Serum Leptin and Triglyceride Levels in Patients on Treatment With Atypical Antipsychotics

Murad Atmaca, M.D.; Murat Kuloglu, M.D.; Ertan Tezcan, M.D.; and Bilal Ustundag, M.D.

Received June 5, 2002; accepted Sept. 11, 2002. *From the Departments of Psychiatry (Drs. Atmaca, Kuloglu, and Tezcan) and Biochemistry (Dr. Ustundag), School of Medicine, Firat University, Elazig, Turkey.*

The authors report no financial affiliation or other relationship relevant to the subject matter of this article.

Corresponding author and reprints: Murad Atmaca, M.D., Firat (Euphrates) Universitesi, Firat Tip Merkezi, Psikiyatri Anabilim Dali, 23119 Elazig, Turkey (e-mail: matmaca_p@yahoo.com).

Background: Weight gain is a common adverse effect associated with the use of most antipsychotic drugs. Leptin has been reported to be associated with antipsychotic-induced weight gain. Previous studies have demonstrated a relationship between the atypical antipsychotics clozapine and olanzapine and serum leptin levels. We planned to comparatively investigate the effects of the atypical antipsychotics quetiapine, olanzapine, risperidone, and clozapine on leptin and triglyceride levels and weight gain.

Method: The study population comprised 56 patients with DSM-IV schizophrenia, who were divided into 4 treatment groups: quetiapine (N = 14), olanzapine (N = 14), risperidone (N = 14), or clozapine (N = 14) monotherapy, and a control group of 11 patients receiving no psychopharmacologic treatment. The patients were evaluated at baseline and at the sixth week according to the Positive and Negative Syndrome Scale (PANSS), body mass index (BMI), weight, and fasting serum leptin and triglyceride levels. Data were gathered in 2001 and 2002.

Results: Olanzapine and clozapine caused a marked increase in weight and serum triglyceride and leptin levels, though increases in these variables were modest in the patients receiving quetiapine and minimal in those receiving risperidone. There were positive correlations between serum leptin levels and BMI and triglyceride levels. Clinical efficacy, as indicated by decrease in total PANSS scores, was associated with leptin levels in all atypical antipsychotic groups.

Conclusion: Our results suggest that leptin may be associated with olanzapine- and clozapine-induced weight gain and that quetiapine appears to have modest influence and risperidone appears to have minimal influence on leptin and triglyceride levels and weight gain compared with olanzapine and clozapine.

(J Clin Psychiatry 2003;64:598–604)

Weight gain is a common adverse effect associated with both typical and atypical antipsychotics.[1,2] In schizophrenic patients on treatment with these drugs, many factors, such as inactivity, social isolation, and unemployment, may contribute to weight gain. On the other hand, changes in reproductive hormones have contributed to weight gain in patients on chronic antipsychotic treatment.[3]

Leptin is an adipocyte hormone regulating food intake and energy balance and providing the hypothalamus with information on the amount of body fat.[4] It is released from white adipose tissue and other tissues, including brown adipose tissue, the human placenta, and breast tissue.[5] A growing number of studies have focused on leptin levels in the various psychiatric disorders recently.[6–10] Plasma levels of leptin are considerably correlated with body mass index (BMI) and body fat percentage. It has been reported that leptin affects the intracellular lipid concentration via a decrease in the synthesis of fatty acid and triglycerides and an increase in lipid oxidation.[11] Leptin administration has been shown to reduce food intake and weight, suggesting its role in weight regulation.[12,13] Obesity has been thought to be associated with leptin resistance in hypothalamus.[14]

The 5-HT_{2C} receptor–blocking effect of antipsychotics has been regarded as a possible cause of increase in food intake and related weight gain. Various psychotropic agents (e.g., tricyclic antidepressants, novel antipsychotics) antagonize the 5-HT_{2C} receptor, while some, such as haloperidol, have minimal effect on this receptor and produce minimal weight gain.[15] On the other hand, an interaction between leptinergic and serotonergic systems in the central nervous system has been shown.[16] The weight gain induced by clozapine and olanzapine has been reported to be associated with an increase in both leptin and triglyceride levels.[2,17,18] Therefore, leptin may

be associated with antipsychotic-induced weight gain. To explore the pathophysiology of weight gain during atypical antipsychotic treatment, we planned to comparatively investigate the effects of the atypical antipsychotics quetiapine, olanzapine, risperidone, and clozapine on leptin and triglyceride levels and weight gain.

