Diabetes Mellitus Among Outpatients Receiving Clozapine: Prevalence and Clinical-Demographic Correlates

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Background: Treatment with antipsychotic drugs has been associated with increased risk for developing diabetes mellitus. Recent consensus statements suggest that clozapine may pose an especially high risk. The purpose of this study is to examine the prevalence and clinical-demographic correlates of diabetes among outpatients with DSM-IV–diagnosed schizophrenia or schizoaffective disorder receiving clozapine.

Method: One hundred one outpatients receiving clozapine at the University of Rochester Department of Psychiatry, Rochester, N.Y., were evaluated between September 2002 and September 2003. Demographic data were collected from medical records, and body mass index (BMI) and body fat measurements were conducted. Diagnosis of diabetes was established through review of medical records and fasting blood glucose testing. Associations between clinical and demographic variables and diabetes were examined using t tests, Fisher exact tests, and logistic regression.

Results: Mean (SD) age of patients was 40.4 (9.5) years, and 79% were white. Mean (SD) dose and duration of clozapine treatment were 426 (164) mg/day and 5.7 (3.6) years, respectively. Point prevalence of diabetes was 25.7%. Mean (SD) BMI was 32.6 (8.0) kg/m^2, and mean (SD) body fat was 34.0% (11.0%). Logistic regression revealed significant associations between diabetes and nonwhite race/ethnicity and family history of diabetes (p = .02 and .002, respectively). No significant associations were found between diabetes prevalence and BMI or body fat.

Conclusion: Patients receiving clozapine are at substantial risk for developing diabetes, although the level of risk relative to other antipsychotic medications has not been fully determined. Clinicians should monitor all severely mentally ill patients receiving antipsychotic drugs for diabetes, with closer monitoring of patients with established demographic risk factors.

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Growing evidence suggests that clozapine treatment is associated with an increased risk for developing diabetes mellitus. Since publication of the first report of hyperglycemia associated with clozapine in 1994,[1] 37 additional cases have been described in case reports and small case series.[2–28] These reports describe cases of transient hyperglycemia,[1,8,11,20,21,24] diabetic ketoacidosis,[2–4,6,7,10,13–18,23–28] new onset diabetes mellitus,[7,10,12,19,22] and exacerbation of preexisting diabetes.[7,9] In addition to case reports, recently published clinical studies have examined the association between clozapine, insulin levels, glucose abnormalities, and diabetes.[29–49] The prevalence of diabetes in these studies has ranged from 4% in a Medicaid claims study of 531 patients[44] to 36.6% in a 5-year naturalistic study of 82 patients.[36]

Some studies suggest that clozapine is associated with a greater risk of diabetes than other antipsychotic medications,[31–37] while other studies do not.[42–48,50] Despite inconsistencies in the literature, a consensus is emerging that clozapine treatment is associated with an especially high risk of diabetes relative to other medications.[51,52] Yet clozapine remains a valuable treatment for schizophrenia because of its superior effectiveness.[52] Research is therefore needed to identify risk factors for diabetes among patients requiring clozapine therapy.

The relationship between established risk factors for diabetes mellitus and the likelihood of developing clozapine-associated diabetes is unclear. Increasing age is a known risk factor for diabetes in general,[53] and some

studies have reported a higher prevalence of glucose abnormalities among older clozapine-treated patients.[34–36] However, in a U.S. Food and Drug Administration (FDA) database study,[37] Koller et al. found the highest frequency of clozapine-associated diabetes among 31 to 50 year olds. This finding contrasted with the general population, where the frequency of diabetes peaks in the 65- to 74-year-old cohort.[37] Lund et al.[44] found an increased risk of diabetes with clozapine only among patients aged 20 to 34 years, while Buse et al.[46] failed to find a significant hazard ratio of diabetes for age with clozapine. Likewise, Sernyak et al.[33] found clozapine to be associated with an increased prevalence of diabetes in patients younger than 50 years, while no significant increase was found in patients older than 60.

