Adjunctive Fluvoxamine Inhibits Clozapine-Related Weight Gain and Metabolic Disturbances

Mong-Liang Lu, M.D., M.S.; Hsien-Yuan Lane, M.D., Ph.D.; Shih-Ku Lin, M.D.; Kun-Po Chen, M.D.; and Wen-Ho Chang, M.D.

Background: Adjunctive fluvoxamine inhibits clozapine metabolism and decreases plasma norclozapine (a toxic metabolite of clozapine) to clozapine ratios. This study aimed to demonstrate the effects of fluvoxamine on clozapine-related weight gain, hyperglycemia, and lipid abnormalities.

Method: Sixty-eight treatment-resistant inpatients with a DSM-IV diagnosis of schizophrenia were randomly assigned to 2 treatment groups for 12 weeks. The monotherapy group (N = 34) received clozapine (≤ 600 mg/day). The coadministration group (N = 34) received fluvoxamine (50 mg/day) plus low-dose clozapine (≤ 250 mg/day). The study was conducted from August 1999 to October 2002.

Results: The 2 groups were similar in demographic data; baseline body weight and body mass index (BMI); baseline serum glucose, triglyceride, and cholesterol levels; and steady-state plasma clozapine concentration. The monotherapy patients (but not the coadministration patients) had significantly higher ($p < .05$) body weight, BMI, and serum glucose and triglyceride levels after treatment than at baseline. At week 12, the monotherapy patients also had significantly higher glucose ($p = .035$), triglyceride ($p = .041$), and norclozapine ($p = .009$) (and numerically higher cholesterol) levels than the cotreatment patients. The changes in weight and serum glucose and triglyceride levels were significantly correlated ($p = .026$, $p = .005$, and $p = .028$, respectively) with the plasma concentration of norclozapine but not with plasma levels of clozapine.

Conclusion: These results suggest that fluvoxamine cotreatment can attenuate weight gain and metabolic disturbances in clozapine-treated patients. Plasma levels of norclozapine, but not clozapine, are associated with increases in weight and serum glucose and triglyceride levels. Of note, coadministration of fluvoxamine could increase plasma clozapine levels markedly and carry the risk of adverse events. If this combined treatment is applied, conservative introduction with reduced clozapine dosage and careful therapeutic drug monitoring of clozapine concentration is recommended.

(J Clin Psychiatry 2004;65:766–771)

Received Oct. 7, 2003; accepted Jan. 5, 2004. From the Department of Psychiatry, Taipei Medical University-Wan Fang Hospital, Taipei (Dr. Lu); the Department of Psychiatry, China Medical University and Hospital, Taichung (Dr. Lane); the Department of Adult Psychiatry, Taipei City Psychiatric Center, Taipei (Drs. Lin and Chen); and the Department of Psychiatry, Dalin Tzu-Chi General Hospital and Tzu-Chi University, Hualien (Dr. Chang), Taiwan.

Supported by grants NSC 92-2314-B-038-055 (Dr. Lu), NSC 91-2314-B-039-033 (Dr. Lane), and NSC 91-2314-B-320-005 (Dr. Chang) from the National Science Council, Taipei; grant NHRI-EX-92-9134PI (Dr. Lane) from the National Health Research Institutes, Taipei; and grant CMU92-TH-03 (Dr. Lane) from the China Medical University, Taichung, Taiwan.

The authors thank Shaw-Tein Wu, B.S., and Su-Chen Chang, B.S., for technical support.

Corresponding author and reprints: Hsien-Yuan Lane, M.D., Department of Psychiatry, China Medical University Hospital, No. 2, Yuh-Der Road, Taichung 404, Taiwan (e-mail: hylane@pchome.com.tw).

Clozapine, an atypical antipsychotic drug, can improve the clinical outcome of refractory schizophrenic patients[1,2] and decrease the economic burden of the disease on society.[3] However, clozapine still fails to elicit sufficient therapeutic response in a substantial portion of patients even if a threshold plasma drug concentration (350–420 mg/dL) has been attained.[4,5] Moreover, usage of clozapine has been limited because of a side effect profile including hypotension, seizure, sedation, and hematologic abnormalities.[6–8] Recently, clozapine-induced weight gain,[9] serum triglyceride elevation,[10] hyperglycemia,[11,12] and new onset of type 2 diabetes mellitus[13,14] have become the focus of attention.

