ƒ ‹ F | Œfia‹ ˙'e›ß• |–M^D‹ ª¤s›p e ƒ¤"G‡ł§i

Clozapine ¤ ¥ ¸ fluvoxamine „ ' ^ł"v«‹"°fl«⁄ ıflg–w" ⁄§

łfi˜‹ ª¤s

›p e^ §¡G §O«‹ ›p e

›p e‰ ¸s„¡GNSC92–2314–B–038–055–

ıƒ · ¶¡¡G92 ƒ~08 ⁄°01 ⁄ ƒ 94 ƒ~07 ⁄°31 ⁄Ø

ıƒ ‡ ƒ ¡G» O ¥´ ˙⁄j ˙"°fl«

›p e¥ D ø⁄¡HG¿ c ˙s¤}

ƒ ƒP¥ D ø⁄¡HG‡ ¢ ´"a

‡ł§i^ «‹¡G"°´†‡ł§i

‡ B † zŁ¡fG¡¥»›p e¥ i ⁄ ‰ ¶‹ d,

⁄⁄ ¥` Œ 94 ƒ~10 ⁄°13 ⁄Ø

Background: Adjunctive fluvoxamine inhibits clozapine metabolism, reduces the clozapine dose needed for schizophrenia treatment, and decreases plasma norclozapine (a toxic metabolite of clozapine) to clozapine ratios. This study aimed to testify fluvoxamine effects on clozapine-related weight gain, hyperglycemia, and lipid abnormalities and to evaluate the influences of plasma clozapine and norclozapine levels on body weight and metabolism changes.

Method: Sixty-eight treatment-resistant schizophrenia inpatients were randomly assigned into two treatments for 12 weeks. The monotherapy group (N = 34) received clozapine alone (≤ 600 mg/day). The coadministration group (N = 34) received fluvoxamine (50 mg/day) plus low-doe clozapine (≤ 250 mg/day).

Results: The two groups were similar in demographic data, baseline body weight and BMI, baseline serum glucose, triglycerides and cholesterol, and steady-state plasma clozapine concentration. The monotherapy patients (but not the coadministration patients) had significantly higher body weight, BMI, serum glucose and triglycerides after treatment than at baseline. At week 12, the monotherapy patients also had significantly higher glucose, triglycerides, and norclozapine (and numerically higher cholesterol) levels than the cotreatment patients. The changes in weight and serum levels of sugar and triglycerides were significantly correlated to the plasma norclozapine concentration, but not to plasma 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 the increases in weight and serum levels of sugar and triglycerides.

Key words: Clozapine, Fluvoxamine, Metabolic Disturbance, Weight Gain.

INTRODUCTION

Clozapine, an atypical antipsychotic drug, can improve the outcome of refractory schizophrenic patients[1,2] and decrease the economic burden on society.[3] However, it still fails to bring 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, its usage has been limited because of side-effect profiles including hypotension, seizure, sedation, and hematological abnormalities.[6-8] Recently, clozapine induced weight gain,[9] serum triglycerides elevation,[10] hyperglycemia,[11,12] and new onset of Type II diabetes mellitus[13,14] have become the focus of attention.

Weight gain has been a documented side effect of antipsychotic drug use for over 40 years.[15,16] The consequences of excessive weight gain associated with antipsychotic drugs include poor compliance or even discontinuation of therapy by the patients.[17] Poor adherence almost always leads to relapse and a worsened long-term outcome. Since obesity is a common comorbid condition with schizophrenia,[18] schizophrenic patients are inherently at increased risk of developing obesity-related conditions such as cardiovascular disease and type II diabetes.[19] Fontaine et al.[20] found that 492 suicide deaths per 100,000 schizophrenic patients would be prevented over 10 years with the use of clozapine compared to 416 additional deaths due to antipsychotic induced weight gain. They suggested that the lives saved via clozapine may essentially be offset by the deaths due to weight gains.[20]

Accumulated experience has led experts to emphasize how difficult it is to achieve a stable normal weight once obesity is well established.[21] There are some inherent difficulties for schizophrenic patients to adhere to strict weight-loss programs. Therefore, management with specific diets[22] or adjuvant drugs to prevent or decrease antipsychotics-induced weight gain is a logical strategy. The agents that have been tested in antipsychotics-treated schizophrenic patients include amantadine,[23-25] metformin,[26,27] nizatidine,[28] orlistat,[29] and topiramate.[30,31] 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 to already poly-medicated patients.