The prevalence of diabetes is approximately 2-fold greater in African Americans, Hispanic Americans, and Native Americans compared with non-Hispanic whites,[53] but few studies have examined the role of race/ethnicity in clozapine-associated diabetes. Of FDA database cases in which racial information was provided, 58% of patients with clozapine-associated diabetes were of African descent.[37] Also, African Americans and African Caribbeans are overrepresented in case reports of clozapine-associated glucose abnormalities, totaling nearly half of all reported cases.[1,2,4,7,10,13,14,17,21,24,26]

Family history is another well-established risk factor for diabetes mellitus within the general population.[53] Of 23 case reports that contained information about family history, 6 patients had a positive family history of diabetes.[2–4,7,10,16] Also, 4 of 13 diabetic clozapine-treated patients in a study by Hägg et al.[32] had positive family histories. However, Henderson et al.[36] reported a positive family history of diabetes in only 2 of 82 clozapine-treated patients, of which 30 developed diabetes. Results regarding gender as a risk factor for clozapine-associated diabetes have also been mixed. While 32 of 38 published case reports have involved male patients, increased prevalence of clozapine-associated diabetes among women has been reported by both Koller et al.[37] and Hägg et al.[32]

Obesity is a strong predictor of diabetes in the general population.[53] However, few published studies have examined the relationship between clozapine-associated obesity and diabetes to date. In Henderson and colleagues' 5-year study[36] of 82 outpatients receiving clozapine, weight and body mass index (BMI) were not associated with the development of diabetes. Also, Lindenmayer and colleagues' 14-week study[49] that included 27 clozapine-treated patients found no treatment interaction for the relationship between glucose change and weight gain at endpoint.

Our current understanding of clozapine-associated diabetes is limited by available data that primarily consist of case reports and small clinical studies. This article presents a study of a sizeable group of persons with schizophrenia or schizoaffective disorder receiving clozapine within an outpatient treatment setting. The goal of the study is to examine the relationship between the presence of diabetes mellitus and established clinical-demographic risk factors within this cohort.

METHOD

Subjects

This study was conducted at Strong Ties Community Support Program, an outpatient clinic of the University of Rochester Medical Center Department of Psychiatry, Rochester, N.Y., specializing in care of severely mentally ill adults. In addition to outpatient psychiatric treatment and case management services, Strong Ties offers pharmacy and primary medical care services to all enrolled patients. The study was approved by the University of Rochester Medical Center Research Subjects Review Board.

Patients receiving clozapine were identified through review of the Strong Ties pharmacy database and were contacted and given a complete description of the study. Written informed consent was subsequently obtained from 101 patients who participated in the study between September 2002 and September 2003. Patients receiving clozapine less than 3 months or with a documented history of diabetes prior to age 18 were excluded from study participation.

Data Collection

Medical records were reviewed, and the following data were obtained for all subjects: age, race/ethnicity, gender, presence or absence of diabetes diagnosis, clozapine dose and start date, date of first antipsychotic drug use, and number and type of concomitant medications. Family history of diabetes was determined by review of medical records and by subject interview in the absence of documentation. All patients had received a DSM-IV clinical diagnosis of either schizophrenia (N = 62) or schizoaffective disorder (N = 39) from their treating psychiatrists.

For subjects with documented diabetes, date of diabetes diagnosis, presence of diabetes treatment, and the date of the last normal fasting blood glucose prior to diabetes diagnosis were recorded. Whenever pertinent dates in the medical record were unclear, either the last day of the month or the last month of the year was used. When dates of psychiatric hospitalizations were available without information about drug therapy at the time, the date of discharge from the second hospitalization was used as the date of first antipsychotic use. The first documentation in the chart of diabetes was used as the date of diagnosis whenever the actual date of diagnosis was unclear.

Subjects received BMI and percentage body fat measurements using a Tanita Body Composition Analyzer model TBF-300 (Tanita Corp. of America, Inc., Arlington

Heights, Ill.). This device is accurate within ± 5% of dual energy X-ray absorptiometry (DEXA),[54] the institutional standard of body composition analysis. Subjects without a documented history of diabetes mellitus underwent fasting blood glucose testing using standard procedures. Diagnosis of diabetes was made for subjects having a fasting blood glucose level equal to or greater than 126 mg/dL on 2 occasions, consistent with American Diabetes Association diagnostic criteria.[55] All data were transcribed into data collection forms and entered into a secure Microsoft Access (Microsoft Corp., Redmond, Wash.) database.

