Olanzapine Increases Weight and Serum Triglyceride Levels

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Background: Previous studies have suggested that clozapine is associated with increases in both weight and serum triglyceride (but not cholesterol) levels. Because of the pharmacologic similarities between clozapine and olanzapine, we decided to evaluate if olanzapine use was associated with an increase in triglycerides.

Method: Twenty-five inpatients (21 men, 4 women) were treated with olanzapine, and their outcomes were tracked prospectively in a medication utilization evaluation study.

Results: After 12 weeks on a mean ± SD dose of 13.8 ± 4.4 mg/day, weight increased a mean of 12 lb (5.4 kg; from 190 ± 37 lb [85.5 ± 16.7 kg] to 202 ± 30 lb [90.9 ± 13.5 kg]), while fasting triglycerides increased a mean of 60 mg/dL (from 162 ± 121 mg/dL to 222 ± 135 mg/dL). Both increases were significant at $p < .05$. Fasting total cholesterol did not increase. The triglyceride increase was even larger when we excluded 8 patients who received various interventions to lower lipid levels (e.g., pravastatin, low-fat diet) during the olanzapine trial. There was a strong association between weight change and triglyceride change ($p < .02$); after controlling for weight, analysis of covariance showed no independent increase in triglycerides.

Conclusion: These results suggest olanzapine has significant effects on weight and serum triglyceride levels. Clinical implications are discussed.

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The work of Padideh Ghaeli, Pharm.D., inspired the concept of this project.

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Weight gain is associated with most antipsychotic agents to varying degrees,[1–3] but the most weight gain appears to occur with clozapine and olanzapine.[3–5] Clozapine also has been reported to increase serum triglyceride (but not cholesterol) levels,[6,7] which may add another risk factor for cardiovascular disease.[8] Given the pharmacologic similarity of olanzapine to clozapine, we thought that olanzapine might also increase serum triglyceride levels.

METHOD

Data are reported on 25 white patients who completed 12 weeks of treatment with olanzapine while they were inpatients at Taunton State Hospital (Taunton, Mass.). Twelve other patients were started on olanzapine treatment during the same period, but were excluded from the study. Reasons for exclusion were early discharge (N = 4), discontinuation due to intolerance (N = 4), and inability to cooperate with data collection (N = 4). Mean ± SD age of study patients was 38 ± 12 years, and clinicians' diagnoses (DSM-IV) included schizophrenia (N = 13), schizoaffective disorder (N = 4), and other psychoses (N = 8). There were 21 males and 4 females, and the mean dose of olanzapine at 12 weeks was 13.8 ± 4.4 mg/day. The following were measured at baseline and 12 weeks: weight, total cholesterol, and triglycerides. All patients received instructions to fast the night before their blood tests, and a phlebotomist took the samples before patients were brought to breakfast the next morning.

We attempted to collect data after 6 weeks of olanzapine treatment, but we were successful in only 17 of the 25 patients, so these data are not reported. All subjects were inpatients during the study because most were treatment-resistant, severely ill, or partially compensated individuals. Many of these patients had a history of dangerous behavior in the community. Descriptive data on the patients are shown in Table 1.

Since this was an evaluation of naturalistic treatment, medications other than olanzapine were used in treating these patients. The use of other drugs that could affect lipid levels was recorded. Four patients were taking divalproex sodium at some point, 7 patients were taking lithium, and 1 was taking both.

