Association of Weight Gain and Metabolic Syndrome in Patients Taking Clozapine: An 8-Year Cohort Study

Ya Mei Bai, MD, PhD; Chao-Cheng Lin, MD; Jen-Yeu Chen, MD; Tzu Ting Chen, MD; Tung-Pine Su, MD; and Pesus Chou, DPH

Introduction: Metabolic syndrome is an important side effect associated with clozapine. It has been hypothesized that weight gain contributes to the development of metabolic syndrome, but a direct diabetogenic effect has also been suggested. We conducted an 8-year cohort study to determine the association between weight gain and metabolic parameters among schizophrenic patients taking clozapine.

Method: This study is a retrospective cohort study combining a cross-sectional survey of metabolic syndrome and retrospective chart review. The subjects were hospitalized schizophrenic patients (*DSM-IV*) who began to receive clozapine at least 3 months before the survey (March to September 2005) and subsequently had monthly body weight monitoring. Anthropometric and biochemical measurements were performed to determine the presence of metabolic syndrome. The chart reviews were conducted to obtain gender, age at initiation of clozapine treatment, baseline body mass index (BMI), BMI changes after the initiation of clozapine treatment, treatment duration with clozapine, and concomitant psychotropic medications.

Results: One hundred eighty-nine patients were maintained on clozapine for a mean ± SD treatment duration of 57.6 ± 27.3 months (range, 5–96). The prevalence of metabolic syndrome was 28.4%. The cohort regression models showed that baseline BMI ($P < .01$) and BMI change after clozapine treatment ($P < .01$) were significant factors for metabolic syndrome and 4 metabolic parameters except hyperglycemia, which was related to treatment duration ($P < .05$).

Conclusions: For patients treated with clozapine, metabolic syndrome and most metabolic parameters were related to weight gain; however, glucose dysregulation was associated with treatment duration independent of weight gain. The results confirm that monitoring body weight is important, but periodic monitoring of blood sugar may also be required for clozapine patients who do not have significant weight gain.

J Clin Psychiatry 2011;72(6):751–756

Submitted: *May 29, 2009; accepted November 5, 2009.*
Online ahead of print: *November 30, 2010 (doi:10.4088/JCP.09m05402yel).*
Corresponding author: *Ya Mei Bai, MD, PhD, Department of Psychiatry, Taipei Veterans General Hospital, Taiwan, No. 201, Sec 2, Shih-Pai Rd, Taipei 112, Taiwan (ymbi@mail2000.com.tw).*

The metabolic syndrome associated with antipsychotic treatment has gained much attention in recent years; however, the pharmacologic basis for the metabolic changes is not fully understood.[1] Previous studies have indicated that clozapine and olanzapine were associated with the highest risk of treatment-related metabolic dysfunction, quetiapine and risperidone with intermediate risk, and ziprasidone and aripiprazole with the least risk of metabolic side effects.[2,3] In general, the rank order of risk observed for these second-generation antipsychotic medications suggests that the differing weight gain liability of atypical agents contributes to the differing relative risk of metabolic side effects.[3] This is consistent with effects observed in nonpsychiatric samples in that the risk for adverse metabolic changes tends to increase with increasing adiposity. In the general population, obesity has been recognized as an independent cardiometabolic risk factor that impacts morbidity and mortality and contributes to the development of other cardiometabolic risk factors, such as dyslipidemia, hypertension, and insulin resistance.[4] In a cross-sectional study of 5,278 Japanese men aged 40–59 years, Yatsuya[5] found that components of metabolic syndrome tended to cluster more in individuals with large weight gain on a physiologic basis characterized by high fasting insulin concentration. Berrahmoune et al[6] found that there was a strong linear trend between increasing body mass index (BMI) and the worsening of various metabolic parameters in a 5-year study of 1,099 middle-aged adults. McLaughlin et al[7] have demonstrated that people with a BMI greater than 27 have a 50% probability of being in the top tertile of insulin resistance. This increases to a 70% probability when triglyceride levels are greater than 130 mg/dL, and a 78% probability when criteria are met for the metabolic syndrome. Lamberti et al[8] found the prevalence of the metabolic syndrome was significantly higher among clozapine patients (53.8%) than among the comparison group (20.7%), and body mass index was associated with the prevalence of metabolic syndrome in both groups. On the basis of these data, it has been suggested that antipsychotic-induced changes in weight are responsible for antipsychotic-related metabolic side effects.

