Orlistat in Clozapine- or Olanzapine-Treated Patients With Overweight or Obesity: A 16-Week Randomized, Double-Blind, Placebo-Controlled Trial

Grigori Joffe, M.D., Ph.D.; Pirjo Takala, M.D.; Evgueni Tchoukhine, M.D.; Helinä Hakko, Ph.D.; Mirjam Raidma, M.D.; Hanna Putkonen, M.D., Ph.D.; Markku Eronen, M.D., Ph.D.; and Pirkko Räsänen, M.D., Ph.D.

Objective: Undesirable metabolic effects of modern antipsychotics, especially clozapine and olanzapine, merit development of new weight-control strategies, including pharmacologic ones. We investigated the feasibility of treatment with orlistat, a weight-control drug with no central effects, for overweight/obesity in clozapine- or olanzapine-treated male and female patients.

Method: Add-on orlistat was prescribed for 16 weeks in a randomized, double-blind, placebo-controlled clinical trial to patients who were receiving stable clozapine or olanzapine medication and were aged 18 to 65 years, with no compliance with nonpharmacologic programs or hypocaloric diet required. The primary efficacy variable was body weight change. The study was conducted from 2004 through 2005.

Results: Of 71 randomly assigned subjects, 63 were eligible for modified intent-to-treat analysis. While no statistically significant effect was observed in the whole population, male (but not female) patients benefited from treatment with orlistat (–2.36 kg vs. 0.62 kg on placebo, $p = .011$). There were 5 responders (16.1%) (those with ≥ 5% weight loss) that received orlistat versus 2 responders (6.3%) that received placebo (number needed to treat = 11), but the difference was not statistically significant.

Conclusions: Without a hypocaloric diet, the effect of orlistat in overweight/obese clozapine- or olanzapine-treated patients is modest and may only be seen in men. More studies should define the optimal length of treatment and feasibility of combination of orlistat with behavioral programs in this population.

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Received Feb. 21, 2007; accepted Sept. 17, 2007. *From Kellokoski Hospital (Drs. Joffe, Tchoukhine, and Raidma); Vanha Vaasa Hospital, Vaasa (Drs. Takala, Putkonen, and Eronen); Department of Psychiatry, Oulu University Hospital (Dr. Hakko); and Department of Psychiatry, University of Oulu (Dr. Räsänen), Finland.*

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Corresponding author and reprints: Dr. Grigori Joffe, Kellokoski Hospital, 04500 Kellokoski, Finland (e-mail: grigori.joffe@hus.fi).

A common adverse effect of atypical antipsychotics, particularly clozapine and olanzapine, associated with increased morbidity, mortality, and noncompliance[1,2] is weight gain. Even moderate weight reduction may yield health benefits.[3] In antipsychotic-treated patients, however, behavioral weight-control programs show only a limited effect[4] or have high dropout rates.[5] A switch to a weight-neutral antipsychotic is fraught with risk for psychotic exacerbation, especially in regard to clozapine or olanzapine, probably the most effective antipsychotics.[6,7]

Data on weight-control pharmacotherapy in clozapine- or olanzapine-related overweight/obesity have been limited. Some studies aimed at pharmacotherapeutic prevention of antipsychotic-induced weight gain, such as metformin therapy, showed equivocal results with olanzapine[8] or other atypicals.[9] In patients already suffering from olanzapine-related overweight/obesity, reboxetine, sibutramine, and amantadine proved effective in several randomized control trials,[10–12] whereas fluoxetine and nizatidine did not.[13,14] In a randomized controlled trial by Ko and colleagues,[15] topiramate was efficacious, but the majority of their patients were receiving other atypicals. In the only randomized controlled trial we were able to locate that studied clozapine-associated weight gain, sibutramine showed no effect.[16]

In clinical practice, the use of weight-control drugs is limited by their propensity to alter central neurotrans-

mitter balance, leading to risk for clinical destabilization. Orlistat, which blocks absorption of ingested fat by inhibiting pancreatic lipase within the intestinal lumen, is a novel weight-control drug with no central effects. In nonpsychiatric populations, orlistat therapy with hypocaloric diet produced significant weight loss.[17]

While some clinical observations,[18] including our own (a body mass index [BMI] reduction from 31.5 to 26.3 in 1 olanzapine-treated patient; unpublished), favor augmentation of olanzapine or clozapine[19] with orlistat, no studies have reported this issue with appropriate scientific methodology. Here, we tested the hypothesis that orlistat is more effective than placebo for clozapine- or olanzapine-related overweight/obesity.