Since obesity is a common comorbid condition with schizophrenia,[15] schizophrenic patients are inherently at increased risk of developing obesity-related conditions such as cardiovascular disease and type 2 diabetes.[16] Also, the consequences of excessive weight gain associated with antipsychotic drugs may include poor compliance with or even discontinuation of therapy by the patient.[17] Therefore, management with specific diets[18] or adjuvant drugs to prevent or decrease antipsychotic-induced weight gain is a logical strategy. The agents that have been tested in antipsychotic-treated schizophrenic patients include amantadine,[19–21] metformin,[22,23] nizatidine,[24] orlistat,[25] and topiramate.[26,27] However, there is an understandable concern about the economic burden of adding another drug, often expensive, with its own side effects and with potential drug interaction in poly-medicated patients.

Add-on selective serotonin reuptake inhibitors (SSRIs) may be tried when clozapine fails to bring sufficient thera-

peutic response,[8,28–30] especially with respect to depressive or negative symptomatology. Although several SSRIs, particularly fluvoxamine, interact pharmacokinetically and pharmacodynamically with clozapine,[31–34] several pilot studies reported that addition of fluvoxamine to clozapine treatment was well tolerated and could improve the psychopathology of schizophrenic patients.[35–37] The 2 principal metabolites of clozapine, norclozapine and clozapine N-oxide, represent most of the total metabolite formation.[7] In comparison with clozapine, norclozapine produces lower therapeutic activity and perhaps more adverse effects, whereas clozapine N-oxide is almost inactive.[38] Norclozapine may be responsible for the myelotoxicity of clozapine treatment.[39–41] In addition, norclozapine, a more potent 5-HT_{2C} antagonist than clozapine itself,[42] may be more likely to generate such side effects as weight gain or convulsion.[43] Recent studies by our group[37,44] showed that coadministration of fluvoxamine could increase steady-state plasma clozapine levels, decrease plasma norclozapine/clozapine ratios, and reduce clozapine dose (and thus cost) needed in refractory schizophrenic patients.

Hinze-Selch et al.[45] compared the effects of coadministration of clozapine and fluvoxamine (N = 11) versus clozapine monotherapy (N = 12) on plasma levels of cytokines and body weight in schizophrenic patients after 6 weeks of medication. The results showed that coadministration of fluvoxamine enhanced and accelerated the clozapine-induced increase in plasma leptin levels without significant effect on clozapine-induced weight gain. Due to the relatively small sample size and the short duration of the study,[45] the effects of coadministered fluvoxamine on clozapine-induced weight changes and metabolic disturbances require further elucidation. We hypothesized that fluvoxamine cotreatment could attenuate weight gain and serum levels of glucose, triglycerides, and cholesterol in clozapine recipients.

METHOD

Subjects and Procedures

The institutional review board of the Taipei City Psychiatric Center, Taipei, Taiwan, approved this prospective, randomized, open-label study. After a description of the study to the patients, written informed consent was obtained. Patients were evaluated by the research psychiatrists after a thorough medical and neurologic workup. The Structured Clinical Interview for DSM-IV[46] was conducted to determine the diagnosis. All enrolled patients fulfilled the DSM-IV diagnosis of schizophrenia and were treatment-resistant to typical antipsychotics.[1] None of the patients were receiving clozapine or other atypical antipsychotics prior to initiation of clozapine treatment. None of the patients had been pretreated with depot antipsychotics for at least 6 months before study entry. Patients with an Axis I diagnosis other than schizophrenia or with a medical or neurologic illness were excluded, as were patients with medical conditions that could confound metabolic assessments. The study was conducted from August 1999 to October 2002.

A total of 68 Han Chinese inpatients aged 18 to 60 years were included in this study and were randomly assigned to 2 treatment groups: clozapine monotherapy (N = 34) and fluvoxamine-clozapine coadministration (N = 34). The monotherapy patients received clozapine (up to 600 mg/day). The coadministration patients received a fixed dose of fluvoxamine (50 mg/day) and low doses of clozapine (up to 250 mg/day). Clozapine dosage was individually titrated in all patients according to clinical efficacy and adverse effects. Since adjunctive fluvoxamine can increase plasma clozapine concentration by approximately 2.3 times,[37] we thus utilized a lower dose range of clozapine in the coadministration group. Medications (e.g., lithium, carbamazepine, valproic acid, propranolol, tricyclic antidepressants, or other SSRIs) that may influence body weight, glucose/lipid metabolism, or clozapine disposition were not allowed.[47] Among the 68 patients, 53 did not smoke, but the other 15 smoked more than 10 cigarettes per day.

All patients were hospitalized during the study period and received a routine hospital diet. The patients' body weight was measured every week. Fasting serum glucose, triglyceride, and cholesterol levels were assayed at baseline and at week 12 of treatment. We defined clinical significance as fasting glucose ≥ 126 mg/dL, total cholesterol ≥ 200 mg/dL, and triglycerides ≥ 200 mg/dL on the basis of standard guidelines of the American Diabetes Association[48] and the National Cholesterol Education Program.[49] We then determined the percentage of patients who had clinically significant changes in glucose or lipid measurements. At week 12, plasma levels of clozapine, norclozapine, and clozapine N-oxide were also analyzed. All blood samples were drawn in the fasting state and collected in the morning prior to breakfast and medication.

