Orlistat in Clozapine- or Olanzapine-Treated Patients With Overweight or Obesity: A 16-Week Open-Label Extension Phase and Both Phases of a Randomized Controlled Trial

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Objective: To explore long-term effects of orlistat in adult clozapine- or olanzapine-treated patients with *DSM-IV*–diagnosed schizophrenia and overweight or obesity who tolerate orlistat.

Method: Orlistat or placebo was added to clozapine or olanzapine in stable doses in a 16-week randomized controlled trial. Open-label orlistat was added to the antipsychotics during a 16-week extension phase for those completing the double-blind phase. No low-calorie diet or participation in behavioral programs was required. Body weight (primary outcome) and some metabolic parameters were measured prospectively. Analyses were performed for those completing both phases (ie, population differing from that reported earlier). The study was conducted from 2004 through 2005.

Results: During the open-label phase, the 44 patients experienced mean ± SD body weight loss of −1.29 ± 3.04 kg, $P = .007$. During both phases, men (but not women) showed a weight loss of −2.39 ± 5.45 kg, $P = .023$. Some subgroups showed desirable changes in several metabolic parameters. Prolonged (32 weeks) orlistat treatment yielded no additional benefits as compared to short (16 weeks) treatment.

Conclusions: In clozapine- or olanzapine-treated overweight or obese patients able to take orlistat on a long-term basis, the drug, with no concomitant hypocaloric diet or behavioral interventions, caused moderate weight loss only in men. However, some metabolic benefits may be achieved independently of weight changes. In patients who do not respond to orlistat within the first 16 weeks, continuation treatment may provide no additional benefits.

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Weight gain is a common undesirable side effect of many antipsychotics,[1] especially olanzapine and clozapine.[2,3] Excessive weight gain or obesity leads to important untoward clinical consequences—increased morbidity and mortality,[4] noncompliance with antipsychotic medication,[5] and decreased quality of life.[6] Overweight is often accompanied by metabolic disturbances, including hypercholesterolemia, hyperglycemia, and diabetes.

A number of behavioral[7] or pharmacologic weight control interventions have been studied,[8,9] but in antipsychotic-related weight gain or obesity, these interventions have yielded conflicting results.[10]

Orlistat, a lipase inhibitor that hinders absorption of fat from the intestinal lumen,[11] is the only existing weight control medication with no central effects. Orlistat is thus tempting as a medication for overweight or obesity in patients receiving antipsychotics, since they usually suffer from serious mental disease, and additional central nervous system–active medications may unsettle the pharmacodynamic and clinical balance achieved.

In our previously reported 16-week randomized controlled trial in clozapine- or olanzapine-treated patients,[12] only males treated with orlistat showed weight loss (−2.36 kg vs weight gain of 0.62 kg in males taking placebo, $P = .011$), while no statistically significant differences appeared in females or in the whole group. There were 5 responders (those with > 5% weight loss; 16.1%) in the orlistat group versus 2 patients (6.3%) in the placebo group.

In overweight or obesity, longstanding weight loss is crucial for enduring health effects. Indeed, in the nonpsychiatric population, long-term orlistat treatment produced favorable results regarding weight loss and prevention of diabetes.[13] In patients with severe mental disorders, however, data on long-term treatments are lacking.

We proposed that, in our study, 16 weeks might be too short of a period and more benefits could be achieved with a prolonged treatment. To test this hypothesis, we prescribed orlistat in open-label fashion to those completing the double-blind phase for an additional 16 weeks. Here, we report the results of this open-label phase, as well as both (double-blind and open-label) phases, resulting in a total length of 32 weeks. Only those completing the extension phase were included in the analysis, since the aim of this continuation study was to explore whether orlistat deserves a trial longer than 16 weeks among patients who are able to follow simple dietary instructions and who tolerate orlistat medication.