METHOD

The study protocol was approved by the Ethics Committee of the Hospital District of Helsinki and Uusimaa, the Ethics Committee of Vaasa Hospital District, and the National Agency for Medicines, Helsinki, Finland.

The subjects were included in the study if they were inpatients or outpatients aged 18 to 65 years, had a BMI of 28 to 43 kg/m^2, and suffered from a serious mental condition that was relatively stable with ongoing clozapine or olanzapine treatment. The BMI limits were used to obtain homogeneous data, i.e., to exclude patients with only mild overweight or extreme obesity. Exclusion criteria included the following: (1) contraindications for orlistat, (2) receiving concomitant medication considerably affecting body weight (preexisting therapies able to affect weight could be continued provided that both the medication and weight had remained stable during ≥ 4 weeks prior to enrollment; these medications had to remain unchanged throughout the trial), (3) serious medical illness, (4) type 1 diabetes mellitus, (5) substance-related disorders, (6) expected poor compliance, (7) significant body weight change within the last ≥ 4 weeks, (8) conditions associated with rapid weight swings (polydipsia, bulimia, binge eating), (9) clinically significant abnormalities in laboratory tests, (10) fertile women who are pregnant or breastfeeding, or (11) fertile women who are unable/unwilling to use appropriate contraception. These exclusion criteria were applied due to their possibly confounding effect on weight and other metabolic issues (criteria 2, 3, 4, 7, 8, and 10), reliability of obtained data (5 and 6), or patients' (1 and 9) or fetus' (11) safety. After a complete description of the study, subjects gave written informed consent, and after a 1-week placebo run-in period, all those eligible were randomly assigned, half to orlistat, half to placebo, in a double-blind fashion for 16 weeks.

The doses of clozapine and olanzapine remained unchanged for the last ≥ 4 weeks before the trial. During the trial, only a minimal (according to investigators' clinical judgment) increase (but not decrease) in clozapine and olanzapine doses was allowed if essential. Orlistat or placebo was taken in identical gelatin capsules t.i.d. during the main fat-containing meals, with each orlistat capsule containing 120 mg. Adherence to study medication was monitored by capsule count at each visit. Patients with poor compliance (i.e., those taking less than 80% of their study medication during 2 or more consecutive or 3 or more cumulative weeks) were withdrawn. All patients were instructed at baseline visit and reinstructed at week 1 as to the mechanism of action of orlistat, and they were encouraged to limit their dietary fat and calorie consumption and to increase their exercise, but they were given no formal diet or exercise program. The patients thus continued to receive their usual meals in the hospital restaurant (approximately 1800 calories/day, 25%–35% from fat) and, if wanted, could purchase additional food elsewhere with no external control or restrictions. At each visit, patients were asked about adverse events.

The primary efficacy variable was body weight change. Secondary efficacy parameters included the number of patients achieving a response (≥ 5% body weight loss). Assessments were performed at weeks 0 (baseline), 1, 4, 8, and 16. Fasting glucose, total cholesterol, high- and low-density lipoprotein cholesterol, and triglyceride levels underwent standard measurement at weeks 0, 8, and 16.

The data were analyzed on a modified intent-to-treat basis with last observations carried forward. Modified intent to treat was predefined by study protocol and comprised patients with at least week 4 assessments (i.e., at least 1 on-medication assessment; the assessments at week 1 were performed only to reinforce the instructions and check patients' ability to follow them).

Statistical significance of weight change over time by gender was examined post-hoc with the paired sample t test (2 repeated measures) and Friedman test (3 or more repeated measures). A $p < .05$ for a 2-tailed interpretation was considered significant. Significance of between-group differences in categorical variables was assessed with the Pearson χ^2 or Fisher exact test and in continuous variables with Student t test. We used the software SPSS for Windows, version 13.0 (SPSS, Inc.; Chicago, Ill.).

