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ORIGINAL INVESTIGATION

Attenuating effect of reboxetine on appetite and weight gain in olanzapine-treated schizophrenia patients: a double-blind placebo-controlled study

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Abstract
Rationale Search for safe and effective strategies to diminish weight gain associated with second generation antipsychotics (SGAs) is imperative. In the present study, we sought to replicate our preliminary findings, which indicated that coadministration of the selective norepinephrine reuptake inhibitor reboxetine attenuates olanzapine-induced weight gain.
Materials and method Fifty-nine patients hospitalized for first-episode DSM-IV schizophrenic disorder participated in this randomized double-blind study. Reboxetine (4 mg/day; 31 patients) or placebo (29 patients) was coadministered with olanzapine (10 mg/day) for 6 weeks. Analysis was by intention-to-treat.
Results Nine patients in each group prematurely discontinued the trial. Olanzapine/reboxetine-treated patients showed a significantly lower increase in body weight (mean=3.31 kg, SD=2.73) than their olanzapine/placebo-treated counterparts (mean=4.91 kg, SD=2.45). Significantly fewer olanzapine/reboxetine-treated patients gained at least 7% of their initial weight, the cutoff for clinically significant weight gain (6 [19.4%] of 31 patients vs 13 [46.4%] of 28 patients). Seven (22.6%) olanzapine/reboxetine-treated patients compared to only one patient (3.6%) in the olanzapine/placebo group revealed no weight change or even modest weight loss. Appetite increase was significantly lower in the olanzapine/reboxetine than olanzapine/placebo group and was correlated with attenuation of weight gain. Reboxetine addition was safe and well tolerated.
Conclusions The results confirm that coadministration of reboxetine promotes a clinically meaningful attenuation of olanzapine-induced weight gain in schizophrenia patients. If substantiated in long-term studies, along with behavioral management and diet counseling, reboxetine may have a clinical utility in controlling SGA-induced weight gain.

Keywords Second generation antipsychotics · Olanzapine · Reboxetine · Weight gain

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Introduction

Weight gain is one of the major drawbacks of treatment with second generation antipsychotic agents (SGAs). SGA-

induced weight gain is associated with patient nonadherence to medication, reduced quality of life, increased morbidity (e.g., cardiovascular disease, type 2 diabetes), and mortality (Newcomer and Haupt 2006).

Olanzapine, along with clozapine, has the greatest propensity of all available SGAs to induce weight gain. Despite extensive research during the last decade, a pathophysiological mechanism underlying olanzapine-induced weight gain remains unclear. Neurotransmitter systems, primarily serotonergic (5-HT), noradrenergic (NE), and histaminergic (H), apparently play a role (Elman et al. 2006). It was suggested that the antagonistic effect of olanzapine on NE neurotransmission contributes, along with its 5-HT_{2C} and H_1 receptor blockade, to its high propensity to cause weight gain (Kroeze et al. 2003; Poyurovsky et al. 2003). In contrast, phentermine and sibutramine, both potent appetite suppressants and antiobesity agents, facilitate adrenergic tone by stimulating NE release and NE and 5-HT reuptake inhibition (Henderson et al. 2005). Increased NE neurotransmission has consistently been implicated in regulation of food intake, body weight, and energy expenditure in preclinical models of obesity (Ste Marie et al. 2005).

Reboxetine, a selective norepinephrine reuptake inhibitor (NRI), is broadly used as an antidepressant and antianxiety agent. Overall, in these patient populations, reboxetine produced a neutral effect on body weight, but weight loss has also been reported (Schatzberg 2000; Bertani et al. 2004). Based on the assumption that stimulation of NE activity by the selective NRI reboxetine may diminish olanzapine-induced weight gain, we conducted a pilot study in which reboxetine was coadministered with olanzapine in schizophrenia patients (Poyurovsky et al. 2003). In accordance with our assumption, patients given olanzapine and reboxetine demonstrated a significantly lower increase in body weight than those given olanzapine with placebo. The addition of reboxetine to olanzapine treatment was safe and well tolerated by the patients. Noteworthy, the participants were young first-episode schizophrenia patients previously unexposed to antipsychotic medication who seem to be particularly vulnerable to olanzapine-induced weight gain (Kinon et al. 2001).