METHOD

Patients

The study population comprised 56 patients (age range, 19–46 years) with schizophrenia who had consecutively applied for treatment in the Department of Psychiatry at the Firat University School of Medicine (Elazig, Turkey). Data were gathered in 2001 and 2002. From the initial sample of 71 patients who had been free of psychotropic drugs at least for 2 weeks, 9 were excluded from the study because of comorbid Axis I disorders (obsessive-compulsive disorder in 2 patients and major depressive disorder in 1 patient), a history of alcohol abuse (1 patient), and physical reasons (diabetes mellitus in 2 patients, autoimmune disease in 1 patient, hepatoma in 1 patient, and pregnancy in 1 patient). In fact, 62 patients were started on atypical antipsychotic treatment during the study period, but 6 were excluded from the study due to requirement of additional drug (N = 4; chlorpromazine use) or discontinuation because of intolerance (N = 2). Thus, 15 patients were excluded from the initial sample, leaving 56 patients participating in the study. All patients were admitted to the psychiatry clinic.

The patients were randomly divided into 4 treatment groups: quetiapine (N = 14), olanzapine (N = 14), risperidone (N = 14), and clozapine (N = 14) monotherapy. The only concomitant medications permitted were biperiden hydrochloride (in 3 patients receiving risperidone) and benzodiazepines (in 4 patients receiving quetiapine, 2 patients receiving olanzapine, 2 patients receiving risperidone, and 1 patient receiving clozapine). Nineteen patients had never taken any psychotropic drugs (6 from the risperidone group, 5 from the olanzapine group, 5 from the clozapine group, and 3 from the quetiapine group). The other 37 patients had been on the following current (the last treatment before the present study) drug treatments: classical antipsychotics (9 from the olanzapine group, 8 from the clozapine group, 7 from the quetiapine group, and 6 from the risperidone group), clozapine (5 patients from the olanzapine group, 3 from the clozapine group, 3 from the risperidone group, and 3 from the quetiapine group), risperidone (5 patients from the quetiapine group, 5 from the clozapine group, 4 from the olanzapine group, and 3 from the risperidone group), olanzapine (4 patients from the quetiapine group, 4 from the clozapine group, 3 from the olanzapine group, and 3 from the risperidone group), and quetiapine (5 patients from the quetiapine group and 3 from the risperidone group), but had been off medication treatment for 15 days to $1^1/_2$ years. In addition, they had received prior treatment with the following drugs: classical neuroleptics (N = 17), depot neuroleptics (N = 9), clozapine (N = 4), olanzapine (N = 3), and risperidone (N = 1).

Eleven patients suffering from a variety of psychiatric disorders received no psychopharmacologic treatment because of pregnancy (N = 3), diagnostic purposes (N = 3), or treatment with cognitive and behavioral psychotherapeutic approaches (N = 5). These controls were selected from people who were among the consecutive "applicants" for treatment at the Department of Psychiatry, School of Medicine, Firat University, and gave written informed consent.

Procedure

The clinical evaluation was performed by 1 trained psychiatrist (M.K.) within 2 days after admission for all patients. The Structured Clinical Interview for DSM-IV[19] was administered to establish DSM-IV diagnosis. Patients with comorbid Axis I disorders were excluded. All participants were free of all medications for at least the previous 2 weeks. Exclusion criteria included the presence of a severe physical illness, a history of alcohol and substance abuse or dependence, a history of lipid-lowering treatment, and the presence of any endocrinologic disorder. All participants were carefully assessed to exclude those with autoimmune, pulmonary, or infectious diseases or neoplasms. All subjects were evaluated using a semistructured questionnaire form that was arranged by the authors in accordance with clinical experience and available information sources to examine sociodemographic and clinical characteristics. In addition, BMI was calculated by dividing the patient's weight (in kilograms) by the squared height (in meters) ($BMI = kg/m^2$). After the complete description of the study to the subjects, written informed consent was obtained from each patient. The study was approved by the Local Ethics Committee of the Firat University School of Medicine.

All patients received a routine hospital diet. The patients were evaluated at baseline and at the sixth week with respect to the Positive and Negative Syndrome Scale (PANSS),[20] BMI, weight, and serum leptin and triglyceride levels. The raters were blind to drug assignment, although the prescribing physician was not blind to assignment.