Clinical Assessment

Drug safety was rigorously evaluated by the investigators throughout the study period. Patients' vital signs were measured daily. Hematologic, physical, and neurologic examinations were repeated weekly. The Udvalg for Kliniske Undersogelser (UKU) Side Effect Rating Scale[50] was used biweekly to monitor extrapyramidal symptoms and other side effect profiles. Electrocardiograms, urinalyses, and biochemistry values were checked at baseline and at endpoint. General psychopathology and functioning were assessed biweekly with the Clinical Global Impressions scale (CGI)[51] and the Global Assessment of Functioning (GAF) (DSM-IV Axis V). The clinical assessments involving these 2 efficacy scales and the UKU Side Effect Rating Scale were performed by a research psychiatrist throughout the study.

Laboratory Assessment

Plasma levels of clozapine, norclozapine, and clozapine N-oxide were determined by high-performance liquid chromatography with ultraviolet detection.[52] The intraassay and interassay coefficients of variation were < 10% for clozapine and its metabolites. The lower limit of detection was 1 mg/dL for clozapine and 2 mg/dL for the metabolites. The serum levels of glucose, triglycerides, and cholesterol were measured by using the Ciba-Corning 550 express chemistry analyzer (Ciba Corning Diagnostics Corp., East Walpole, Mass.).

Statistical Analyses

Kolmogorov-Smirnov testing revealed a trend toward normality of distribution for all variables. Subgroups were compared using t test for continuous variables and χ^2 test for categorical variables. To explore the effect of the 2 treatment modalities on the time course of the variables, multivariate analysis of variance with repeated measurements and a between-subject factor (for the 2 treatment modalities) was applied. When significant effects emerged, analysis of variance for repeated measures was applied to analyze the effect of time in each of the 2 treatment groups. To identify the time points of significant differences compared with baseline, within-group tests with simple contrasts were conducted. To identify the time points of significant differences between groups, between-group t tests were performed. A p value of less than .05 was considered statistically significant.

RESULTS

The 2 groups were similar in gender, age, height, age at illness onset, smoking status, and plasma clozapine concentration (Table 1). The coadministration group, however, had significantly lower plasma levels of norclozapine and clozapine N-oxide (Table 1). This result supports previous study findings that add-on fluvoxamine decreases plasma norclozapine to clozapine ratios.[37,44] Baseline body weight, body mass index (BMI), and fasting serum glucose, triglyceride, and cholesterol levels were also comparable in the 2 groups (Tables 2 and 3). All subjects completed the 12-week trial.

Clozapine dose increased significantly across time in both treatment groups but was significantly lower in the patients in the coadministration treatment group from week 2 onward (Table 2). In accordance, antecedent studies suggest that add-on fluvoxamine can decrease the clozapine dose needed.[37,44]

Changes in Weight, BMI, Glucose, Cholesterol, and Triglycerides

As shown in Table 2, both body weight and BMI remained rather constant after treatment in the coadministration group. In the clozapine monotherapy group, however, body weight and BMI at weeks 4, 8, and 12 were significantly higher than the baseline values. No statistically significant difference in body weight or BMI was found between the 2 groups at any time point. Eleven subjects in the clozapine monotherapy group gained ≥ 7% in weight at week 12 compared with 3 subjects in the coadministration group (p = .03).

Table 1. Patient Demographics at Baseline and Plasma Levels of Clozapine and Metabolites at Endpoint (week 12)

Variable	Coadministration Group	Monotherapy Group
Gender, N		
Male	10	10
Female	24	24
Age, mean ± SD, y	32.9 ± 8.5	35.1 ± 9.4
Height, mean ± SD, cm	165.3 ± 8.7	163.6 ± 6.0
Age at onset, mean ± SD, y	21.6 ± 4.8	21.0 ± 4.5
Smokers, N	8	7
Nonsmokers, N	26	27
Plasma clozapine, mean ± SD, mg/dL	509.8 ± 281.1	502.0 ± 220.6
Plasma norclozapine, mean ± SD, mg/dL[a]	179.0 ± 95.8	242.8 ± 100.3
Plasma clozapine N-oxide, mean ± SD, mg/dL[b]	28.6 ± 15.9	61.2 ± 28.4

[a]Significant difference between treatment groups at week 12 (p = .009).
[b]Significant difference between treatment groups at week 12 (p < .001).