In the present double-blind placebo-controlled study, we sought to replicate, in a larger sample, our preliminary findings indicating that reboxetine coadministration attenuates olanzapine-induced weight gain. In addition, as increased appetite and food intake seem to be a major behavioral pathway by which olanzapine produces weight gain (Gothelf et al. 2002; Kinon et al. 2005; Cope et al. 2005), we also assessed the effect of reboxetine on appetite and its relationship to weight gain. To increase comparability of the results, similar to the previous study, we recruited first-episode predominantly drug-naïve schizophrenia patients for whom olanzapine treatment was indicated.

Subjects and methods

Subjects and study design

This study was conducted in Tirat Carmel Mental Health Center (Tirat Carmel, Israel) between October, 2003 and October, 2006. The study protocol was approved by the local ethics committee and was undertaken in accordance with Good Clinical Practice and the provisions of the International Conference on Harmonization, with all patients providing written informed consent after they received a full explanation of the study procedures. Patients hospitalized for a first psychotic episode were enrolled in the study. All met the DSM-IV criteria for schizophrenia or schizophreniform disorder. The diagnosis was based on information obtained from the Structured Clinical Interview for DSM-IV Axis-I Disorders, Patient Edition (First et al. 1995). Similar to the previous pilot study, inclusion criteria in the present study were none or less than 4 weeks of antipsychotic drug exposure and a recommendation for olanzapine treatment by the treating physician. Exclusion criteria included major mood disorders, aggressive or suicidal behavior, medical illnesses that could affect body weight (e.g., diabetes mellitus and hypothyroidism), and obesity (body mass index [BMI]≥30 kg/m^2). Of the 85 patients who were screened for participation in the study, 69 met entry criteria, 59 patients (38 men, 21 women) were randomized, whereas ten patients refused to participate (Fig. 1). There were no differences in socio-demographic or clinical variables between participants (N=59) and those who refused to participate (N=10).

The olanzapine/reboxetine group consisted of 31 patients (23 men, 8 women; age 30.3±8.5 years, range 19–48 years), and the olanzapine/placebo group consisted of 28 patients (15 men, 13 women; age 29.5±7.2 years, range 19–46 years). Before the beginning of the study, 13 patients in the olanzapine/reboxetine group were drug-naïve, eight patients received risperidone (2–4 mg/day), five patients received haloperidol (5–10 mg/day), and five patients received perphenazine (8–24 mg/day). In the olanzapine/placebo group, 12 patients were drug-naïve, five patients received risperidone (2–6 mg/day), five patients received haloperidol (10 mg/day), five patients received perphenazine (8–16 mg/day), and one patient received quetiapine (600 mg/day). None of the participants received medications other than psychotropic agents during the study. None of them had abnormal findings on routine physical examination and laboratory tests, including electrocardiography and drug screening, when appropriate.

A double-blind placebo-controlled randomized design was used in the present study. The participants were allocated according to entries on a table of random numbers to receive olanzapine (fixed dose of 10 mg at 8:00 P.M.)

