Clozapine, Diabetes Mellitus, Hyperlipidemia, and Cardiovascular Risks and Mortality: Results of a 10-Year Naturalistic Study

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Objective: The goal of this 10-year naturalistic study was to examine, in clozapine-treated patients, the change in cardiovascular risk factors following clozapine initiation and the mortality estimates from cardiovascular disease.

Method: Data were collected from medical records from January 1992 to December 2003 and included age, gender, race, diagnosis, family history of diabetes, and age at clozapine initiation for clozapine-treated patients with schizophrenia or schizoaffective disorder (DSM-IV criteria). Clozapine dosage and laboratory results were recorded at 12-month intervals.

Results: At the time of clozapine initiation, the mean ± SD age of the 96 patients studied was 36.5 ± 7.9 years; 28% (N = 27) were women. The Kaplan-Meier estimate for 10-year mortality from cardiovascular disease was 9%. African American and Hispanic American patients exhibited elevated risk of cardiovascular disease–related mortality (odds ratio [OR] = 7.2, p = .09; OR = 11.3, p = .04, respectively) compared to white patients. Body mass index (BMI) significantly increased the odds ratio of mortality (OR = 1.2, p < .01). The Kaplan-Meier estimate for new-onset diabetes mellitus was approximately 43%, and Hispanic American (OR = 4.3, p = .027) and African American (OR = 11.5, p = .0001) patients showed elevated risks of developing diabetes mellitus compared to white patients. Additionally, BMI (OR = 1.11, p = .0006), total cholesterol level (OR = 1.006, p = .04), and serum triglyceride level (OR = 1.002, p = .04) modestly increased the odds ratio for the development of diabetes mellitus.

Conclusions: These results support the hypothesis that clozapine-treated patients appear to be at risk for death from cardiovascular disease secondary to clozapine-associated medical disorders such as obesity, diabetes, hypertension, and hyperlipidemia.

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High rates of medical morbidity and increased risk of mortality have long been associated with schizophrenia. Clozapine remains the treatment of choice for treatment-resistant schizophrenia and associated disorders because of its greater efficacy and relative lack of extrapyramidal side effects compared to conventional antipsychotic medications.[1] Growing concerns with clozapine treatment are related to side effects such as weight gain, hyperglycemia, hyperlipidemia, and hypertension.[2,3] Fontaine et al.[4] estimated the expected impact of antipsychotic-induced weight gain on mortality rates and incidence of impaired glucose tolerance (IGT) and hypertension using raw data from 5209 respondents from the Framingham Heart Study. Results indicated that the estimated deleterious effects of weight gain were greater for people with higher body mass index (BMI) at baseline, people with greater degrees of weight gain, men, and older persons. Additionally, the effect of weight gain on IGT and hypertension was deleterious regardless of baseline BMI.

Psychotropic medications, in general, may produce significant weight gain.[5] In our 5-year naturalistic study, we found that weight gain with clozapine did not plateau until the fourth year.[3] Umbricht and colleagues[6] reported that almost half of 82 patients gained 20% or more of their

body weight during clozapine treatment for up to 90 months. A 7% or greater increase in weight is considered the standard indicator for extreme weight gain in clinical trials. An increase in body weight of 7% or greater is generally regarded as a high-risk event.

A large number of published case reports have also linked treatment-emergent type 2 diabetes mellitus to the use of atypical agents, with clozapine and olanzapine most frequently cited.[7] Clozapine treatment has been associated with insulin resistance independent of adiposity in schizophrenia patients.[8] When insulin resistance occurs, the body attempts to overcome this resistance by secreting more insulin, resulting in hyperinsulinemia. Abnormalities associated with insulin resistance include glucose intolerance, hypertension, a prothrombic state, and dyslipidemia. These metabolic abnormalities have been associated with metabolic syndrome and cardiovascular disease individually and together have been found to greatly increase cardiovascular mortality.[9]

Several risk factors for coronary disease, including cigarette smoking, obesity, hypertension, elevated serum lipids, and diabetes mellitus, have been identified in the general population. Because these factors are supra-additive, the risk for cardiac disease is increased almost 12-fold in individuals who have all 5 risk factors compared to those who have none.[10] The purpose of the present study was to examine in clozapine-treated subjects the change in risk factors for cardiovascular disease, as well as the rate and estimates of diabetes mellitus and cardiovascular disease–related mortality, after clozapine initiation, over a 10-year period.

