Schizophrenia Research 161 (2015) 478–483

Contents lists available at ScienceDirect

Schizophrenia Research

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

Cognitive Enhancement Therapy in substance misusing schizophrenia: Results of an 18-month feasibility trial

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ARTICLE INFO

Article history:
Received 16 September 2014
Received in revised form 13 November 2014
Accepted 17 November 2014
Available online 12 December 2014

Keywords:
Cognitive remediation
Cognitive rehabilitation
Substance use
Social cognition
Drug use

ABSTRACT

Substance use is a frequent problem in schizophrenia, and although many substance misusing patients with the disorder also experience considerable cognitive impairments, such individuals have been routinely excluded from clinical trials of cognitive remediation that could support their functional and addiction recoveries. This study conducted a small-scale feasibility trial of Cognitive Enhancement Therapy (CET) in substance misusing schizophrenia patients to assess the feasibility and efficacy of implementing comprehensive neurocognitive and social-cognitive remediation in this population. A total of 31 schizophrenia outpatients meeting addiction severity criteria for alcohol and/or cannabis use were randomized to 18 months of CET or usual care. Feasibility findings indicated high degrees of satisfaction with CET, but also presented significant challenges in the recruitment and retention of substance misusing patients, with high levels of attrition (50%) over the study period, primarily due to positive symptom exacerbation. Intent-to-treat efficacy analyses showed large and significant improvements in neurocognition ($d = .86$), social cognition ($d = 1.13$), and social adjustment ($d = .92$) favoring CET. Further, individuals treated with CET were more likely to reduce alcohol use (67% in CET vs. 25% in usual care) during treatment ($p = .021$). These results suggest that once engaged and stabilized, CET is a feasible and potentially effective treatment for cognitive impairments in patients with schizophrenia who misuse alcohol and/or cannabis. Substance misusing patients who are able to engage in treatment may be able to benefit from cognitive remediation, and the treatment of cognitive impairments may help improve substance use outcomes among this underserved population.

1. Introduction

Schizophrenia is characterized by marked impairments in social cognition (Green et al., 2012; Horan et al., 2012) and non-social cognition (Heinrichs and Zakzanis, 1998) that significantly limit functional recovery from the disorder (Green et al., 2000; Fett et al., 2011). Cognition remediation has emerged as an effective intervention for addressing cognitive deficits in schizophrenia, with recent meta-analyses indicating small to medium-size effects on cognition and functional outcome, particularly for strategic approaches that are integrated into broader psychosocial treatment programs (McGurk et al., 2007; Wykes et al., 2011; Keshavan et al., 2014). Cognitive Enhancement Therapy (CET; Hogarty and Greenwald, 2006) is one approach to the remediation of cognitive impairments in schizophrenia that we have previously shown can produce significant improvements in neurocognitive and social-cognitive function in both chronic (Hogarty et al., 2004) and early course (Eack et al., 2009) patients with schizophrenia, with generalizable and durable benefits to social and vocational functioning (Hogarty et al., 2006; Eack et al., 2010a, 2011). When applied as an early intervention approach, CET has also been shown to protect against gray matter loss in service of cognitive enhancement in the disorder (Eack et al., 2010b).

While evidence is steadily growing to support the efficacy of CET and other cognitive remediation interventions in treating cognitive deficits in schizophrenia, such evidence has been largely limited to patients who do not experience comorbid substance use problems. As many as 65% of patients with schizophrenia misuse substances (Volkow, 2009), and most trials of cognitive remediation have excluded substance misusing patients (see McGurk et al., 2005 for a notable exception). Such individuals are frequently unstable (Schmidt et al., 2011) and have challenges with medication adherence (Perkins et al., 2008), making them less ideal candidates for clinical trials of new interventions. There has also been controversy over the degree to which cognitive deficits are present in patients with substance use problems (Yücel

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http://dx.doi.org/10.1016/j.schres.2014.11.017
0920-9964/

et al., 2012), although larger studies using carefully assessed samples indicate impairments similar to those individuals not misusing substances (Wobrock et al., 2013; Bahorik et al., 2014). Given the general lack of efficacy of antipsychotic treatment on cognitive impairment in schizophrenia (Keefe et al., 2007), some patients may turn to substances to cope with residual cognitive deficits and associated social dysfunction (Blanchard et al., 2000; Gregg et al., 2007). At the same time, executive and problem-solving impairments may limit the decision-making abilities needed to prevent or recover from substance misuse problems in the disorder (Chambers et al., 2001).