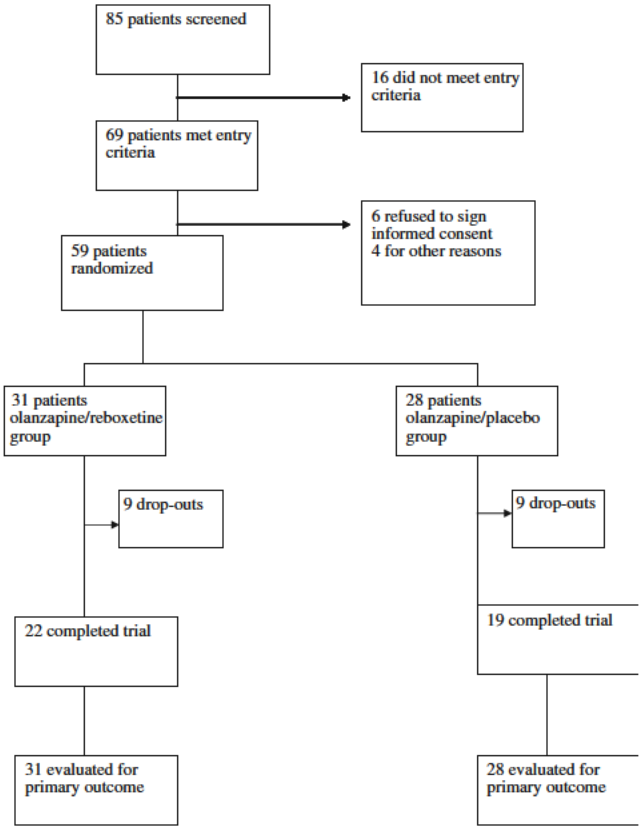

Fig. 1 Trial profile. Primary analysis was done on the intention to treat population

with either reboxetine (4 mg/day, administered in 2-mg doses twice daily) or placebo (twice daily) for 6 weeks. All study medications were dispensed in identical capsules, and patients received two capsules per day. Clinical and research staff and patients were unaware of and could not determine the study drug assignment by appearance or otherwise. The reboxetine dose was determined based on our previous report (Poyurovsky et al. 2003). Administration of an anticholinergic agent (trihexyphenidyl 5 mg/day; biperiden 2–4 mg/day) for extrapyramidal side effects (extrapyramidal symptoms, EPS) and benzodiazepines (lorazepam 1–3 mg/day; diazepam 5 mg/day) for insomnia or agitation were allowed on an as-needed basis; no other antipsychotics, antidepressants, or mood stabilizers were permitted. The doses of all medications remained unchanged during the entire study period. Meals were served three times a day, and patients were not placed on a special diet or physical exercise program for weight reduction.

Assessments

Body weight and BMI were measured before breakfast at baseline and then weekly. All weight measurements were performed by a research assistant blinded to the patients' treatment assignment. To assess a change of appetite, we used a visual analog scale with the following scores: 0, no change; 1, minimal increase; 2, moderate increase; 3, substantial increase; −1, minimal decrease; −2, moderate decrease; −3, substantial decrease. Appetite ratings were completed at the end of the trial. Clinical assessment instruments included the Scale for the Assessment of Positive Symptoms (SAPS; Andreasen 1984), Scale for the Assessment of Negative Symptoms (SANS; Andreasen 1983), Clinical Global Impression scale for psychosis (CGI; Guy 1976), and the Hamilton Rating Scale for Depression (HAM-D; Hamilton 1960). EPS were assessed using the Barnes Akathisia Scale (BAS; Barnes 1989) and Simpson–Angus Scale (SAS; Simpson and Angus 1970). Emergent non-EPS drug-induced side effects were closely monitored. Clinical ratings were completed at baseline and at week 6 by the same trained psychiatrist (A. Pashinian) who was blinded to the patients' treatment assignments.

Statistical analysis

Statistical analysis was carried out using SPSS for Windows 13 (SPSS, Chicago, III). The sample size of approximately 30 in each group was determined to provide 80% power in detecting a between-group difference of at least 2 kg, when the significance level of the two-sided test is α=0.05, and the pooled SD is 2.9, as obtained in our previous pilot study (Poyurovsky et al. 2003), and allowing for a 25% attrition rate. The primary statistical analysis was by intention to treat and included all randomized participants. A complementary analysis of weight/BMI changes in completers was also performed. We used analysis of variance with repeated measurements (ANOVA-RM) to evaluate between-group differences in weight and BMI during the 6-week trial with time as a within-subject factor and group as a between-subject factor. In addition, similar to the previous study, the mean changes in weight/BMI during the trial period (difference between baseline and each time point) were analyzed for each group.