Table 3 reveals the metabolic profiles of the 2 treatment groups. In the coadministration patients, fasting glucose, total cholesterol, and triglyceride levels did not change significantly after treatment. In contrast, the monotherapy patients had significant increases in fasting glucose and triglyceride levels and trend (insignificant) increase in total cholesterol levels after treatment. Compared with the cotreatment patients, the monotherapy patients also had significantly higher levels of glucose and triglycerides at week 12. There is a consistency in the direction of the results across measures in Tables 2 and 3, which could decrease the necessity for raising the p value. We therefore did not perform the correction here. Certainly, for a more rigorous analysis, an adjustment of the p value could still be utilized.

In both treatment groups, the weight change was correlated with the change in serum glucose levels (r = 0.70, p < .001), triglyceride levels (r = 0.35, p = .003), and total cholesterol levels (r = 0.40, p = .001). The glucose level change was correlated with the changes in triglyceride levels (r = 0.49, p < .001) and in total cholesterol levels (r = 0.62, p < .001).

In the clozapine monotherapy group, the rates of hypertriglyceridemia increased from 8.8% (N = 3) at baseline to 11.8% (N = 4) at week 12 ($\chi^2 = 4.63$, df = 1, p = .03). In the coadministration group, the rates of hypertriglyceridemia were unchanged: 11.8% (N = 4) at baseline and at week 12. The rate of hypercholesterolemia did not change significantly in either group. In the monotherapy group,

Table 2. Body Weight, BMI, and Dosage of Clozapine in Coadministration and Monotherapy Groups

Variable	Baseline	Week 2	Week 4	Week 8	Week 12
Body weight, mean ± SD, kg					
Coadministration group	67.9 ± 14.1	68.1 ± 14.1	68.3 ± 14.0	68.6 ± 13.7	68.8 ± 13.5
Monotherapy group	65.3 ± 12.1	65.8 ± 12.1	66.3 ± 12.0[a]	67.2 ± 12.0[a]	68.5 ± 12.0[a]
BMI, mean ± SD, kg/m^2					
Coadministration group	24.8 ± 4.6	24.9 ± 4.6	24.9 ± 4.6	25.0 ± 4.4	25.1 ± 4.3
Monotherapy group	24.3 ± 3.3	24.5 ± 3.3	24.6 ± 3.3[a]	25.0 ± 3.2[a]	25.4 ± 3.2[a]
Clozapine dosage, mean ± SD, mg/d					
Coadministration group	NA	102.2 ± 9.5	121.3 ± 40.9[b,c]	128.7 ± 52.3[b,c]	130.1 ± 56.3[b,c]
Monotherapy group	NA	159.6 ± 44.0[c]	266.2 ± 74.6[b,c]	297.1 ± 104.9[b,c]	307.4 ± 120.8[b,c]

[a]Significant difference from baseline ($p < .05$).
[b]Significant difference from week 2 ($p < .05$).
[c]Significant difference between treatment groups at the same time point ($p < .05$).
Abbreviations: BMI = body mass index, NA = not applicable.

Table 3. Serum Glucose, Total Cholesterol, and Triglyceride Levels at Baseline and Endpoint (week 12)

Variable	Baseline	Endpoint
Glucose, mean ± SD, mg/dL		
Coadministration group	91.9 ± 7.3	92.3 ± 6.0
Monotherapy group	91.2 ± 7.1	95.6 ± 6.7[a,b]
Total cholesterol, mean ± SD, mg/dL		
Coadministration group	178.8 ± 19.5	180.2 ± 23.9
Monotherapy group	181.8 ± 16.6	190.4 ± 21.5
Triglycerides, mean ± SD, mg/dL		
Coadministration group	107.7 ± 46.9	109.8 ± 46.2
Monotherapy group	108.6 ± 32.2	132.5 ± 45.9[b,c]

[a]Significant difference from baseline ($p = .035$).
[b]Significant difference between treatment groups at the same time point ($p < .001$).
[c]Significant difference from baseline ($p = .041$).

the rates of hypercholesterolemia were 17.6% (N = 6) at baseline and 20.6% (N = 7) at week 12. In the coadministration group, the rates of hypercholesterolemia were 11.8% (N = 4) at baseline and at week 12. During the 12-week study, no patients developed hyperglycemia or diabetes mellitus.

Influence of Plasma Norclozapine Levels

In both treatment groups, the weight change was correlated with the plasma level of norclozapine (N = 68, r = 0.27, p = .026), whereas no correlation was found between weight change and plasma clozapine level. The changes in blood sugar and triglyceride levels were also correlated with the plasma concentration of norclozapine (r = 0.34, p = .005; and r = 0.27, p = .028), but not with the plasma clozapine level. There was a tendency toward a correlation between the change in the total cholesterol level and the plasma level of norclozapine (r = 0.21, p = .07).