Although a close relationship between drug-induced weight gain and the risk of diabetes was reported in the general population, some psychiatric studies have suggested that glucose dysregulation may be independent of adiposity. Clozapine and olanzapine were suggested to have a direct effect on glucose regulation by limiting the capacity of β cells to secrete appropriate amount of insulin.[9] Avella et al[10] reported on 3 patients treated with olanzapine who died suddenly and unexpectedly with hyperglycemic ketoacidosis without significant weight gain. Hundreds of patients developed new-onset diabetes or exacerbation of preexisting disease within 6 months of the initiation of clozapine or olanzapine therapy. Improved glycemic control was noted after discontinuation or dose reduction of the drugs, and hyperglycemia recurred

with rechallenge; therefore, a causal relationship between clozapine/olanzapine treatment and diabetes was suggested.[11,12]

In addition to these case reports and surveillance data, some case-control studies also suggested the glucose dysregulation was independent of body weight. Newcomer et al[13] compared oral glucose tolerance tests among patients treated with clozapine, olanzapine, risperidone, or typical antipsychotics and untreated healthy control subjects. These patients were matched for age and adiposity. The results showed that clozapine- and olanzapine-treated patients still showed significant glucose elevations, although their BMIs were similar to those of patients taking risperidone or typical antipsychotics and of untreated healthy control subjects. Melkersson and Hulting[14] also found higher insulin levels in patients receiving olanzapine than in those receiving conventional antipsychotics despite similar BMI results. Henderson et al[15,16] reported that both nonobese clozapine- and olanzapine-treated groups displayed significant insulin resistance and impairment of glucose effectiveness by intravenous glucose tolerance test. Howes et al[17] found 11 of 20 patients (55%) treated with clozapine developed impaired glucose control within 4 months of the onset of treatment, independent of BMI. Lamberti et al[18] evaluated the fasting blood glucose levels of 101 outpatients treated with clozapine for an average duration of 5.7 years and found no significant associations between the prevalence of diabetes and BMI or body fat. In Chiu and colleagues' prospective study,[19] 26 atypical-naive schizophrenic patients were randomly assigned to therapy with olanzapine or risperidone for 14 days, and the insulin secretion level significantly increased only in the olanzapine group, but there were no significant within-group changes in weight or body mass index between the 2 groups. However, Haupt et al[20] found a positive correlation between adiposity and insulin resistance. Their study subjects included 63 nondiabetic patients receiving olanzapine, risperidone, ziprasidone, or first-generation antipsychotics and 14 healthy controls. Subject groups were matched for BMI and age. They found that BMI and waist circumference significantly predicted insulin sensitivity and acute plasma insulin response to the glucose challenge.

Whether antipsychotic-associated weight gain contributes to glucose dysregulation is important for clinical practice. The American Diabetes Association, American Psychiatric Association, American Association of Clinical Endocrinologists, and the North American Association for the Study of Obesity recommend that all patients receiving second-generation antipsychotics receive appropriate baseline screening and ongoing monitoring.[21] However, a recent report showed a very low prevalence of monitoring, with only 10.5% lipid testing and 21.8% glucose testing after the guidelines were established.[22] Because patients with schizophrenia require life-long maintenance on antipsychotics, the cost of periodically monitoring all patients will be expensive. If we can validate that weight gain is a predictor for all metabolic side effects, then the monitoring protocol can focus on patients who show significant weight gain in order to reduce cost. If antipsychotic drug–associated glucose dysregulation is independent of adiposity, then periodic monitoring of glucose would be suggested for all patients, even for those without significant weight gain. The association between weight gain and glucose dysregulation is still unclear. Most previous studies have been limited by small sample size or cross-sectional design without data of baseline BMI and BMI change. Furthermore, the subjects in previous studies received different antipsychotics with different effects on glucose control. Mixed data from different antipsychotics may complicate the interpretation. Because clozapine is associated with the highest risk of weight gain and metabolic side effects, we focused only on the subjects treated with this drug in the present cohort study. We followed the long-term weight gain of institutionalized patients taking clozapine for up to 8 years to investigate the association between weight gain and metabolic side effects. During the study period, all the patients were confined to the same hospital, and body weight was monitored monthly. Because these were inpatients, variables relating to drug adherence, diet content, and activity level were optimally controlled.