We used the regression method to treat missing data. In this method, for each week with missing weight/BMI, the values were substituted by those obtained from the fitted values based on the regression of the values of the participants with complete data for the given week on the data for the previous week. This imputation method takes into account the direction and the effect size of weight/BMI changes in the group to which the patients with missing data were ascribed. We also carried out an alternative method of imputation based on the last observation carried forward (LOCF).

We used the changes in weight and BMI as the primary continuous outcome variable and the proportion of patients who gained 7% of their initial body weight, the established cut-off for clinically significant weight gain (Kanders et al. 1991), as a primary categorical outcome variable. Between-

group differences in the proportion of patients who gained 7% of their initial body weight were tested by χ^2 test and odd ratios. Between-group differences in demographic and clinical variables and in changes from baseline to endpoint in the appetite visual analog scale, SAPS, SANS, CGI, HAM-D, SAS, and BAS scores were analyzed using *t* test or χ^2 test, as appropriate. Pearson's correlation analysis was used to assess the relationship between appetite and weight changes at the end of the trial and the relationship between baseline weight and weight change at the end of the trial. All tests were two-tailed with a significance level of α=0.05. Measures are given as mean±SD.

Role of the funding source

The study was funded by the Stanley Medical Research Institute. The funding source had no role in gathering, analyzing, or interpreting the data or in deciding to submit the paper for publication in Psychopharmacology.

Results

Figure 1 depicts the flow of patients through the study. There were no significant between-group differences in demographics, baseline clinical characteristics, body weight, and BMI (Table 1). Nine patients in each group discontinued the study medication because of a lack of efficacy of olanzapine (seven patients in each group), withdrew consent (olanzapine/reboxetine: one patient; olanzapine/placebo: two patients), and discharge from the hospital (olanzapine/reboxetine: one patient). The missing data patterns for weight/BMI values were similar between the two groups. None of the patients discontinued the study because of weight gain, and the majority (olanzapine/reboxetine: eight of nine patients; olanzapine/placebo: six of nine patients) dropped out before the fourth assessment (third week). There were no differences in demographic or clinical characteristics or weight/BMI values between the patients who dropped out of the study and those who did not.

Body weight/BMI changes from baseline in both groups are presented in Table 2. ANOVA-RM revealed a highly significant effect of time (weight: F=88.89; df=5,287, p<0.01; BMI: F=84.35; df=5, 287, p<0.01) and effect of group (weight: F=6.46, df=1, p=0.014; BMI: F=6.37; df=1, 57, p=0.014) but not the interaction between time and group (weight: F=1.77, df=5, 287, p=0.12; BMI: F=1.83; df=5,287, p=0.11). Analysis of the changes in weight gain in the two groups (Table 2) revealed a gradual cumulative effect in weight gain from the baseline in favor of reboxetine, resulting in statistically significant between-group differences in each of the weeks starting from week 2 through the end of the 6-week trial. Although the cumulative effect from baseline was significant, the between-group week-to-week differences in weight were relatively small and not statistically significant, accounting for the failure of ANOVA-RM to detect significant group × time interaction for the sample sizes. Overall, at the end of the trial, patients in the olanzapine/reboxetine group gained significantly less weight than their counterparts in the olanzapine/placebo group (3.31±2.73 and 4.91±2.45 kg, respectively; t=2. 55; df=57; p=0.013), namely, a between-group difference in mean weight gain of 1.61±0.62 kg. The corresponding increase in BMI was 1.12±0.87 kg/m^2 in the olanzapine/reboxetine group and 1.71±0.91 kg/m^2 in the olanzapine/placebo group (t=2.56, df=57, p=0.013), with a between-group mean difference of 0.59±0.23 kg/m^2. Table 2 highlights the statistically significant between-group difference in body weight and BMI in favor of reboxetine, which was evident in the first week, strengthened by the third week and which remained significant until the end of the trial. The LOCF analysis also yielded a