Safety and Efficacy

The frequencies of other treatment-emergent adverse events in the coadministration and monotherapy groups were similar: sedation (N = 10 and N = 12), hypersalivation (N = 6 and N = 9), constipation (N = 8 and N = 6), postural hypotension (N = 4 and N = 7), tachycardia (N = 4 and N = 5), accommodation disturbances (N = 2 and N = 5), and nausea (N = 2 and N = 0), respectively. These events were all mild and many of them dis appeared spontaneously. Extrapyramidal symptoms, seizures, or agranulocytosis did not occur in any patients.

The mean ± SD CGI scores in the coadministration and monotherapy groups were similar (baseline: 4.54 ± 0.53 and 4.60 ± 0.51; endpoint: 4.04 ± 0.25 and 3.98 ± 0.27) as were the GAF scores (baseline: 47.6 ± 9.3 and 47.0 ± 8.9; endpoint: 60.2 ± 3.4 and 59.5 ± 3.3), respectively.

DISCUSSION

As expected, the clozapine monotherapy group had statistically significant increases in weight, BMI, and serum glucose and triglyceride levels and a trend increase in serum levels of total cholesterol from baseline. Our data further suggest that add-on fluvoxamine attenuates the effects of clozapine on body weight, BMI, and serum glucose and triglyceride levels (and possibly total cholesterol levels).

One possible explanation for the between-group differences could be that fluvoxamine itself can decrease body weight and serum levels of glucose and triglycerides (and possibly total cholesterol). Fluvoxamine could modulate corticotropin-releasing hormone (CRH) or CRH-like peptides and thus lead to significant weight loss in animal studies.[53] Some investigators have also reported weight reduction effects and increased metabolic rates with fluvoxamine,[54,55] but others have not supported such results.[56] The ability of clozapine to stimulate insulin secretion directly from the beta cells may explain its weight-gain and diabetogenic effects.[57,58] Insulin levels in the Zucker rats model were reduced following fluvoxamine administration.[53] Also, fluvoxamine might have a cholesterol-lowering effect.[56] Therefore, this coadministration strategy may neutralize the metabolic disturbances of clozapine medication. However, 2 recent studies suggest that coadministration of fluoxetine (another SSRI) cannot lessen olanzapine-induced weight gain.[59,60] Further studies are required to substantiate the weight effect of adjunctive fluvoxamine.

Another possible explanation for the between-group differences is that fluvoxamine alters pharmacokinetic and/or pharmacodynamic characteristics of clozapine. Five cytochrome P450 (CYP) isoenzymes, 1A2, 2C9, 2C19, 2D6, and 3A4, are able to mediate the demethylation of clozapine, whereas only CYP3A4 catalyzes the formation of clozapine N-oxide.[61–63] Fluvoxamine inhibits the activities of all 5 of these isoenzymes.[34] The inhibition of clozapine metabolism is at least partly due to the inhibition of CYP isoforms.[34] Several studies reported that clozapine led to significant increases in serum levels of triglycerides and/or total cholesterol.[11,58,64] The effect of serotonin 5-HT_{2C} antagonism has been postulated as a pharmacologic mechanism underlying generally greater weight gain experienced with atypical antipsychotics. Norclozapine is a more potent 5-HT_{2C} antagonist than clozapine itself.[42] Fluvoxamine coadministration can decrease the plasma norclozapine/clozapine ratio[37,44] and may thus attenuate the metabolic abnormalities in clozapine recipients. In accordance, the changes in weight and in serum glucose, triglyceride, and, perhaps, total cholesterol levels in our subjects were correlated with plasma levels of norclozapine but not with plasma levels of clozapine.

In the current study, the coadministration group had significantly lower clozapine dosages than the monotherapy group. Several studies reported that the correlations between clozapine dose and weight gain were not significant.[65,66] However, stepwise multiple regression analysis showed that clozapine dose contributed to final body mass.[67] This may also explain in part why the coadministration group, which had a lower dose of clozapine, gained less weight. The relationships between clozapine dosage and serum glucose, total cholesterol, or triglyceride levels remain unclear.[12,58] It has been suggested that the metabolic abnormalities associated with clozapine are probably concentration-dependent rather than dose-dependent.[68] In our study, we further found that the changes in body weight and blood sugar and triglyceride levels were correlated with the plasma levels of norclozapine but not with clozapine levels. The sum plasma levels of clozapine, norclozapine, and clozapine N-oxide were not correlated with weight changes or any of the metabolic measures (not shown).