Determination of Serum Leptin and Triglyceride Levels

To determine serum levels of leptin and triglyceride, venous blood samples were obtained at 8:00 a.m. after overnight fasting. Leptin levels were measured using the DRG Diagnostics kit (DRG Instruments GmbH, Marburg, Germany) in enzyme-linked immunoassay

Table 1. Mean ± SD Weight, PANSS Score, Triglyceride and Leptin Levels, and BMI at Baseline and Week 6 in Schizophrenia Patients and Controls

Variable	Quetiapine (I) (N = 14)	Olanzapine (II) (N = 13)	Risperidone (III) (N = 13)	Clozapine (IV) (N = 13)	No Treatment (V) (N = 11)	p Value
Body weight, kg						
Baseline	61.93 ± 2.43	61.60 ± 3.77	63.26 ± 4.41	62.93 ± 3.65	64.23 ± 4.67	.18
Treatment	66.34 ± 5.34	70.52 ± 5.51	63.80 ± 3.48	69.40 ± 4.93	62.91 ± 4.13	< .05 (I-III, V) < .01 (II-I, III, V; IV-I, III, V)
Change	4.41 ± 2.21	8.92 ± 3.13	0.54 ± 0.72	6.52 ± 3.41	–1.32 ± 0.93	
p Value	< .05	< .01	.91	< .01	.82	
PANSS score						
Baseline	94.93 ± 4.66	93.53 ± 5.93	94.41 ± 4.52	94.61 ± 3.51	…	.85
Treatment	77.24 ± 6.08	74.86 ± 6.41	78.26 ± 4.62	77.06 ± 5.28	…	.38
p Value	< .01	< .001	< .01	< .01	…	…
Triglyceride, mg/dL						
Baseline	162.32 ± 18.26	164.48 ± 13.21	158.52 ± 14.27	160.53 ± 11.78	161.42 ± 17.25	.12
Treatment	173.96 ± 10.23	195.71 ± 11.45	162.39 ± 9.88	196.81 ± 17.33	159.31 ± 10.87	< .05 (I-III, V) < .01 (I-II, IV; II-I, III, V), (IV-I,III,V)
Change	11.64 ± 4.58	31.23 ± 9.87	3.87 ± 1.45	36.28 ± 5.61	–2.11 ± 1.02	
p Value	< .05	< .001	.76	< .001	.85	
Leptin, mg/dL						
Baseline	6.12 ± 1.74	6.52 ± 1.97	6.36 ± 2.48	6.34 ± 2.75	5.81 ± 2.01	.11
Treatment	8.38 ± 2.27	11.98 ± 4.11	7.24 ± 1.61	11.22 ± 3.37	4.75 ± 1.98	< .05 (I-II, IV, V) < .01 (II-III, V; IV-III, V)
Change	2.26 ± 1.58	5.46 ± 2.15	0.88 ± 0.51	4.88 ± 2.17	–1.06 ± 0.81	
p Value	< .05	< .001	.91	< .001	.62	
BMI						
Baseline	22.86 ± 1.35	22.35 ± 2.87	24.41 ± 2.72	23.06 ± 2.77	25.12 ± 3.49	.25
Treatment	23.46 ± 2.89	26.97 ± 2.84	23.65 ± 2.94	26.91 ± 3.67	24.73 ± 4.01	< .05 (II-I, III, V; IV-I, III, V)
p Value	.96	< .05	.71	< .05	.62	

Abbreviations: BMI = body mass index, PANSS = Positive and Negative Syndrome Scale.

method. The limit of detection was 0.2 ng/mL. Triglyceride levels were measured with an Olympus AU 600 autoanalyzer (Olympus, Tokyo, Japan), using the Randox kit (Randox Laboratories, Crumlin, United Kingdom).

Statistical Analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS/PC 9.05 version, 1998, SPSS Inc., Chicago, Ill.). The Wilcoxon test was used to compare values at baseline and at 6 weeks within groups. Analysis of variance was used to compare the BMI, weight, total PANSS scores, and biochemical parameters among groups. The General Linear Model command of the SPSS was used when controlling for covariates. Correlation analysis was performed using Pearson correlations and the Spearman rank correlations test, whenever appropriate. Differences were considered significant at $p < .05$ for all of these tests.

