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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 (20mg/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.

Keywords

rimonabant; cognition; schizophrenia; CB1 receptor antagonist; probabilistic learning

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Contributors: Drs. Conley and Kelly conceived the idea for the study; Drs. Conley, Kelly, Gorelick, and Buchanan were responsible for the design of the study; Drs. Kelly, Boggs, Gold, and Buchanan and Mr. Linthicum were responsible for the conduct of the study; Dr. McMahon and Ms. Liu were responsible for the statistical analyses; Drs. Conley, Kelly, Boggs, Gold, Gorelick, Huestis, McMahon, Waltz, and Buchanan were responsible for the interpretation of the data; and Dr. Boggs wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

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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; Horder et al, 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/m², or ≥ 27 kg/m² plus Adult Treatment Panel III hyperlipidemia or hypertriglyceridemia (National Cholesterol Education Program, 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 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 group exhibiting a small worsening on this measure ($F=4.92$; $df=1,11$; $p=0.048$; $ES=-0.64$; $CI: -1.24, -0.01$). There

was no statistically significant variation in the effect of treatment across RBANS domains ($F=0.80$; $df=4,8.44$; $p=0.56$).

3.2.2. IGT—The treatment main effect was not significant ($F=0.20$; $df=1,10$; $p=0.66$; $ES=0.21$; $CI: -1.40, 1.80$).

3.2.3. N-Back Task—The overall treatment main effect ($F=1.25$; $df=1,8.23$; $p=.30$; $ES: 0.46$; $CI: -0.27, 1.17$) and treatment by condition interaction ($F=0.97$; $df=1,8.88$; $p=.97$) were not significant.

3.2.4. PL (see Figure 1)—Rimonabant participants were significantly more likely to choose the most frequently rewarded item ($F=5.45$; $df=1,10.7$; $p=0.04$; $ES: 1.29$; $CI: -2.07, 4.60$); this finding was largely driven by the increased likelihood of rimonabant participants choosing the more frequently rewarded item in the 80:20 ($t=1.75$; $df=10$; $p=0.11$) and 70:30 ($t=2.07$; $df=10$; $p=0.065$) reward probability conditions. Participants treated with rimonabant exhibited a marked improvement in the use of positive feedback (i.e., staying with rewarded choices; $t=-3.22$; $df=10$; $p=0.009$; $ES=1.88$; $CI: 0.01, 3.68$); there was less change in the use of negative feedback ($t=-1.21$; $df=10$; $p=0.25$; $ES=0.68$; $CI: -1.69, 3.03$).

There were no significant group differences in adverse events (see Kelly et al, 2011 for details).

4. DISCUSSION

We found suggestive evidence that rimonabant enhances reinforcement learning, especially the response to positive reinforcement, without improving other aspects of cognitive function. The effect of rimonabant on positive reinforcement learning is hypothesized to be mediated by the modulation of striatal dopamine release and subsequent increase in D1 dopamine receptor transmission (Garcia-Arencibia et al, 2008; Tadaiesky et al, 2010).

The IGT is similar to the PL task, but unlike the latter, successful IGT performance may depend primarily on punishment sensitivity. Increased striatal DA transmission in people with Parkinson's Disease (through the administration of L-dopa) has been shown to benefit reward-driven learning at the expense of punishment-driven learning (Frank et al, 2004), which may account for the observed effects of rimonabant on the two tasks.

We did not find a treatment effect of rimonabant on the N-Back task. The lack of observed effect suggests either that rimonabant is unable to sufficiently increase GABAergic-mediated inhibition of prefrontal pyramidal neurons or the observed impairment in N-back performance is not related to a CB1-mediated disruption of the interaction between GABAergic interneurons and glutamatergic pyramidal cells.

We found a significant treatment effect for the RBANS total score. Placebo-treated participants generally had slight improvements, while rimonabant-treated participants exhibited mild to modest worsening on individual domain scores. This pattern of improvement was most marked for the attention domain. Improvement in the placebo group could be attributed to a placebo-potentiated practice effect, because practice effects have not been observed outside of placebo-controlled randomized clinical trials (Wilk et al, 2002).

The major study limitation is the small sample size, secondary to the early termination of the study. While some findings achieved statistical significance, this study should be regarded as hypothesis generating until larger studies confirm that our findings were not the result of Type I error. Although the future of CB1 antagonists remains uncertain, it is important to

continue to determine how the endocannabinoid system relates to the psychopathology and neuropsychiatric deficits in schizophrenia and whether alteration of this system can lead to novel therapeutic treatments.

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Figure 1. Performance on the Probabilistic Learning Task (PL)

A) Overall percent correct (SD) for the three conditions during baseline and end of study. The x-axis lists the probability of reinforcement for each of the two decks. Blue diamonds are rimonabant-treated participants and red squares are placebo-treated participants. B) Overall accuracy (SD) at baseline and end of study illustrating how feedback was used in determining which deck to choose after feedback was given averaged over all three conditions. “Stay Driven by Wins” indicates the participant selected the same deck based on the fact the previous response was correct. “Shifts Driven by Loses” indicate the participant selected the other deck based on the fact the previous response was incorrect. Blue indicates rimonabant-treated participants and red indicates placebo-treated participants.

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

Table 2

Baseline and End of Study (EOS) Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) Total and Domain Scores (Mean $\pm$ SD)

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

Table 3
Baseline and End of Study (EOS) Iowa Gambling Task and N-Back Scores (Mean $\pm$ SD)

	Rimonabant (n = 7)		Placebo (n = 7)		Effect Size	95% C.I.
	Baseline	EOS	Baseline	EOS		
Iowa Gambling Task: Rewarded minus Punished score	5.1 $\pm$ 19.8	-0.3 $\pm$ 25.2	1.3 $\pm$ 22.7	-9.0 $\pm$ 29.7	0.21	-1.40, 1.80
N-Back: d-prime						
0-Back	3.8 $\pm$ 0.5	3.9 $\pm$ 0.6	3.6 $\pm$ 0.6	3.6 $\pm$ 0.4	0.26	-0.69, 1.19
1-Back	3.2 $\pm$ 0.8	3.3 $\pm$ 0.7	3.2 $\pm$ 0.6	2.8 $\pm$ 0.2	0.76	-0.30, 1.78
2-Back	1.5 $\pm$ 0.6	1.5 $\pm$ 0.4	1.6 $\pm$ 0.6	1.6 $\pm$ 0.4	0.09	-0.87, 1.04