Letters to the Editor

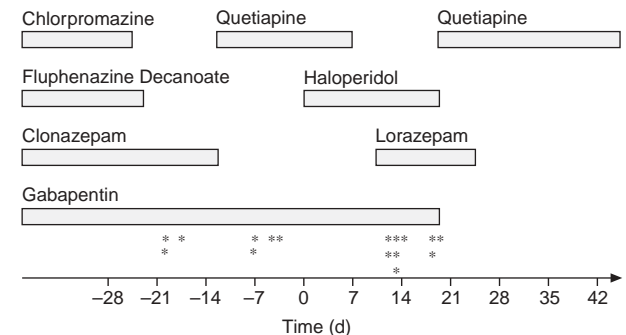## Antiaggressive Effect of Quetiapine in a Patient With Schizoaffective Disorder

Sir: Clozapine and other atypical antipsychotics may have antiaggressive effects. Cantillon and Goldstein's findings[1] suggested antiaggressive effects of quetiapine in psychosis. We observed a beneficial effect of quetiapine in a persistently aggressive 45-year-old white woman with a DSM-IV diagnosis of schizoaffective disorder.

Case report. Ms. A had repeated psychiatric hospitalizations for DSM-IV schizoaffective disorder since the age of 20 years. During the current hospitalization, she was intermittently agitated, threatening, and throwing or toppling objects. She consented to participate in a randomized double-blind study comparing several antipsychotics in an effort to reduce her aggressive behaviors. In the 4-week period prior to randomization, she had 7 incidents of overt aggression (Figure 1). Ms. A's medication regimen at the time included chlorpromazine, 50 mg b.i.d. (last dose 24 days prior to randomization); fluphenazine decanoate, 50 mg i.m. every 2 weeks (last dose 22 days prior to randomization); quetiapine (for 11 days immediately prior to randomization, maximum dose of 500 mg/day); clonazepam, 1 mg b.i.d. (last dose 11 days prior to randomization); gabapentin, 100 mg t.i.d.; and sedatives, p.r.n. Her baseline Positive and Negative Syndrome Scale (PANSS)[2] score totaled 89, with a hostility item score of 6 ("severe"). Her baseline akathisia rating (according to the Extrapyramidal Symptom Rating Scale[3]) was "mild" (2 on a scale from 0 to 6). Ms. A was randomly assigned and cross-titrated from quetiapine to haloperidol (20 mg/day) over a 1-week period and continued taking gabapentin. After randomization, she had 9 incidents of overt aggression and received 25 doses of diphenhydramine, p.r.n., or chloral hydrate, p.r.n., over a 19-day period. Lorazepam, 2 mg t.i.d., was provided for the last 7 days, with no effect on her aggressive behavior. She was therefore discontinued from the study at day 19. Her endpoint PANSS total score was 103, and her hostility score remained "severe"; her akathisia rating of 4 was "moderately severe." She complained of restlessness.

A retrospective review of the events before and after randomization revealed that Ms. A's behavior improved slightly with the addition of quetiapine, but worsened after quetiapine was completely discontinued once the cross-titration to haloperidol was completed. Thus, after she was terminated from the protocol, she was again prescribed quetiapine, this time as her only antipsychotic (titrated to 500 mg/day over 3 days). Gabapentin was discontinued, and lorazepam was gradually discontinued. Her aggressive behavior disappeared completely with no incidents noted since receiving quetiapine, 500 mg/day. Ms. A's 4-week follow-up PANSS total score was 40; hostility and akathisia were scored as "absent."

Quetiapine may have had a nonspecific effect on aggression through its antipsychotic action; it may have also exerted a spe-

Figure 1. Medication Timeline and Occurrence of Overt Aggression[a]

[a]Day 0 = day of randomization. Symbol: * = incident of overt aggression.

cific antiaggressive effect. More likely, the switch to quetiapine alone eliminated akathisia; this effect may have indirectly contributed to the reduction of aggression.[4] This case suggests that quetiapine may be useful for some psychotic patients exhibiting aggressive behavior. Controlled studies should follow.

