannabinoids produce impairments in memory and attention. Furthermore, chronic cannabis exposure is known to disrupt attention, behavioral inhibition, verbal memory, and working memory/executive function (Ranganathan and D'Souza 2006). Acute administration of delta-9-tetrahydrocannabinol (THC), the main psychoactive component of cannabis and CB1R partial agonist, produces robust deficits in verbal learning, attention, and working memory (D'Souza et al. 2004), and schizophrenia patients are more vulnerable to the cognitive-impairing effects of THC compared to healthy controls (D'Souza et al. 2005). In summary, given that the endocannabinoid system is implicated in schizophrenia and CB1R agonists produce robust cognitive deficits, we hypothesized that manipulation of brain endocannabinoid function via CB1R antagonism/inverse agonism or modulating endocannabinoid levels might offer a novel target for reducing CIAS.

Cannabidiol (CBD), one of over 100 plant cannabinoids or phytocannabinoids isolated from *Cannabis sativa*, (ElSohly et al. 2017), is a constituent in herbal cannabis (Izzo et al. 2009), and unlike THC, it does not produce any psychotomimetic effects (Zuardi et al. 1993).THC, and other CB1Rs agonists, reliably produce robust deficits in verbal memory on the HVLT (D'Souza et al. 2004; Ranganathan and D'Souza 2006) in healthy volunteers and schizophrenia patients (D'Souza et al. 2005), and verbal memory deficits also occur in chronic users of cannabis (Morgan et al. 2010). Further, amongst cannabis users, a higher concentration of CBD in the cannabis used was correlated with lesser verbal memory impairments (Morgan et al. 2010) representing either a neuroprotective or pro-cognitive effect. In addition, non-human primate studies have also shown a protective effect of CBD for acute cognitive deficits produced by THC (Murphy et al. 2017). However, the effects of CBD on CIAS has not been studied to our knowledge.

Preclinical studies suggest that CBD may also have antipsychotic properties (Gomes et al. 2015; Moreira and Guimaraes 2005). Consistent with this, Leweke et al. 2012 demonstrated that CBD was as effective as amisulpride in ameliorating psychotic symptoms in decompensated patients with schizophrenia (Leweke et al. 2012). Further, Leweke et al. suggest that FAAH inhibition may underlie CBD's antipsychotic effects (Hallak et al. 2010; Leweke et al. 2012; Zuardi et al. 2006; Zuardi et al. 1995). However, CBD may have many different pharmacological effects on the endocannabinoid system (Ibeas Bih et al. 2015). Further, whether CBD has antipsychotic effects in patients with schizophrenia that are psychiatrically stable has not been studied in placebo controlled trials.

The current study aimed to examine the effects of CBD on CIAS using the MATRICS Consensus Cognitive Battery (MCCB) and on psychotic symptoms using the Positive and Negative Syndrome Scale (PANSS).

Methods

Study design

In this 6-week, randomized, placebo-controlled, parallel group, double-blinded, fixed-dose trial, the effects of oral CBD 300 mg BID, (600 mg/daily), added to a stable dose of antipsychotic medication were studied in 36 patients diagnosed with schizophrenia. Adherence to study medication was monitored each week by self-report. The study was conducted in the Schizophrenia Neuropharmacology Research Group at Yale (SNRGY) spanning VA Connecticut Healthcare System, West Haven, Connecticut, and the Abraham Ribicoff Research Facilities, Connecticut Mental Health Center, New Haven, Connecticut. The study was conducted under the purview of the Institutional Review Boards of both Yale University and VA Connecticut Healthcare System, and the US FDA (IND #101,185) and in compliance with ICH guidelines. CBD was obtained from STI Pharmaceuticals. The study was registered with clinicaltrials.gov (NCT 00588731). Subjects were recruited using local advertisements and word of mouth and were paid for their participation in the research.

Consent process

Subjects who met entry criteria were invited to meet with the research staff, who explained risks and procedures as outlined in the consent form. After reviewing this information and answering questions, informed consent was obtained from all subjects. A copy of the consent form was provided to all subjects.

Sample size

In the absence of controlled data showing medication-induced improvement in HVLT total immediate recall improvement in schizophrenia, we determined, based on the mean total recall scores from the CATIE study, that for a two-tailed independent *t* test with alpha = 0.05 and 80% statistical power to detect a 12% or greater increase in total recall due to add-on CBD treatment compared to the levels with antipsychotic treatment alone (18.7 ± 2.11), we would need 15 subjects per group. With an expected dropout rate of 20%, a total number of 36 subjects were studied over 3 years.