Add-on selective serotonin reuptake inhibitors (SSRIs) may be tried when clozapine fails to bring sufficient therapeutic response,[8,32-34] especially with respect to depressive or negative symptomatology. Although several SSRIs, particularly fluvoxamine, interact pharmacokinetically and phramacodynamically with clozapine,[35-38] several pilot studies reported that addition of fluvoxamine to clozapine treatment was well tolerated and could improve the psychopathology of schizophrenic patients.[39-41] The two principal metabolites of clozapine, norclozapine and clozapine N-oxide, represent most of the total metabolite formation.[7] Clozapine N-oxide is a rather inactive compound.[7] Norclozapine, however, produces lower therapeutic activity and perhaps more adverse effects than the parent drug.[42] Norclozapine may be responsible for the myelotoxicity of clozapine treatment.[43-45] In addition, norclozapine, a more potent 5-HT_{2C} antagonist than clozapine itself,[46] may be more likely to generate such side effects as weight gain or convulsion.[47] In recent studies by our group,[41,48] 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.[49] 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, 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 facility's institutional review board 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 neurological workup. The Structured Clinical Interview for DSM-IV[50] was conducted for the diagnosis. All enrolled patients fulfilled the DSM-IV diagnosis of schizophrenia and were "treatment-resistant" to typical antipsychotics.[1] None were receiving clozapine or other atypical antipsychotics prior to initiation of clozapine treatment. None of the patients had been pretreated with depot antipsychotics during at least 6 months before study entry. Patients with Axis I diagnosis other than schizophrenia or medical or neurological illness were excluded. Subjects were excluded for medical conditions that could confound metabolic assessments. All were Han Chinese inpatients and aged 18-60 years.

A total of 68 inpatients were included into this study and were randomized into two treatment groups: clozapine monotherapy (N = 34) and fluvoxamine-clozapine coadministration (N = 34). The monotherapy patients received clozapine alone (up to 600 mg/day). The coadministration 34 patients received a fixed dose of fluvoxamine (50 mg/day) and low doses of clozapine (up to 250 mg/day). Clozapine dosage in each patient of both groups was individually titrated according to clinical efficacy and adverse effects. Since adjunctive fluvoxamine can increase plasma clozapine concentration by around 2.3 times,[41] 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.[51] Among the 68 patients, 53 did not smoke but the other 15 consumed more than ten cigarettes per day.

All patients were hospitalized during the study period and received a routine hospital diet. The body weight was measured every week. Fasting serum glucose, triglycerides, and cholesterol levels were assayed at baseline and the 12th week of treatment. Based on the standard guidelines set forth by the American Diabetes Association[52] and the National Cholesterol Education Program,[53] we defined clinical significance as fasting glucose ≥ 126 mg/dL, total cholesterol ≥ 200 mg/dL, and triglycerides ≥ 200 mg/dL. 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. Fasting blood samples and body weight were obtained in the morning, 12 hours after the bedtime drug administration.

Clinical assessment

Drug safety was rigorously evaluated by the investigators at baseline (day 0) and under the fluvoxamine-clozapine coadministration. Daily vital signs were measured. Hematology, physical and neurological examinations were repeated weekly. The Udvalg for Kliniske Undersogelser (UKU) Side Effect Rating Scale[54] was used biweekly for monitoring both exprapyramidal symptoms and other side-effect profiles. Electrocardiogram (ECG), urinalysis, and biochemistry were checked at baseline and endpoint. General psychopathology and functioning were biweekly assessed with Clinical Global Impression Scale (CGI)[55] and Global Assessment of Functioning Scale (GAF) (DSM-IV axis V). The clinical assessment involving these two efficacy scales and the UKU Side Effect Rating Scale was performed by a research psychiatrist throughout.

Laboratory assessment

Plasma levels of clozapine, norclozapine, and clozapine N-oxide were determined by high performance liquid chromatography with ultraviolet detection.[56] The intraassay and interassay coefficients of variation were < 10% for clozapine and its metabolites. The lower limit of detection for clozapine was 1 mg/dL, and for the metabolites was 2 mg/dL. The serum levels of glucose, triglycerides, and cholesterol were measured by using the Ciba-Corning 550 express chemistry analyzer.