RESULTS

All but 3 patients (1 patient from the olanzapine group, 1 patient from the risperidone group, and 1 patient from the clozapine group) completed the 6-week study period as inpatients. The mean ± SD age was 30.1 ± 8.4 years in the quetiapine group, 29.6 ± 8.1 years in the olanzapine group, 27.9 ± 7.8 years in the risperidone group, 31.3 ± 7.2 years in the clozapine group, and 32.1 ± 6.2 years in the group receiving no psychopharmacologic treatment ($p = .21$). The mean duration of illness was 5.9 ± 3.7 years in the quetiapine group, 6.3 ± 3.3 years in the olanzapine group, 5.6 ± 4.1 years in the risperidone group, and 6.6 ± 3.8 years in the clozapine group ($p = .24$). With respect to sex distribution, there were 8 women and 6 men in the quetiapine group, 7 women and 6 men in the olanzapine group, 6 women and 7 men in the risperidone group, 8 women and 5 men in the clozapine group, and 6 women and 5 men in the no-treatment group ($p = .62$). As can be seen, there were no significant differences among groups in mean age, female/male ratio, or duration of illness. At the week 6 evaluation, the mean doses were 535.7 ± 110.5 mg/day for the quetiapine group, 15.7 ± 4.8 mg/day for the olanzapine group, 6.7 ± 3.6 mg/day for the risperidone group, and 207.1 ± 62.4 mg/day for the clozapine group.

Weight, PANSS score, triglyceride and leptin levels, and BMI at baseline and week 6 in all antipsychotic groups are presented in Table 1. There were no statistically significant differences among the treatment groups with respect to weight at baseline ($p = .18$). The mean changes in weight for the treatment groups were quetiapine, 4.41 ± 2.21 kg (9.80 ± 4.91 lb); olanzapine, 8.92 ± 3.13 kg (19.82 ± 6.95 lb); risperidone, 0.54 ± 0.72 kg (1.20 ± 1.60 lb); clozapine, 6.52 ± 3.41 kg (14.48 ± 7.57 lb); and no psychopharmacologic treatment, –1.32 ± 0.93 kg (–2.93 ± 2.06 lb).

No statistically significant difference regarding decrease in mean PANSS scores among the atypical antipsychotic groups was found ($p = .61$).

There were no statistically significant differences among the treatment groups with respect to mean triglyceride levels at baseline ($p = .12$). The mean changes in triglyceride levels for the quetiapine, olanzapine, risperidone, clozapine, and no psychopharmacologic treatment groups were 11.64 ± 4.58, 31.23 ± 9.87, 3.87 ± 1.45, 36.28 ± 5.61, and –2.11 ± 1.02 mg/dL, respectively. At the week 6 evaluation, a significant difference in mean serum triglyceride levels among groups was found after BMI and age adjustment ($F = 7.43$, $p < .001$ adjusted for BMI; $F = 3.21$, $p < .05$ adjusted for age). In addition, when the mean triglyceride levels were compared between the sexes within each group, a statistically significant difference was found in the olanzapine ($p < .05$), clozapine ($p < .05$), and no-treatment groups ($p < .05$) (higher in women compared with men in all 3 groups), but not in the quetiapine ($p = .23$) or risperidone ($p = .45$) groups.

There were no statistically significant differences among the treatment groups with respect to mean leptin levels at baseline ($p = .11$). The mean changes in leptin levels for the quetiapine, olanzapine, risperidone, clozapine, and no psychopharmacologic treatment groups were 2.26 ± 1.58, 5.46 ± 2.15, 0.88 ± 0.51, 4.88 ± 2.17, and –1.06 ± 0.81 mg/dL, respectively. At the week 6 evaluation, a significant difference in the mean serum leptin levels was found after BMI or age adjustment ($F = 6.1$, $p < .001$ adjusted for BMI; $F = 3.9$, $p < .05$ adjusted for age). In addition, when the mean leptin levels were compared between sexes within each group, a statistically significant difference was found only in the clozapine group (higher in women compared with men; $p < .05$).

There were no statistically significant differences among groups with respect to mean BMI at baseline ($p = .25$). At the week 6 evaluation, a significant difference in mean BMI among groups was found after sex adjustment and age adjustment ($F = 4.4$, $p < .05$ adjusted for sex; $F = 3.3$, $p < .05$ adjusted for age).