Screening

During screening, cognitive ability was measured using the Hopkins Verbal Learning Test (HVLT) (Brandt 1991), and IQ was measured by the Wechsler Adult Intelligence Scale (WAIS) (Wechsler 1955). Verbal memory deficits represent the largest effect size difference in schizophrenia compared to the general population (Heinrichs and Zakzanis 1998); the CATIE study found that the mean HVLT total immediate recall score was 18.73 (out of a maximum possible score of 36) in antipsychotic-treated patients with schizophrenia as compared to 28.16 for the general population (Keefe et al. 2006; Riley et al. 2000; Rund et al. 2004). Subjects who scored less than or equal to 1 standard deviation below the mean for the general population on HVLT (Brandt 1991) total immediate recall were included in the study. Since the composite MCCB score is recommended as the gold standard for determining cognitive-enhancing effects of medications (Harvey and Bowie 2012), it was used as the primary cognitive outcome.

Inclusion/exclusion criteria

Male and female subjects 18–65 years of age, with a DSM-IV-TR diagnosis of schizophrenia, were included in the study. Subjects had at least 3 months of treatment with stable doses (no dose change in 4 weeks) of antipsychotic medication. Subjects were excluded for any other past or current DSM-IV-TR axis I diagnosis that required pharmacologic treatment, DSM-IV-TR diagnosis of substance abuse in the past 3 months or dependence in the past 6 months (excluding nicotine), any serious medical or neurological disorder, pregnant or nursing females or those not willing to use appropriate birth control, history of electroconvulsive treatment in the past 3 months, currently enrolled in a weight loss program, previous recent exposure to the HVLT, and treatment with clozapine, cognitive enhancers, or other investigational agents during the study.

Outcome measures

Cognitive Assessments Cognition was assessed using the *T* score of the MCCB composite and subscales at baseline and end of study after 6 weeks of study medication (Nuechterlein et al. 2008). An increase in MCCB *T* score indicates an improvement in cognitive ability.

Psychiatric Assessments Psychotic symptoms were assessed using the PANSS at baseline, week 2, week 4, and week 6 to measure symptom severity (Kay et al. 1987).

Safety Assessments Motor side effects were measured using the Barnes Akathisia Scale (BAS) (Barnes 1989), Simpson Angus Scale (SAS) (Simpson and Angus 1970), and the Abnormal Involuntary Movements Scale (AIMS) (Guy 1976) every 2 weeks. Additional side effects were measured weekly using the UKU-Side Effect Scale (Lingjaerde et al. 1987).

Statistical analysis

Linear mixed models with treatment (placebo, CBD) included as a between-subject factor and time as a within-subject factor were used to analyze each outcome. The interaction between treatment and time was also modeled. PANSS outcomes were analyzed at baseline, 2, 4, and 6 weeks; all other outcomes were analyzed at baseline and 6 weeks. The best-fitting variance-covariance structure was chosen based on the Schwartz-Bayesian Information Criterion (BIC). Least square means were estimated and plotted to assess significant effect. All analyses were conducted using SAS, version 9.4 (Cary, NC).

Results

Subjects

The study was conducted between September 2009 and May 2012. In total, 41 participants were randomized in the study and 39 received study medication: CBD ($n = 20$), placebo ($n = 19$) (see Fig. 1). Subject demographics and ratings during screening, for each arm of the study, can be seen in Table 1. In the CBD arm, one subject had a medication change in his antipsychotic after randomization, a protocol violation, and was thus withdrawn from the study before week 2. A second subject in the CBD group reported significant sedation and withdrew before week 2 assessments. In the placebo arm,