RESULTS

Of 81 consenting patients, 10 failed screening due to withdrawn consent (N = 4), inability to follow routine protocol procedures (N = 3), worsened psychosis (N = 1), or protocol issues (N = 2). The other 71 received orlistat (N = 35) or placebo (N = 36). Within the first week, 1 placebo patient discontinued (due to protocol violation) as did 2 orlistat patients (1 due to diarrhea and 1 due to suicide [not study-related]). Prior to week 4 assessment, 5 more patients discontinued: in the placebo group, 1 was

Table 1. Body Weight and Metabolic Parameters in 63 Clozapine-Medicated Patients (N = 50) or Olanzapine-Medicated Patients (N = 13) With Serious Mental Conditions and Overweight/Obesity During Add-On Treatment With Orlistat (N = 31; males, N = 23) or Placebo (N = 32; males, N = 18)[a]

	Baseline Characteristics (week 0)					Change From Baseline (week 0 through week 16)									
						Orlistat				Placebo					
			Statistic[c]				Statistic[d]				Statistic[d]			Statistic[c]		
Measure[b]	Orlistat	Placebo	t	df	p[e]	Value	t	df	p[e]	Value	t	df	p[e]	t	df	p[e]
Male																
Body weight	105.6 ± 11.2	102.8 ± 12.6	–0.75	39	.456	–2.36 ± 2.99	–3.78	22	**.001**	0.62 ± 4.10	0.64	17	.532	2.68	39	**.011**
Cholesterol total	4.7 ± 0.7	5.1 ± 1.4	1.12	39	.270	–0.15 ± 0.86	–0.76	17	.460	–0.17 ± 0.43	–1.60	16	.129	–0.06	33	.953
LDL	2.8 ± 0.7	3.0 ± 1.1	0.77	35	.447	–0.37 ± 0.75	–1.99	15	.065	–0.13 ± 0.61	–0.87	15	.399	1.00	30	.324
HDL	0.8 ± 0.2	0.8 ± 0.3	–0.77	39	.448	0.02 ± 0.16	0.64	17	.534	0.02 ± 0.12	0.65	16	.527	–0.11	33	.914
Fasting glucose	6.2 ± 0.7	6.2 ± 0.7	0.06	38	.955	–0.14 ± 1.18	–0.50	17	.625	0.16 ± 1.05	0.64	16	.529	0.80	33	.429
Female																
Body weight	92.4 ± 14.5	93.1 ± 16.5	0.11	20	.916	1.94 ± 6.05	0.91	7	.395	0.22 ± 3.32	0.25	13	.807	–0.87	20	.397
Cholesterol total	4.7 ± 0.4	5.6 ± 1.5	1.68	20	.108	0.004 ± 0.51	0.02	7	.984	–0.31 ± 0.90	–1.20	11	.256	–0.89	18	.383
LDL	2.7 ± 0.3	3.4 ± 1.3	1.53	18	.144	–0.15 ± 0.62	–0.66	7	.531	–0.63 ± 0.64	–3.08	9	**.013**	–1.60	16	.129
HDL	1.3 ± 0.3	1.1 ± 0.3	–1.20	20	.244	–0.10 ± 0.17	–1.70	7	.133	0.02 ± 0.13	0.58	11	.572	1.82	18	.085
Fasting glucose	5.3 ± 0.7	5.9 ± 0.9	1.66	20	.113	0.55 ± 0.50	3.12	7	**.017**	0.15 ± 0.48	1.09	11	.300	–1.80	18	.088
Total																
Body weight	102.2 ± 13.3	98.6 ± 15.0	–1.01	61	.314	–1.25 ± 4.33	–1.60	30	.119	0.44 ± 3.73	0.67	31	.506	1.66	61	.101
Cholesterol total	4.7 ± 0.7	5.3 ± 1.5	2.17	61	**.034**	–0.11 ± 0.77	–0.70	25	.489	–0.22 ± 0.66	–1.86	28	.073	–0.64	53	.527
LDL	2.7 ± 0.6	3.2 ± 1.2	1.69	55	.097	–0.32 ± 0.70	–2.06	23	.051	–0.32 ± 0.66	–2.50	25	**.019**	–0.13	48	.896
HDL	1.0 ± 0.3	0.9 ± 0.3	–0.30	61	.764	–0.01 ± 0.17	–0.45	25	.658	0.02 ± 0.12	0.89	28	.383	0.89	53	.379
Fasting glucose	5.9 ± 0.8	6.0 ± 0.8	0.64	60	.525	0.07 ± 1.06	0.35	25	.728	0.16 ± 0.85	1.00	28	.324	0.33	53	.742