METHOD

Following institutional review board approval, 96 patients with schizophrenia or schizoaffective disorder (DSM-IV criteria) who had been treated with clozapine for up to 10 years from January 1992 to December 2003 were examined for known diabetes and cardiovascular risk factors.[10] Cardiovascular risk was tabulated using the following criteria: race (African American, Hispanic/Latino American, Asian American) = 1 point; BMI ≥ 27 kg/m^2 = 1 point; hypertension (systolic blood pressure ≥ 140 mm Hg or diastolic blood pressure ≥ 90 mm Hg) = 1 point; diabetes mellitus = 1 point; cigarette smoking = 1 point; history of left ventricular hypertrophy, myocardial infarction, or cerebrovascular accident = 1 point; total cholesterol level ≥ 200 mg/dL or serum triglyceride level ≥ 150 mg/dL = 1 point; and male gender = 1 point. Cardiovascular risk factors were tabulated at 1-year intervals over a 10-year period.

Autopsy reports and all medical records were reviewed by a research psychiatrist (D.C.H.) to determine the cause of death. When cardiovascular disease was identified, all records were carefully reviewed to determine if any evidence of clozapine-associated myocarditis or cardiomyopathy was present prior to the death such as persistent tachycardia, left ventricular hypertrophy, a prolonged corrected QT interval, eosinophilia, dyspnea on exertion, exercise intolerance, or edema.[11,12]

Statistical Analysis

This study examined time to development of diabetes mellitus and death from cardiovascular disease associated with clozapine treatment at 12-month intervals over a 10-year period. Baseline and follow-up descriptive statistics were tabulated. Weight, serum cholesterol level, and serum triglyceride level were treated as continuous variables and analyzed by means of longitudinal methods. The Cox proportional hazards regressions were used to test the association between the covariates (age, ethnicity, BMI, total cholesterol level, serum triglyceride level, systolic and diastolic blood pressure, smoking, and diabetes mellitus) and death from cardiovascular disease and the development of diabetes mellitus. Age, race, and gender were analyzed as baseline covariates, and BMI, total cholesterol level, clozapine total daily dose, serum triglyceride level, and weight were analyzed as time-dependent covariates. Each covariate was analyzed separately.

Time was used as a stratum and ties were handled with the discrete option in the SAS PHREG procedure (SAS Institute Inc., Cary, N.C.). This replaces the proportional hazards model with the discrete logistic model so that odds ratios rather than hazard ratios are computed. The Kaplan-Meier estimate of time to development of diabetes mellitus and cardiovascular death were computed. Changes from baseline in weight, BMI, total cholesterol level, and serum triglyceride level were analyzed by using a mixed-effects model. This model has fixed linear term for time and random intercept and linear term for time for each patient. The fixed effects estimate the mean trajectory of the change from baseline, and the random effects allow a separate trajectory for each patient. All p values are 2-tailed, and a p value < .05 was considered evidence for statistical significance.

RESULTS

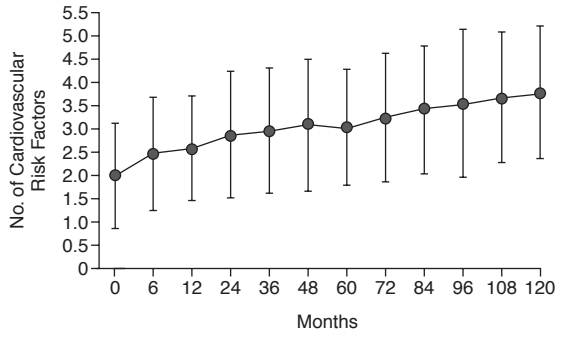
Baseline demographic and laboratory measures are presented in Table 1. Sixty-nine subjects (72%) were men and 27 (28%) were women. The mean ± SD age at clozapine initiation was 36.5 ± 7.9 years; 6 subjects (6%) were African Americans, 4 (4%) were Hispanic Americans, and 1 (1%) was an Asian American. The mean length of treatment with clozapine was 90 ± 37 months.