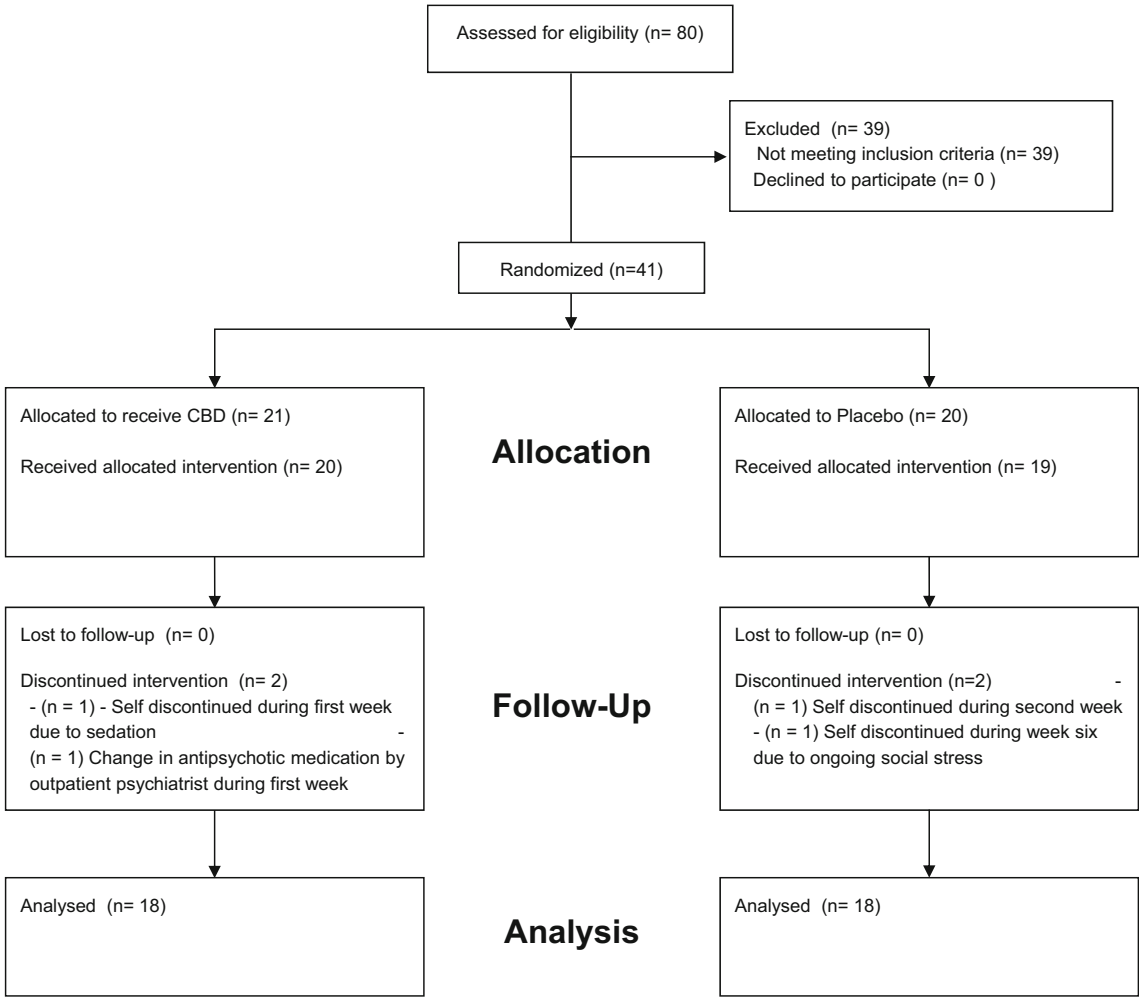

Fig. 1 CONSORT Flow Diagram

two subjects voluntarily withdrew, one before week 2 assessments and another before week 6 assessments. This resulted in 18 participants in each arm having at least one assessment after baseline. The progression of subjects from recruitment through the end of study is shown in Fig. 1.

Cognition

Baseline HVLTs, the primary variable for randomization, were similar at baseline between the two groups (see Fig. 2a). There was no main effect of Drug or Time on MCCB Composite score, but a significant drug × time effect was observed (F (1, 32) = 5.94; $p = 0.02$)(see Fig. 2b). Post hoc analyses revealed that only placebo-treated subjects improved over time (F (1, 32) = 4.84; $p = 0.03$).

For MCCB subscales, on the Reasoning and Problem Solving domain, there was a trend toward a main effect of time (F (1, 33) = 3.48; $p = 0.07$) and a drug × time interaction (F (1, 33) = 4.47; $p = 0.04$) (see Table 2). Post hoc analyses revealed that only placebo-treated subjects improved over time (F (1, 33) = 7.71; $p = 0.009$).

