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Rimonabant for neurocognition in schizophrenia: A 16-week double blind randomized placebo controlled trial

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ABSTRACT

Objective: To examine the effect of rimonabant on neurocognitive impairments in people with schizophrenia.
Methods: Participants entered a 16-week double-blind, placebo-controlled, randomized clinical trial. A neurocognitive battery was administered at baseline and end of study.
Results: In comparison to rimonabant (20 mg/day), placebo-treated participants exhibited a significant improvement on the Repeatable Battery for the Assessment of Neuropsychological Status total score. In contrast, rimonabant was associated with significant improvement on a probabilistic learning task. There were no other significant treatment effects.
Conclusions: Rimonabant did not improve global cognitive functioning, but did improve a specific learning deficit based on response to positive feedback.

1. Introduction

Several lines of evidence suggest that cannabinoid-1 (CB1) antagonists may enhance cognition in people with schizophrenia. CB1 mRNA and receptor protein expression is decreased in the prefrontal cortex, which may represent a compensatory response to the decrease in prefrontal GABAergic tone (Eggan et al., 2008; Lewis and Sweet, 2009). CB1 antagonists could decrease GABAergic interneuron inhibition, increase GABAergic-mediated inhibition of prefrontal pyramidal neurons, and consequently enhance cognition in people with schizophrenia.

Alternatively, CB1 antagonists may exert pro-cognitive effects through their actions on dopaminergic activity. CB1 receptors are highly concentrated in the basal ganglia and modulate dopamine (DA) release (Andre et al., 2010). Pharmacological modulation of striatal DA release has been shown to influence performance on probabilistic reinforcement learning (PL) tasks (Frank and O'Reilly, 2006); people with schizophrenia show impaired performance on these tasks (Waltz et al., 2011). A CB1 antagonist could enhance striatal DA release, with a subsequent increase in reward-seeking behavior and overall PL task performance.

Rimonabant is a CB1 receptor antagonist/inverse agonist (Sim-Selley et al., 2001). In animal studies, rimonabant has mixed effects on social and spatial memory (Terranova et al., 1996; Lichtman, 2000; Varvel and Lichtman, 2002; Shiflett et al., 2004; Varvel et al., 2005). The examination of rimonabant effects on human cognition has been limited to the study of affective stimuli in normal healthy controls (Horder et al., 2009, 2010). There are no published studies of the cognitive effects of rimonabant in schizophrenia.

2. Methods

The full study description, including inclusion/exclusion criteria, is presented in the primary study report (Kelly et al., 2011). In brief, participants were inpatients or outpatients, aged 18–55 years old, with DSM-IV-TR schizophrenia or schizoaffective disorder (American Psychiatric Association, 2000). Participants were required to be treated with a second generation antipsychotic for at least eight weeks, with the same dose for at least four weeks; clinically stable; and to have a body mass index ≥ 30 kg/m^2, or ≥ 27 kg/m^2 plus Adult Treatment Panel III hyperlipidemia or hypertriglyceridemia (National Cholesterol Education Program, NCEP, 2002). Exclusion criteria included a diagnosis of DSM-IV substance abuse within the last month or DSM-IV substance dependence within the last 6 months; cannabis use greater than once weekly; Calgary Depression Rating Scale (CDS) total score > 7; suicidality

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Table 1
Baseline demographic information and clinical ratings.

	Rimonabant (n = 7)	Placebo (n = 7)	p-value
Age (years)	45.9 ± 6.9	44.9 ± 12.2	0.94
Sex (Male)	5 (71.4%)	4 (57.1%)	1.00
Race			1.00
African-American	3 (43%)	4 (57%)	
Caucasian	4 (57%)	3 (43%)	
Hispanic	0	0	
Education (years)	14.0 ± 1.6	14.4 ± 1.8	0.58
BPRS total score	33.5 ± 7.5	34.3 ± 4.9	0.85
Positive Symptom Subscale	9.4 ± 4.3	11.9 ± 3.2	0.31
Hostility Subscale	4.9 ± 1.2	4.8 ± 1.0	0.52
Anxiety/Depression Subscale	6.1 ± 2.5	5.5 ± 1.2	0.65
Activation Subscale	4.1 ± 0.6	3.5 ± 0.8	0.10
SANS total score	28.5 ± 11.2	21.9 ± 7.9	0.18
Anhedonia Subscale	1.8 ± 1.1	1.5 ± 0.9	0.48
Blunting Subscale	1.3 ± 0.8	0.7 ± 0.4	0.31
Alogia Subscale	0.5 ± 0.5	0.4 ± 0.3	0.70
Avolition Subscale	2.6 ± 1.1	2.3 ± 1.1	0.70
CDS total score	3.0 ± 2.2	3.3 ± 2.5	0.80
Antipsychotics			
Clozapine	3 (43%)	0	
Clozapine + SGA	0	2 (28.5%)	
SGA + SGA	4 (57%)	3 (43%)	
SGA	0	2 (28.5%)	

Data expressed as (mean ± S.D.).
BPRS = Brief Psychiatric Rating Scale; CDS = Calgary Depression Scale; SANS = Scale for Assessing Negative Symptoms; SGA = non-clozapine second generation antipsychotic.

or hospitalization for depression in prior 6 months; the use of any medication known to alter weight or appetite; and pregnant or nursing women.