The changes in leptin levels were correlated with the change in BMI in all groups ($r = 0.54$, $p < .05$ for the quetiapine group; $r = 0.63$, $p < .05$ for the olanzapine group; and $r = 0.60$, $p < .05$ for the clozapine group) except the risperidone ($r = 0.22$, $p = .13$) and no-treatment groups ($r = 0.06$, $p > .05$). Additionally, there was a significant correlation between the changes in leptin levels and those in weight in the olanzapine ($r = 0.57$, $p < .05$) and clozapine groups ($r = 0.78$, $p < .01$), but not in the quetiapine ($r = 0.22$, $p = .13$), risperidone ($r = 0.12$, $p > .05$), or no psychopharmacologic treatment groups ($r = 0.08$, $p = .76$). There were significant positive correlations between the changes in leptin levels and triglyceride levels in all groups ($r = 0.58$, $p < .05$ for the quetiapine group; $r = 0.62$, $p < .05$ for the olanzapine group; $r = 0.55$, $p < .05$ for the risperidone group; $r = 0.60$, $p < .05$ for the clozapine group; and $r = 0.52$, $p < .05$ for the controls). Between the changes in triglyceride levels and BMI, there was a positive correlation in the quetiapine ($r = 0.63$, $p < .05$), olanzapine ($r = 0.80$, $p < .01$), and clozapine groups ($r = 0.78$, $p < .01$). On the other hand, between the changes in weight and BMI, there was a positive correlation only in the olanzapine ($r = 0.64$, $p < .05$) and clozapine ($r = 0.60$, $p < .05$) groups. Changes in total PANSS scores were correlated with changes in leptin levels in all antipsychotic groups ($r = 0.58$, $p < .05$ for the quetiapine group; $r = 0.60$, $p < .05$ for the olanzapine group; $r = 0.56$, $p < .05$ for the risperidone group; and $r = 0.64$, $p < .05$ for the clozapine group); with changes in weight in the olanzapine ($r = 0.83$, $p < .01$), clozapine ($r = 0.78$, $p < .01$), and quetiapine ($r = 0.57$, $p < .05$) groups; and with changes in triglyceride levels in the olanzapine ($r = 0.58$, $p < .05$) and clozapine ($r = 0.60$, $p < .05$) groups.

DISCUSSION

The major findings of our study were as follows: (1) olanzapine and clozapine caused a marked increase in weight and serum triglyceride and leptin levels, though increases in these variables were modest in patients receiving quetiapine and minimal in those receiving risperidone; (2) there were positive correlations between serum leptin levels and BMI and triglyceride levels; and (3) clinical efficacy, as indicated by decrease in total PANSS scores, was associated with leptin levels in all antipsychotic groups.

The mechanism of antipsychotic-induced weight gain remains incompletely understood. The factors influencing weight gain in patients receiving an antipsychotic are probably complex. An important theory is that of histamine-1 (H_1) receptor blockade by antipsychotics, since H_1 receptors are considered to be involved in the regulation of food intake, and, moreover, a robust correlation was found between novel antipsychotic affinity for the histamine receptor and antipsychotic-induced weight gain.[21,22] Apart from this theory, however, there have been many approaches to account for antipsychotic-related weight gain. Many factors, including changes in reproductive hormones,[3] gastric misperception of satiety,[23] and cortisol elevation,[24] have been proposed. It has been reported that antipsychotic-induced imbalance in reproductive hormones may play a role in the development of obesity. However, there are also contrary findings indicating that changes in reproductive hormones with antipsychotic treatment are in contrast to primary obesity.[25] Furthermore, it has been reported that antagonism of serotonin, dopamine, and norepinephrine receptors may be associated with weight gain.[26] Antipsychotics constitute a heterogeneous group of drugs that demonstrate diverse

influences on hormonal systems such as prolactin[27] and brain monoamines related to feeding and drinking behaviors.[28]

An important finding of our study is that of greater increases in triglyceride and leptin levels in the olanzapine and clozapine groups compared with the quetiapine and especially the risperidone groups. We should note that if higher doses of clozapine (usual doses of about 400 mg/day in the United States) had been used, the clozapine figures for the variables of interest might have been larger. Olanzapine- and clozapine-induced increases in triglyceride and leptin levels have been reported.[2,18,29] A positive correlation has been shown between serum leptin concentration and triglyceride,[30] as evidenced by the present study. Leptin has been considered to interact with some neurotransmitters, including histamine and serotonin.[31,32] Serotonin is an important, well-known satiety factor. Despite the fact that it has not been well understood which serotonin receptors are critical, increase in serotonin at different serotonin receptors has been demonstrated to decrease food intake, and serotonin blockade causes increased energy intake.[33,34] The 5-HT_{2C} receptor has been reported as a candidate receptor for psychotropic-induced weight gain, and the antagonists of this receptor produce weight gain.[35,36] It has been shown to interact with leptinergic and serotonergic systems in the central nervous system.[16] Fluoxetine, a selective serotonin reuptake inhibitor, has been reported to reduce plasma leptin levels in rats,[31] and it has been noted that leptin administration stimulated serotonin turnover,[37] suggesting further evidence for this association.