METHOD

This study is a retrospective cohort study combining a cross-sectional survey of metabolic syndrome and retrospective chart review. The study sample consisted of hospitalized patients with schizophrenia who were admitted to the largest mental hospital in Taiwan and had received clozapine for at least 3 months at the time the survey was conducted (March–September 2005). During hospitalization, the body weight of all patients was monitored monthly and recorded. Chart reviews established the demographic data, age and baseline BMI, BMI change after the initiation of clozapine treatment, treatment duration, and concomitant use of other antipsychotics and mood stabilizers. Anthropometric and biochemical assessments were performed in September 2005 to investigate the prevalence of metabolic syndrome according to the 2005 International Diabetes Federation (IDF) Asia criteria[23]: waist circumference > 90 cm in men or > 80 cm in women as the essential criteria of central obesity, plus 2 of the following 4 criteria: (1) fasting serum triglyceride levels ≥ 150 mg/dL, (2) fasting high-density lipoprotein (HDL) cholesterol < 40 mg/dL in men or < 50 mg/dL in women, (3) blood pressure ≥ 130/85 mm Hg, and (4) fasting glucose ≥ 100 mg/dL. Overnight fasting blood samples were drawn between 7:00 and 8:00 AM from all patients. Serum glucose, triglyceride, and cholesterol levels were measured using a glucose oxidase autoanalyzer, a triglyceride enzyme autoanalyzer, and a cholesterol oxidase autoanalyzer, respectively (Dimension RxL, DADE Behring Company, Inc, Newark, Delaware).

The study was performed in accordance with the Declaration of Helsinki and was approved by the Ethics Review Committee of Yu-Li Veterans Hospital. All elements of the study were completely described to all patients,

 © Copyright 2010 Physicians Postgraduate Press, Inc.

and all patients provided written informed consent before participating.

Descriptive statistics were performed for continuous and categorical variables for the characteristics of the subjects. Multivariate regression analysis was performed to establish the cross-sectional and cohort logistic regression model to find the factors associated with metabolic syndrome (2005 IDF Asia criteria), as well as for 5 metabolic parameters (waist circumference, fasting serum triglyceride level, fasting HDL cholesterol, blood pressure, fasting glucose) and diabetes mellitus specifically. Seven cross-sectional regression models and 7 cohort logistic regression models were performed separately. The cross-sectional regression model was to find the predictors for the presence of metabolic syndrome at the survey time, and the present BMI was an independent variable. The cohort regression model was to find the predictors of metabolic syndrome from cohort variables, including baseline BMI and BMI change after clozapine treatment. The 2 types of regression models were to cross-validate the results for the association between metabolic syndrome and BMI or BMI change. All *P* values were 2-tailed at the .05 significance level. All tests were analyzed using SPSS, version 13.0 for Windows (SPSS Inc, Chicago, Illinois).

RESULTS

The study sample consisted of 189 hospitalized patients with schizophrenia (*DSM-IV*) treated with clozapine, with mean ± SD dosage of 330.3 ± 106 mg/d. During the study period, all patients were hospitalized and maintained on clozapine for a mean ± SD duration of 57.6 ± 27.3 months (range, 5–96). Table 1 shows the demographics, treatment characteristics, data on metabolic parameters, and prevalence of metabolic syndrome among the subjects. The prevalence of metabolic syndrome (IDF) was 28.4%.

Table 2 integrates 7 cross-sectional logistic regression models to show the factors related to the presence of metabolic syndrome, 5 metabolic parameters, and diabetes mellitus. The independent variables included gender, age and BMI at survey, treatment duration of clozapine, mean dosage of clozapine, and concomitant use of other antipsychotics and mood stabilizers. The results show that BMI at survey was a significant factor for presence of metabolic syndrome and 4 metabolic parameters except hyperglycemia and diabetes mellitus. The treatment duration was a significant factor for both hyperglycemia and diabetes mellitus. The concomitant use of mood stabilizers was associated with a higher risk of hypertension (blood pressure ≥ 130/85 mm Hg) by 2005 IDF criteria for metabolic syndrome.