If substance misusing schizophrenia patients can be successfully engaged in cognitive remediation interventions that are sensitive to addiction problems, this may help support the recovery of these individuals. Unfortunately, little is known about cognitive remediation in this population. This study sought to examine the feasibility of applying an adapted version of CET to patients with schizophrenia and comorbid alcohol and/or cannabis misuse problems, the two most commonly misused substances in the disorder (Volkow, 2009), and evaluate its initial efficacy compared to usual care in a small-scale randomized-controlled trial.

2. Method

2.1. Participants

Participants included 31 substance misusing patients with schizophrenia ($n = 17$) or schizoaffective disorder ($n = 14$) enrolled in an 18-month randomized feasibility trial (NCT01292577) of Cognitive Enhancement Therapy (CET) or treatment as usual (TAU).

Patients were enrolled if they (1) were between the age of 18 and 60 years, (2) were diagnosed with schizophrenia or schizoaffective disorder according to the Structured Clinical Interview for DSM-IV (SCID; First et al., 2002), (3) met criteria for moderate or higher (≥4) addiction severity for cannabis or alcohol on the Addiction Severity Index (McLellan et al., 1980), (4) were stabilized on antipsychotic medications, (5) had an IQ ≥ 80, (6) were able to read and speak fluent English, (7) were not abusing or dependent on cocaine or opioids, (8) did not have another persistent medical condition producing significant cognitive impairment, (9) were not receiving any substance abuse pharmacotherapies (e.g., naltrexone), (10) did not experience persistent homicidality or suicidality, and (11) displayed significant cognitive and social disability on the Cognitive Styles and Social Cognition Eligibility Interview (Hogarty et al., 2004). Eligibility criteria focused on including participants misusing the two most common substances of abuse in schizophrenia, reducing heterogeneity by excluding cocaine and opioid users, and avoiding concomitant substance abuse pharmacotherapies that could impact outcomes.

Table 1 presents the characteristics of enrolled participants, who were mostly male, ethnically diverse, and ill for many years. All but 2 individuals met full SCID criteria for at least one substance abuse or dependence diagnosis, and all individuals met ASI criteria for moderate or greater addiction severity. Moderate ASI severity criteria can be achieved through frequent use and/or significant need for substance use treatment. The majority (68%) of enrolled participants were actively using either alcohol or cannabis at study enrollment, with the remaining individuals meeting ASI criteria based on treatment need. No significant differences were observed between treatment groups in the number of patients actively using substances at enrollment, $\chi^2(1, N = 31) = .26$, $p = .614$, and no significant differences emerged between treatment groups with regard to any demographic, clinical, substance use, or cognitive characteristics prior to treatment (see Table 1). Service use data collected at 18 months on exposure to community substance use treatments in the last 6 months indicated that only 3 patients (2 in CET/PT and 1 in TAU) participated in dual diagnosis, Alcoholics Anonymous, or Narcotics Anonymous treatment programs, with no significant differences between treatment groups ($p = 1.000$).

Table 1
Characteristics of substance misusing schizophrenia patients enrolled in an 18-month feasibility trial of Cognitive Enhancement Therapy (CET) or treatment as usual (TAU).