REFERENCES

1. Cantillon M, Goldstein JM. Quetiapine fumarate reduces aggression and hostility in patients with schizophrenia. In: New Research Program and Abstracts of the 151st Annual Meeting of the American Psychiatric Association; June 3, 1998; Toronto, Ontario, Canada. Abstract NR444:188
2. Kay SR, Fiszbein A, Opler LA. The Positive and Negative Syndrome Scale (PANSS) for schizophrenia. Schizophr Bull 1987;13:261–276
3. Chouinard G, Ross-Chouinard A, Annable L, et al. The Extrapyramidal Symptom Rating Scale [abstract]. Can J Neurol Sci 1980;7:233
4. Keckich WA. Neuroleptics: violence as a manifestation of akathisia. JAMA 1978;240:2185

Leslie Citrome, M.D., M.P.H.
Menahem Krakowski, M.D., Ph.D.
William M. Greenberg, M.D.
Elsie Andrade, B.A.
Jan Volavka, M.D., Ph.D.
Nathan S. Kline Institute for Psychiatric Research
Orangeburg, New York

Body Weight Gain, Insulin, and Leptin in Olanzapine-Treated Patients

Sir: There is growing interest regarding antipsychotic drug–induced weight gain and metabolic abnormalities. The recent article by Melkersson et al.[1] is pertinent given the increasing concern about these side effects among the mental health staff, the patients, and their families.[2]

The authors conclude that olanzapine induces excessive body weight gain; insulin resistance, expressed as elevated glucose and insulin levels (with the consequent increased risk of diabetes development); and hyperleptinemia. While it is not formally stated, the uninformed reader may deduce that during antipsychotic drug treatment, insulin and leptin abnormalities are mainly (or more easily) induced by olanzapine (and clozapine as shown in their previous study[3]) and that insulin and leptin are remarkably pathogenic.

Provided the impact on public health, it may be useful to assess the available information about the "causal" relationship between olanzapine and metabolic abnormalities and the pathogenic role of insulin and leptin. As suggested by Hill,[4] heuristic criteria for causality are strength, consistency, specificity, temporality, biological gradient, plausibility, coherence and analogy, and experimental support. After considering some methodological limitations of the article by Melkersson et al.,[1] we present empirical evidence that suggests that the causality criteria are still not properly met.

The authors acknowledge that the sample was too small, that there was not a comparison group (apart from normalized data from the general population), and that there were no records of values for pretreatment variables. We would like to emphasize that, when needed, the initial body weight was obtained from the patients' self-reports and not from an objective record. Considering how unaware a subject with severe and fluctuating psychosis can be of his or her precise body weight, this method appears problematic. In addition, 3 patients were already overweight before starting olanzapine therapy. Patients 1 and 4 might also have been overweight prior to treatment, but their weight changes were unavailable. If perhaps 5 of 8 subjects were previously overweight before the drug treatment, the presented frequency of obesity in olanzapine-treated subjects is misleading.

More importantly, 42% of the sample had a family history of diabetes; the sample appears to be an overrepresentation of high-risk subjects. Two of these subjects (subjects 9 and 11) displayed such abnormal values of insulin and leptin in spite of a normal weight that one may seriously consider whether they were prediabetic or had pilocystic ovary before the olanzapine treatment. A different picture emerges if these patients are considered outsiders and are excluded from the analysis (see below). Taken as a whole, these limitations preclude any firm conclusion with regard to the criteria of temporality (the cause preceding[4] or at least being simultaneous to the effect[5]) and specificity.

Finally, leptin levels may be affected by the phase of the menstrual cycle[6] and by race.[7] By observing the women's ages, it can be considered that subjects 8, 9, and 10 may be premenopausal; subjects 11 and 12, perimenopausal; and subjects 13 and 14, postmenopausal. It appears difficult to draw firm conclusions from such a heterogeneous sample, particularly for the correlation analysis. Given the influence of race, it seems more adequate to compare the patients with a carefully selected control group and not with the general population. It is also questionable that the authors did not provide the reference values for leptin.