METHOD

The trial was carried out in Kellokoski and Vanha Vaasa hospitals in Finland. Seventy-one adult patients with schizophrenia (*Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition [*DSM-IV*] criteria) were enrolled, and 63 were randomly assigned to a double-blind treatment with orlistat 360 mg/d or placebo added to stable clozapine or olanzapine medication. Neither compliance with weight control behavioral programs nor any hypocaloric diet was required, but patients were advised to limit their dietary fat and overall calorie intake. The analysis was performed on a modified intent-to-treat (MITT) analysis basis with the last observations carried forward (LOCF). In detail, the methods of the initial double-blind phase appear earlier.[12]

All those completing the double-blind phase who volunteered to participate in the open-label extension phase were given open-label orlistat 360 mg/d for 16 additional weeks. The patients treated initially with placebo (ie, those who received orlistat treatment during the 16 weeks of the extension phase only) formed a group referred to as the short-term group, while their counterparts receiving orlistat treatment during both phases (altogether 32 weeks) formed the long-term group. Week 16 (endpoint) of this double-blind study was also the baseline for the extension phase. Body weight (the primary outcome) was measured at weeks 17, 20, 24, 28, and 32, and fasting glucose, total cholesterol, high-density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol, and triglyceride levels (secondary outcomes) were performed with standard means at weeks 20, 24, 28, and 32. The secondary efficacy variables also included the number of patients achieving a response (≥ 5% body weight loss). The efficacy analyses were performed for completers of both double-blind and open-label phases. Body weight changes (LOCF; week 32 minus week 16) were also calculated for the MITT population of the open-label phase (patients with at least week 20 observations) as a secondary analysis. The safety population for the adverse events analysis comprised all patients enrolled in the open-label phase.

The study was conducted from 2004 through 2005 and approved by the Ethics Committee of the Hospital District of Helsinki and Uusimaa; the Ethics Committee of the Vaasa Hospital District; the National Agency for Medicines, Helsinki, Finland; and institutional authorities. All study procedures followed the Good Clinical Practice, the Helsinki Declaration, and national and international rules and regulations. All patients received complete information about the study and gave their informed consent. The patients were informed that they could discontinue at any time if they wished to, with no negative consequences for their usual treatment.

Statistical significance of weight change over time was examined 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.

The software SPSS for Windows, version 13.0 (SPSS Inc, Chicago, Illinois) was used.

RESULTS

A total of 55 patients completed the double-blind phase. Three patients in the short-term group and 1 patient in the long-term group discontinued prematurely between weeks 17 and 20 due to adverse events (see below). Three patients (1 patient in the short-term and 2 patients in the long-term group) discontinued between weeks 20 and 24 due to withdrawal of consent. Two patients, both in the long-term group, discontinued at week 20 due to lack of efficacy (1 patient) or noncompliance (1 patient). Finally, 1 patient in the long-term group discontinued at week 17 due to uncooperativeness. In addition, 1 patient in the short-term group was excluded from data analysis due to a protocol violation. Eventually, 44 patients (21 patients in the short-term and 23 patients in the long-term group) completed the study protocol and were eligible for the data analysis. Thirty-three men (18 in the long-term group and 15 in the short-term group) and 18 women (10 and 8, correspondingly) formed the MITT population for the open-label phase.

At baseline 1 (week 0), triglycerides were statistically significantly higher in the short-term group (2.99 mmol/L vs 2.03 mmol/L in the long-term group, $t = 2.44$, $P = .019$). Other demographic or clinical data (percent taking clozapine, age, sex, duration of illness, clozapine or olanzapine doses, body weight, total cholesterol, LDL, HDL, fasting glucose) did not differ between the groups.

During both phases (32 weeks), mean doses of clozapine increased from 481 mg/d to 488 mg/d. The doses increased in 1 patient in the short-term group (by 100 mg/d) and 7 patients in the long-term group (6 by 50 mg/d and 1 by 200 mg/d).

Open-Label Extension Phase

During the open-label extension phase (weeks 16 to 32), an absolute mean body weight drop of > 1 kg occurred in all subgroups except among women in the long-term group. This change reached statistical significance for the whole population and for the short-term group but not for the long-term group (Table 1). By gender, this change occurred in men (both in the short-term and long-term groups) but not in women (though with a similar trend in women in the short-term group) (Figure 1). Of secondary measures (total cholesterol, LDL, HDL, triglycerides, fasting glucose, C-peptide), only HDL decreased statistically significantly in the short-term group (mean ± SD = −0.10 ± 0.14 mmol/L from initial 0.88 ± 0.28 mmol/L, $t = 3.02$, $P = .008$), and triglycerides (−0.54 ± 0.44 mmol/L from 2.33 ± 1.12 mmol/L, $t = -2.97$, $P = .031$) and fasting glucose (−0.43 mmol/L from 5.88 ± 0.41 mmol/L, $t = -3.14$, $P = .026$) decreased statistically significantly in women in the long-term group. The mean ± SD body weight change in the MITT population was −1.14 ± 2.96 kg ($t = -2.76$, $P = .008$). For the long-term group, the change was −0.85 ± 3.37 kg ($t = -1.28$, $P = .21$), and for the