[a]Modified intent-to-treat population, last observation carried forward.
[b]Body weight (kg) and cholesterol and fasting glucose (mmol/L) are expressed as mean ± SD.
[c]Independent samples t test (between groups).
[d]Paired t test (within group).
[e]Significant values are shown in boldface.
Abbreviations: HDL = high-density lipoprotein, LDL = low-density lipoprotein.

noncompliant, 1 withdrew consent, and 1 experienced an intolerable side effect; in the orlistat group, 1 experienced psychotic deterioration and 1, diarrhea.

The other 63 patients (58 inpatients and 5 outpatients) formed the modified intent-to-treat population. Baseline demographic and clinical characteristics (mean ± SD) did not differ significantly between orlistat (N = 31) and placebo (N = 32) in regard to age (38.3 ± 9.4 vs. 37.1 ± 9.7 years, t = –0.50, df = 61, p = .622), duration of olanzapine or clozapine treatment (40.0 ± 36.5 vs. 28.8 ± 27.9 months, t = –1.37, df = 61, p = .175), total Positive and Negative Syndrome Scale[20] score (84.1 ± 15.1 vs. 78.0 ± 17.9, t = –1.46, df = 61, p = .149), male gender (N = 23 [74.2%] vs. N = 18 [56.3%], $\chi^2 = 2.23$, df = 1, p = .135), clozapine medication (N = 25 [80.6%] vs. N = 25 [78.1%], $\chi^2 = 0.27$, df = 1, p = .604), body weight (102.2 ± 13.3 kg vs. 98.6 ± 15.0 kg; t = –1.01, df = 61, p = .314), or BMI (32.6 ± 3.5 vs. 33.3 ± 3.7; t = 0.75, df = 61, p = .457). Likewise, stratified analysis by gender revealed no significant differences in these variables between orlistat and placebo.

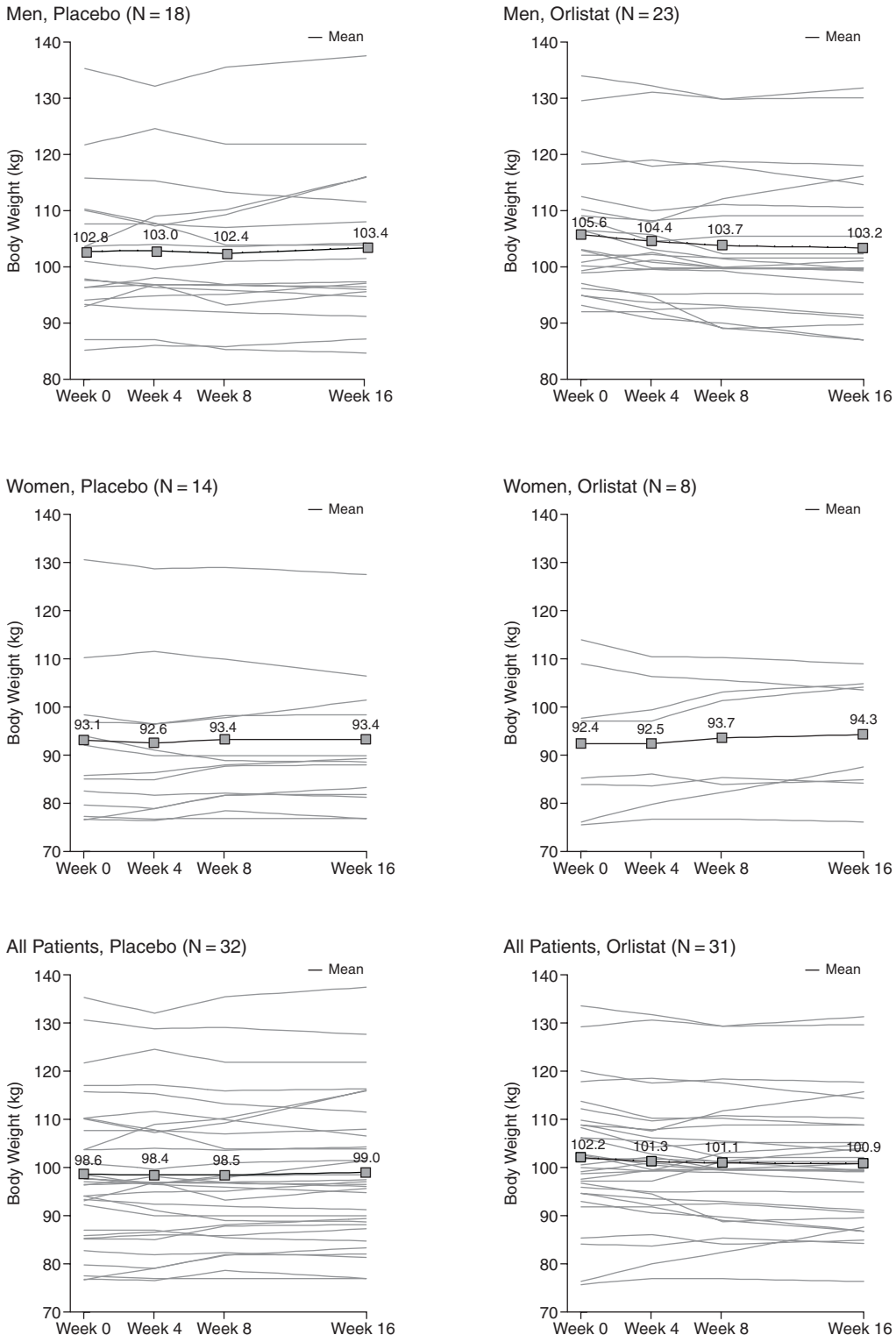
In all randomly assigned patients, no differences occurred in dropout rates (each group: 7 patients, of which 1 was due to noncompliance), but all 4 patients discontinuing due to diarrhea were taking orlistat. The doses of olanzapine remained unchanged in both groups, and the mean dose of clozapine did not change in the placebo group and increased by 2.4% in the orlistat group.