Psychopathology

Overall, there was a main effect of time, such that there was a significant decrease in PANSS Total scores over time (F (3, 101) = 10.62; $p < 0.0001$) but there was no significant drug × time interaction (F (3, 101) = 1.66; $p = 0.18$) (see Fig. 3). Similarly, there was a significant effect of time for PANSS General (F (3, 101) = 4.55; $p = 0.005$), PANSS Negative (F (3, 101) = 2.63; $p = 0.05$), and PANSS Positive (F (3, 101) = .11; $p < 0.001$) scores, such that the scores decreased with time, but there was no drug × time interaction ($p = 0.56$, $p = 0.26$, $p = 0.55$; respectively).

Side effects

There were no significant time, drug, or drug × time interactive effects on the movement side effects as measured by the SAS: CBD (baseline 2.6 ± 2.9, endpoint 2.3 ± 2.8; mean ± SD) versus placebo (baseline 2.9 ± 3.4, endpoint 1.6 ± 1.9); (F (8, 129) = 0.35; $p = 0.94$); BAS: CBD (baseline 0.58 ± 0.96, endpoint 0.35 ± 0.86) versus placebo (baseline 0.44 ± 0.78,

Table 1 Demographics and screening clinical symptom rating scores

Characteristics	Cannabidiol ($n = 18$)	Placebo ($n = 18$)	p value
Age (years ± SD)	48.4 ± 9.3	46.4 ± 9.5	0.53
Sex (male %)	66.7%	72.2%	0.72
Race (%)			
African American	38.9%	66.7%	0.22
Caucasian	55.6%	27.8%	
Other	5.5%	5.5%	
Length of diagnosis (years ± SD)	25.6 ± 12.7	28.2 ± 8.5	0.89
Intelligence quotient (IQ) (mean ± SD)	91.6 ± 18.4	82.3 ± 15.4	0.12
Education (years ± SD)	13.2 ± 1.6	12.8 ± 2.0	0.57
Smoking status (yes %)	50%	55.6%	0.67
Hopkins Verbal Learning Test *T* score (mean ± SD)	32.5 ± 6.3	34.5 ± 6.0	0.34
Clinical screening assessments			
PANSS Total Score (mean ± SD)	76.6 ± 17.0	82.7 ± 8.8	0.18
PANSS Positive Subscale (mean ± SD)	18.8 ± 4.7	20.6 ± 3.8	0.21
PANSS Negative Subscale (mean ± SD)	20.7 ± 4.6	20.9 ± 4.7	0.89
PANSS General Subscale (mean ± SD)	37.1 ± 10.3	41.2 ± 5.6	0.15
Medications (%)			
First generation antipsychotics	50%	27.8%	0.17
Second generation antipsychotics	55.5%	72.2%	0.30
Multiple antipsychotics	11%	38.9%	0.05
Long-acting injectable antipsychotics	16.7%	33.3%	0.25
Antidepressant	16.7%	22.2%	0.64
Anticholinergic	38.9%	38.9%	1.0
Anticonvulsants/mood stabilizers	16.7%	33.3%	0.25
Benzodiazepine	11.1%	16.7%	0.63