For the remaining discussion, we will use data from studies conducted by our research group. Even if the olanzapine- or clozapine-induced metabolic abnormalities were actually confirmed in rigorously designed studies, we still would like to propose that other antipsychotics also induce (or further promote) such metabolic disturbances and that their pathogenic effects are controversial (particularly for leptin).

The atypical antipsychotic sulpiride was administered to rats[8] and healthy volunteers.[9–11] In another study, an endocrine/metabolic evaluation was conducted in women chronically treated with typical antipsychotics (phenothiazines and haloperidol) and a control group of healthy, drug-free women matched by body mass index (BMI), age, and menstrual cycle phase.[12] It was found that (1) sulpiride administration significantly increased the area under the glucose tolerance curve in healthy women in spite of not having significantly affected the body weight,[10] (2) sulpiride also induced a small but significant increase in weight along with significant increments in insulin and leptin levels in healthy men,[9,11] and (3) women chronically treated with typical antipsychotics displayed higher glucose basal levels and glucose-stimulated insulin levels than controls; however, leptin levels were similar in both groups.[12]

Hence, the induction of insulin resistance does not appear to be specific for clozapine or olanzapine. An extensive literature is devoted to the glucose metabolism abnormalities induced by phenothiazines and haloperidol (for instance, see references 13–15). In fact, Thonnard-Neumann[13] used the term *phenothiazine diabetes* in 1968. In our last study,[12] it was also shown that, as expected, the obese antipsychotic-treated subjects displayed higher area under the insulin curve than the nonobese patients. This finding brings us to the arena of the pathogenic effects of insulin resistance and its specificity. There appears to be general consensus that insulin resistance is observed in most subjects with primary or secondary obesity.[16] It is possible, however, that the antipsychotics further enhance such an impairment in insulin function (in fact, in study C,[12] we found higher insulin and glucose levels in antipsychotic-treated obese women than in the obese control group). Regarding the typical antipsychotics, converging evidence suggests that impairment in insulin function may be partially related to hyperprolactinemia (see Baptista[16] for review). However, in the case of clozapine or olanzapine, no consistent hypothesis has been offered. Finally, besides its postulated role in human pathology, insulin resistance appears to be a powerful adaptive mechanism to prevent additional body weight gain.[17]

Regarding leptin, Melkersson et al.[1] state that hyperleptinemia may be a mechanism behind olanzapine-induced weight gain. Little empirical information supports that claim (therefore, Hill's criteria of biological plausibility and gradient, coherence, analogy, and experimental support are not yet met). Research on leptin is currently one of the most active scientific fields. As regards human obesity, it appears that leptin increment is a consequence of—or at least correlates with—body weight gain.[18,19] Therefore, with the exception of people with a defect in leptin production or transduction (perhaps less than 10% of persons with primary obesity),[19] a rise in leptin levels is normally expected even after a modest increase in weight (for instance, as reported in Baptista et al.[9]). However, there is not yet experimental evidence that hyperleptinemia itself could be considered a direct "cause" of weight gain. Hyperleptinemia appears to be part of a general adaptation mechanism (obviously defective in obese people) that counteracts weight gain.[18,19] This affirmation has experimental support: female rats rendered obese after chronic sulpiride administration did not display the expected hyperleptinemia.[8] Hence, at least in rats, it appears that it is the lack of increase in leptin level that might be causally

linked to weight gain. However, it is possible that future research will show that hyperleptinemia displays some deleterious (and paradoxical) effect on human metabolism, but currently there are few data to support that contention. Some researchers have proposed that hyperleptinemia might be involved in the arterial hypertension observed in obesity,[20] but their data appear to be preliminary and controversial.

Melkersson et al.[1] found that the positive significant correlation between insulin, leptin, and BMI was absent in olanzapine-treated subjects (marginally significant for insulin, p = .06; and nonsignificant for leptin, p = .13). A positive correlation is observed in subjects with normal weight,[11,12] in people with primary obesity,[19] in sulpiride-treated healthy men,[9] and in women chronically treated with typical antipsychotics.[11,12] This lack of correlation between insulin, leptin, and BMI reported by Melkersson et al. is an important finding because it may point to (1) a subtle impairment in weight regulation and/or (2) the covariation of leptin with other physiologic aspects in psychotic subjects. However, by excluding the above-mentioned atypical subjects (patients 9 and 11, who had very high insulin and leptin levels in spite of a BMI within the normal range), a significant positive correlation was observed in the remaining sample: for insulin and BMI: r = 0.658, p = .02; for leptin and BMI: r = 0.712, p = .009).

