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Effects of the Cannabinoid-1 Receptor Antagonist/Inverse Agonist Rimonabant on Satiety Signaling in Overweight People with Schizophrenia:

A Randomized, Double-Blind, Pilot Study

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AUTHOR DISCLOSURE INFORMATION

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To the Editors

People with schizophrenia have an increased risk of comorbid medical conditions, primarily coronary heart disease, resulting in a 15- to 20-year shorter life expectancy than those without the diagnosis. Coronary heart disease is induced largely by high rates of obesity, insulin resistance and type 2 diabetes, hyperlipidemia, and hypertension¹ compounded by smoking, reduced access to care, inadequate health screening rates, poor diet, and metabolic adverse effects of antipsychotic medications.

Weight gain is a serious adverse effect of several second-generation antipsychotic (SGA) medications² possibly caused by several peripheral and central mechanisms including disturbances in glucose, insulin, leptin, ghrelin, H₁ and 5HT_{2C} receptor antagonism, other hormone signaling or function or secretion, or disturbances in satiety signaling.³ In fact, people with schizophrenia taking SGA medications show lower levels of self-reported satiety after a standardized breakfast than do those not taking SGAs.⁴ Rats taking the SGA olanzapine show impeded behaviorally measured satiety⁵ and hyperphagia is implicated in the SGA induction of body weight gain.⁶ Thus, one key mechanism of weight gain with SGAs may involve disruption or interruption of normal satiety signaling after eating.

Cannabinoid-1 (CB1) antagonists and agonists affect food intake through binding to cannabinoid receptors. Hyperphagia (overeating) can be induced by injection of anandamide, an endogenous cannabinoid (endocannabinoid) neurotransmitter, into the ventral medial hypothalamus or by peripheral administration of exogenous cannabinoids.⁷ In addition, cannabinoids increase rodents' preference for sucrose solution or other palatable substances.⁸ Pretreatment with rimonabant, a CB1 receptor inverse agonist/antagonist, inhibited this hyperphagia and increased food preference in rats,^{7,8} suggesting that cannabinoids are acting via the CB1 receptor. The natural craving of rats for sweet substances is intensified by enhanced endocannabinoid signaling in the nucleus accumbens,⁹ suggesting a relationship between endocannabinoid activity and satiety modulation. Furthermore, endocannabinoids inhibit digestion signals mediated by afferent vagus nerve fibers, such as the release of cholecystokinin, leading to increased food consumption.¹⁰ Because of the potential satiety-inducing effects of cannabinoid receptor antagonism, we hypothesized that rimonabant may enhance satiety signaling in people with schizophrenia taking a SGA. The aim of this study was to directly test the behavioral effects of rimonabant on satiety signaling as measured by a preload-test meal paradigm.

Inpatients and outpatients at the Maryland Psychiatric Research Center with a *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*-defined diagnosis of schizophrenia or schizo-affective disorder who were treated with an SGA for at least eight weeks on a stable dose for at least one month were enrolled in a 16-week, double-blind, randomized, placebo-controlled study of rimonabant (20 mg/d). Full results on psychiatric symptoms and metabolic data are presented elsewhere.¹¹ Participants were between the ages of 18 and 55 years, had a body mass index (BMI) of 30 kg/m² or greater or a BMI of 27 kg/m² or greater plus adult treatment panel III hyperlipidemia or hypertriglyceridemia,¹² no recent depressive symptoms/suicidality, no current substance abuse/dependence (with the exception of nicotine), no more than weekly cannabis use, and were clinically stable (baseline characteristics, Table 1). An exercise and dietary counseling group was offered weekly during the study.

The participants were assessed at baseline, midpoint, and end of study using a preload-test meal paradigm designed to assess satiety signaling. After an overnight fast, the participants were given a standardized breakfast preload of 12-oz. vanilla Ensure. The preload was consumed, in its entirety, within 5 minutes. A preweighed test meal (Wheat Thins, Nilla

Wafers, and 12-oz. water) was served an hour later. After 30 minutes, the test meal was removed and weighed. The amount consumed was considered a behavioral index of satiety.

Rimonabant-placebo differences in test meal consumption were evaluated using mixed models for analysis of covariance to combine data across repeated visits and to adjust for observed between-group differences in baseline consumption. The models took the following form: treatment phase measure = baseline measure + treatment + week + treatment $\times$ week. In this model, week is a categorical indicator of week 7 versus week 16; the main effect of treatment estimates the average of the rimonabant-placebo differences at weeks 7 and 16; and the treatment $\times$ week interaction term tests whether the magnitude of treatment effects varies significantly between the follow-up 2 weeks. The models were fitted using SAS PROC MIXED (version 9.1.3, SAS Institute, Cary, NC), and degrees of freedom for hypothesis tests were estimated using the Kenward-Roger¹³ method. Similar models were fitted to evaluate rimonabant effects on body weight and BMI.

The target sample size was 60 participants (30 in each group); however, the study was terminated prematurely when rimonabant was withdrawn from worldwide marketing due to concerns over psychiatric symptoms and suicidality. We excluded participants with depressive symptoms or suicidality at baseline and did not see any increase in suicidality or depressive symptoms throughout the trial. In fact, total Brief Psychiatric Rating Scale (BPRS) scores improved in the rimonabant group compared to the placebo group over the 16 weeks.