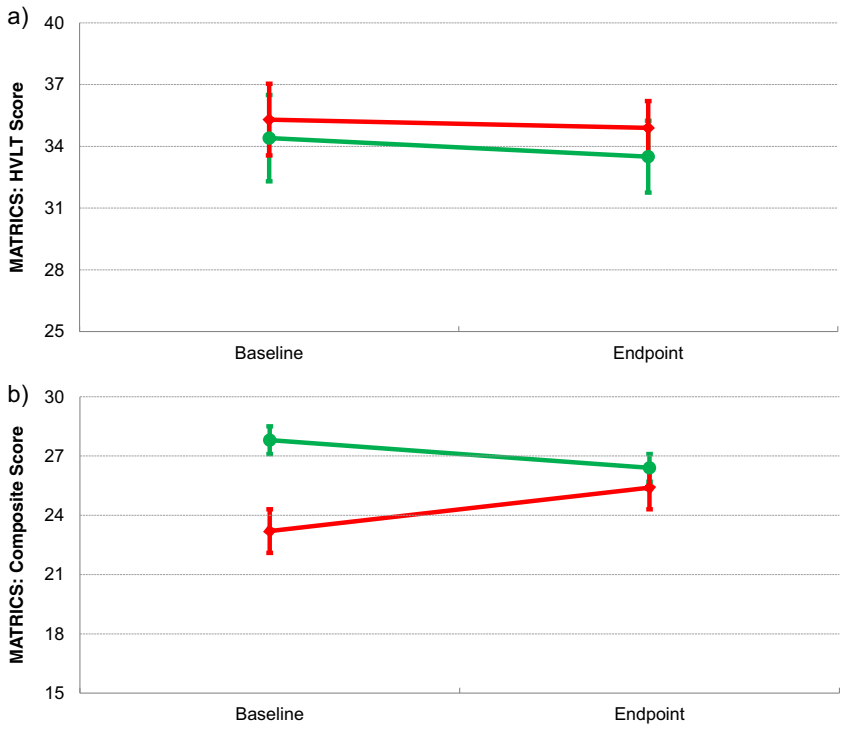

Fig. 2 MATRICS Scores at Baseline and Endpoint with Cannabidiol or Placebo. **a** MATRICS Hopkins Verbal Learning mean (SE) at beginning of study and after 6 weeks of treatment. **b** MATRICS mean (SE) at beginning of study and after 6 weeks of treatment; green square (cannabidiol), red diamond (placebo)

Table 2 *T* score results of subjects receiving cannabidiol or placebo on the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery after 6 weeks of treatment

	Cannabidiol ($n = 18$)			Placebo ($n = 18$)			Drug effect	Time effect	Drug × time effect
	Baseline (mean ± SD)	Endpoint (mean ± SD)	Cannabidiol time effect	Baseline (mean ± SD)	Endpoint (mean ± SD)	Placebo time effect			
Speed of Processing									
Brief Assessment of Cognition in Schizophrenia (BACS): symbol coding	36.3 ± 9.3	35.9 ± 10.3	(F (1, 33) = 0.13; $p = 0.73$)	36.2 ± 8.6	37.2 ± 9.6	(F (1, 33) = 0.27; $p = 0.61$)	(F (1, 34) = 0.02; $p = 0.90$)	(F (1, 33) = 0.02; $p = 0.90$)	(F (1, 32) = 0.38; $p = 0.54$)
Verbal fluency	40.6 ± 9.7	42.2 ± 9.1	(F (1, 33) = 1.3; $p = 0.26$)	40.4 ± 6.3	39.7 ± 5.4	(F (1, 33) = 0.15; $p = 0.70$)	(F (1, 34) = 0.29; $p = 0.60$)	(F (1, 33) = 0.27; $p = 0.61$)	(F (1, 33) = 1.15; $p = 0.29$)
Trail Making Test: part A	48.5 ± 13.0	45.2 ± 11.3	(F (1, 33) = 2.58; $p = 0.12$)	41.0 ± 10.8	39.8 ± 9.4	(F (1, 33) = 0.07; $p = 0.79$)	(F (1, 34) = 3.12; $p = 0.09$)	(F (1, 33) = 1.72; $p = 0.20$)	(F (1, 33) = 0.87; $p = 0.36$)
Attention/vigilance									
Continuous Performance Test	37.9 ± 12.7	37.1 ± 15.0	(F (1, 33) = 0.21; $p = 0.65$)	33.6 ± 12.8	36.5 ± 13.5	(F (1, 33) = 2.31; $p = 0.14$)	(F (1, 33) = 0.32; $p = 0.58$)	(F (1, 33) = 0.59; $p = 0.45$)	(F (1, 33) = 1.99; $p = 0.17$)
Reasoning and Problem Solving									
Neuropsychological Assessment Battery: mazes	43.7 ± 9.7	43.6 ± 10.8	(F (1, 33) = 0.03; $p = 0.86$)	37.9 ± 7.4	40.8 ± 8.5	(F (1, 33) = 7.71; $p = 0.009$)	(F (1, 34) = 2.14; $p = 0.15$)	(F (1, 33) = 3.48; $p = 0.07$)	(F (1, 33) = 4.47; $p = 0.04$)