Table 1. Patient Characteristics

Gender	Age, y	Diagnosis	Weight Change, lb (kg)	Triglyceride Change, mg/dL	Cholesterol Change, mg/dL	Medications	Intervention
M	33	Schizophrenia	33 (14.8)	150	17		
F	38	Schizoaffective disorder	27 (12.2)	90	10	Valproate	
M	32	Bipolar disorder	3 (1.4)	175	8	Lithium	
M	45	Bipolar disorder	–3 (–1.4)	–104	–29	Lithium	
F	34	Schizophrenia	15 (6.8)	45	–30		
M	26	Schizophrenia	4 (1.8)	–57	–51	Lithium, valproate	Simvastatin at 8 weeks
M	43	Schizophrenia	3 (1.4)	–1	53	Lithium	
M	64	Schizophrenia	0 (0)	–8	–8		
M	33	Schizophrenia	–7 (–3.2)	3	3	Lithium	
M	27	Schizophrenia	28 (12.6)	236	48	Lithium	
M	29	Schizoaffective disorder	26 (11.7)	42	–85	Valproate	
F	26	Schizophrenia	47 (21.2)	157	23		
M	31	Schizoaffective disorder	8 (3.6)	210	68		
M	48	Pedophilia	1 (0.4)	46	–9	Lithium	Gemfibrozil (before treatment)
M	36	Bipolar disorder	4 (1.8)	–125	–24	Lithium	Pravastatin started at 7 weeks
M	37	Schizophrenia	13 (5.8)	–54	2		Low fat at 6 weeks
M	69	Bipolar disorder	–23 (–10.4)	–88	–61		Low fat before treatment
M	41	Schizophrenia	5 (2.2)	11	42		
M	19	Schizophrenia	24 (10.8)	213	61		
M	44	Schizophrenia	14 (6.3)	4	11	Valproate	
M	60	Bipolar disorder	–2 (–0.9)	268	4		Diabetic; pravastatin at 9 weeks
M	23	Impulse-control disorder	4 (1.8)	11	–30		Low fat; pravastatin around last laboratory tests
F	32	Schizoaffective disorder	20 (9.0)	–31	–17		
M	39	Schizophrenia	30 (13.5)	301	61	Valproate	Pravastatin from start of treatment
M	42	Schizophrenia	25 (11.2)	10	12		

Analysis of variance with repeated measures was used to evaluate the changes in weight and lipid levels, and analysis of covariance with repeated measures was performed to see if the lipid changes were significant after controlling for the effects of weight gain. The association between continuous variables was tested using a Pearson correlation with a corresponding t test.

RESULTS

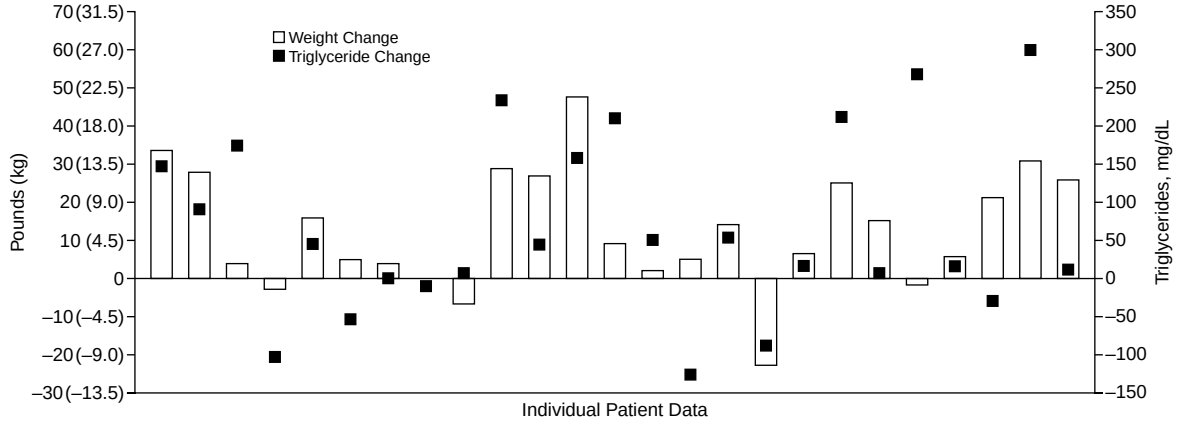
The use of olanzapine for 12 weeks was associated with significant increases in mean weight and serum triglyceride levels, while serum cholesterol levels were not significantly altered. During the olanzapine treatment period, weight increased from a mean ± SD of 190 ± 37 lb (85.5 ± 16.7 kg) to 202 ± 30 lb (90.9 ± 13.5 kg), an increase of 12 lb (5.4 kg) ($p < .02$). Triglycerides increased from a mean of 162 ± 121 mg/dL to 222 ± 135 mg/dL, an increase of 60 mg/dL ($p < .04$). Cholesterol levels increased only 3 mg/dL, from a mean of 186 ± 36 mg/dL to 189 ± 40 mg/dL during the same period ($p = .76$, not significant).