Table 3 integrated 7 cohort logistic regression models to find the predictors related to the presence of metabolic syndrome, 5 metabolic parameters, and diabetes mellitus. The independent variables included gender, age at the initiation of clozapine treatment, baseline BMI, BMI change after clozapine treatment, treatment duration of clozapine, mean dosage of clozapine, and concomitant use of other antipsychotics and mood stabilizers. The cohort regression models showed that baseline BMI and BMI change after clozapine treatment were significant factors for central obesity, elevations of fasting triglycerides and blood pressure, low HDL, and metabolic syndrome. Fasting glucose was not related to obesity but was instead related to duration of treatment with clozapine. The concomitant use of mood stabilizers was associated with a higher risk of hypertension (blood pressure ≥ 130/85 mm Hg) by 2005 IDF criteria for metabolic syndrome.

Table 1. Characteristics in Study Subjects Treated With Clozapine (N = 189)

Characteristic	Value[a]
Retrospective chart review data	
Dosage, mg/d	330.3 ± 106.4
Age at survey, y	43.3 ± 8.7
Age at initiation of index antipsychotic treatment, y	38.1 ± 8.5
Male gender, n (%)	120 (63.5)
Treatment duration, mo	57.6 ± 27.3
BMI at survey	25.5 ± 4.6
BMI at initiation of clozapine	24.3 ± 4.5
BMI increase after initiation of clozapine treatment	1.1 ± 3.5
Concomitant use of mood stabilizer, n (%)	49 (25.9)
Concomitant use of other antipsychotics, n (%)	23 (12.2)
Metabolic syndrome survey data	
Waist circumference, cm	85.4 ± 12.7
Hip circumference, cm	94.2 ± 9.0
Systolic blood pressure, mm Hg	116.9 ± 14.1
Diastolic blood pressure, mm Hg	73.6 ± 9.8
Triglyceride, mg/dL	124.5 ± 80.4
HDL, mg/dL	38.5 ± 12.5
Cholesterol, mg/dL	153.1 ± 33.2
Fasting glucose, mg/dL	95.0 ± 37.0
Insulin, μU/mL	10.1 ± 12.5
Central obesity, n (%)[b,c]	79 (43.6)
Fasting triglyceride ≥ 150 mg/dL, n (%)[b]	53 (28.0)
Fasting HDL < 40 mg/dL in men or < 50 mg/dL in women, n (%)[b]	137 (73.3)
Blood pressure ≥ 130/85 mm Hg, n (%)[b]	47 (25.1)
Fasting glucose ≥ 100 mg/dL, n (%)[b]	44 (23.4)
Diabetes mellitus ≥ 126 mg/dL, n (%)	31 (16.5)
Metabolic syndrome (IDF), (%)	28.4

[a]Values are shown as mean ± SD unless stated otherwise.
[b]Metabolic syndrome components of 2005 International Diabetes Federation (IDF) Asia criteria.
[c]Central obesity: waist circumference > 90 cm in men or > 80 cm in women.
Abbreviations: BMI = body mass index, HDL = high-density lipoprotein.

DISCUSSION

Our results showed that the prevalence of metabolic syndrome for the 189 Chinese patients with schizophrenia treated with clozapine was 28.4%. The prevalence of metabolic syndrome in the general Taiwanese population, according to Chuang and colleagues' study[24] was 12.9% (15.5% in men and 10.5% in women) of 24,329 people who had received health check-ups at Health Screening Centers. The mean age of our study sample was 43.3 years old. Another Taiwanese nationwide cross-sectional population-based survey of 5,936 participants showed the age-specific percentage of the metabolic syndrome for age between 40–49 years was 14.3%.[25] Therefore, our results showed twice the risk of metabolic syndrome in our patients than that in the general

Table 2. Cross-Sectional Multivariate Regression Model for Factors Associated With Metabolic Parameters According to the 2005 International Diabetes Federation (IDF) Asia Criteria in Patients Treated With Clozapine

Factor	Central Obesity,[a] OR	Hypertriglyceridemia,[b] OR	Low HDL,[c] OR	High Blood Pressure,[d] OR	Hyperglycemia,[e] OR	Diabetes Mellitus,[f] OR	Metabolic Syndrome (IDF), OR
Age at survey	1.001	1.040	1.009	1.040	1.011	0.996	1.053
Male gender	0.674	1.747	1.427	1.883	0.682	0.993	1.876
BMI at survey	1.665**	1.278***	1.214***	1.203***	1.063	1.066	1.458***
Treatment duration of clozapine	1.007	1.003	1.009	0.990	1.017*[h]	1.020*[h]	1.001
Clozapine dosage (mg/d)	0.999	1.000	0.998	1.003	0.998	0.998	0.998
Concomitant use of other antipsychotics	0.807	0.542	0.568	0.543	0.476	0.799	0.917
Concomitant use of mood stabilizers	1.746	1.041	1.228	2.535*[g]	0.468	0.495	1.568