Several pilot studies reported that addition of fluvoxamine to clozapine treatment was well tolerated and could improve the psychopathology of schizophrenic patients.[35–37] Of note, caution should be exercised with this combination, as the clozapine concentration may increase by a factor of 5–10 in some subjects. The pronounced increase in clozapine level might carry the risk of worsening psychosis[69] or even sudden death.[70] If this combined treatment is applied, conservative introduction with reduced clozapine dosage and careful therapeutic drug monitoring of clozapine concentration are recommended.

Several limitations in our study deserve attention. First, clinical variables (e.g., adverse reaction and psychopathology) were compared between the clozapine monotherapy and fluvoxamine-clozapine coadministration groups under an open-label design. Second, some laboratory measurements (e.g., insulin, leptin, low-density lipoprotein, and high-density lipoprotein) were unavailable. Third, the study duration was limited to 12 weeks. Long-term effects of adjuvant fluvoxamine on clozapine-induced metabolic disturbances remain unclear.

Drug names: amantadine (Symmetrel), carbamazepine (Carbatrol, Tegretol, and others), clozapine (Clozaril and others), fluoxetine (Prozac and others), lithium (Eskalith, Lithobid, and others), metformin (Metaglip, Glucovance, and others), nizatidine (Axid), olanzapine (Zyprexa), orlistat (Xenical), propranolol (Inderide, Inderal, and others), topiramate (Topamax), valproic acid (Depakene).

REFERENCES

1. Kane J, Honigfeld G, Singer J, et al. Clozapine for the treatment-resistant schizophrenic: a double-blind comparison with chlorpromazine. Arch Gen Psychiatry 1988;45:789–796
2. Rosenheck R, Cramer J, Xu W, et al. A comparison of clozapine and haloperidol in hospitalized patients with refractory schizophrenia. Department of Veterans Affairs Cooperative Study Group on Clozapine in Refractory Schizophrenia. N Engl J Med 1997;337:809–815
3. Meltzer HY, Cola PA. The pharmacoeconomics of clozapine: a review. J Clin Psychiatry 1994;55(9,suppl B):161–165
4. Perry PJ, Miller DD, Arndt SV, et al. Clozapine and norclozapine plasma concentrations and clinical response of treatment-refractory schizophrenic patients. Am J Psychiatry 1991;148:231–235
5. Lane HY, Chang WH. Clozapine versus risperidone in treatment-refractory schizophrenia: possible impact of dosing strategies [letter]. J Clin Psychiatry 1999;60:487–488
6. Buchanan RW. Clozapine: efficacy and safety. Schizophr Bull 1995;21:579–591
7. Jann MW, Grimsley SR, Gray EC, et al. Pharmacokinetics and pharmacodynamics of clozapine. Clin Pharmacokinet 1993;24:161–176
8. Lieberman JA. Maximizing clozapine therapy: managing side effects. J Clin Psychiatry 1998;59(suppl 3):38–43
9. Allison DB, Mentore JL, Heo M, et al. Antipsychotic-induced weight gain: a comprehensive research synthesis. Am J Psychiatry 1999;156:1686–1696
10. Gaulin BD, Markowitz JS, Caley CF, et al. Clozapine-associated elevation in serum triglycerides. Am J Psychiatry 1999;156:1270–1272
11. Henderson DC, Cagliero E, Gray C, et al. Clozapine, diabetes mellitus, weight gain, and lipid abnormalities: a five-year naturalistic study. Am J Psychiatry 2000;157:975–981
12. Lindenmayer JP, Nathan AM, Smith RC. Hyperglycemia associated with the use of atypical antipsychotics. J Clin Psychiatry 2001;62(suppl 23):30–38
13. Popli AP, Konicki PE, Jurjus GJ, et al. Clozapine and associated diabetes mellitus. J Clin Psychiatry 1997;58:108–111
14. Hagg S, Joelsson L, Mjorndal T, et al. Prevalence of diabetes and impaired glucose tolerance in patients treated with clozapine compared with patients treated with conventional depot neuroleptic medications. J Clin Psychiatry 1998;59:294–299
15. Allison DB, Fontaine KR, Heo M, et al. The distribution of body mass index among individuals with and without schizophrenia. J Clin Psychiatry 1999;60:215–220
16. Mukherjee S, Decina P, Bocola V, et al. Diabetes mellitus in schizophrenic patients. Compr Psychiatry 1996;37:68–73
17. Perkins DO. Predictors of noncompliance in patients with schizophrenia. J Clin Psychiatry 2002;63:1121–1128
18. Lane HY, Jann MW, Chang YC, et al. Repeated ingestion of grapefruit juice does not alter clozapine's steady-state plasma levels, effectiveness, and tolerability. J Clin Psychiatry 2001;62:812–817
19. Correa N, Opler LA, Kay SR, et al. Amantadine in the treatment of neuroendocrine side effects of neuroleptics. J Clin Psychopharmacol 1987;7:91–95
20. Floris M, Lejeune J, Deberdt W. Effect of amantadine on weight gain