In the same direction, Melkersson et al. state that the "gender difference that normally exists, in that women have higher circulating levels than men, was also lacking in our patients."[1(p747)] Again, this might point to an interesting subtle dysregulation of the leptin system. However, given the reported strong correlation between leptin and BMI,[11,12,19] future studies should consider comparing leptin levels between men and women, pairing by BMI.

It is now clear that clozapine, olanzapine, and thioridazine are the antipsychotics that induce the highest weight gain after short-term administration,[21] but the lifetime prevalence of severe obesity (BMI > 30) is also significantly higher than in the general population in subjects chronically treated with diverse typical antipsychotics (see references 2 and 16 for review). We must also acknowledge the increasing number of reports dealing with carbohydrate and lipid metabolism abnormalities in clozapine- or olanzapine-treated subjects compared with the paucity of publications linking risperidone[22] or quetiapine[23] with those side effects. However, future studies might consider in their design that (1) subjects with schizophrenia and bipolar disorders appear to display an elevated prevalence of diabetes[24–26] and other endocrine anomalies relevant for weight regulation (see Baptista[16] for review) and (2) the typical antipsychotics also appear to impair insulin sensitivity.[12–15]

REFERENCES

1. 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
2. Green AI, Patel JK, Goisman RM, et al. Weight gain from novel antipsychotic drugs: need for action. Gen Hosp Psychiatry 2000;22:224–235
3. Melkersson KI, Hulting A-L, Brismar KE. Different influences of classical antipsychotics and clozapine on glucose-insulin homeostasis in patients with schizophrenia or related psychoses. J Clin Psychiatry 1999;60:783–791
4. Hill AB. The environment and disease: association or causality? Proc R Soc Med 1965;58:295–300
5. Weed DL. On the logic of causal inference. Am J Epidemiol 1986; 123:965–979
6. Quinton ND, Laird SM, Okon MA, et al. Serum leptin levels during the menstrual cycle of healthy fertile women. Br J Biomed Sci 1999; 56:16–19
7. Nicklas BJ, Toth MJ, Goldberg AP, et al. Racial differences in plasma leptin concentrations in obese postmenopausal women. J Clin Endocrinol Metab 1997;82:315–317
8. Lacruz A, Baptista T, Mendoza S, et al. Body weight induced by antipsychotic drugs in rats: correlation between leptin and insulin during sulpiride administration. Mol Psychiatry 2000;5:70–77
9. Baptista T, Alastre T, Contreras Q, et al. Effects of the antipsychotic drug sulpiride on reproductive hormones in healthy men: relationship with body weight regulation. Pharmacopsychiatry 1997;30:250–255
10. Baptista T, Alastre T, Contreras Q, et al. Effects of the antipsychotic drug sulpiride on reproductive hormones in healthy women: relationship with body weight regulation. Pharmacopsychiatry 1997;30:256–262
11. 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
12. Baptista T, Lacruz A, Angeles F, et al. Endocrine and metabolic abnormalities involved in obesity associated with typical antipsychotic drug administration. Pharmacopsychiatry. In press
13. Thonnard-Neumann E. Phenothiazines and diabetes in hospitalized women. Am J Psychiatry 1968;124:138–142
14. Korenyi C, Lowenstein B. Chlorpromazine induced diabetes. Dis Nerv Syst 1968;29:827–828
15. Brambilla F, Guastalla A, Guerrini A. Glucose-insulin metabolism in chronic schizophrenia. Dis Nerv Syst 1976;37:98–103
16. Baptista T. Body weight gain induced by antipsychotic drugs: mechanisms and management. Acta Psychiatr Scand 1999;100:3–16
17. Eckel RH. Insulin resistance: an adaptation for weight maintenance. Lancet 1992;340:1452–1453
18. Campfield LA, Smith FJ, Burn P. The OB protein (leptin) pathway: a link between adipose tissue mass and central neural networks. Horm Metab Res 1996;28:619–632
19. Friedman JM, Halaas JL. Leptin and the regulation of body weight in mammals. Nature 1998;22:763–770
20. Aizawa-Abe M, Ogawa Y, Masuzaki H, et al. Pathophysiological role of leptin in obesity-related hypertension. J Clin Invest 2000;105:1243–1252
21. Allison DB, Mentore JL, Heo M, et al. Antipsychotic-induced weight gain: a comprehensive research synthesis. Am J Psychiatry 1999;156:1686–1696
22. Croarkin PE, Jacobs KM, Bain BK. Diabetic ketoacidosis associated with risperidone? Psychosomatics 2000;41:369–370
23. Sobel M, Jaggers ED, Franz MA. New-onset diabetes mellitus associated with the initiation of quetiapine treatment [letter]. J Clin Psychiatry 1999;60:556–557
24. Schimmelbusch WH, Mueller PS, Sheps J. The positive correlation between insulin resistance and duration of hospitalization in untreated schizophrenia. Br J Psychiatry 1971;118:429–436
25. Dixon L, Weiden P, Delahanty J, et al. Prevalence and correlates of diabetes in national schizophrenia samples. Schizophr Bull 2000;26:903–912
26. Cassidy F, Ahearn E, Carroll BJ. Elevated frequency of diabetes mellitus in hospitalized manic-depressive patients. Am J Psychiatry 1999;156:1417–1420