[a]Waist circumference > 90 cm in men or > 80 cm in women. [b]Fasting triglyceride ≥ 150 mg/dL. [c]Fasting HDL < 40 mg/dL in men or < 50 mg/dL in women. [d]Blood pressure ≥ 130/85 mm Hg. [e]Fasting glucose ≥ 100 mg/dL. [f]Fasting glucose ≥ 126 mg/dL. [g]$P = .021$. [h]$P = .020$.
*$P < .05$. **$P < .01$. ***$P < .001$.
Abbreviations: BMI = body mass index, HDL = high-density lipoprotein, OR = odds ratio.

Table 3. Cohort Regression Model for Factors Associated With Presence of Metabolic Parameters According to the 2005 International Diabetes Federation (IDF) Asia Criteria in Patients Treated With Clozapine

Factor	Central Obesity,[a] OR	Hypertriglyceridemia,[b] OR	Low HDL,[c] OR	High Blood Pressure,[d] OR	Hyperglycemia,[e] OR	Diabetes Mellitus,[f] OR	Metabolic Syndrome (IDF), OR
Age at initiation of clozapine	0.998	1.034	1.010	1.744	1.012	0.996	1.048
Male gender	0.724	1.863	1.426	2.046**	0.771	1.196	2.168
Baseline BMI	1.662**	1.262***	1.236***	1.170***	1.073	1.076	1.471***
BMI change after the initiation of clozapine treatment	1.653**	1.332***	1.254***	1.240***	1.101	1.126	1.492***
Treatment duration of clozapine	1.008	1.004	1.010	0.990	1.018*[h]	1.019*[i]	1.004
Clozapine dosage (mg/d)	0.999	1.000	0.997	1.003	0.998	0.998	0.998
Concomitant use of other antipsychotics	0.574	0.329	0.554	0.489	0.320	0.541	0.536
Concomitant use of mood stabilizers	1.728	1.152	1.120	2.732*[g]	0.505	0.551	1.767

[a]Waist circumference > 90 cm in men or > 80 cm in women. [b]Fasting triglyceride ≥ 150 mg/dL. [c]Fasting HDL < 40 mg/dL in men or < 50 mg/dL in women. [d]Blood pressure ≥ 130/85 mm Hg. [e]Fasting glucose ≥ 100 mg/dL. [f]Fasting glucose ≥ 126 mg/dL. [g]$P = .014$. [h]$P = .020$. [i]$P = .029$.
*$P < .05$. **$P < .01$. ***$P < .001$.
Abbreviations: BMI = body mass index, HDL = high-density lipoprotein, OR = odds ratio.

Taiwanese population. The result was consistent with previous reports of white populations.[26–29] Another important issue is that the 28.4% prevalence of metabolic syndrome in our study sample was much lower than other white reports, such as 53.8% in Lamberti's study.[8] This may be related to the racial/ethnic, sociocultural differences. A report of representative 2006 national survey data from Hong Kong, Taiwan, Thailand, and the United States showed that the age-standardized prevalence of metabolic syndrome in the general population was lowest in Taiwan (11% in men, 12% in women), and highest in the United States (31% in men, 35% in women).[30]

Our results showed that BMI at survey can predict the presence of metabolic syndrome by cross-sectional regression models. Furthermore, the cohort regression model controlling for pretreatment characteristics showed that baseline BMI and BMI change after initiation of clozapine were factors associated with metabolic syndrome. The results were consistent with other cross-sectional or short-term studies. Tirupati and Chua[31] suggested that BMI was a quick and easy measure, and they used it as a screening test for metabolic syndrome in 202 patients with chronic schizophrenia and schizoaffective disorders who were taking antipsychotic medications. Van Gaal[32] also suggested measurement of waist circumference as a good indicator of overall cardiovascular and metabolic risk. Our data support the observation that antipsychotic-associated weight gain contributes to metabolic syndrome, and monitoring a patient's body weight is important in order to identify patients at higher risk for metabolic side effects. For patients with significant weight gain, the metabolic parameters should be monitored.