Data Analysis

Data analysis was conducted using SAS version 8.2 (SAS Institute, Inc., Cary, N.C.). The following continuous variables were examined on study subjects: age, percentage body fat, BMI, total years of antipsychotic drug treatment, years of clozapine treatment, clozapine dose, and age when clozapine was first prescribed. To determine if the means of the continuous variables varied between diabetics and nondiabetics, t tests were performed on each variable. Categorical variables collected on each of the patients included gender, race/ethnicity, family history, use of a selective serotonin reuptake inhibitor (SSRI), use of divalproex sodium, and use of a second antipsychotic drug. Fisher exact tests were used to test for associations between the categorical variables and diabetes status.

All tests performed were 2-sided, with significance level α = .05, unless noted otherwise. A stepwise selection logistic regression model with the response variable diabetes (yes/no) was used to determine all significant predictors of the presence of diabetes.

RESULTS

Mean (SD) age of subjects was 40.4 (9.5) years, and 66.3% were male. Eighty subjects (79.2%) were white, and the remaining 21 (21.8%) were African American (16 subjects), Hispanic (2 subjects), Native American (2 subjects), and other race/ethnicity (1 subject). Twenty-six subjects (25.7%) had a positive family history of diabetes. Mean (SD) age upon initiation of clozapine treatment was 34.6 (8.9) years, and mean (SD) age at time of diabetes diagnosis was 38.9 (8.04) years. Mean (SD) dose of clozapine at the time of study enrollment was 426 (164) mg/day. Mean (SD) duration of clozapine treatment was 5.7 (3.6) years, and mean (SD) total duration of antipsychotic drug treatment was 15.4 (7.9) years. The most commonly prescribed concomitant medications were benzodiazepines (31.7%, 32 subjects), divalproex sodium (26.7%, 27 subjects), and SSRIs (21.8%, 22 subjects). In addition, 25.7% (26 subjects) were receiving a second antipsychotic medication in addition to clozapine at the time of enrollment. Of the 26 subjects receiving a second

Table 1. Diabetes Prevalence by Demographic and Clinical Categories Among Patients With Schizophrenia and Schizoaffective Disorder Taking Clozapine (N = 101)

Category	N/N	Prevalence, %	p Value[a]
Age group, y			.23
18–30	2/16	12.5	
31–40	9/35	25.7	
41–50	8/34	23.5	
Over 50	7/16	43.8	
Gender			.34
Male	15/67	22.4	
Female	11/34	32.4	
Race/ethnicity			.02
White	16/80	20.0	
Nonwhite	10/21	47.6	
Family history			.002
Positive	13/26	50.0	
Negative/unknown	13/75	17.3	
Body mass index, kg/m²			.77
≥ 30	17/59	28.4	
< 25	4/17	23.5	
Body fat, men			.75
≥ 30%	10/37	27.0	
< 25%	4/20	20.0	
Body fat, women			.33
≥ 25%	10/32	31.3	
< 20%	1/1	100.0	

[a]p Values are based on Fisher exact test.

antipsychotic medication, 12 received quetiapine, 7 received risperidone, 3 received haloperidol, 2 received ziprasidone, 1 received thiothixene, and 1 received olanzapine. No subjects were receiving corticosteroids or protease inhibitors, both medications known to cause diabetes.

Point prevalence of diabetes mellitus in the study group was 25.7% (26 subjects). Twenty-one of the 26 subjects had a documented diagnosis of diabetes in their medical records at the time of study enrollment, with 5 subjects being newly diagnosed by fasting blood glucose testing under the study protocol. Among patients diagnosed with diabetes after clozapine initiation, mean (SD) time to diabetes diagnosis following initiation was 3.7 (3.1) years (range, 0.04–9.7 years). Prevalence rates of diabetes by age, gender, race/ethnicity, family history of diabetes, body mass index, and percentage body fat appear in Table 1. Mean (SD) BMI for the group was 32.6 (8.0) kg/m². Mean (SD) percentage body fat was 34.0% (11.0%), with percentages for men and women of 29.2% (9.1%) and 43.7% (7.2%), respectively. Analyses of the continuous variables and diabetes status resulted in only 1 significant association. Mean (SD) age at clozapine initiation was significantly older for patients with diabetes (37.6 years [7.9]) than for those without (33.6 years [9.1]) (t test, p = .05), although mean ages of the groups did not differ significantly.