The random slopes model indicated that BMI increased significantly over time; the linear coefficient was 0.033 kg/m^2/month, (SE = 0.005, t = 6.48, df = 94, p < .0001). Weight also increased significantly over time (linear coefficient of 0.21 lb/month, SE = 0.03, t = 6.29,

Table 1. Demographic Characteristics and Baseline Values for 96 Patients With Schizophrenia Treated With Clozapine Over a 10-Year Period

Variable	N (%)	Mean (SD)
Age, y		36.5 (7.9)
Gender		
Male	69 (72)	
Female	27 (28)	
Race		
White	85 (89)	
African American	6 (6)	
Hispanic American	4 (4)	
Asian American	1 (1)	
Diagnosis		
Schizophrenia	66 (69)	
Schizoaffective disorder	30 (31)	
Smoking status		
Smoker	61 (64)	
Nonsmoker	35 (36)	
Baseline measures		
Weight, lb		174.2 (35.5)
Body mass index, kg/m^2		27.3 (5.2)
Glucose level, mg/dL		93 (12)
Blood pressure, mm Hg		
Systolic		114 (13)
Diastolic		76 (9)
Total cholesterol level, mg/dL		196 (47)
Serum triglyceride level, mg/dL		180 (136)
Cardiovascular risk factors		2.0 (1.1)
Diabetes risk factor		1.4 (1.1)

Figure 1. Number of Cardiovascular Risk Factors (mean ± SD) During a 10-Year Period in 96 Clozapine-Treated Patients



df = 92, p < .0001). The mean increase in weight was approximately 30 lb. Unlike in most previous reports of weight stability after an early weight gain,[13,14] many patients experienced a second prolonged period of weight gain following a leveling off after several months or years. Fifteen of these patients had a significant change in lifestyle such as moving from a residential program (where diet was closely monitored) to an independent apartment. There was a significant increase in serum triglyceride levels (linear coefficient of 0.5 mg/dL/month, SE = 0.238, t = 2.08, df = 89, p = .04) but not total cholesterol levels (linear coefficient of –0.1, SE = 0.567, t = –1.55, df = 90, p = .13).

There was a significant increase in number of cardiovascular risk factors (mixed-effects model, t = 9.3, df = 95, p < .0001) over time. Figure 1 shows the change in cardiovascular risk factors over the 10-year period. Table 2 provides demographic and background information for patients who experienced a cardiovascular-related event. Five confirmed cardiovascular disease–related deaths occurred during the 10-year period. Of these 5 patients who died, 2 were less than 30 years of age, 3 were smokers, and 2 received treatment for diabetes mellitus following clozapine initiation. In addition, 3 patients experienced nonfatal myocardial infarctions and 1 suffered a cerebrovascular accident. Two additional patients experienced cardiovascular disease–related deaths but were excluded from the overall sample since baseline cardiovascular risk assessments, prior to clozapine initiation, were not available. One of these patients was a smoker and developed diabetes mellitus following clozapine initiation. In total, 7 patients experienced a fatal myocardial infarction, 3 experienced a nonfatal myocardial infarction, and 1 experienced a cerebrovascular accident.

The Kaplan-Meier estimate for 10-year mortality from cardiovascular disease was 9% (Figure 2). The Cox proportional odds model revealed that compared to white patients, African American and Hispanic American patients exhibited an elevated risk of cardiovascular mortality (odds ratio [OR] = 7.2, 95% confidence interval [CI] = 0.7 to 69.9; OR = 11.3, 95% CI = 1.1 to 118.1, respectively; Table 3). Change in BMI significantly increased the odds ratio (OR = 1.2, 95% CI = 1.059 to 1.400). Age (OR = 1.0, 95% CI = 0.868 to 1.124), total cholesterol level (OR = 1.0, 95% CI = 0.97 to 1.01), serum triglyceride level (OR = 1.0, 95% CI = 0.995 to 1.004), systolic (OR = 1.02, 95% CI = 0.96 to 1.09) and diastolic blood pressure (OR = 1.1, 95% CI = 0.99 to 1.20), smoking (OR = 1.4, 95% CI = 0.23 to 8.49), clozapine dose (OR = 1.0, 95% CI = 0.99 to 1.00), and treatment with valproate (OR = 0.99, 95% CI = 0.99 to 1.00) did not significantly increase the odds ratio. Though the difference was not statistically significant, patients who developed diabetes had approximately 3 times the odds of cardiovascular death.