Table 1. Changes in Body Weight (kg) and Metabolic Parameters in Clozapine-Treated (n = 32) or Olanzapine-Treated (n = 12) Patients With Overweight or Obesity Who Completed 16-Week, Double-Blind Treatment With Orlistat or Placebo and 16-Week, Open-Label Treatment With Orlistat[a]

	Long-Term Group (n = 23)[b]				Short-Term Group (n = 21)[c]				Total (n = 44)			
	Mean (± SD)	Change (± SD)	*t*	*P*	Mean (± SD)	Change (± SD)	*t*	*P*	Mean (± SD)	Change (± SD)	*t*	*P*
Open-label orlistat extension phase	Week 16	Weeks 16–32			Week 16	Weeks 16–32			Week 16	Weeks 16–32		
Weight, total, kg	102.49 (13.28)	−0.93 (3.44)	−1.29	.210	100.25 (13.08)	**−1.69 (2.54)**	−3.04	**.007**	101.42 (13.08)	**−1.29 (3.04)**	−2.82	**.007**
Weight, men, kg	103.71 (14.30)	−1.38 (3.04)	−1.87	.080	101.88 (8.93)	−1.43 (2.47)	−2.09	.059	102.91 (12.11)	**−1.40 (2.76)**	−2.78	**.010**
Weight, women, kg	99.03 (10.12)	0.35 (4.46)	0.19	.855	97.61 (18.41)	−2.10 (2.78)	−2.14	.070	98.22 (14.92)	−1.05 (3.66)	−1.07	.302
Total cholesterol, mmol/L	4.39 (0.69)	−0.11 (0.49)	−1.07	.296	4.71 (1.06)	0.09 (0.76)	−0.53	.605	4.54 (0.88)	−0.10 (0.62)	−1.06	.296
LDL cholesterol, mmol/L	2.41 (0.57)	0.03 (0.57)	0.27	.793	2.75 (0.89)	−0.19 (0.62)	−1.32	.204	2.57 (0.74)	−0.07 (0.60)	−0.75	.459
Triglycerides, mmol/L	2.37 (0.90)	−0.30 (0.93)	−1.49	.151	2.71 (1.28)	0.23 (0.84)	1.16	.261	2.53 (1.08)	0.06 (0.92)	−0.41	.685
Fasting glucose, mmol/L	5.90 (0.59)	−0.06 (0.54)	−0.55	.586	6.38 (1.18)	−0.34 (1.06)	−1.35	.195	6.11 (0.92)	−0.19 (0.82)	−1.45	.156
Double-blind and open-label phases	Week 0	Weeks 0–32			Week 0	Weeks 0–32			Week 0	Weeks 0–32		
Weight, total, kg	103.69 (13.67)	−2.13 (7.41)	−1.38	.182	100.07 (13.28)	−1.50 (5.43)	−1.27	.219	101.96 (13.45)	−1.83 (6.47)	−1.88	.067
Weight, men, kg	106.20 (12.98)	**−3.87 (5.17)**	−3.09	**.007**	100.90 (8.53)	−0.45 (5.38)	−0.30	.766	103.90 (11.41)	**−2.39 (5.45)**	−2.40	**.023**
Weight, women, kg	96.58 (14.17)	2.80 (10.80)	0.64	.553	98.73 (19.38)	−3.21 (5.41)	−1.68	.137	97.81 (16.75)	−0.64 (8.37)	−0.28	.781
Total cholesterol, mmol/L	4.53 (0.68)	−0.25 (0.74)	−1.60	.125	5.09 (1.18)	**−0.47 (0.82)**	−2.54	**.021**	4.78 (0.98)	**−0.35 (0.77)**	−2.94	**.005**
LDL cholesterol, mmol/L	2.77 (0.57)	**0.03 (0.71)**	−2.14	**.045**	3.07 (0.92)	**−0.51 (0.86)**	−2.53	**.022**	2.91 (0.76)	**−0.41 (0.78)**	−3.33	**.002**
Triglycerides, mmol/L	1.90 (0.81)	0.18 (0.77)	1.08	.294	2.94 (1.33)	−0.01 (0.84)	0.06	.954	2.37 (1.30)	0.09 (0.80)	−0.73	.471
Fasting glucose, mmol/L	5.97 (0.66)	−0.14 (0.38)	−1.68	.107	6.07 (0.85)	0.03 (0.59)	0.20	.844	6.01 (0.74)	0.09 (0.48)	−1.15	.257

[a]Bold denotes significance. [b]Long-term group = patients who received orlistat treatment during both double-blind and open-label phases (altogether, 32 weeks; 6 women and 17 men). [c]Short-term group = patients who received placebo treatment during double-blind phase (ie, only 16-week, open-label orlistat treatment; 8 women and 13 men).
Abbreviation: LDL = low-density lipoprotein.