Analyses of the categorical variables and diabetes status resulted in significant associations with race/ethnicity and with family history. Race/ethnicity was first categorized into 5 groups: white, African American, Hispanic,

Native American, and other. The prevalence of diabetes for each group was 20.0% (16 of 80 subjects), 43.8% (7 of 16), 50.0% (1 of 2), 100.0% (2 of 2), and 0%, respectively. A significant difference between groups was found using Fisher exact test (p = .029). As shown in Table 1, significant differences in diabetes prevalence were also noted comparing the categories white and nonwhite, and family history positive and negative. Presence of a second antipsychotic drug was associated with a trend toward a higher prevalence of diabetes compared with the absence of a second antipsychotic drug (38.5% vs. 21.3%, respectively; p = .118). No association was noted between prevalence of diabetes and use of divalproex sodium, benzodiazepines, or SSRIs.

Logistic regression was used to examine variables that were associated with diagnosis of diabetes. By initially including the variables years of antipsychotic drug treatment, years of clozapine treatment, BMI, percentage body fat, age at the time of clozapine initiation, divalproex, race/ethnicity (white vs. nonwhite), gender, family history, current age, SSRIs, second antipsychotic drug, and benzodiazepines, the stepwise model selection procedure was used to trim the variables in the initial model. The final reduced model included only race/ethnicity (p = .02) and family history (p = .002). The odds of a nonwhite patient having diabetes were 3.6 times the odds of a white patient when all other variables were held constant (95% CI = 1.2 to 11.1 times). The odds of a patient with a family history of diabetes having diabetes were 5.5 times the odds of a patient with a negative or unknown family history when all other variables were held constant (95% CI = 2.0 to 14.9 times).

DISCUSSION

Our results appear to confirm previous reports of an increased risk for developing diabetes mellitus among patients receiving clozapine. The 25.7% diabetes prevalence is considerably higher than the 7.9% general adult population rate, a difference that extends across comparable age categories.[56] This prevalence rate also exceeds the 14.9% rate found among adults in the general population with BMIs between 30 and 39.9, considering the 32.6 BMI of the study cohort.[56]

While previous studies examining clozapine-associated weight gain and diabetes[36,49] as well as the present study have found no relationship, these negative results are likely due to methodologic limitations of each study. Studies to date have failed to account for the significant delay between weight gain and the onset of diabetes that typically occurs in genetically vulnerable patients. It is well established that increases in adiposity are associated with decreased insulin sensitivity that leads to compensatory hyperinsulinemia.[53,57] This process allows plasma glucose to remain well controlled over many years before the

emergence of diabetes in susceptible individuals. The present study is also limited by other methodological weaknesses. Specifically, analysis was performed by using a cutoff of 126 mg/dL for the diagnosis of diabetes rather than considering fasting glucose as a continuous variable that changes over time. In addition, the study's substantially obese patient sample provided little opportunity to compare obese with nonobese patients. Also, the study examined associations between previous diagnoses of diabetes and current BMIs. Given the strong association between increased adiposity and decreased insulin sensitivity and diabetes within the general population,[53,57] it seems unlikely that this relationship would not exist in severely mentally ill patients with clozapine-associated obesity. Optimal evaluation of associations between diabetes and body weight requires a prospective randomized study in which relationships between diabetes incidence rates and changes in weight and adiposity are examined over an extended period of time.

Race/ethnicity and family history of diabetes are well established risk factors within the general population.[53] Study findings of increased diabetes prevalence rates among nonwhite patients and those with positive family histories are consistent with previous reports suggesting that these variables are important risk factors among clozapine-treated patients. In addition, the 25.7% rate of family history of diabetes in this study is consistent with previous reports of positive family history rates ranging from 18% to 30% among patients with schizophrenia.[58] These rates are substantially higher than the 1.2% to 6.3% rates among the general population[59] and may be indicative of vulnerability to diabetes among patients with schizophrenia. The lack of association between age and diabetes prevalence is somewhat surprising given the established role of age as a general population risk factor. Considering that numeric differences were found between age categories, it is possible that significant differences may have emerged with a larger sample size.