However, the predictor was different for hyperglycemia and diabetes mellitus. Instead of BMI and BMI change, treatment duration was the significant predictive factor for hyperglycemia and diabetes mellitus from both cross-sectional and cohort regression models. The clinical implication is that we may have to monitor blood sugar periodically for patients treated with clozapine, even for those without significant weight gain. The diabetogenic potential of olanzapine and clozapine has been supported by many clinical reports,[10–16,18,19] but the exact cause of glucose dysregulation by these atypical antipsychotics is unclear. It has been hypothesized that serotonin-1A receptor (5-HT_{1A}) antagonism may decrease the responsiveness of the pancreatic β cells.[33] This would then result in inappropriately low insulin secretion and, therefore, hyperglycemia.[34] Animal studies have demonstrated that low concentrations of clozapine and olanzapine can markedly and selectively impair cholinergic-stimulated

insulin secretion by blocking muscarinic M_2 receptors, which could be one of the contributing factors to their higher risk for producing hyperglycemia and diabetes in humans.[1,35,36] Melkersson and Hulting[14] reported that insulin levels were correlated with the clozapine serum concentration, indicating a likely influence of clozapine on insulin secretion. Our results showing that longer treatment duration with clozapine increases the risk of glucose dysregulation may support the hypothesis of clozapine's diabetogenic effect. This hypothesis has been further supported by the reversibility of antipsychotic treatment–related new-onset diabetes. The data from the US Food and Drug Administration MedWatch surveillance program showed improved glycemic control after discontinuation or dose reduction of clozapine among 46 patients who developed hyperglycemia within 6 months of the onset of clozapine treatment.[11] Seven cases of recent-onset diabetes were reversed after a change to aripiprazole.[37,38] Periodic monitoring of glucose may be required for patients receiving clozapine treatment, even for those without significant weight gain. Once glycemic dysregulation is found, changing to other antipsychotics or other managements is important for these patients.

Some reports also suggest a direct effect of clozapine and olanzapine on lipid metabolism. Case reports in which treatment with olanzapine resulted in the elevation of the serum triglyceride level despite the absence of weight gain were noted.[39] In a cross-sectional study of 242 patients with severe mental disorders who were on monotherapy with olanzapine, clozapine, or other antipsychotics or who were unmedicated, Birkenaes et al[40] found that, independent of body mass, dyslipidemia was significantly associated with olanzapine and clozapine. But their study is a cross-sectional design without a control for baseline BMI and BMI change. Our study with cohort pretreatment characteristics showed BMI and weight gain were significant predictors for hyperlipidemia by both cross-sectional and cohort regression models. Because of its cost, lipid monitoring could be limited to patients with significant weight gain.

The main limitation of this study is the lack of metabolic parameters before subjects received clozapine treatment, although the pretreatment characteristics, including gender, age at initiation of clozapine, and baseline BMI were controlled in the cohort regression model. Prospective cohort study with periodic collection of metabolic data is still required to validate our results.

In conclusion, our study supported that weight gain is the predictor for metabolic syndrome and most metabolic parameters for patients treated with clozapine; however, glucose dysregulation is associated with treatment duration independent of weight gain. These results will be important for future schizophrenia treatment guidelines. Monitoring weight is required for all patients. If the patients have significant weight gain, they should have more frequent monitoring for metabolic syndrome. But periodic monitoring of blood sugar may also be required for all patients treated with clozapine, even for those who do not have significant weight gain.

Drug names: aripiprazole (Abilify), clozapine (Clozaril, FazaClo, and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal and others), ziprasidone (Geodon).

Author affiliations: Department of Psychiatry, Taipei Veterans General Hospital, and Department of Psychiatry, College of Medicine (Drs Bai and Su), and Community Medicine Research Center and Institute of Public Health (Dr Chou), National Yang-Ming University, Taipei; Department of Psychiatry, National Taiwan University Hospital, and Graduate Institute of Medical Informatics, Taipei Medical University (Dr Lin), Taipei; and Department of Psychiatry, Yu-Li Veterans Hospital, Hua-Lien (Drs J. Y. Chen and T. T. Chen), Taiwan.

Potential conflicts of interest: The authors report no conflict of interest.

Funding/support: The study was supported by grants from National Science Council, Taiwan (NSC 96-2314-B-075-009, 97-2314-B-075-003-MY2).