Analysis of covariance with repeated measures was performed with the weight change over the period as covariant and serum triglyceride levels at baseline and 12 weeks as the dependent variables. The triglyceride change was highly associated with the weight change ($r = 0.484$, $F = 6.985$, $p < .02$); the change in serum triglyceride levels independent of weight was not significant. The association of cholesterol with weight change was not significant ($r = 0.12$, $p = .09$). The association between the serum cholesterol levels less the triglyceride component and weight was even weaker ($r = 0.06$, not significant). Thus, much of the cholesterol change probably was due to change in the triglyceride component of the total cholesterol. The use of lithium in 8 of the 25 patients was associated with higher triglycerides throughout the study ($F = 6.329$, $p < .02$), but was not associated with differential increases in weight.

The 6 (of 25) patients who received lipid-lowering agents during the study had no increase in serum triglyceride levels (121 mg/dL at baseline and 125 mg/dL at 12 weeks). When these patients were removed from the analysis, the remaining 19 patients, as expected, showed a greater numerical increase in serum triglyceride levels (278 ± 121 mg/dL at baseline rising to 352 ± 125 mg/dL after 12 weeks; $F = 5.061$, $p < .05$).

Most of the increase in triglycerides that occurred in the group as a whole came from a subgroup of 8 patients who had increases between 150 mg/dL and 300 mg/dL. Three patients had decreases of about 100 mg/dL and the rest had smaller changes up or down. Figure 1 displays the association between weight change and serum triglyceride level in the entire sample. There was no difference in the frequency of concomitant medication in the high triglyceride increase subgroup compared with the remaining patients. While 3 (38%) of 8 with high triglycerides were taking concomitant medications, 9 (53%) of 17

Figure 1. Change in Serum Triglyceride Level and Weight After 12 Weeks of Olanzapine Treatment



without major changes in triglycerides were also taking other medications ($\chi^2 = 0.52$, df=1, not significant).

DISCUSSION

The mean weight gain after 12 weeks of olanzapine treatment (at a final mean dose of 13.8 mg) was about 12 pounds (5.4 kg). This is comparable to the 8-pound (3.5 kg) gain seen in the 6-week North American acute phase olanzapine study[4] and suggests that the weight gain of our patients was not unusual.

The mechanism whereby antipsychotics cause weight gain is unknown. One theory attributes this phenomenon to blockade of the histamine-1 (H_1) receptor, which is thought to be involved in the regulation of appetite.[9] Clozapine and olanzapine are among the most potent antipsychotics at blocking H_1 receptors, as contrasted with molindone, which is the least potent.[9] These differences in receptor activity generally correspond to the findings of a recent meta-analysis of differential weight gain occurring during 78 clinical trials of antipsychotics.[3] This review found that clozapine and olanzapine caused the most weight gain of all antipsychotics. At 10 weeks (estimated by regression analysis), mean weight gain on clozapine treatment was 4.5 kg, and on olanzapine treatment, it was 4.2 kg. This was significantly higher than risperidone (2.1 kg) and ziprasidone (0.9 kg). Among the conventional antipsychotics, thioridazine produced a mean weight gain of 3.2 kg, compared with haloperidol at 1.1 kg and molindone with a loss of 0.4 kg.

There are numerous other theories to explain antipsychotic-induced weight gain. Other central neurotransmitter mechanisms that may be involved in weight gain include serotonin, dopamine, and norepinephrine receptor antagonism.[10,11] Peripheral contributions could come from cortisol elevation,[12] alterations in fat cell metabolic processes,[11] gastric misperception of satiety,[13] and better appetite associated with improvement in psychosis.[14] Patients who are underweight prior to treatment do tend to have the largest weight gains, but final weights often go above "normal" levels.[15]