Many additional factors are likely to have contributed to the high prevalence rate of diabetes found in this study. Although not assessed in this study, poor diet, lack of exercise, and substance abuse may have contributed to the high prevalence of diabetes found in the study group.[60] Schizophrenia itself may also be a risk factor for diabetes mellitus. Studies prior to the discovery of chlorpromazine have documented impaired glucose tolerance among patients with schizophrenia, although fasting blood glucose was usually normal in these studies.[61–67] This finding was recently replicated by Ryan and colleagues,[68] who found increased fasting blood glucose levels and insulin resistance but no diabetes in their comparison of drug-naive patients to controls. While Mukherjee et al.[69] reported higher rates of diabetes among patients without antipsychotic drugs than those receiving them, the medication-free group contained only 8 patients. Conclusive evidence

that diabetes is more common in schizophrenia independent of medications is lacking, but the literature suggests that adults with schizophrenia are vulnerable to developing diabetes.

Although antipsychotic medications have long been associated with diabetes, certain lines of evidence suggest that clozapine may pose an especially high level of risk. Some clinical studies have shown high rates of diabetes among clozapine-treated patients, either alone[34,36,37] or in comparison to patients receiving other drugs.[32,33,35] Clozapine causes the most weight gain of any antipsychotic drug,[70] and obesity is a well-established risk factor for diabetes in the general population.[53] Clozapine levels have also been shown to correlate positively with insulin levels, suggesting a stimulating effect of clozapine on insulin secretion from pancreatic β cells.[31,71] This correlation was not observed with other antipsychotic drugs studied. A similar finding was noted in vitro, where clozapine, but not typical drugs, olanzapine, or risperidone, was associated with increased basal insulin release.[72] Reviewing available data, the American Psychiatric Association Practice Guideline for the Treatment of Patients with Schizophrenia[52] and the national Consensus Development Conference[51] of the American Diabetes Association have placed clozapine in a higher risk category than all other antipsychotic drugs except olanzapine. Controlled prospective studies are needed to determine whether this categorization is accurate. Such studies are necessary to control for the tendency of clinicians to look for diabetes preferentially among clozapine-treated patients[73,74] as well as other potentially confounding variables.

It should be noted that the retrospective design and lack of a control group in this study prevent determination of the extent to which clozapine is an independent risk factor for diabetes. Possible confounding factors include diet, level of exercise, drug and alcohol abuse, cigarette smoking, and medication nonadherence. Disease severity may also have impacted the risk of developing diabetes, but it was not assessed in this study. In addition, impedance measurement tends to underestimate abdominal adiposity relative to lower extremity adiposity,[75] which may result in gender-related measurement errors. Also, subjects who were the most engaged in treatment were probably overrepresented among those who provided informed consent for study participation. For these reasons, study results should be interpreted with caution. Large controlled prospective studies are needed to establish the level of risk for diabetes attributable to clozapine treatment and how this risk interacts with established clinical and demographic factors.

Patients receiving clozapine are at increased risk of developing diabetes mellitus. Despite this problem, clozapine maintains a special place in the treatment of schizophrenia. Decisions to use clozapine require a careful risk-benefit assessment, as well as a commitment to long-term

monitoring of patients for development of diabetes. Although definitive studies have yet to be done, the existing literature suggests that antipsychotic drugs in general are associated with some degree of increased risk for diabetes.[76] Given that persons with schizophrenia appear vulnerable to developing diabetes independent of antipsychotic drugs, all patients receiving antipsychotics should be monitored regularly for diabetes. Current guidelines suggest that patients should receive fasting blood glucose testing at baseline, 3 to 4 months later, and annually thereafter.[51,52] Results of this study suggest that nonwhite patients and those with positive family histories of diabetes receiving clozapine should be monitored more closely. In the absence of evidence-based guidelines, clinicians should consider monitoring clozapine-treated patients with multiple established risk factors on a quarterly or semiannual basis rather than annually.

Drug names: chlorpromazine (Thorazine, Sonazine, and others), clozapine (Clozaril, FazaClo, and others), divalproex sodium (Depakote), haloperidol (Haldol and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal), thiothixene (Navane and others), ziprasidone (Geodon).

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