during olanzapine treatment. Eur Neuropsychopharmacol 2001;11: 181–182
21. Gracious BL, Krysiak TE, Youngstrom EA. Amantadine treatment of psychotropic-induced weight gain in children and adolescents: case series. J Child Adolesc Psychopharmacol 2002;12:249–257
22. Baptista T, Hernandez L, Prieto LA, et al. Metformin in obesity associated with antipsychotic drug administration: a pilot study [letter]. J Clin Psychiatry 2001;62:653–655
23. Morrison JA, Cottingham EM, Barton BA. Metformin for weight loss in pediatric patients taking psychotropic drugs. Am J Psychiatry 2002; 159:655–657
24. Sacchetti E, Guarneri L, Bravi D. H_2 antagonist nizatidine may control olanzapine-associated weight gain in schizophrenic patients. Biol Psychiatry 2000;48:167–168
25. Anghelescu I, Klawe C, Benkert O. Orlistat in the treatment of psychopharmacologically induced weight gain [letter]. J Clin Psychopharmacol 2000;20:716–717
26. Dursun SM, Devarajan S. Clozapine weight gain, plus topiramate weight loss [letter]. Can J Psychiatry 2000;45:198
27. Levy E, Margolese HC, Chouinard G. Topiramate produced weight loss following olanzapine-induced weight gain in schizophrenia [letter]. J Clin Psychiatry 2002;63:1045
28. Centorrino F, Baldessarini RJ, Frankenburg FR, et al. Serum levels of clozapine and norclozapine in patients treated with selective serotonin reuptake inhibitors. Am J Psychiatry 1996;153:820–822
29. Chong SA, Remington G. Clozapine augmentation: safety and efficacy. Schizophr Bull 2000;26:421–440
30. Buckley P, Miller A, Olsen J, et al. When symptoms persist: clozapine augmentation strategies. Schizophr Bull 2001;27:615–628
31. Jefferson JW. Drug interactions: friend or foe? J Clin Psychiatry 1998;59(suppl 4):37–47
32. Greenblatt DJ, von Moltke LL, Harmatz JS, et al. Drug interactions with newer antidepressants: role of human cytochromes P450. J Clin Psychiatry 1998;59(suppl 15):19–27
33. Chang WH, Augustin B, Lane HY, et al. In-vitro and in-vivo evaluation of the drug-drug interaction between fluvoxamine and clozapine. Psychopharmacology (Berl) 1999;145:91–98
34. Olesen OV, Linnet K. Fluvoxamine-clozapine drug interaction: inhibition in vitro of five cytochrome P450 isoforms involved in clozapine metabolism. J Clin Psychopharmacol 2000;20:35–42
35. Szegedi A, Anghelescu I, Wiesner J, et al. Addition of low-dose fluvoxamine to low-dose clozapine monotherapy in schizophrenia: drug monitoring and tolerability data from a prospective clinical trial. Pharmacopsychiatry 1999;32:148–153
36. Lammers CH, Deuschle M, Weigmann H, et al. Coadministration of clozapine and fluvoxamine in psychotic patients: clinical experience. Pharmacopsychiatry 1999;32:76–77
37. Lu ML, Lane HY, Chen KP, et al. Fluvoxamine reduces the clozapine dosage needed in refractory schizophrenic patients. J Clin Psychiatry 2000;61:594–599
38. Spina E, Avenoso A, Facciola G, et al. Relationship between plasma concentrations of clozapine and norclozapine and therapeutic response in patients with schizophrenia resistant to conventional neuroleptics. Psychopharmacology (Berl) 2000;148:83–89
39. Gerson SL, Arce C, Meltzer HY. N-desmethylclozapine: a clozapine metabolite that suppresses haemopoiesis. Br J Haematol 1994;86: 555–561
40. Mauri MC, Rudelli R, Bravin S, et al. Clozapine metabolism rate as a possible index of drug-induced granulocytopenia. Psychopharmacology (Berl) 1998;137:341–344
41. Deliliers GL, Servida F, Lamorte G, et al. In vitro effect of clozapine on hemopoietic progenitor cells. Haematologica 1998;83:882–889
42. Kuoppamaki M, Syvalahti E, Hietala J. Clozapine and N-desmethylclozapine are potent 5-HT1C receptor antagonists. Eur J Pharmacol 1993;245:179–182
43. Tecott LH, Sun LM, Akana SF, et al. Eating disorder and epilepsy in mice lacking 5-HT2c serotonin receptors. Nature 1995;374:542–546
44. Lu ML, Lane HY, Jann MW, et al. Dosing strategies of clozapine-fluvoxamine cotreatment. J Clin Psychopharmacol 2002;22:626–628