Statistical analyses

The Kolmogorov-Smirnov testing revealed a trend toward normality of distribution for all variables. Subgroups were compared using t-test for continuous variables and chi-square test for categorical variables. To explore the effect of the two treatment modalities on the time course of the variables, multivariate analysis of variance with repeated measurements and with a between-subject factor (for the two treatment modalities) was applied. When significant effects emerged, analysis of variance for repeated measures was applied to analyse the effect of time in each of the two treatments, respectively. To identify the time points of significant differences compared to baseline, within-group tests with simple contrasts were conducted. To identify the time points of significant differences, between-group t-tests were performed. A p-value of less than 0.05 was considered to have statistical significance.

RESULTS

The two groups were similar in gender, age, height, age of 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 finding that add-on fluvoxamine decreases plasma norclozapine to

clozapine ratios.[41,48] Baseline body weight and BMI and fasting serum levels of glucose, triglycerides, and cholesterol were also comparable in the two 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 on the coadministration treatment from week 2 onwards (Table 2). In accordance, antecedent studies suggest that add-on fluvoxamine can decrease the clozapine dose needed.[41,48]

Changes in weight, BMI, glucose, cholesterol, and triglycerides

As shown in Table 2, both body weight and BMI kept 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 two groups at each time point. Eleven subjects in clozapine monotherapy group gained ≥ 7% in weight at 12 weeks compared to 3 subjects in coadministration group ($p = .03$).

Table 3 reveals the metabolic profiles. In the coadministration patients, fasting glucose, total cholesterol, and triglycerides levels did not have significant changes after treatment. In contrast, the monotherapy patients had significant increases in fasting glucose and triglycerides levels and trend (insignificant) increase in total cholesterol levels after treatment. Compared to the cotreatment patients, the monotherapy patients also had significantly higher levels of glucose and triglycerides at week 12.

The weight change was correlated to the change in serum glucose levels ($r = 0.70$, $p < .001$), in triglycerides ($r = 0.35$, $p = .003$), and in total cholesterol levels ($r = 0.40$, $p = .001$). The glucose level change was correlated to the changes in triglycerides ($r = 0.49$, $p < .001$) 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 (X^2 = 4.63, df = 1, p = .03). In the coadministration group, the rates of hypertriglyceridemia were unchanged: 11.8% (N = 4) at baseline and 11.8% (N = 4) at week 12. The rate of hypercholesterolemia did not have significant change in both groups. In the monotherapy group, 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 11.8% (N = 4) at week 12 too. During the 12-week study, no patients experienced hyperglycemia.

Influence of plasma norclozapine levels

The weight change was correlated to 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 triglycerides levels were also correlated to the plasma concentration of norclozapine (r = 0.34, p = .005; and r = 0.27, p = .028), but not to 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 cotreatment and monotherapy groups were similar: sedation (N = 10 and 12, respectively), hypersalivation (N = 6 and 9), constipation (N = 8 and 6), postural hypotension (N = 4 and 7), tachycardia (N = 4 and 5), accommodation disturbances (N = 2 and 5), and nausea (N = 2 and 0). These events were all mild and many of them disappeared spontaneously. Extrapyramidal symptoms, seizures or agranulocytosis did not occur in our patients.

The CGI scores in the cotreatment and monotherapy groups were similar (baseline: 4.54 ± 0.53 and 4.60 ± 0.51 in the 2 groups, respectively; endpoint: 4.04 ± 0.25 and 3.98 ± 0.27); and so were the GAF scores (baseline: 47.6 ± 9.3 and 47.0 ± 8.9; endpoint: 60.2 ± 3.4 and 59.5 ± 3.3).

DISCUSSION

Compared with the general population, schizophrenic patients suffer not only neurocognitive and functional impairments but also increased medical morbidity and mortality. Atypical antipsychotics may be contributors to the medical morbidity of schizophrenia patients. It has been recognized that there are differential effects among these agents on metabolic outcomes. The dibenzodiazepine-derived atypical antipsychotics (clozapine, olanzapine) are associated with greater adverse reactions on weight, glucose, and serum lipids than ziprasidone (benzisothiazolyl) or risperidone (benzisoxazole).[57] This study mainly aimed to compare the effects of clozapine monotherapy and clozapine-fluvoxamine coadministration on body weight and metabolic profiles.

As expected, the clozapine monotherapy group had statistically significant increases in weight, BMI, and serum levels of glucose and triglycerides 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 levels of glucose and triglycerides (and possibly levels of total cholesterol).