Characteristic	TAU ($N = 9$) N (%)	CET ($N = 22$) N (%)	p[a]
Age–mean (*SD*)	34.67 (12.99)	39.68 (13.64)	.354
Male	7 (78%)	15 (68%)	.689
White	3 (33%)	13 (59%)	.252
Attended college	7 (78%)	14 (64%)	.677
Employed	1 (11%)	5 (23%)	.642
Primary diagnosis			1.000
Schizophrenia	5 (56%)	12 (55%)	
Schizoaffective disorder	4 (44%)	10 (45%)	
Substance abuse or dependence diagnosis	8 (89%)	21 (95%)	.503
Alcohol abuse	3 (33%)	4 (18%)	.384
Alcohol dependence	3 (33%)	14 (64%)	.233
Cannabis abuse	1 (11%)	0 (0%)	.290
Cannabis dependence	7 (78%)	16 (73%)	1.000
Daily substance use among active users, mean (SD)			
Alcohol usage occasions per day	1.67 (1.11)	1.15 (.84)	.355
Cannabis usage occasions per day	3.88 (.47)	4.30 (1.69)	.681
Addiction Severity Index score, mean (SD)			
Alcohol	4.22 (2.05)	4.00 (2.60)	.821
Drugs	4.78 (1.79)	4.41 (2.34)	.676
Schizophrenia illness duration, mean (*SD*)	11.78 (11.26)	15.18 (11.40)	.455
IQ, mean (*SD*)	99.33 (10.45)	99.32 (12.18)	.997
BPRS total, mean (*SD*)	42.67 (12.32)	43.27 (9.30)	.882
Antipsychotic dose (cpz equivalent), mean (*SD*)	450.00 (306.19)	400.30 (329.00)	.700
Receiving second generation antipsychotic	9 (100%)	18 (82%)	.295
Medication adherent	9 (100%)	19 (86%)	.537

Note. BPRS = Brief Psychiatric Rating Scale, cpz = chlorpromazine.
[a] Results of independent sample *t*-test or Fisher's exact test, two-tailed.

2.2. Measures

A comprehensive battery of cognitive and behavioral assessments was collected to examine the impact of CET on neurocognition, social cognition, dysfunctional cognitive style, social adjustment, symptomatology, and substance use. Neurocognition was assessed using the NIMH MATRICS Consensus Cognitive Battery (Green et al., 2004). Social cognition was assessed using the Mayer–Salovey–Caruso Emotional Intelligence Test (MSCEIT: Mayer et al., 2003), the Penn Emotion Recognition Test-40 (Kohler et al., 2003), and the Hinting Task (Corcoran et al., 1995). Dysfunctional cognitive style was assessed using the Cognitive Style and Social Cognition Eligibility Interview and the Cognitive Styles Inventory (Hogarty et al., 2004). Social adjustment was assessed using the Social Adjustment Scale-II (Schooler et al., 1979), Major Role Adjustment Inventory (Hogarty et al., 1974b), and the Global Assessment Scale (Endicott et al., 1976). Symptomatology was assessed using the Brief Psychiatric Rating Scale (Overall and Gorham, 1962), Wing Negative Symptom Scale (Wing, 1961), Raskin Depression Scale (Raskin et al., 1969), and Covi Anxiety Scale (Lipman, 1982). Finally, previous 30-day substance use was assessed using the Timeline Follow-Back interview (Sobell and Sobell, 1992), which has been shown to be a reliable and valid measure of substance use in psychosis (Hjorthøj et al., 2012).

2.3. Treatments

2.3.1. Medication

All participants were maintained on antipsychotic medication indicated for the treatment of schizophrenia or schizoaffective disorder by their treating psychiatrist. The majority of patients (87%) were maintained on second-generation antipsychotic medication. There were no significant differences between treatment groups with regard to

antipsychotic medication dose, type, or clinician-estimated medication adherence at study entry (see Table 1).