Figure 1. Body Weight in Clozapine- or Olanzapine-Treated Patients With Overweight or Obesity During Double-Blind Treatment With Placebo or Orlistat (weeks 0–16) and Open-Label Orlistat Treatment (weeks 16–32)

short-term group, the change was −1.45 ± 2.49 kg ($t = -2.91$, $P = .008$).

Both Phases

Body weight. During both phases (weeks 0 to 32), body weight in all 44 patients showed a downward trend that did not, however, reach statistical significance. Men in the whole completer population and in the long-term group (but not in the short-term group) demonstrated statistically significant body weight loss, while no women in any population or subpopulation did so (see Table 1 and Figure 1).

Metabolic variables. Total cholesterol and LDL decreased in the total population and in the short-term group (see

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Table 1). In the latter, HDL also decreased (−0.10 ± 0.14 mmol/L from 0.88 ± 0.28 mmol/L, $t = -3.02$, $P = .008$). In men, a decrease occurred in total cholesterol and LDL (−0.35 ± 0.80 mmol/L from 4.81 ± 1.06 mmol/L, $t = -2.30$, $P = .030$, and −0.44 ± 0.84 mmol/L from 2.95 mmol/L, $t = -2.72$, $P = .012$), but this difference was not statistically significant either in the short-term or in the long-term group. In women, total cholesterol diminished −0.46 ± 0.69 mmol/L from 4.81 ± 0.77 mmol/L ($t = -2.20$, $P = .043$), with a statistically significant change also observed in the short-term (−0.66 ± 0.48 mmol/L from 5.01 ± 1.01 mmol/L, $t = -3.38$, $P = .020$) but not in the long-term group. High-density lipoprotein cholesterol decreased by −0.17 ± 0.13 mmol/L from 1.11 ± 0.36 mmol/L, $t = -3.22$, $P = .024$, in women in the short-term group. No statistically significant changes were observed in other metabolic variables in analyses of other populations or subpopulations.

In the comparison of changes from week 0 to week 32 between the long-term and short-term groups, no statistically significant differences appeared in body weight or any other variables either in the total population ($t = 0.32$, $P = .753$) or in the by-gender subgroups. Nor did the number of responders differ (8, 34.8% in the long-term group, vs 6, 28.6% in the short-term group, $t = 0.19$, $P = .66$).

Adverse Events

Among the safety population, 23 adverse events were registered in the short-term group and 25 adverse events in the long-term group. Diarrhea occurred in 4 patients, all in the short-term group (from these, 3 emerged in 1 week after the shift from placebo to orlistat). All of these 4 patients discontinued. None of the patients discontinued due to other adverse events in either group. Other adverse events were mild and rare.

DISCUSSION

This study presents data from a total of 44 patients who completed both phases in a 32-week extension of our earlier study of overweight or obese patients treated with clozapine or olanzapine at stable doses.

During the open-label phase (final 16 weeks), mean ± SD body weight change was −1.29 ± 3.04 kg ($P = .007$), with essentially similar results for the MITT group. In the secondary analyses by subgroups, the change reached statistical significance only in men and in the short-term group. During both phases (32 weeks), men (but not women) demonstrated a statistically significant weight loss (change −2.29 kg, $P = .023$). Women in the long-term group showed, however, a desirable decrease in triglycerides and fasting glucose. After both phases, the whole completer population showed only a trend toward a weight loss. Longer treatment revealed no benefits in either population or subpopulation.