The University of Maryland School of Medicine, State of Maryland DHMH, and NIDA IRBs approved the study protocol and informed consent procedures. Written informed consent was obtained from all participants after the full explanation of study procedures and prior to study participation. Participant ability to provide valid informed consent was documented using study specific procedures. In February 2009, the above-referenced IRBs suspended this study and all active participants were withdrawn from the study (see Kelly et al., 2011 for study cessation details).

The study was registered with clinical trial.gov (NCT00547118).

2.1. Neurocognitive assessments

The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS; Gold et al., 1999; Hobart et al., 1999) measures attention, episodic memory, language performance, and visual–spatial skills. The Iowa Gambling Task (IGT; Bechara et al., 1994) measures risk-reward decision-making; the IGT outcome measure was the number of rewarded minus punished card choices. The N-Back task is a sequential letter working memory task (Cohen et al., 1997). D-prime was used to measure accuracy on the 0-back, 1-back, and 2-back conditions (Macmillan and Creelman, 1990). In the probabilistic learning task (PL; Frank et al., 2004), participants used performance feedback to choose the most frequently rewarded item in each of three pairs of stimuli (reward probabilities: 80 versus 20; 70 versus 30; 60 versus 40). The frequencies with which participants repeated an item choice that was rewarded on the previous presentation (win-stay) or changed their choice for unrewarded items (lose-shift) were calculated to assess the use of positive and negative feedback.

2.2. Study design

In the 2-week Evaluation Phase, participants underwent baseline cognitive, symptom and safety assessments. Participants who continued to meet inclusion criteria entered the 16-week, parallel group, double-blind Treatment Phase. Participants were randomized to rimonabant 20 mg/day or matching placebo. The baseline neurocognitive assessments were administered prior to randomization and the end-of-study (EOS) assessments were conducted upon completion of the double-blind treatment phase or study termination for those subjects who had not completed the Treatment Phase at the time of study suspension (see above).

2.3. Statistical analyses

Analysis of covariance (ANCOVA) was used to estimate treatment differences on EOS RBANS total score, adjusted for baseline score. Similar ANCOVA models were used to assess treatment differences on IGT, N-Back, and PL tests. ANCOVA was also used to estimate treatment differences in the probability of repeating a choice after a reward (win-stay) or changing a choice after a loss (lose-shift) during the PL task. The procedures outlined by Lai and Kelley (in press) were used to calculate treatment effect size estimates and corresponding 95% confidence intervals (CI).

3. Results

3.1. Study participants (see Table 1)

Eighteen participants signed consent and 17 were randomized to study medication (rimonabant n = 8, placebo n = 9). One participant from each group was withdrawn prior to the receipt of study medication. One placebo participant refused the neurocognitive assessments. The remaining 14 participants (rimonabant n = 7, placebo n = 7) completed baseline and EOS RBANS evaluations; 1 placebo participant failed to complete the other EOS neurocognitive tests. Five rimonabant participants and 4 placebo participants completed the 16-week treatment phase; the other 2 rimonabant participants completed 11 and 13 weeks and 3 placebo participants completed 13 (n = 2) and 15 weeks (n = 1). There were no significant baseline differences between rimonabant and placebo participants (Table 1).

3.2. Neurocognitive measures (see Tables 2 and 3)

3.2.1. RBANS

There was significant treatment effect for RBANS total score, with the placebo group exhibiting a small improvement and the rimonabant

Table 2
Baseline and end of study (EOS) Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) total and domain scores (mean ± SD).

RBANS measure	Rimonabant (n = 7)		Placebo (n = 7)			
	Baseline	EOS	Baseline	EOS	Effect size	95% C.I.
Total score	85.0 ± 19.8	83.0 ± 11.8	78.3 ± 10.2	84.3 ± 12.6	−0.64	−1.24, −0.01
Attention	79.9 ± 16.8	77.9 ± 16.2	81.5 ± 16.4	97.1 ± 23.1	−0.82	−2.89, 1.29
Delayed memory	88.1 ± 8.3	86.6 ± 18.6	72.5 ± 14.9	77.1 ± 19.0	0.03	−4.17, 4.22
Immediate memory	89.7 ± 11.3	87.6 ± 17.9	87.5 ± 15.3	81.7 ± 18.3	−0.46	−1.42, 0.52
Language	92.6 ± 7.2	92.3 ± 7.6	90.0 ± 3.6	90.9 ± 8.6	−0.15	−2.87, 2.58
Visuospatial	94.9 ± 15.8	92.9 ± 18.0	81.7 ± 18.3	82.3 ± 13.9	0.02	−5.04, 5.08