Probable disparate receptor-binding profiles between typical and atypical antipsychotics and even among atypical antipsychotics may account for their differential effects on leptin levels and related weight gain. Actually, although they have some similarities in regard to receptor-binding profiles, such as greater affinity for 5-HT_2 receptors than dopamine-2 receptors, atypical antipsychotics differ in some pharmacologic properties; for example, quetiapine has weak 5-HT_2 and moderate antihistaminergic antagonism; olanzapine has a rather similar receptor-binding profile to that of clozapine, except that it has a slightly higher affinity than clozapine to all sites except α_1 receptors, with especially high affinity for H_1 and 5-HT_2 receptors; and risperidone's pharmacologic profile includes somewhat lower affinity for H_1 receptors.[38] Olanzapine and clozapine have strong affinity to serotonin and histamine receptors (5-HT_{2A}, 5-HT_{2C}, and H_1). There is strong evidence that blockade of these receptors is associated with weight gain.[24] On the other hand, it seems that talking about other mechanisms related to both leptin and weight gain will be beneficial.

It has been reported that various cytokines and soluble cytokine receptors, in particular, tumor necrosis factor-α (TNF-α), soluble TNF receptors p55 and p75, and soluble interleukin-2 receptor, are involved in weight regulation, and clozapine has increased these biological markers,[39] but olanzapine, which shares many pharmacologic characteristics with clozapine, has not.[40] Leptin shares many features with endogenous peptides known as cytokines including signaling via a cytokine-type receptor.[11] In addition, leptin is induced by TNF-α, suggesting an interaction between leptin and cytokines.[41] Moreover, the neurotransmitters serotonin and histamine, which may be involved in weight regulation, have been shown to be linked with the TNF system.[42]

We should note that some evidence suggests that leptin increases whenever there is an increase in body weight, relatively independent of the kind of antipsychotic drug administered; for example, it has been reported that sulpiride administration increased leptin levels[3] and that obese patients on typical antipsychotic treatment showed higher leptin levels compared with obese controls.[25] However, the major finding of our study, that olanzapine- and clozapine-treated patients exhibited significantly higher leptin levels while those receiving risperidone displayed significantly lower leptin levels after 6 weeks of treatment, even after adjustment for BMI, supports the opinion that other mechanisms besides weight gain might be involved in the leptin increase found in the present study. Baptista et al.[3,25] proposed that insulin might be one of these probable mechanisms. Leptin secretion is induced by insulin, and the two are positively correlated in both healthy people and patients receiving antipsychotic treatment.[3,25] Since olanzapine and clozapine may lead to increase in appetite, they might increase insulin and leptin secretion, irrespective of increase in body weight. This possibility was supported by Melkersson et al.[29] As proposed by Baptista and Beaulieu,[43] it is possible that future research will show that hyperleptinemia displays some deleterious effect on metabolism despite not enough current supportive evidence. It seems that the exact roles of triglyceride, leptin, insulin, cytokines, and serotonin, which seem to be related, have been obscured due to the lack of investigations and that trials in which these biological markers are used together are required.

It has been reported that weight gain has some predictive value for a positive response to clozapine treatment.[44] Some evidence shows that increased triglycerides elevate brain cell membrane fluidity, leading to increased serotonin reuptake and decreased serotonin function. This can enhance the decrease in postsynaptic serotonergic function that results from the 5-HT_2 receptor blockade related to a majority of atypical antipsychotics.[45] On the other hand, it has been proposed that leptin mediates the beneficial effects of antipsychotics.[17] In our study, decrease in total PANSS scores was positively correlated with increase in leptin levels in all antipsychotic groups, weight gain in all antipsychotic groups except the quetiapine group, and increases in triglyceride levels in the olanza-

pine and clozapine groups, although the study period was limited. This finding was not supported by Herrán and colleagues'[46] study, despite the chronic nature of their sample. Therefore, the relationships between leptin, triglyceride, and psychopathology require evaluation by comprehensive studies.

Several limitations should be taken into consideration when interpreting our results. First, the relatively small sample size might not be representative of patients treated with atypical antipsychotics. Second, some factors that might be related to body weight, e.g., glucose, insulin, cholesterol fractions, cytokines, and soluble cytokine receptors, were not assessed in the present study. Furthermore, we could not test whether poor economic status and other psychosocial factors might be related to serum triglyceride or leptin levels.