Verbal Learning									
Hopkins Verbal Learning Test	34.4 ± 8.9	33.5 ± 7.4	(F (1, 33) = 0.32; $p = 0.57$)	35.3 ± 7.4	34.9 ± 5.5	(F (1, 33) = 0.07; $p = 0.79$)	(F (1, 34) = 0.28; $p = 0.60$)	(F (1, 33) = 0.35; $p = 0.56$)	(F (1, 33) = 0.04; $p = 0.84$)
Visual Learning									
Brief Visuospatial Memory Test	36.2 ± 10.4	35.2 ± 11.3	(F (1, 33) = 0.16; $p = 0.69$)	31.3 ± 14.9	36.1 ± 14.5	(F (1, 33) = 3.33; $p = 0.08$)	(F (1, 34) = 0.27; $p = 0.60$)	(F (1, 33) = 1.06; $p = 0.31$)	(F (1, 33) = 2.51; $p = 0.12$)
Working Memory									
Wechsler Memory Scale—spatial span	37.3 ± 12.5	39.4 ± 13.2	(F (1, 33) = 1.44; $p = 0.24$)	35.3 ± 8.3	39.3 ± 9.4	(F (1, 33) = 3.85; $p = 0.06$)	(F (1, 34) = 0.15; $p = 0.70$)	(F (1, 33) = 5.02; $p = 0.03$)	(F (1, 33) = 0.32; $p = 0.57$)
Letter-number span	35.4 ± 11.5	33.4 ± 12.2	(F (1, 33) = 0.80; $p = 0.38$)	32.1 ± 8.3	33.9 ± 9.5	(F (1, 33) = 0.63; $p = 0.43$)	(F (1, 34) = 0.21; $p = 0.65$)	(F (1, 33) = 0.00; $p = 0.96$)	(F (1, 33) = 1.42; $p = 0.24$)
Social cognition									
The Mayer-Salovey-Caruso Emotional Intelligence Test (MSCEIT)	29.7 ± 13.8	27.7 ± 15.5	(F (1, 33) = 1.52; $p = 0.23$)	30.7 ± 14.3	29.5 ± 11.5	(F (1, 33) = 0.21; $p = 0.64$)	(F (1, 34) = 0.12; $p = 0.73$)	(F (1, 33) = 1.42; $p = 0.24$)	(F (1, 33) = 0.28; $p = 0.60$)
Speed of processing composite	39.2 ± 12.0	38.2 ± 10.2	(F (1, 33) = 0.53; $p = 0.47$)	35.8 ± 9.2	35.3 ± 8.1	(F (1, 33) = 0.04; $p = 0.84$)	(F (1, 34) = 0.87; $p = 0.36$)	(F (1, 33) = 0.42; $p = 0.52$)	(F (1, 33) = 0.13; $p = 0.72$)
Working memory composite	33.5 ± 13.5	33.6 ± 12.6	(F (1, 33) = 0.00; $p = 0.98$)	30.2 ± 8.4	33.6 ± 9.8	(F (1, 33) = 2.76; $p = 0.11$)	(F (1, 34) = 0.25; $p = 0.62$)	(F (1, 33) = 1.47; p = 0.23)	(F (1, 33) = 1.37; $p = 0.25$)
MATRICS Composite Score	27.8 ± 14.0	26.4 ± 12.2	(F (1, 32) = 1.48; $p = 0.23$)	23.2 ± 13.3	25.4 ± 12.5	(F (1, 32) = 4.84; $p = 0.03$)	(F (1, 33) = 0.35; $p = 0.56$)	(F (1, 32) = 0.59; $p = 0.45$)	(F (1, 32) = 1.48; $p = 0.02$)