45. Hinze-Selch D, Deuschle M, Weber B, et al. Effect of coadministration of clozapine and fluvoxamine versus clozapine monotherapy on blood cell counts, plasma levels of cytokines and body weight. Psychopharmacology (Berl) 2000;149:163–169
46. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. Washington, DC, American Psychiatric Association; 1994
47. Lane HY, Su KP, Chang WH, et al. Elevated plasma clozapine concentrations after phenobarbital discontinuation [letter]. J Clin Psychiatry 1998;59:131–133
48. American Diabetes Association. Screening for type 2 diabetes. Diabetes Care 2000;23(suppl 1):S20–S23
49. Summary of the second report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel II). JAMA 1993;269:3015–3023
50. Lingjaerde O, Ahlfors UG, Bech P, et al. The UKU Side Effect Rating Scale: a new comprehensive rating scale for psychotropic drugs and cross-sectional study of side effects in neuroleptic-treated patients. Acta Psychiatr Scand Suppl 1987;334:1–100
51. Guy W. ECDEU Assessment Manual for Psychopharmacology. US Dept Health, Education, and Welfare publication (ADM) 76-338. Rockville, Md: National Institute of Mental Health; 1976; 218–222
52. Lane HY, Chang YC, Chang WH, et al. Effects of gender and age on plasma levels of clozapine and its metabolites: analyzed by critical statistics. J Clin Psychiatry 1999;60:36–40
53. Wieczorek I, Schulz C, Jarry H, et al. The effects of the selective serotonin reuptake-inhibitor fluvoxamine on body weight in Zucker rats are mediated by corticotropin-releasing hormone. Int J Obes Relat Metab Disord 2001;25:1566–1569
54. Abell CA, Farquhar DL, Galloway SM, et al. Placebo controlled double-blind trial of fluvoxamine maleate in the obese. J Psychosom Res 1986;30:143–146
55. Fernstrom MH, Massoudi M, Kupfer DJ. Fluvoxamine and weight loss [letter]. Biol Psychiatry 1988;24:948–949
56. de Zwaan M, Nutzinger DO. Effect of fluvoxamine on total serum cholesterol levels during weight reduction. J Clin Psychiatry 1996;57:346–348
57. Umbricht DS, Pollack S, Kane JM. Clozapine and weight gain. J Clin Psychiatry 1994;55(9, suppl B):157–160
58. Henderson DC. Clozapine: diabetes mellitus, weight gain, and lipid abnormalities. J Clin Psychiatry 2001;62(suppl 23):39–44
59. Poyurovsky M, Pashinian A, Gil-Ad I, et al. Olanzapine-induced weight gain in patients with first-episode schizophrenia: a double-blind, placebo-controlled study of fluoxetine addition. Am J Psychiatry 2002;159:1058–1060
60. Bustillo JR, Lauriello J, Parker K, et al. Treatment of weight gain with fluoxetine in olanzapine-treated schizophrenic outpatients. Neuropsychopharmacology 2003;28:527–529
61. Pirmohamed M, Williams D, Madden S, et al. Metabolism and bioactivation of clozapine by human liver in vitro. J Pharmacol Exp Ther 1995;272:984–990
62. Linnet K, Olesen OV. Metabolism of clozapine by c-DNA expressed human cytochrome P450 enzymes. Drug Metab Dispos 1997;25: 1379–1382
63. Prior TI, Chue PS, Tibbo P, et al. Drug metabolism and atypical antipsychotics. Eur Neuropsychopharmacol 1999;9:301–309
64. Wirshing DA, Boyd JA, Meng LR, et al. The effects of novel antipsychotics on glucose and lipid levels. J Clin Psychiatry 2002;63:856–865
65. Melkersson KI, Hulting AL, 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
66. Melkersson KI, Hulting AL. Insulin and leptin levels in patients with schizophrenia or related psychoses: a comparison between different antipsychotic agents. Psychopharmacology (Berl) 2001;154:205–212
67. Frankenburg FR, Zanarini MC, Kando J, et al. Clozapine and body mass change. Biol Psychiatry 1998;43:520–524
68. Melkersson KI, Dahl ML. Relationship between levels of insulin or triglycerides and serum concentrations of the atypical antipsychotics clozapine and olanzapine in patients on treatment with therapeutic doses. Psychopharmacology (Berl) 2003;170:157–166
69. Chong SA, Tan CH, Lee HS. Worsening of psychosis with clozapine and selective serotonin reuptake inhibitor combination: two case reports. J Clin Psychopharmacol 1997;17:68–69
70. Tie H, Walker BD, Singleton CB, et al. Clozapine and sudden death. J Clin Psychopharmacol 2001;21:630–632