Fifteen participants were randomized to medication (7 participants, rimonabant; and 8 participants, placebo); 5 participants in each group completed the 16-week trial. Because of early study termination, 2 participants on rimonabant (at weeks 11 and 13) and 2 participants on placebo (both at week 13) did not complete the 16-week trial but completed end-of-study assessments. No participant discontinued because of adverse events. One participant on placebo did not complete the satiety paradigm. At baseline, mean (SD) test meal consumption was lower in the participants randomized to rimonabant for total kilocalories (64.4 [68.0]) and Wheat Thins (40.6 [53.1]) compared to placebo (101.0 [55.4] and 58.0 [44.4], respectively). After statistically adjusting for these baseline differences, least square mean (SE) rimonabant-placebo differences in test meal consumption were -42.7 (19.7) for total kcal ($F = 4.70$; $df = 1, 10.8$; $P = 0.053$) and -17.8 (9.3) for Wheat Thins kcal, ($F = 3.64$; $df = 1, 8.93$; $P = 0.089$), giving estimated treatment effect sizes of 0.73 and 0.44, respectively. Rimonabant-placebo differences did not vary significantly between weeks 7 and 16 (treatment $\times$ interaction tests, $P = 0.51$ for total kilocalories and $P = 0.82$ for Wheat Thins). Nilla Wafer consumption did not differ between groups. There were no significant group differences in weight change ($F = 0.05$; $df = 1, 11.4$; $P = 0.82$) or BMI ($F = 0.27$; $df = 1, 11.9$; $P = 0.61$). Rimonabant effects on psychiatric symptoms and adverse events are reported elsewhere.¹¹

DISCUSSION

In this pilot study, rimonabant failed to produce any significant changes in satiety as measured by the preload-test meal paradigm. However, there was a trend toward lower caloric consumption in the rimonabant group compared to the placebo group, and the effect size of this difference was robust (0.73 for total kcal). This trend may have failed to reach statistical significance because the study was underpowered owing to its premature termination. In addition, the placebo group had a significantly higher baseline BMI, which may have inflated the amount of test meal consumption seen in this group. An effect of decreased caloric consumption would be consistent with a prior human laboratory study in which rimonabant (20 mg/d) reduced subjective measures of hunger and desire to eat during

test meals while having no effect on ratings of fullness after the meals.¹⁴ Over the course of that study, rimonabant significantly reduced participants' frequency and strength of food cravings. Cannabinoid-1 receptor blockade reducing caloric consumption and hunger would be functionally consistent with the clinical use of CB1 receptor agonists such as 9-tetrahydrocannabinol to enhance appetite and weight gain in individuals with cachexia due to serious illness, such as cancer and acquired immune deficiency syndrome.¹⁵

Animal studies suggest an important role for the endocannabinoid system in stimulating eating and motivation to eat and increasing both the "wanting"¹⁶ and "liking"¹⁷ of food. This influence on normal satiety signaling may explain the mechanism of action of rimonabant and other CB1 receptor antagonists in producing weight loss.¹⁸ However, little work has been done in humans to understand the effects of cannabinoids on motivation to eat or satiety. This topic is of significant interest to the field of schizophrenia because abnormalities in both metabolic processes and weight regulation and in the endocannabinoid system may be present in this condition.¹¹ For example, the CB1 receptor gene may be associated with antipsychotic-induced weight gain in people with schizophrenia.¹⁹ Future human research will likely focus on medications with less central and more peripheral effects to minimize the psychiatric adverse effects that led to the withdrawal of rimonabant and related CB1 receptor antagonist/inverse agonist.

The major limitation of our study is the small sample size, with resulting low power to detect significant differences between treatments. This may have accounted for the failure to observe any significant weight loss over 16 weeks of rimonabant treatment at a dose (20 mg/d) that produced significant weight loss in several large-scale controlled clinical trials of overweight or obese people without serious mental illness.²⁰ However, there are no other comparable published data on the effects of any CB1 receptor antagonist on satiety signaling in people with schizophrenia. Thus, these preliminary results may guide research on the potential effects of CB1 receptor antagonists on food wanting or caloric consumption.

In this small sample of people with schizophrenia, rimonabant failed to produce any statistically significant changes in body weight or eating behavior. However, there was a trend toward lower caloric consumption in the rimonabant group compared to the placebo group, with a moderate to large effect size. This suggests that the endocannabinoid system may be involved with satiety signaling. The endocannabinoid system remains a very interesting target for weight-altering treatments.

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TABLE 1

Demographic and Baseline Clinical Characteristics of 14 Study Participants Completing Satiety Testing

	Rimonabant (n = 7)	Placebo (n = 7)	Significance*
Age, y	45.9 ± 6.9	44.9 ± 12.2	$\chi^2 = 0.004$; df = 1; $P = 0.95$
Sex, male	5 (71%)	4 (57%)	$P = 1.0$
Race, white	4 (57%)	3 (43%)	$P = 1.0$
Weight, mean (SD), kg	94.4 (10.2)	120.0 (30.5)	$\chi^2 = 2.2$; df = 1; $P = 0.14$
BMI, kg/m ² *, mean (SD)	31.3 (3.2)	43.8 (14.2)	$\chi^2 = 3.4$; df = 1; $P = 0.06$
Concurrent antipsychotic medication, n (%)			
Clozapine	3 (43)	0 (0)	$P = 0.19$
Clozapine + SGA	0 (0)	2 (25)	$P = 0.47$
Olanzapine + SGA	1 (14)	0 (0)	$P = 0.47$
Risperidone +/- SGA (not clozapine or olanzapine)	3 (43)	2 (25)	$P = 0.61$
Quetiapine +/- SGA (not clozapine or olanzapine)	0 (0)	1 (13)	$P = 1.0$
Ziprasidone	0 (0)	2 (25)	$P = 0.47$

* Significance testing by the Fisher exact test unless otherwise indicated.