The more surprising finding in this study was the triglyceride elevation of 60 mg/dL, which represented a 37% increase over the baseline mean of 162 mg/dL. A literature review found no previous reports of triglyceride elevations with olanzapine. Inquiry of the manufacturer revealed that triglycerides were not routinely monitored in the premarketing studies (however, cholesterol was monitored, and there was a clinically insignificant increase in those levels) (data on file, Eli Lilly and Company, Indianapolis, Ind., 1999). Thus, little information is available on whether our triglyceride data for olanzapine are unusual. The package insert for olanzapine lists hyperlipidemia as a "rare" side effect (i.e., occurring in fewer than 1/1000 patients).[16] The package insert for clozapine[17] also fails to mention increased triglyceride levels. By contrast, the quetiapine package insert[18] describes cholesterol and triglyceride elevations under "precautions," and reports that pooled 3- to 6-week data showed an 11% increase in cholesterol from baseline and a 17% increase in triglycerides. There were slight decreases of both lipids in placebo-treated patients. Future trials of olanzapine and clozapine should include full lipid profiles as part of their safety protocols.

There may be differences in the relative propensity of the different antipsychotics to elevate triglycerides; this is suggested by a report of 4 patients with elevated triglycerides on clozapine treatment who were switched to risperidone.[19] All had a rapid drop in triglyceride levels. Two of the patients had to be restarted with clozapine owing to clinical deterioration or intolerance of risperidone, and the triglyceride levels increased to previous levels. The clinical outcomes of the other 2 patients were not reported.

Regarding conventional neuroleptics, we found 1 report[20] of 8 new-onset patients with schizophrenia treated with phenothiazines (chlorpromazine, levomepromazine, perphenazine) in which triglycerides were measured. No differences from baseline were found after 10 weeks of treatment.[20]

The potential consequences of hypertriglyceridemia are significant. It is now well established that it is a significant risk factor for exacerbation of coronary artery disease.[8] Also, triglyceride elevations seem to precipitate or exacerbate diabetes.[8] Case reports of insulin resistance and the development of new-onset diabetes during treatment with olanzapine have recently appeared.[21] Unfortunately, triglyceride levels were not reported, which would have been of interest as an opportunity to demonstrate the significance of our findings. Other antipsychotics have been associated with impaired glucose tolerance, but clozapine seems more frequently associated with this effect than are conventional neuroleptics.[22,23] It is possible that this is related in part to clozapine's proposed effect on triglycerides.[6]

Interestingly, antipsychotic effects of these drugs also may be mediated in part through an effect on triglycerides. There is some evidence that elevated triglycerides increase brain cell membrane fluidity, resulting in increased presynaptic serotonin reuptake and decreased postsynaptic serotonin function.[24] This could augment the decrease in postsynaptic serotonin function that results from the serotonin-2 receptor blockade associated with many of the atypical antipsychotics.

In conclusion, we have found large triglyceride level elevations along with weight gain in a substantial proportion of patients taking olanzapine. Our data suggest that the triglyceride elevations and weight gain associated with olanzapine treatment occur together, compounding the health risks to the patient. Caution is required in interpreting these results due to the uncontrolled, naturalistic nature of this medication utilization evaluation study. Controlled studies should be conducted with larger patient samples. More frequent lipid measurements could determine the time course of any lipid elevations and whether early elevations could predict later lipid and weight outcomes. Also, it would be useful to obtain data on all cholesterol fractions: in one study of phenothiazine treatment, high density lipoprotein levels declined.[20]

At this point, it appears appropriate to suggest that clinicians monitor these variables more routinely, especially if other cardiovascular risk factors are present (smoking, hypertension, diabetes, obesity). For patients who develop large triglyceride elevations, it would also seem advisable to consider medical treatment options (e.g., use of lipid-lowering agents). Switching to a different antipsychotic that does not elevate triglycerides may be considered. However, as in the 2 clozapine-treated patients switched to risperidone,[19] this may result in loss of benefits in some patients.

Drug names: chlorpromazine (Thorazine and others), clozapine (Clozaril and others), divalproex sodium (Depakote), gemfibrozil (Lopid and others), haloperidol (Haldol and others), molindone (Moban), olanzapine (Zyprexa), perphenazine (Trilafon and others), pravastatin (Pravachol), quetiapine (Seroquel), risperidone (Risperdal), simvastatin (Zocor), thioridazine (Mellaril and others).

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