2.3.2. Cognitive Enhancement Therapy

CET is a comprehensive developmental approach to the treatment of social and non-social cognitive impairments that limit the functional recovery of patients with schizophrenia. Detailed descriptions of the intervention are provided elsewhere (Hogarty et al., 2004; Hogarty and Greenwald, 2006; Eack, 2012). Over the course of 18 months, CET integrates 60 h of computer-based training in attention, memory, and problem-solving with 45 structured social-cognitive groups that target the achievement of such adult social milestones as perspective-taking, social context appraisal, and emotion management. Neurocognitive training takes place in pairs to facilitate socialization, engagement, and providing support to each other. Social-cognitive groups are highly structured with an educational and participation focus, and include in-group social-cognitive exercises, psychoeducational lectures, and homework assignments designed to facilitate the transfer of learning. Because of the nature of the substance misusing population, additional psychoeducational content on substance use and schizophrenia was developed for this study, and a greater emphasis was placed on applying the stress management principles of Personal Therapy (Hogarty, 2002) and enhancing motivation for treatment in individual therapy appointments.

2.3.3. Treatment as usual

The contrasting treatment condition for this feasibility trial of CET in substance misusing schizophrenia was treatment as usual (TAU), which consisted of a range of mental health and social services including psychiatry services, case management, individual supportive therapy, vocational rehabilitation services, dual diagnosis treatments, and community-driven substance use treatments. Every effort was made to connect all participants in the study, regardless of treatment assignment, to needed mental health and substance use services.

2.4. Procedures

Participants were recruited from Western Psychiatric Institute and Clinic, Pittsburgh, PA and nearby community clinics. Upon recruitment, participants were screened for eligibility by project clinicians and an expert diagnostician. Eligible participants were then randomized to 18 months of CET or TAU, weighted toward a greater proportion of CET assignments to facilitate the formation of the social-cognitive groups, and assessed every six months on the aforementioned clinical and cognitive assessments. With the exception of cognitive styles measures, all assessments were completed by trained raters and neuropsychological testers who were blind to treatment assignment. Study clinicians completed cognitive styles assessments for assigned cases in CET or TAU. Participants received payment for eligibility and outcome assessments, and those assigned to CET also received compensation to defray the costs of session attendance and to facilitate adherence to the treatment protocol. This research was conducted between September, 2010 and May, 2014, and was approved annually by the University of Pittsburgh Institutional Review Board. All participants provided written informed consent prior to study participation.

2.5. Data analysis

The effects of CET compared to TAU on cognition and behavior were examined using a series of linear mixed-effect intent-to-treat models, including all randomized participants who completed at least baseline assessments, adjusting for the effects of age, gender, IQ, illness duration, and baseline drug use severity on outcome. Age, gender, IQ, and illness duration were included as a priori covariates, and drug use severity was included due to its association with attrition. Mixed models made use of an auto-regressive error structure (Raudenbush and Bryk, 2002), when appropriate, and missing data were handled at the time of parameter estimation using the expectation–maximization approach (Dempster et al., 1977). To avoid excessive univariate testing, composite indexes of neurocognition, social cognition, cognitive style, social adjustment, and symptomatology were formed from respective test and interview items. The neurocognitive composite consisted of the overall composite for the MATRICS Consensus Cognitive Battery, which has been shown to be reliable in previous studies (Nuechterlein et al., 2008), and was log transformed due to high skewness. The remaining composite indexes were computed by averaging across *z*-scaled items, scaled with a mean (*SD*) of 50 (10), and demonstrated minimally adequate internal consistency (range of $\alpha = .68$ to .79). Effects on substance use outcomes were examined using Fisher's exact test comparing the number of people in each treatment group who were abstinent in the past month from alcohol or cannabis, as well as the proportion of individuals in CET and TAU who either increased, decreased, or did not change the number of days of use of substances during the course of their participation in the study.

3. Results

A total of 222 individuals from a broad range of sources were screened for the study, 31 of whom were eligible, randomized, and completed baseline assessments. Recruitment for the study was feasible, but challenging, with many individuals showing little interest in the possibility of receiving additional treatment, and others demonstrating significant psychiatric instability and medication non-adherence. Fig. 1 describes the flow of participants throughout the study. Attrition was considerable in the CET group and larger than any other study of CET conducted to date, although attrition rates were not significantly different from TAU ($p = .148$). Treatment engagement was challenging, and individuals who completed the study had lower pre-treatment drug addiction severity scores ($p = .002$). Most attrition occurred early (usually in the first several months of the study), and was primarily due to increased positive symptoms resulting from high levels of substance use or medication non-adherence, as observed by the treatment team. Cognitive impairment was substantial in randomized and treated patients, with average MATRICS composite percentile scores of 11.62% ($SD = 17.75\%$). Individuals who engaged in CET appeared to be satisfied with the treatment, with all those who completed the study rating CET on a 1 ("Very Helpful") to 5 ("Harmful") scale as "Very Helpful".