In the whole modified intent-to-treat population, no statistically significant differences between orlistat and placebo were observed within or between groups (primary outcome). Nevertheless, a significant change in body weight over time (weeks 0, 4, 8, and 16) occurred in men taking orlistat (Friedman test: $\chi^2 = 17.7$, df = 3, p = .001) but not in those taking placebo ($\chi^2 = 2.3$, df = 3, p = .507) nor in women taking orlistat ($\chi^2 = 0.7$, df = 3, p = .866) or placebo ($\chi^2 = 3.9$, df = 3, p = .269). Furthermore, a significant change in body weight from week 0 through week 16 occurred in men receiving orlistat but not in men receiving placebo nor in women within either group (Table 1, Figure 1).

There were 5 responders (16.1%) receiving orlistat versus 2 responders (6.3%) receiving placebo, but the difference was not statistically significant (Fisher exact test, p = .257). For response, the number needed to treat was 11.

No differences appeared within or between groups regarding changes in fasting glucose, total cholesterol, or HDL levels, but low-density lipoprotein (LDL) decreased significantly with placebo, with the same trend seen with orlistat. In the secondary analysis by gender, no metabolic changes were found in men while in women, fasting glucose increased with orlistat and LDL decreased with placebo. No differences between clozapine and olanzapine were observed in body weight change (data not shown).

Figure 1. Body Weight in Clozapine- or Olanzapine-Medicated Patients With Serious Mental Conditions and Overweight/Obesity During Add-On Treatment With Orlistat or Placebo[a]



[a]Modified intent-to-treat population, last observation carried forward.

Per protocol population (all patients randomly assigned), the groups did not differ in terms of adverse events. Eleven patients receiving placebo versus 9 receiving orlistat complained of diarrhea. Overall, patients (27 receiving placebo and 19 receiving orlistat) complained of only mild gastrointestinal side effects.

DISCUSSION

To our knowledge, this is the first randomized controlled trial testing orlistat in clozapine- or olanzapine-related overweight/obesity. Beneficial effects of orlistat on body weight appeared only in males. The magnitude of this effect (3 kg difference from placebo) was close to that found in the nonpsychiatric population. (For a review of 28 randomized controlled trials, see Padwal et al.[17]) No differences in body weight change between orlistat and placebo appeared in women or in the whole modified intent-to-treat sample. Response (weight loss of ≥ 5%) was achieved in 5 patients (16.1%) receiving orlistat versus 2 patients (6.3%) receiving placebo (number needed to treat = 11); i.e., 84% of patients taking orlistat did not respond, nor was the difference statistically significant. LDL decreased in the placebo group, with the same trend seen in the orlistat group. In women, LDL decreased with placebo and fasting glucose increased with orlistat.