Trino Baptista, M.D., Ph.D.
Serge Beaulieu, M.D., Ph.D., F.R.C.P.C.
Douglas Hospital Research Center
Verdun, Québec, Canada

Drs. Melkersson and Colleagues Reply

Sir: We appreciate the opportunity to reply to the letter by Baptista and Beaulieu regarding our article.[1] This study,[1] together with our previous study,[2] may point to the possibility that, among antipsychotic drugs, atypical agents such as olanzapine and clozapine especially induce insulin and leptin abnormalities. Even though Baptista and Beaulieu claim the contrary in their comments, these abnormalities, which are induced by

antipsychotic medications often used for long periods, are probably both clinically relevant and important, since they are associated with an increased risk of development of diabetes and cardiovascular disease.[3,4]

Moreover, Baptista and Beaulieu comment that they apprehend the "presented frequency of obesity in olanzapine-treated subjects" in our study as "misleading." The fact is that we concluded in our article that "57% [8/14] of the patients . . . exhibited elevated BMI after a median of 5 months of treatment with olanzapine."[1(p746)] This frequency of 57% could then be compared with the estimated rate of elevated BMI in the patients before beginning with olanzapine (25% [3/12]; or, if patients 1 and 4 were also included, 36% [5/14]) (see Table 1 in our article[1]).

Regarding the family history of type 2 diabetes in our sample, it is important to emphasize that all 8 patients with no family history of diabetes, together with 2 of the 6 patients with a family history of diabetes, exhibited insulin and/or leptin abnormalities in the study.[1] Thus, the majority (i.e., 8) of the 10 patients who had these abnormalities were not high-risk subjects with a family history of diabetes.

It is also worth noting for the reader that patients 9 and 11 in our study[1] had no known prediabetes, polycystic ovaries, or other physical illness before beginning the olanzapine treatment. Therefore, there is no reason for considering these 2 patients as outliers and excluding them from the analysis, as is suggested by Baptista and Beaulieu.

Concerning the influence of race on leptin levels, all 14 of our patients were white.[1] Their leptin levels were compared with BMI- and sex-adjusted reference values, based on samples from a group of 103 men and women, in which a subgroup analysis showed a similar mean concentration of leptin in white and black subjects.[5] Therefore, it seems reasonable to make a comparison between leptin levels in our patients and levels in that reference group of 103 subjects.[5]

Regarding the influence on leptin levels of hormonal changes due to menopause or the menstrual cycle, of the 7 women included in our study, 5 women were premenopausal and 2 women were postmenopausal.[1] However, serum leptin concentrations have been shown to be higher in both premenopausal and postmenopausal women compared with men.[6] In addition, the difference in serum leptin levels during the luteal and follicle phases of the menstrual cycle is small to moderate and is not found in all fertile women.[7] Thus, there appears to be weak ground for the assumption made by Baptista and Beaulieu that our sample of women would be heterogeneous.