Table 1 Demographics and baseline clinical characteristics of the study participants

Variables	Olanzapine/reboxetine (n=31)	Olanzapine/placebo (n=28)	Statistic	p
Age (years)	30.3 (8.5)	29.5 (7.2)	$t_{(57)}$=0.40	0.69
Gender (male/female)	23/8	15/13	χ^2=2.73	0.10
Education (years)	11.7 (1.8)	11.6 (1.7)	$t_{(57)}$=0.08	0.94
Duration of illness (years)	4.0 (5.6)	3.0 (4.0)	$t_{(57)}$=0.75	0.46
No. of hospitalizations	1.7 (1.3)	1.3 (0.5)	$t_{(57)}$=1.78	0.08
Weight (kg)	67.1 (12.0)	68.4 (13.2)	$t_{(57)}$= 0.38	0.71
BMI (kg/m^2)	22.6 (3.21)	23.3 (3.36)	$t_{(57)}$=0.82	0.42
Rating scales				
SAPS	6.4 (3.2)	5.8 (2.4)	$t_{(57)}$=0.82	0.42
SANS	12.9 (3.6)	12.9 (3.0)	$t_{(57)}$= 0.06	0.96
CGI	4.2 (0.5)	4.1 (0.6)	$t_{(57)}$=0.13	0.90
HAM D	10.0 (3.5)	(4.3)	$t_{(57)}$=0.67	0.50
SAS	11.3 (2.7)	11.5 (2.6)	$t_{(57)}$= 0.31	0.76
BAS	0.7 (1.0)	0.6 (1.0)	$t_{(57)}$=0.55	0.59

BMI Body Mass Index; *SAPS* Scale for the Assessment of Positive Symptoms; *SANS* Scale for the Assessment of Negative Symptoms; *CGI* Clinical Global Impression for psychosis; *HAM D* Hamilton Rating Scale for Depression; *SAS* Simpson Angus Scale; *BAS* Barnes Akathisia Scale

Table 2 Weight/BMI values (mean±SD); changes from baseline in olanzapine/reboxetine and olanzapine/placebo groups

Weight: difference from baseline							Body Mass Index (BMI): difference from baseline					
Week	Olanzapine/ reboxetine (n=31)	Olanzapine/ placebo (n=28)	Olanzapine/ reboxetine (n=31)	Olanzapine/ placebo (n=28)	t Statistics[a] (df=57)	p	Olanzapine/ reboxetine (n=31)	Olanzapine/ placebo (n=28)	Olanzapine/ reboxetine (n=31)	Olanzapine/ placebo (n=28)	t Statistics[a] (df=57)	p
Baseline	67.13 (11.97)	68.36 (13.18)					22.55 (3.21)	23.34 (3.36)				
Week 1	67.81 (11.90)	69.73 (13.05)	0.68 (1.01)	1.36 (1.58)	2.00	0.051	22.78 (3.16)	23.82 (3.45)	0.23 (0.37)	0.49 (0.58)	2.06	0.044
Week 2	68.33 (11.88)	70.63 (13.09)	1.19 (1.77)	2.26 (1.92)	2.23	0.030	22.96 (3.20)	24.13 (3.43)	0.40 (0.62)	0.80 (0.69)	2.25	0.028
Week 3	68.77 (11.96)	71.40 (13.12)	1.64 (2.15)	3.01 (2.03)	2.51	0.015	23.11 (3.25)	24.38 (3.39)	0.56 (0.78)	1.04 (0.73)	2.46	0.017
Week 4	69.35 (11.94)	71.90 (13.19)	2.22 (2.29)	3.53 (2.04)	2.31	0.024	23.31 (3.27)	24.56 (3.42)	0.76 (0.83)	1.22 (0.72)	2.29	0.026
Week 5	69.95 (11.80)	72.58 (13.04)	2.81 (2.26)	4.21 (2.33)	2.34	0.022	23.51 (3.27)	24.80 (3.45)	0.96 (0.82)	1.47 (0.84)	2.33	0.023
Week 6	70.44 (12.25)	73.28 (13.00)	3.31 (2.73)	4.91 (2.45)	2.55	0.013	23.80 (3.37)	25.05 (3.53)	1.12 (0.87)	1.71 (0.91)	2.56	0.013