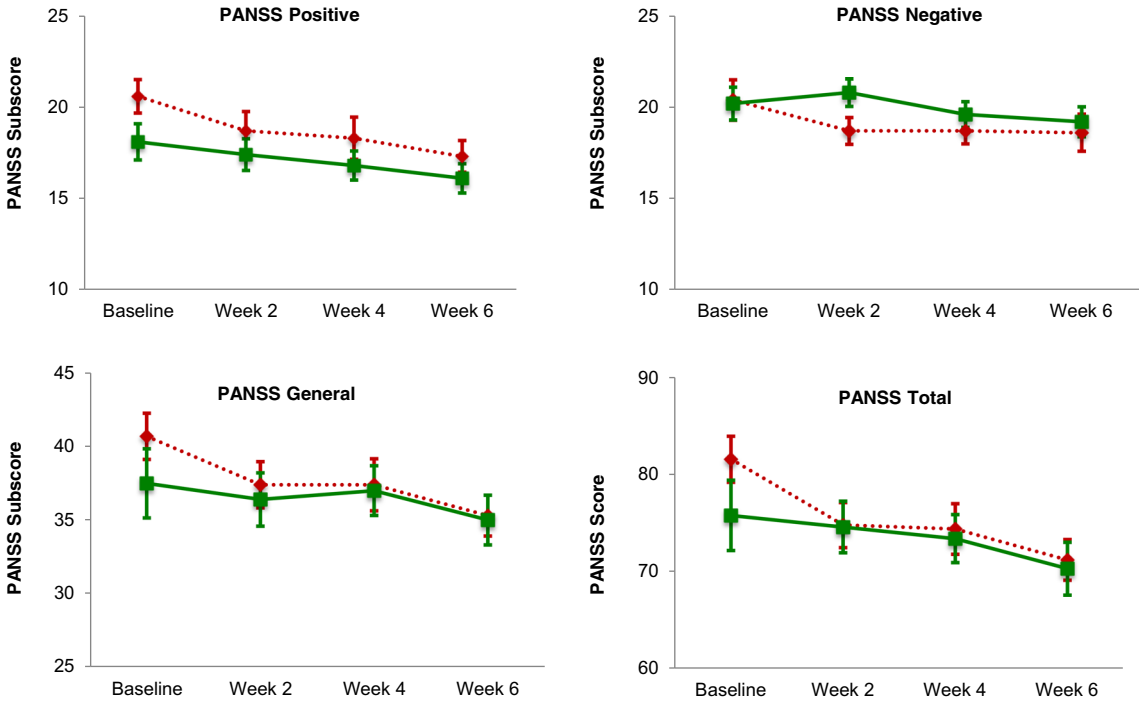

Fig. 3 Positive and Negative Syndrome Scale (PANSS) scores over 6 weeks with cannabidiol or placebo. **a** PANSS Positive subscale mean (SD) scores. **b** PANSS Negative subscale mean (SD) scores. **c** PANSS General subscale mean (SD) scores. **d** PANSS Total score mean (SD) scores; green square (cannabidiol), red diamond (placebo)

endpoint 0.07 ± 0.26); (F (8, 130) = 0.857; p = 0.55); or AIMS: CBD (baseline 6.6 ± 8.4, endpoint 4.5 ± 7.2) versus placebo (baseline 6.8 ± 8.1, endpoint 5.5 ± 6.5); (F (7, 131) = 0.32; p = 0.94). Other reported sided effects were similar between CBD and placebo, with the one exception being sedation (see Supplemental Table 1), which was more prevalent in the CBD group. One subject in the CBD arm withdrew early in the study due to sedation. During the study, approximately 20% of participants in the CBD arm reported sedation (mild) and 5% reported sedation in the placebo arm.

Discussion

This study was designed to examine the effects of augmentation of CBD on CIAS and psychotic symptoms in chronically ill, stable outpatients with schizophrenia. At the dose tested, CBD augmentation for 6 weeks did not improve MCCB performance or psychotic symptoms in this sample of patients.

Although patients in the CBD arm had no change in MCCB performance, patients in the placebo arm did show improvements on the MCCB Composite Score and Reasoning and Problem Solving domain (see Table 2). These improvements were small (Cohen's d: MCCB Composite = 0.28, Reasoning and Problem Solving = 0.33) and of questionable clinical significance. Both the MCCB Composite Score and Reasoning and Problem Solving domain scores were higher at baseline and endpoint for the CBD-treated group, suggesting that the observed improvement in the placebo arm could also represent a regression to the mean. A second explanation for the improvement on placebo may be practice effects that have been previously noted on the MCCB (Nuechterlein et al. 2008). The fact that CBD treatment was not associated with a similar improvement could be related to the greater sedation (20% of subjects) observed with CBD as compared to placebo (5%). Although the presence/absence of sedation was noted in this study, the degree of sedation was not systematically quantified during cognitive testing and therefore not covaried for, which should be assessed in future studies. An alternative explanation is that CBD hampered the expected practice-related learning on the MCCB unrelated to its effects on sedation. This, however, is contrary to the expected effects of CBD based on preclinical and clinical data (Fagherazzi et al. 2012; Magen et al. 2010; Morgan et al. 2010) suggesting that CBD may have pro-cognitive effects. For instance, CBD has been shown to attenuate induced cognitive deficits both in mice (Magen et al. 2010; Murphy et al. 2017) and rats (Fagherazzi et al. 2012) and to enhance the expression of hippocampal brain-derived neurotropic factor (BDNF) and has been shown to have benefits in neurodegenerative conditions (Iuvone et al. 2009).