The overall degree of weight loss in our male patients was modest as compared to studies in nonpsychiatric populations, in which it ranged from 5.4 kg to 10.8 kg (or 3.9%–10.2%) with orlistat compared to 2.7 kg to 7.3 kg (0.2%–7.5%) with placebo.[17] However, the following considerations should be taken into account: First, in previous studies, orlistat has been prescribed as an adjunct to nonpharmacologic treatments of patients having already achieved considerable weight reduction. In our own patients, no such adherence to nonmedical regimens was required. Second, in earlier studies, a concomitant hypocaloric diet continued during the trial, whereas our patients, although encouraged to limit their caloric intake, continued their usual diet. Third, our trial duration (16 weeks) was less than that of the majority of those trials (6 to 12 months or longer), and weight loss in men taking orlistat was still continuing at the endpoint. It is thus plausible that clinically more meaningful weight reduction may be achieved with prolonged treatment. These issues were our limitations, but they enabled exploration of direct effects of orlistat while minimizing the confounding effect of behavioral interventions.

Another limitation was the small sample size, especially regarding secondary analyses by subgroups (gender). Therefore, the study was possibly underpowered, leading to the possibility of type II error. Furthermore, the risk of spurious findings (i.e., type I error) may exist, since several statistical tests have been performed and some could thus have achieved significance by chance alone. This possibility might be especially true for the metabolic parameters in females. However, there is a consistent pattern in the results regarding the primary outcome.

In serious mental conditions, metabolic disadvantages for women have recently been reported. In the Clinical Antipsychotic Trials of Intervention Effectiveness, the waist circumference criterion for abdominal obesity was met by 72% of females (vs. 37% of males).[21] Furthermore, females with psychosis had a higher risk for weight gain in a Finnish cohort study.[22] Likewise, women in our study responded worse to active medication than did men. Given the gender-neutral mechanism of action of orlistat, the better response seen in men in our study was unlikely due to biological issues. Since orlistat has repeatedly shown efficacy in combination with behavioral interventions rather than alone, it is more likely in our study that men receiving orlistat had a better ability to follow dietary/exercise recommendations than their female counterparts. Richelsen et al.[23] arrived at a similar behavior explanation for a worse response in women taking placebo in a nonpsychiatric population in the only study with gender differences in response to orlistat we were able to locate. The gender issue in patients with serious mental conditions and overweight/obesity should be explored in further intervention studies, especially due to the small number of women in our trial.

Between the groups, the incidence of diarrhea, a common adverse effect of orlistat, did not differ. Nevertheless, all 4 patients who discontinued due to diarrhea were receiving orlistat. Education about the possible side effects of study medication or concomitant use of laxatives, common with clozapine (and to a lesser extent, olanzapine), might increase the incidence of diarrhea with placebo, but this could be true for the orlistat group, too. The overall incidence of diarrhea was, however, too small to draw statistical analysis and conclusions.

In conclusion, orlistat may be a safe treatment for obese/overweight patients treated with clozapine or olanzapine, but, without a hypocaloric diet, its effect is modest and may only be seen in men. Further studies should define the optimal length of treatment and feasibility of combination of orlistat with behavioral programs in this population.

Drug names: amantadine (Symmetrel and others), clozapine (FazaClo, Clozaril, and others), fluoxetine (Prozac and others), metformin (Riomet, Fortamet, and others), nizatidine (Axid and others), olanzapine (Zyprexa), orlistat (Xenical), sibutramine (Meridia), topiramate (Topamax).