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 CRH or CRH-like peptides and thus lead to significant weight loss in animal studies.[58] Some investigators also reported weight reduction effects and increased metabolic rates of fluvoxamine,[59,60] but others did not support it.[61] The ability of clozapine to stimulate insulin secretion directly from the beta cells may explain its

weight-gain and diabetogenic effects.[62,63] Insulin levels in the Zucker rats model were reduced following fluvoxamine administration.[58] Besides, fluvoxamine might also have a cholesterol-lowering effect.[61] Therefore, this coadministration strategy may neutralize the metabolic disturbances of clozapine medication. However, two recent studies suggest that coadministration of fluoxetine (another SSRI) cannot lessen olanzapine-induced weight gain.[64,65] Further studies are required to substantiate the weight effect of adjunctive fluvoxamine.

Another possible explanation 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.[66-68] Fluvoxamine inhibits the activities of all of these five isoenzymes.[38] The inhibition of clozapine metabolism is at least partly due to the inhibition of CYP isoforms.[38] Several studies reported that clozapine led to significant increases in serum levels of triglycerides and/or total cholesterol.[11,63,69] The effect of serotonin 5-HT_{2C} antagonism has been postulated as a pharmacological mechanism underlying generally greater weight gain experienced with atypical antipsychotics. Norclozapine is a more potent 5-HT_{2C} antagonist than clozapine itself.[46] Fluvoxamine coadministration can decrease the plasma norclozapine/clozapine ratio[41,48] and may thus attenuate the metabolic abnormalities in clozapine receivers. In accordance, the changes in weight and in serum levels of glucose, triglycerides, and perhaps total cholesterol in our subjects were correlated to plasma norclozapine levels, but not to plasma clozapine levels.

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 cotreatment groups under an open-label design. Second, some laboratory measurements (e.g., insulin, leptin) 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: clozapine (Clozaril and others), fluvoxamine (Luvox).

REFERENCES

1. Kane JM, Honigfeld G., Singer J, et al. Clozapine for 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 P. 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. J Clin Psychiatry 1999; 60:487-8
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. Mefferd RB, Labrosse EH, Gawienowski AM, et al. Influence of chlorpromazine on certain biochemical variables of chronic male schizophrenics. J Nerv Ment Dis 1958; 127:167-179
16. Planansky K. Changes in weight in patients receiving a “tranquilizing” drug. Psychiatr Q 1958; 32:289-303
17. Perkins DO. Predictors of noncompliance in patients with schizophrenia. J Clin Psychiatry 2002; 63:1121-1128
18. Allison DB, Fontaine KR, Heo M, et al. The distribution of body mass index among individuals with and without schizophrenia. J Clin Psychiatry 1999; 60:215-20
19. Mukherjee S, Decina P, Bocola V, et al. Diabetes mellitus in schizophrenic patients. Compr Psychiatry 1996; 37:68-73
20. Fontaine KR, Heo M, Harrigan EP, et al. Estimating the consequences of anti-psychotic induced weight gain on health and mortality rate. Psychiatry Res 2001; 101:277-288
21. Bray GA, Greenway FL. Current and potential drugs for treatment of obesity. Endocr Rev 1999; 20:805-875
22. 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
23. 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

24. Floris M, Lejeune J, Deberdt W. Effect of amantadine on weight gain during olanzapine treatment. Eur Neuropsychopharmacol 2001;11:181-182
25. 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
26. Baptista T, Hernandez L, Prieto LA, et al. Metformin in obesity associated with antipsychotic drug administration: a pilot study. J Clin Psychiatry 2001; 62:653-655
27. Morrison JA, Cottingham EM, Barton BA. Metformin for weight loss in pediatric patients taking psychotropic drugs. Am J Psychiatry 2002; 159:655-657
28. 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
29. Anghelescu I, Klawe C, Benkert O. Orlistat in the treatment of psychopharmacologically induced weight gain. J Clin Psychopharmacol 2000; 20:716-717
30. Dursun SM, Devarajan S. Clozapine weight gain, plus topiramate weight loss. Can J Psychiatry 2000; 45:198
31. Levy E, Margolese HC, Chouinard G. Topiramate produced weight loss following olanzapine-induced weight gain in schizophrenia. J Clin Psychiatry 2002; 63:1045
32. 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
33. Chong SA, Remington G. Clozapine augmentation: safety and efficacy. Schizophr Bull 2000; 26:421-440
34. Buckley P, Miller A, Olsen J, et al. When symptoms persist: clozapine augmentation strategies. Schizophr Bull 2001; 27:615-628
35. Jefferson JW. Drug interactions--friend or foe? J Clin Psychiatry 1998; 59 (suppl 4):37-47