According to a recent Cochrane meta-analysis of 16 orlistat trials—ones performed in nonpsychiatric populations totaling 10,631—orlistat treatment resulted in a mean weight loss of 2.9 kg (95% CI, 2.5–3.2).[8] Moreover, in another systematic review of 17 orlistat randomized controlled trials in nonpsychiatric populations totaling 10,041, relative risks of weight loss of 5% and 10% (often considered as clinically significant) were, respectively, 1.74 (95% CI, 1.57–1.91) and 1.96 (95% CI, 1.74–2.21).[14] In the earlier studies, orlistat has most often been a treatment for patients compliant with a low-calorie diet or those participating in behavioral programs, or both. Our patients, although educated about the mechanism of action of orlistat and about healthy habits, were not required to strictly follow any dietary limitations or structured behavioral programs. This could explain our less-impressive results. Moreover, our population included patients with body mass index ≥ 28 (vs body mass index ≥ 30 in the majority of the previous trials), which could have diminished the possible range of weight loss and thus weakened the statistical power. In addition, our patients continued to receive their clozapine or olanzapine treatment, which, as medications affecting body weight, might counteract the effects of orlistat on body weight.

Nevertheless, in our trial, men experienced weight loss comparable to that of the nonpsychiatric population. In men, orlistat showed the expected effects; those who initially received placebo treatment began to lose their weight only after their shift to orlistat, and those who initially received orlistat treatment showed a trend toward a further weight loss during the continuation orlistat treatment. Women, however, showed less consistent results, since those who initially received placebo treatment seemed to experience a nonsignificant weight loss, and those who initially received orlistat treatment experienced rather a weight gain in both phases. We have reported similar gender differences earlier, on the basis of our double-blind phase data.[12] The extension phase thus confirms the same finding—again, changes in body weight in women appeared not to have been related to orlistat treatment and could thus more likely be explained by dietary and behavioral factors. Women responded worse to and had 2.4 times lower probability of a successful completing of a dietary and exercise program than men did also in some other,[15] though not all,[16] studies in nonpsychiatric patients. In our study, women in the short-term and long-term groups might have expressed differing attitudes to the dietary recommendations. However, the small sizes of the subgroups make it difficult to draw firm conclusions regarding the secondary analysis by gender.

Orlistat seemed, in a number of our groups or subgroups, to modestly diminish lipid levels. The clinical significance of our reduction in total cholesterol of 0.35 mmol/L is unclear, but a decrease of 0.5 mmol/L can result in a 10.4% decrease of coronary heart disease events.[17] Women in our study demonstrated some statistically significant changes in lipid levels, with a drop of 0.46 mmol/L for total cholesterol. Interestingly enough, some desirable metabolic changes (ie, decrease in triglycerides and fasting glucose) occurred also in women in the long-term group, despite the absence of any effect of orlistat on body weight.

Doses of clozapine had to be increased in 8 patients (25%)—7 patients in the long-term group and 1 patient in

the short-term group. It would be intriguing to speculate that orlistat may counteract some of the effects of the antipsychotic drugs. Indeed, the outcome of clozapine and olanzapine medication tends to positively correlate with weight gain.[18] This finding might have rather a pharmacodynamic than pharmacokinetic explanation, since orlistat does not seem to interfere with the plasma levels of clozapine.[19] Here, such speculations should be made cautiously, however, since the dose changes and number of cases were small.

The main limitation of this study was its small sample size and thereby probably its insufficient statistical power. Nevertheless, our primary outcome (body weight change) pointed to a desirable effect of orlistat in an extension phase, with a similar trend for both phases. The open-label design of the extension phase was another limitation. This design aimed, however, to improve patient retention and thus enlarge the number completing the trial and thus being available for analysis. The nature of our data did not allow for separating overweight or obesity due to clozapine- or olanzapine-induced weight gain and those due to other reasons. To address this issue, future studies should differentiate between overweight or obesity preceding antipsychotic treatment and the overweight or obesity developed during antipsychotic treatment.

Absence of a diet and a behavioral program leads to possibilities for speculations. According to recent data, even patients with serious psychiatric conditions may be capable of successful participation in behavioral weight-control programs.[10,20] Therefore, the main principles of orlistat therapy for nonpsychiatric patients (ie, concomitant diet and exercise requirements) may also apply to the psychiatric population—a hypothesis to be tested in future research.

CONCLUSIONS

In clozapine- or olanzapine-treated psychiatric patients with overweight or obesity who are able to take orlistat for 32 weeks, this medication, if not accompanied by behavioral modification, may yield moderate weight reduction only in men. Other studies should comprise larger samples of patients treated with antipsychotics other than clozapine and olanzapine and should explore relations between orlistat, weight, and metabolic parameters on the one hand and changes in psychopathology on the other hand.

Drug names: clozapine (FazaClo, Clozaril, and others), olanzapine (Zyprexa), orlistat (Xenical).

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