Although limited, the existing preclinical and epidemiological data suggest that CBD may improve cognition. That CBD did not improve MCCB performance in this study, however, is consistent with data from other clinical trials with CBD in schizophrenia. For instance, Hallak et al. examined the effects

of a single dose of CBD (600 mg, 300 mg, or placebo) on the STROOP color word task in a randomized study in patients with schizophrenia (Hallak et al. 2010) and found no benefits. Further, a recently published study of CBD (1000 mg) in schizophrenia over 6 weeks also failed to demonstrate cognitive benefits on the Brief Assessment of Cognition in Schizophrenia (BACS) (McGuire et al. 2017). Thus, the current data suggest that CBD at a wide range of doses tested does not have beneficial effects on cognition in schizophrenia.

CBD did not improve psychotic symptoms in the subjects in our study. These results are in contrast to the published case reports (Zuardi et al. 2006; Zuardi et al. 1995), and the two published clinical trials in schizophrenia (Leweke et al. 2012)(McGuire et al. 2017). Leweke et al. found CBD (800 mg) to be as efficacious as amisulpride in reducing positive psychotic symptoms in 42 acutely decompensated patients with schizophrenia (Leweke et al. 2012). More recently, in a larger study in antipsychotic-treated outpatients with schizophrenia ($n = 86$), McGuire et al. found that CBD augmentation resulted in a small although statistically significant improvement in PANSS positive scores (1.5 points) with CBD compared to placebo (McGuire et al. 2017). However, our results are similar to a separate study also by Leweke et al. who tested the effects of the same dose (600 mg) of CBD in schizophrenia. At this dose, CBD only produced very small improvements in PANSS total scores (~ 2.4) that were not statistically significant (Leweke et al. 2014). Although, this dose (600 mg/day) has been shown to attenuate psychosis-like effects in acute laboratory studies (Bhattacharyya et al. 2010), it appears that a higher dose may be needed to produce beneficial effects on psychotic symptoms in schizophrenia.

A second consideration worth discussing is the stage of illness being tested. Our study included patients with chronic schizophrenia unlike those studied in Leweke et al. who have also demonstrated that patients demonstrate alterations in endocannabinoid levels during early psychosis (Koethe et al. 2009; Leweke et al. 2012). Thus, it is possible that CBD may be even more effective during this critical period rather than in chronic schizophrenia and more studies are needed on the benefits of CBD earlier in the course of psychosis, perhaps even during the prodromal stage. This may be particularly relevant to CIAS. In our study, the mean age of participants was in their mid- to late-40s and mean illness duration was greater than 25 years similar to McGuire et al. 2017 (mean age 41 years) who also failed to demonstrate any benefits on CIAS in their study (McGuire et al. 2017). Interestingly, given the data that cannabis use during adolescence may be associated with a less cognitively severe form of schizophrenia (Yucel et al. 2012), more studies are needed to fully examine the endocannabinoid system as a potential target for the cognitive deficits of schizophrenia.

Overall, subjects in our study tolerated CBD treatment well with no worsening of psychosis, mood, or suicidality. One subject in the CBD arm withdrew within the first 2 weeks due to sedation, and overall, more subjects reported sedation with CBD than placebo. These data are consistent with the previous studies with CBD, suggesting that CBD is well tolerated and not associated with significant motor side effects or laboratory abnormalities (Leweke et al. 2012; McGuire et al. 2017).

Strengths and limitations

A major strength of the study is the design and use of the widely accepted MCCB to measure cognitive deficits. However, there are some limitations to this study. While the CBD dose of 600 mg/day has been used in previous studies, it is lower than Leweke et al. 2012 and McGuire et al. 2017 who used 800 and 1000 mg, respectively. Given that CBD has a low oral bioavailability of about 15% (Scuderi et al. 2009) and higher doses have been tolerated in other studies (Zuardi et al. 2006; Zuardi et al. 1995), it is possible that higher doses may have had beneficial effects on psychosis and possibly CIAS. Second, it is possible that pharmacotherapy alone may be insufficient to produce improvements in CIAS and recent studies combine pharmacotherapy with a cognitive remediation strategy; however, this was not included in this study (D'Souza et al. 2013).

Conclusions

While adjunctive CBD with antipsychotic treatment was well tolerated, it was not effective in treating CIAS. Future studies should assess if CBD treatment earlier in the course of illness is beneficial. Finally, more studies should be conducted to determine an optimal oral dose of CBD for treatment of symptoms and cognitive deficits in schizophrenia.

Compliance with ethical standards

Conflict of interest Support granted by the Stanley Medical Research Institute.

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