Since every measured leptin level in our patients was individually compared with a BMI- and sex-adjusted reference level, it is not questionable, as Baptista and Beaulieu write in their comments, that instead of providing the article with a total of 12 different reference values, we referred to the source used.[5]

In reply to the description by Baptista and Beaulieu of results from their own studies, we agree that antipsychotic drugs such as typical agents (phenothiazines, haloperidol) and sulpiride also may induce metabolic abnormalities, e.g., insulin resistance, and that such an insulin function impairment may be partially related to hyperprolactinemia (for review, see Baptista[8]). However, in our study,[1] we found elevated insulin levels in 10 (71%) of 14 olanzapine-treated patients, i.e., an unexpectedly high rate of hyperinsulinemia, which was not explained by con-

comitant hyperprolactinemia (data not described in the study). In another recent study,[9] we also compared the median insulin level in this olanzapine group with that in a group of patients treated with typical agents (perphenazine or zuclopenthixol) and found a significantly higher median insulin level in the olanzapine group, despite similar BMI and sex distribution between the 2 groups. In contrast to Baptista and Beaulieu, we do not consider a lack of a complete hypothesis on the mechanism(s) behind the hyperinsulinemia found in our olanzapine-treated patients[1] to be a reason for ignoring this finding.

Regarding leptin, we have suggested, not stated as Baptista and Beaulieu claim, that hyperleptinemia *may* be a mechanism behind olanzapine-induced weight gain (see the abstract and p. 747 of our article[1]). In their comments, Baptista and Beaulieu also point out that our finding of a lack of correlation between leptin and BMI in the olanzapine-treated patients "is important." However, we call their motive into question for then excluding patients 9 and 11 (as clarified above, these 2 patients cannot be considered as outliers) and making a reanalysis just to achieve this correlation!

Finally, despite some limitations of our study, which are already acknowledged in the article,[1] we see our findings of elevated levels of insulin, leptin, and blood lipids in olanzapine-treated patients as clinically relevant and worth noting. Moreover, further studies are needed to confirm these results.

REFERENCES

1. 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
2. Melkersson KI, Hulting A-L, Brismar KE. Different influences of classical antipsychotics and clozapine on glucose-insulin homeostasis in patients with schizophrenia or related psychoses. J Clin Psychiatry 1999;60:783–791
3. Fajans SS. Classification and diagnosis of diabetes. In: Porte D, Sherwin RS, eds. Diabetes Mellitus. 5th ed. Stamford, Conn: Appleton & Lange; 1997:357–372
4. Söderberg S, Ahren B, Jansson JH, et al. Leptin is associated with increased risk of myocardial infarction. J Intern Med 1999;246:409–418
5. Ma Z, Gingerich RL, Santiago JV, et al. Radioimmunoassay of leptin in human plasma. Clin Chem 1996;42:942–946
6. Rosenbaum M, Nicolson M, Hirsch J, et al. Effects of gender, body composition, and menopause on plasma concentrations of leptin. 0J Clin Endocrinol Metab 1996;81:3424–3427
7. Quinton ND, Laird SM, Okon MA, et al. Serum leptin levels during menstrual cycle of healthy fertile women. Br J Biomed Sci 1999;56:16–19
8. Baptista T. Body weight gain induced by antipsychotic drugs: mechanisms and management. Acta Psychiatr Scand 1999;100:3–16
9. Melkersson KI, Hulting AL. Insulin and leptin levels in patients with schizophrenia or related psychoses: comparison between different antipsychotic agents. Psychopharmacology (Berl) 2001;154:205–212

Kristina Melkersson, M.D., Ph.D.
Anna-Lena Hulting, M.D., Ph.D.
Kerstin Brismar, M.D., Ph.D.
Karolinska Hospital
Stockholm, Sweden