Intent-to-treat analyses of the differential effects of CET versus TAU on composite indexes of cognition and behavior are presented in Table 2. Effects on neurocognitive and social-cognitive functioning were large and significant favoring CET, with social cognition also showing an unexpected medium-sized decline in those receiving usual care. The largest areas of neurocognitive change on the MATRICS battery were processing speed ($d = .92$, $p = .114$) and verbal learning ($d = .90$, $p = .062$), neither of which met conventional significance thresholds. The greatest domains of social-cognitive improvement were understanding emotions ($d = 1.17$, $p = .015$) and managing emotions ($d = .97$, $p = .019$). Effects on non-blind measures of dysfunctional cognitive style were also large and highly significant. Large differential improvements were observed with regard to blind-rater measures of social adjustment favoring CET, with particularly strong effects on major role functioning ($d = 1.85$, $p = .001$) and global assessment of functioning ($d = 1.02$, $p = .016$). As expected, no significant advantage was observed favoring CET for symptom improvement.

Results regarding the impact of CET compared to usual care on substance use outcomes indicated that there were no significant differences between treatment groups with regard to the number of participants who were abstinent from drugs or alcohol by the end of their participation in the study ($p = .347$). However, patients treated with CET demonstrated significant changes in the number of days they used alcohol in the preceding month compared to usual care, with 67% decreasing

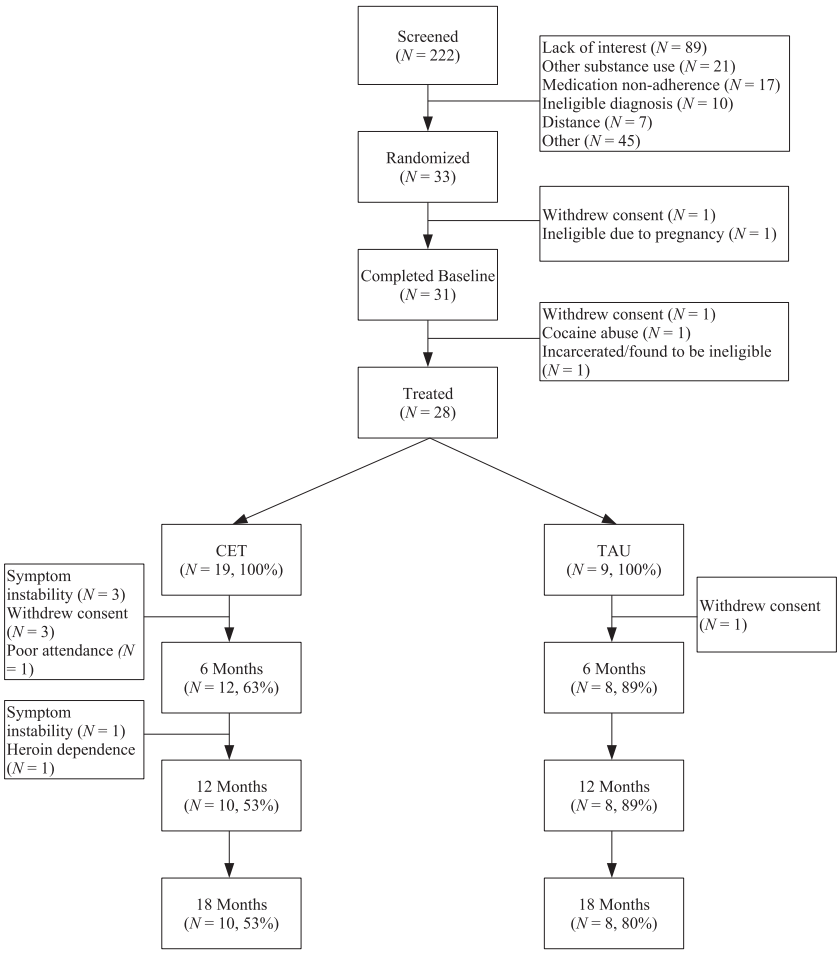

Fig. 1. Enrollment in an 18-month feasibility trial of Cognitive Enhancement Therapy (CET) or treatment as usual (TAU).