[a] Between group differences in weight/BMI

significant between-group to difference in weight gain (olanzapine/reboxetine: 2.68±2.62 kg; olanzapine/placebo: 4.14±2.85 kg; Δweight=1.46±0.61, t=2.05, df=57, p=0.045) and BMI (olanzapine/reboxetine: 0.92±0.96 kg/m^2; olanzapine/placebo: 1.45±1.04 kg/m^2; ΔBMI=0.53±0.26 kg/m^2, t=2.03, df=57, p=0.047). Complementary analysis in completers revealed a similar to intent-to-treat population trajectory and effect size of weight/BMI changes in the olanzapine/reboxetine (N=22) and olanzapine/placebo (N=19) group (Δweight=1.78±0.80 kg; t=2.22, df=37, p=0.032; ΔBMI=0.65±0.30 kg/m^2; t=2.17, df=37, p=0.036).

The two groups were unbalanced with respect to gender, with less women in the olanzapine/reboxetine group than in the olanzapine/placebo group (8 and 13, respectively). Using gender as a fixed factor in a two-way analysis of variance, there was no effect of gender (p=0.96) on the between-group difference in weight gain (Δweight: olanzapine/reboxetine, men=3.38±2.12 kg, women=3.09±3.16 kg; olanzapine/placebo, men=4.81±2.68 kg, women=5.04±2.26 kg).

The weight-attenuating effect of reboxetine is further supported by the fact that significantly less patients in the olanzapine/reboxetine group than in olanzapine/placebo group increased their initial weight by at least 7%, the cut-off for clinically significant weight gain (Kanders et al. 1991; 6/31 [19.4%] and 13/28 [46.4%], respectively; χ^2=4.94, df=1, p=0.026; odds ratio=3.61 [95%CI 1.13–11.52]). These patients did not differ significantly from their counterparts who gained weight in any of demographic or clinical characteristics and baseline weight/BMI indices. Noteworthy, 7 (22.6%) of the 31 olanzapine/reboxetine-treated patients compared to only one patient (3.6%) in the olanzapine/placebo group revealed no weight change from baseline or even minor weight loss (χ^2=4.54, df=1, p=0.033).

No significant correlation between initial BMI and change in body weight at 6 weeks in either group (r=0.02, df=29, p=0.92 for the olanzapine/reboxetine group; r=0.01, df=26, p=0.97 for the olanzapine/placebo group) was found.

Regarding reboxetine's effect on appetite, there was a significantly lower increase in appetite in the olanzapine/reboxetine than in the olanzapine/placebo group (0.82±1.13 and 1.50±0.88, respectively; t=−2.49; df=57, p=0.016). Specifically, less patients in the olanzapine/reboxetine group reported moderate to substantial increase in appetite at the end of the trial, as reflected by the scores "2" and "3" on the appetite scale (olanzapine/reboxetine=8/31 (25.8%); olanzapine/placebo=15/28 (53.5%); χ^2=4.77, df=1, p=0.02; odds ratio=3.32 [95%CI 1.11–9.92]). Notably, there was a strong positive correlation between increase in appetite and weight gain in each group (olanzapine/

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