REFERENCES

1. Houseknecht KL, Robertson AS, Zavadoski W, et al. Acute effects of atypical antipsychotics on whole-body insulin resistance in rats: implications for adverse metabolic effects. *Neuropsychopharmacology*. 2007;32(2):289–297.
2. Newcomer JW. Metabolic considerations in the use of antipsychotic medications: a review of recent evidence. *J Clin Psychiatry*. 2007;68 (suppl 1):20–27.
3. Newcomer JW. Second-generation (atypical) antipsychotics and metabolic effects: a comprehensive literature review. *CNS Drugs*. 2005;19 (suppl 1):1–93
4. Choi KM, Lee J, Lee KW, et al. Serum adiponectin concentrations predict the developments of type 2 diabetes and the metabolic syndrome in elderly Koreans. *Clin Endocrinol (Oxf)*. 2004;61(1):75–80.
5. Yatsuya H. Pathophysiologic mechanisms of obesity and related metabolic disorders: an epidemiologic study using questionnaire and serologic biomarkers. *J Epidemiol*. 2007;17(5):141–146.
6. Berrahmoune H, Herbeth B, Samara A, et al. Five-year alterations in BMI are associated with clustering of changes in cardiovascular risk factors in a gender-dependant way: the Stanislas study. *Int J Obes (Lond)*. 2008;32(8):1279–1288.
7. McLaughlin T, Abbasi F, Cheal K, et al. Use of metabolic markers to identify overweight individuals who are insulin resistant. *Ann Intern Med*. 2003;139(10):802–809.
8. Lamberti JS, Olson D, Crilly JF, et al. Prevalence of the metabolic syndrome among patients receiving clozapine. *Am J Psychiatry*. 2006;163(7):1273–1276.
9. Scheen AJ, De Hert MA. Abnormal glucose metabolism in patients treated with antipsychotics. *Diabetes Metab*. 2007;33(3):169–175.
10. Avella J, Wetli CV, Wilson JC, et al. Fatal olanzapine-induced hyperglycemic ketoacidosis. *Am J Forensic Med Pathol*. 2004;25(2): 172–175.
11. Koller E, Schneider B, Bennett K, et al. Clozapine-associated diabetes. *Am J Med*. 2001;111(9):716–723.
12. Koller EA, Doraiswamy PM. Olanzapine-associated diabetes mellitus. *Pharmacotherapy*. 2002;22(7):841–852.
13. Newcomer JW, Haupt DW, Fucetola R, et al. Abnormalities in glucose regulation during antipsychotic treatment of schizophrenia. *Arch Gen Psychiatry*. 2002;59(4):337–345.
14. Melkersson K, Hulting AL. [Antipsychotic drugs can affect hormone balance: weight gain, blood lipid disturbances and diabetes are important] [Article in Swedish]. *Lakartidningen*. 2001;98(48):5462–5464, 5467–5469.
15. Henderson DC, Copeland PM, Borba CP, et al. Glucose metabolism in patients with schizophrenia treated with olanzapine or quetiapine: a frequently sampled intravenous glucose tolerance test and minimal model analysis. *J Clin Psychiatry*. 2006;67(5):789–797.
16. Henderson DC, Cagliero E, Copeland PM, et al. Glucose metabolism in patients with schizophrenia treated with atypical antipsychotic agents: a frequently sampled intravenous glucose tolerance test and minimal model analysis. *Arch Gen Psychiatry*. 2005;62(1):19–28.
17. Howes OD, Bhatnagar A, Gaughran FP, et al. A prospective study of impairment in glucose control caused by clozapine without changes in insulin resistance. *Am J Psychiatry*. 2004;161(2):361–363.
18. Lamberti JS, Costea GO, Olson D, et al. Diabetes mellitus among outpatients receiving clozapine: prevalence and clinical-demographic correlates. *J Clin Psychiatry*. 2005;66(7):900–906.
19. Chiu CC, Chen KP, Liu HC, et al. The early effect of olanzapine and