In conclusion, our results suggest that leptin seems to be strongly associated with olanzapine- and clozapine-induced weight gain, though our sample is too small to allow us to obtain a clear conclusion, and that quetiapine appears to have modest influence, and risperidone, minimal influence, on leptin and triglyceride levels and weight gain compared with olanzapine and clozapine. Our results need to be confirmed by more comprehensive and detailed further studies to decipher the exact roles of leptin in weight gain related to atypical antipsychotic use.

Drug names: biperiden (Akineton), clozapine (Clozaril and others), fluoxetine (Prozac and others), haloperidol (Haldol and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal).

REFERENCES

1. Brady KT. Weight gain associated with psychotropic drugs. South Med J 1989;82:611–617
2. Osser DN, Najarian DM, Dufresne RL. Olanzapine increases weight and serum triglyceride levels. J Clin Psychiatry 1999;60:767–770
3. Baptista T, Lacruz A, de Mendoza S, et al. Body weight gain after administration of antipsychotic drugs: correlation with leptin, insulin and reproductive hormones. Pharmacopsychiatry 2000;33:81–88
4. Prolo P, Wong M-L, Licinio J. Leptin. Int J Biochem Cell Biol 1998;30:1285–1290
5. Himms-Hagen J. Physiological roles of the leptin endocrine system: differences between mice and humans. Crit Rev Clin Lab Sci 1999;36:575–655
6. Kraus T, Haack M, Schuld A, et al. Low leptin levels but normal body mass indices in patients with depression or schizophrenia. Neuroendocrinology 2001;73:243–247
7. Atmaca M, Kuloglu M, Tezcan E, et al. Serum cholesterol and leptin levels in patients with borderline personality disorder. Neuropsychobiology 2002;45:167–171
8. Atmaca M, Kuloglu M, Tezcan E, et al. Serum leptin levels in the patients with premature ejaculation. Arch Androl 2002;48:345–350
9. Atmaca M, Kuloglu M, Tezcan E, et al. Weight gain and serum leptin levels in patients on lithium treatment. Neuropsychobiology 2002;46: 67–69
10. Atmaca M, Kuloglu M, Tezcan E, et al. Serum leptin and cholesterol values in the suicide attempters. Neuropsychobiology 2002;45:124–127
11. Auwerx J, Steals B. Leptin. Lancet 1998;351:737–742
12. Halaas JL, Gajiwala KS, Maffei M, et al. Weight-reducing effects of the plasma protein encoded by the obese gene. Science 1995;269:543–546
13. Pelleymounter MA, Cullen MJ, Baker MB, et al. Effects of the obese gene product on body weight regulation in ob/ob mice. Science 1995;269:540–543
14. Woods SC, Kaiyala K, Porte D, et al. Food intake and energy balance. In: Porte D, Sherwin RS, eds. Diabetes Mellitus. 5th ed. Stamford, Conn: Appleton and Lange; 1997:175–192
15. McIntyre RS, Mancini DA, Basile VS. Mechanisms of antipsychotic-induced weight gain. J Clin Psychiatry 2001;62:23–29
16. Liebowitz SF, Alexander JT. Hypothalamic serotonin in control of eating behavior, meal size, and body weight. Biol Psychiatry 1998;44:851–864
17. Kraus T, Haack M, Schuld A, et al. Body weight and leptin plasma levels during treatment with antipsychotic drugs. Am J Psychiatry 1999;156:312–314
18. Ghaeli P, Dufresne RL. Serum triglyceride levels in patients treated with clozapine. Am J Syst Pharm 1996;53:2079–2081
19. First MB, Spitzer RL, Gibbon M, et al. Structured Clinical Interview for DSM-IV. New York, NY: Biometric Research, New York State Psychiatric Institute; 1995
20. Kay SR, Opler LA, Fiszbein A. The Positive and Negative Syndrome Scale (PANSS) Manual. North Tonawanda, NY: Multi-Health System; 1986
21. Richelson E. Preclinical pharmacology of neuroleptics: focus on new generation compounds. J Clin Psychiatry 1996;57(suppl 11):4–11
22. Wirshing DA, Wirshing WC, Kysar L, et al. Novel antipsychotics: comparison of weight gain liabilities. J Clin Psychiatry 1999;60:358–363