REFERENCES

1. American Diabetes Association, American Psychiatric Association, American Association of Clinical Endocrinologists, North American Association for the Study of Obesity. Consensus development conference on antipsychotic drugs and obesity and diabetes. Diabetes Care 2004;27:596–601

2. Perkins DO. Predictors of noncompliance in patients with schizophrenia. J Clin Psychiatry 2002;63:1121–1128
3. Wing RR, Koeske R, Epstein LH, et al. Long-term effects of modest weight loss in type II diabetic patients. Arch Intern Med 1987;147: 1749–1753
4. Littrell KH, Hilligoss NM, Kirshner CD, et al. The effects of an educational intervention on antipsychotic-induced weight gain. J Nurs Scholarsh 2003;35:237–241
5. Menza M, Vreeland B, Minsky S, et al. Managing atypical antipsychotic–associated weight gain: 12-month data on a multimodal weight control program. J Clin Psychiatry 2004;65:471–477
6. Kane JM, Honigfeld G, Singer J, et al. Clozapine for the treatment-resistant schizophrenic. A double-blind comparison with chlorpromazine. Arch Gen Psychiatry 1988;45:789–796
7. Lieberman JA, Stroup TS, McEvoy JP, et al. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. N Engl J Med 2005; 353:1209–1223
8. Baptista T, Martinez J, Lacruz A, et al. Metformin for prevention of weight gain and insulin resistance with olanzapine: a double-blind placebo-controlled trial. Can J Psychiatry 2006;51:192–196
9. Klein DJ, Cottingham EM, Sorter M, et al. A randomized, double-blind, placebo-controlled trial of metformin treatment of weight gain associated with initiation of atypical antipsychotic therapy in children and adolescents. Am J Psychiatry 2006;163:2072–2079
10. Poyurovsky M, Isaacs I, Fuchs C, et al. Attenuation of olanzapine-induced weight gain with reboxetine in patients with schizophrenia: a double-blind, placebo-controlled study. Am J Psychiatry 2003;160:297–302
11. Henderson DC, Copeland PM, Daley TB, et al. A double-blind, placebo-controlled trial of sibutramine for olanzapine-associated weight gain. Am J Psychiatry 2005;162:954–962
12. Graham KA, Gu H, Lieberman JA, et al. Double-blind, placebo-controlled investigation of amantadine for weight loss in subjects who gained weight with olanzapine. Am J Psychiatry 2005;162:1744–1746
13. Poyurovsky M, Pashinian A, Gil-Ad I, et al. Olanzapine-induced weight gain in patients with first-episode schizophrenia: a double-blind, placebo-controlled study of fluoxetine addition. Am J Psychiatry 2002;159: 1058–1060
14. Cavazzoni P, Tanaka Y, Roychowdhury SM, et al. Nizatidine for prevention of weight gain with olanzapine: a double-blind placebo-controlled trial. Eur Neuropsychopharmacol 2003;13:81–85
15. Ko YH, Joe SH, Jung IK, et al. Topiramate as an adjuvant treatment with atypical antipsychotics in schizophrenic patients experiencing weight gain. Clin Neuropharmacol 2005;28:169–175
16. Henderson DC, Fan X, Copeland PM, et al. A double-blind, placebo-controlled trial of sibutramine for clozapine-associated weight gain. Acta Psychiatr Scand 2007;115:101–105
17. Padwal R, Li SK, Lau DC. Long-term pharmacotherapy for obesity and overweight. Cochrane Database Syst Rev 2004;3:CD004094
18. Hutton B, Fergusson D. Changes in body weight and serum lipid profile in obese patients treated with orlistat in addition to a hypocaloric diet: a systematic review of randomized clinical trials. Am J Clin Nutr 2004;80: 1461–1468
19. Pavlovic ZM. Orlistat in the treatment of clozapine-induced hyperglycemia and weight gain. Eur Psychiatry 2005;20:520
20. Kay SR, Fiszbein A, Opler LA. The Positive and Negative Syndrome Scale (PANSS) for Schizophrenia. Schizophr Bull 1987;13:261–276
21. McEvoy JP, Meyer JM, Goff DC, et al. Prevalence of the metabolic syndrome in patients with schizophrenia: baseline results from the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) schizophrenia trial and comparison with national estimates from NHANES III. Schizophr Res 2005;80:19–32
22. Hakko H, Komulainen MT, Koponen H, et al. Longitudinal Northern Finland 1966 Birth Cohort Study. Are females at special risk of obesity if they become psychotic? Schizophr Res 2006;84:15–19
23. Richelsen B, Tonstad S, Rössner S, et al. Effect of orlistat on weight regain and cardiovascular risk factors following a very-low-energy diet in abdominally obese patients: a 3-year randomized, placebo-controlled study. Diabetes Care 2007;30:27–32