Table 2
Effects of Cognitive Enhancement Therapy versus treatment as usual on composite indexes of cognition and behavior in substance misusing schizophrenia (N = 31).

		Time point				Analysis[a]			
		Baseline	Month 6	Month 12	Month 18				
Variable	Treatment	*M* (SE)	*M* (SE)	*M* (SE)	*M* (SE)	*p*	d_{CET}	d_{TAU}	*d*
Neurocognition	CET	51.94 (1.82)	55.04 (1.72)	58.14 (1.95)	61.23 (2.43)	.028	.93	.07	.86
	TAU	53.04 (2.83)	53.28 (2.56)	53.52 (2.61)	53.76 (2.97)				
Social cognition	CET	51.13 (1.74)	53.19 (1.70)	55.26 (1.82)	57.32 (2.07)	<.001	.62	−.51	1.13
	TAU	56.58 (2.71)	54.87 (2.59)	53.16 (2.61)	51.45 (2.77)				
Cognitive style	CET	48.21 (2.53)	58.71 (2.17)	69.21 (2.67)	79.71 (3.70)	<.001	3.15	−.08	3.23
	TAU	54.94 (3.93)	54.67 (3.13)	54.40 (3.25)	54.13 (4.22)				
Social adjustment	CET	48.64 (2.19)	52.48 (2.10)	56.31 (2.32)	60.15 (2.76)	.023	1.15	.23	.92
	TAU	55.27 (3.39)	56.03 (3.17)	56.80 (3.24)	57.56 (3.59)				
Symptom	CET	50.90 (2.20)	55.31 (1.97)	59.72 (2.35)	64.14 (3.12)	.637	1.32	1.06	.27
	TAU	50.85 (3.42)	54.37 (2.89)	57.90 (3.01)	61.43 (3.73)				

Note. Composites are scaled with a baseline mean (*SD*) of 50 (10), with higher scores reflecting more favorable outcomes. Means are predicted from linear mixed-effect intent-to-treat models adjusting for demographic characteristics.
CET = Cognitive Enhancement Therapy, TAU = treatment as usual.
[a] Results of linear mixed-effect models evaluating treatment × time interactions, two-tailed, *df* = 46 to 48 depending on the composite.

their days of alcohol use in CET compared to 25% in TAU (see Fig. 2). No significant differences in changes in days of cannabis use for the previous month were observed.

4. Discussion

Substance misuse is a common problem in patients with schizophrenia, and while such individuals frequently experience significant cognitive impairments that may limit their functional and addiction recovery, they have been excluded from most trials of cognitive remediation. This study examined the feasibility of implementing cognitive remediation in substance misusing patients with schizophrenia, and found mixed results regarding feasibility and efficacy. The engagement and retention into treatment proved to be the greatest challenge to feasibility, with many individuals being ambivalent about participating in additional treatment approaches, even though CET was not described as a primary substance use treatment. Attrition was also considerable, but similar to other long-term trials in substance misusing schizophrenia (Bellack et al., 2006; Mueser et al., 2013), with many individuals experiencing significant positive symptom instability leading to withdrawal from the study. Despite these challenges, intent-to-treat analyses indicated significant and large improvements in neurocognitive, social-cognitive, and functional outcomes favoring CET compared to usual care, and those who completed CET found it to be satisfying and helpful. Further, CET was associated with significant reductions in alcohol use, suggesting the potential benefits of treating cognitive impairments to decreasing substance use in this population.