risperidone on insulin secretion in atypical-naïve schizophrenic patients. *J Clin Psychopharmacol*. 2006;26(5):504–507.
20. Haupt DW, Fahnestock PA, Flavin KA, et al. Adiposity and insulin sensitivity derived from intravenous glucose tolerance tests in antipsychotic-treated patients. *Neuropsychopharmacology*. 2007;32(12):2561–2569.
21. American Diabetes Association, American Psychiatric Association, American Association of Clinical Endocrinologists, et al. Consensus development conference on antipsychotic drugs and obesity and diabetes. *J Clin Psychiatry*. 2004;65(2):267–272.
22. Haupt DW, Rosenblatt LC, Kim E, et al. Prevalence and predictors of lipid and glucose monitoring in commercially insured patients treated with second-generation antipsychotic agents. *Am J Psychiatry*. 2009;166(3):345–353.
23. Mannucci E, Monami M, Cresci B, et al. National Cholesterol Education Program and International Diabetes Federation definitions of metabolic syndrome in the prediction of diabetes. Results from the FIrenze-Bagno A Ripoli study. *Diabetes Obes Metab.* 2008;10(5):430–435.
24. Chuang SY, Chen CH, Chou P. Prevalence of metabolic syndrome in a large health check-up population in Taiwan. *J Chin Med Assoc*. 2004;67(12):611–620.
25. Hwang LC, Bai CH, Chen CJ. Prevalence of obesity and metabolic syndrome in Taiwan. *J Formos Med Assoc*. 2006;105(8):626–635.
26. Cohn T, Prud'homme D, Streiner D, et al. Characterizing coronary heart disease risk in chronic schizophrenia: high prevalence of the metabolic syndrome. *Can J Psychiatry*. 2004;49(11):753–760.
27. Ford ES, Giles WH, Dietz WH. Prevalence of the metabolic syndrome among US adults: findings from the third National Health and Nutrition Examination Survey. *JAMA*. 2002;287(3):356–359.
28. De Hert MA, van Winkel R, Van Eyck D, et al. Prevalence of the metabolic syndrome in patients with schizophrenia treated with antipsychotic medication. *Schizophr Res*. 2006;83(1):87–93.
29. McEvoy JP, Meyer JM, Goff DC, et al. Prevalence of the metabolic syndrome in patients with schizophrenia: baseline results from the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) schizophrenia trial and comparison with national estimates from NHANES III. *Schizophr Res*. 2005;80(1):19–32.
30. Patel A, Huang KC, Janus ED, et al. Is a single definition of the metabolic syndrome appropriate? a comparative study of the USA and Asia. *Atherosclerosis*. 2006;184(1):225–232.
31. Tirupati S, Chua LE. Body mass index as a screening test for metabolic syndrome in schizophrenia and schizoaffective disorders. *Australas Psychiatry*. 2007;15(6):470–473.
32. Van Gaal LF. Long-term health considerations in schizophrenia: metabolic effects and the role of abdominal adiposity. *Eur Neuropsychopharmacol*. 2006;16(suppl 3):S142–S148.
33. Bergman RN, Ader M. Atypical antipsychotics and glucose homeostasis. *J Clin Psychiatry*. 2005;66(4):504–514.
34. Bettinger TL, Mendelson SC, Dorson PG, et al. Olanzapine-induced glucose dysregulation. *Ann Pharmacother*. 2000;34(7-8):865–867.
35. Johnson DE, Yamazaki H, Ward KM, et al. Inhibitory effects of antipsychotics on carbachol-enhanced insulin secretion from perifused rat islets: role of muscarinic antagonism in antipsychotic-induced diabetes and hyperglycemia. *Diabetes*. 2005;54(5):1552–1558.
36. Ader M, Kim SP, Catalano KJ, et al. Metabolic dysregulation with atypical antipsychotics occurs in the absence of underlying disease: a placebo-controlled study of olanzapine and risperidone in dogs. *Diabetes*. 2005;54(3):862–871.
37. De Hert M, Hanssens L, van Winkel R, et al. Reversibility of antipsychotic treatment-related diabetes in patients with schizophrenia: a case series of switching to aripiprazole. *Diabetes Care*. 2006;29(10):2329–2330.
38. De Hert M, Hanssens L, van Winkel R, et al. A case series: evaluation of the metabolic safety of aripiprazole. *Schizophr Bull*. 2007;33(3):823–830.
39. Nagamine T. Olanzapine-induced elevation of serum triglyceride levels in a normal weight patient with schizophrenia. *Intern Med*. 2008;47(3):181–182.
40. Birkenaes AB, Birkeland KI, Engh JA, et al. Dyslipidemia independent of body mass in antipsychotic-treated patients under real-life conditions. *J Clin Psychopharmacol*. 2008;28(2):132–137.