36. 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
37. 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
38. 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
39. 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
40. Lammers CH, Deuschle M, Weigmann H, et al. Coadministration of clozapine and fluvoxamine in psychotic patients--clinical experience. Pharmacopsychiatry 1999; 32:76-77
41. 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
42. 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
43. Gerson SL, Arce C, Meltzer HY. N-desmethylclozapine: a clozapine metabolite that suppresses haemopoiesis. Br J Haematol 1994; 86:555-561
44. 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
45. Deliliers GL, Servida F, Lamorte G, et al. In vitro effect of clozapine on hemopoietic progenitor cells. Haematologica 1998; 83:882-889

46. Kuoppamaki M, Syvalahti E, Hietala J. Clozapine and N-desmethylclozapine are potent 5-HT1C receptor antagonists. Eur J Pharmacol 1993; 245:179-182
47. Tecott LH, Sun LM, Akana SF, et al. Eating disorder and epilepsy in mice lacking 5-HT2c serotonin receptors. Nature 1995; 374:542-546
48. Lu ML, Lane HY, Jann MW, et al. Dosing strategies of clozapine-fluvoxamine cotreatment. J Clin Psychopharmacol 2002; 22:626-628
49. 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 2000; 149:163-169
50. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. Washington, DC, American Psychiatric Association, 1994
51. Lane HY, Su KP, Chang WH, et al. Elevated plasma clozapine concentrations after phenobarbital discontinuation. J Clin Psychiatry 1998; 59:131-133
52. American Diabetes Association. Screening for Type 2 Diabetes. Diabetes Care 2000; 23(suppl 1):S1-S116
53. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. 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
54. 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 1987; suppl 334:1-100
55. Guy W. ECDEU Assessment Manual for Psychopharmacology, revised. US Dept Health, Education, and Welfare publication (ADM) 76-338. Rockville, Md: National Institute of Mental Health; 1976; 217-222
56. 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

57. Lane HY, Chang YC, Cheng YC, et al. Effects of patient demographics, risperidone dosage, and clinical outcome on body weight in acutely exacerbated schizophrenia patients. J Clin Psychiatry 2003; 64;316-320
58. 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
59. 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
60. Fernstrom MH, Massoudi M, Kupfer DJ. Fluvoxamine and weight loss. Biol Psychiatry 1988; 24:948-949
61. de Zwaan M, Nutzinger DO. Effect of fluvoxamine on total serum cholesterol levels during weight reduction. J Clin Psychiatry 1996; 57:346-348
62. Umbricht DS, Pollack S, Kane JM. Clozapine and weight gain. J Clin Psychiatry 1994; 55 (suppl B):157-160
63. Henderson DC. Clozapine: diabetes mellitus, weight gain, and lipid abnormalities. J Clin Psychiatry 2001;62 (suppl 23):39-44
64. 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
65. Bustillo JR, Lauriello J, Parker K, et al. Treatment of weight gain with fluoxetine in olanzapine-treated schizophrenic outpatients. Neuropsychopharmacology 2003; 28:527-529
66. 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

67. Linnet K, Olesen OV. Metabolism of clozapine by c-DNA expressed human cytochrome P450 enzymes. Drug Metab Dispos 1997; 25:1379-1382

68. Prior TI, Chue PS, Tibbo P, et al. Drug metabolism and atypical antipsychotics. Eur Neuropsychopharmacol 1999; 9:301-309

69. 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

Table 1. Patient demographics at baseline and plasma levels of clozapine and metabolites at 12th week

	Coadministration Group	Monotherapy Group
Male:female, N	10:24	10:24
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 of onset, mean ± SD, y	21.6 ± 4.8	21.0 ± 4.5
Smokers:nonsmokers, N	8:26	7:27
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[a]	28.6 ± 15.9	61.2 ± 28.4

[a]Significant difference between treatment groups at the 12th week ($p < .05$)

Table 2. Body weight, BMI, and dosage of clozapine

	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	-	102.2 ± 9.5	121.3 ± 40.9[b,c]	128.7 ± 52.3[b,c]	130.1 ± 56.3[b,c]
Monotherapy group	-	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 ($p < .05$)

Table 3. Serum levels of glucose, total cholesterol, and triglycerides at baseline and endpoint (week 12)

	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[a,b]

[a] Significant difference from baseline ($p < .05$)

[b] Significant difference between treatment groups at the same time point ($p < .05$)