The results of this initial trial of CET for substance misusing patients with schizophrenia suggest that cognitive remediation can be feasibly applied to some people with the disorder who have at least moderately severe alcohol and/or cannabis use problems. The challenges we observed in recruitment and retention were not unexpected, nor were they atypical when attempting to engage people with substance use disorders in treatment trials (Dutra et al., 2008). For some individuals, greater psychiatrist involvement may have helped to address stability issues. Other individuals were largely ambivalent about treatment (CET or otherwise), and pre-treatment with motivational interviewing before cognitive remediation might be an effective way to improve engagement in future studies. However, this study suggests that once engaged, cognitive remediation may have significant benefits to long-term cognitive and substance use outcomes beyond usual care. Substance misusing patients may not need to be excluded from clinical trials of cognitive remediation, as cognitive improvement from CET was similar to those observed in previous studies (Hogarty et al., 2004; Eack et al., 2009), indicating that cognition may be able to be enhanced in some patients who are actively using substances.

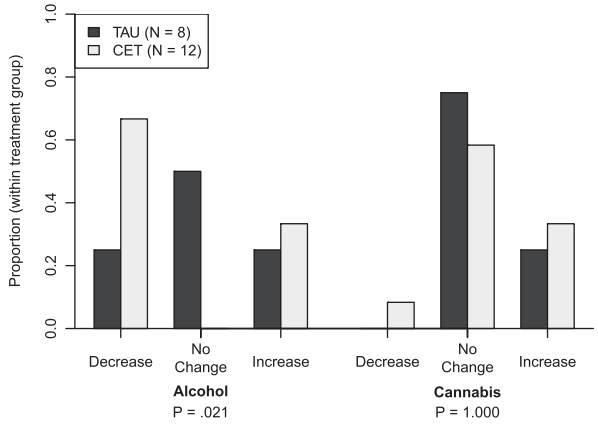

Fig. 2. Effects of Cognitive Enhancement Therapy (CET) versus treatment as usual (TAU) on substance use outcomes.

These findings should be understood in the context of several limitations. First, this was a small-scale trial designed to assess feasibility, and given the modest sample size, it is unknown whether effect sizes and treatment results will generalize to a larger sample. Second, the use of usual care as a control condition is a relatively weak comparator to CET, and it cannot be ruled out that the benefits associated with CET in this study are due to its non-specific effects or compensation for treatment attendance. Third, this study was limited to those patients who met addiction severity criteria for alcohol and/or cannabis use, and it remains unclear whether CET can be equally effective for patients who misuse other substances. Finally, the decline in social cognition in patients receiving usual care was unexpected, and may reflect the negative impact of continued substance use on emotion processing, which will be important for future studies to investigate.

In summary, this initial feasibility trial of CET for substance misusing patients with schizophrenia suggests that cognitive remediation can be feasibly applied to this population, and may hold significant benefits to cognitive and substance use outcomes. Adequately-powered studies that employ active control interventions and assess cognitive mechanisms of substance use change are needed to extend the cognitive remediation evidence base to this significant and underserved population.

Role of funding source

Funding for this research was provided by NIH grants DA-30763 (SME), MH-95783 (SME), and RR-24154 (SME). The funders did not have any further role in study design; in the collection, analysis and interpretation of data; in the writing of the report; or in the decision to submit the paper for publication.

Contributors

This study was designed by Drs. Eack, Cornelius, Pogue-Geile, and Bangalore. Dr. Eack wrote the initial draft of the manuscript, Drs. Cornelius, Pogue-Geile, Newhill, Bangalore, Keshavan, and Greenwald, along with Mrs. Hogarty, Ms. McKnight, and Ms. Litschge provided critical revisions and feedback on the manuscript. Ms. McKnight led cognitive data collection supervised by Dr. Greenwald. Dr. Eack oversaw all data collection and analysis aspects of the study. All authors contributed to and have approved the final manuscript.

Conflict of interest

The authors report no conflicts of interest.

Acknowledgments

This work was supported by NIH grants DA-30763 (SME), MH-95783 (SME), and RR-24154 (SME).

Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.schres.2014.11.017.

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