23. Coddington RD, Bruch H. Gastric perceptivity in normal, obese, and schizophrenic subjects. Psychosomatics 1970;9:571–579
24. Nash JF, Meltzer HY, Gudelsky GA. Elevation of serum prolactin and corticosterone concentrations in the rat after the administration of 3, 4-methylenedioxy/methamphetamine. J Pharmacol Exp Ther 1988; 245:873–879
25. Baptista T, Lacruz A, Angeles F, et al. Endocrine and metabolic abnormalities involved in obesity associated with typical antipsychotic drug administration. Pharmacopsychiatry 2001;34:223–231
26. Stahl SM. Neuropharmacology of obesity: my receptors made me eat it [BRAINSTORMS]. J Clin Psychiatry 1998;59:447–448
27. Baptista T. Body weight gain induced by antipsychotic drugs: mechanisms and management. Acta Psychiatr Scand 1999;100:3–16
28. Wirshing DA, Spellberg BJ, Erhart SM, et al. Novel antipsychotics and new onset diabetes. Biol Psychiatry 1998;44:778–783
29. Melkersson KI, Hulting A-L, Brismar KE. Elevated levels of insulin, leptin, and blood lipids in olanzapine-treated patients with schizophrenia or related psychoses. J Clin Psychiatry 2000;61:742–749
30. Kaplan LM. Leptin, obesity, and liver disease. Gastroenterology 1998;115:997–1001
31. Dryden S, Brown M, King P, et al. Decreased plasma leptin levels in lean and obese Zucker rats after treatment with the serotonin reuptake inhibitor fluoxetine. Horm Metab Res 1999;31:363–366
32. Morimoto T, Yamamoto Y, Mobarakeh JI, et al. Involvement of the histaminergic system in leptin-induced suppression of food intake. Physiol Behav 1999;67:679–683
33. De Vry J, Schreiber R. Effects of selected serotonin 5-HT(1) and 5-HT(2) receptor agonists on feeding behavior: possible mechanisms of action. Neurosci Biobehav Rev 2000;24:341–353
34. Meguid MM, Fetissov SO, Varma M, et al. Hypothalamic dopamine and serotonin in the regulation of food intake. Nutrition 2000;16:843–857
35. Tecott LH, Sun LM, Akana SF, et al. Eating disorder and epilepsy in mice lacking 5-HT_{2C} serotonin receptors. Nature 1995;374:542–546
36. Vickers SP, Benwell KR, Porter RH, et al. Comparative effects of continuous infusion of m-CPP, Ro 60-0175 and d-fenfluramine on food intake, water intake, body weight and locomotor activity in rats. Br J Pharmacol 2000;130:1305–1314
37. Calapai G, Corica F, Corsonello A, et al. Leptin increases serotonin turnover by inhibition of brain nitric oxide synthesis. J Clin Invest 1999;104:975–982
38. Peacock L, Gerlach J. Antipsychotic-induced side effects related to receptor affinity. Handbook Exp Pharmacology 1996;120:359–388
39. Pollmacher T, Hinze-Selch D, Mullington J. Effects of clozapine on cytokines and soluble cytokine receptors. J Clin Psychopharmacol 1996;16:403–409
40. Schuld A, Kraus T, Haack M, et al. Plasma levels of cytokines and soluble cytokine receptors during treatment with olanzapine. Schizophr Res 2000;43:164–166
41. Sarraf P, Frederich RC, Turner EM, et al. Multiple cytokines and acute

inflammation raise mouse leptin levels: potential role in inflammatory anorexia. J Exp Med 1997;185:171–175
42. Müller N, Ackenheil M. Psychoneuroimmunology and the cytokine action in the CNS: implications for psychiatric disorders. Prog Neuropsychopharmacol Biol Psychiatry 1998;22:1–33
43. Baptista T, Beaulieu S. Body weight gain, insulin, and leptin in olanzapine-treated patients [letter with reply]. J Clin Psychiatry 2001;62:902–903
44. Jalenques I, Tauveron I, Albuisson E, et al. Weight gain as a predictor of long term clozapine efficiency. Clin Drug Invest 1996;12:16–25
45. Diebold K, Michel G, Schweizer J, et al. Are psychoactive-drug induced changes in plasma lipid and lipoprotein levels of significance for clinical remission in psychiatric disorders? Pharmacopsychiatry 1998;31:60–67
46. Herrán A, García-Unzueta MT, Amado JA, et al. Effects of long-term treatment with antipsychotics on serum leptin levels. Br J Psychiatry 2001;179:59–62