Thirty-three patients (34%) developed diabetes over the 10-year period. However, the Kaplan-Meier estimate for new-onset diabetes mellitus was approximately 43% if each patient had taken the drug for the full 10-year period (Figure 3). Results from the Cox proportional odds model indicated that African American (OR = 11.5, 95% CI = 3.59 to 36.88) and Hispanic American (OR = 4.3, 95% CI = 1.19 to 15.55) patients showed elevated risks of developing diabetes mellitus compared to white patients. BMI (OR = 1.11, 95% CI = 1.04 to 1.17), total cholesterol level (OR = 1.006, 95% CI = 1.00 to 1.01), and serum triglyceride level (OR = 1.002, 95% CI = 1.000 to 1.003) significantly increased the odds ratio for the development of diabetes mellitus. However, age

Table 2. Cardiovascular Events Over a 10-Year Period in Clozapine-Treated Patients

Patient No.	Duration of Clozapine Treatment, mo	Diagnosis	Gender	Cardiovascular Event	Race	Age at Time of Event, y	Clozapine Dose (mg/d)	BMI (kg/m^2)	Diabetes After Clozapine Initiation	Smoking Status	Other Medications
1	36	Chronic schizophrenia	Male	Nonfatal MI	White	49	525	26.48	No	Yes	Risperidone
2	108	Chronic schizophrenia	Male	Nonfatal MI	White	49	450	34.70	Yes	Yes	None
3	84	Chronic schizophrenia	Female	Nonfatal MI	White	41	350	28.50	No	Yes	None
4	24	Chronic schizophrenia	Female	Fatal MI	African American	25	175	38.70	Yes	No	Atenolol, ipratropium nasal spray
5	60	Chronic schizophrenia	Male	Fatal MI	White	53	300	31.79	No	Yes	None
6	120	Chronic schizophrenia	Female	Fatal MI	White	50	500	50.50	No	Yes	Valproate
7	24	Chronic schizophrenia	Male	Fatal MI	White	49	400	28.95	No	No	None
8	108	Schizoaffective disorder	Male	Fatal MI	Hispanic American	28	425	42.60	Yes	Yes	Valproate, haloperidol decanoate
9[a]	60	Schizoaffective disorder	Male	Fatal MI	White	53	400	35.40	Yes	Yes	None
10[a]	72	Chronic schizophrenia	Female	Fatal MI	White	44	550	33.60	No	No	Lorazepam, sertraline
11	84	Chronic schizophrenia	Male	Nonfatal CVA	White	44	400	22.50	No	Yes	Lithium

[a]Not included in the analysis as baseline data were not available.
Abbreviations: BMI = body mass index, CVA = cerebrovascular accident, MI = myocardial infarction.

Figure 2. Kaplan-Meier Estimates of 10-Year Mortality From Cardiovascular Disease in Clozapine-Treated Patients With Schizophrenia

(OR = 1.02, 95% CI = 0.97 to 1.07), blood pressure (systolic: OR = 1.0, 95% CI = 0.99 to 1.04; diastolic: OR = 1.01, 95% CI = 0.975 to 1.05), clozapine dose (OR = 1.0, 95% CI = 0.99 to 1.00), and treatment with valproate (OR = 1.0, 95% CI = 0.98 to 1.00) did not significantly increase the odds ratio.

Of note, 8 patients developed diabetes mellitus that subsequently resolved following interventions including nutrition and exercise programs (N = 3), lowering of the clozapine dose following the initiation of another antipsychotic agent (N = 3), and discontinuation of clozapine (N = 2). Additionally, 10 subjects were identified as at risk secondary to impaired fasting glucose level (glucose > 110, < 126 mg/dL) or elevated random glucose level (> 160 mg/dL) on several occasions. Interventions were undertaken in these patients to prevent the development of diabetes, including exercise and nutrition programs and the use of appetite-suppressing agents. Overall, 30 patients participated in weight intervention programs or studies that may have reduced their risk for diabetes mellitus. Further, all patients repeatedly received nutrition and exercise counseling between years 5 and 10. Although 64% of patients were smokers at baseline, 10% were able to quit following successful participation in a smoking cessation program.[15–17]

DISCUSSION

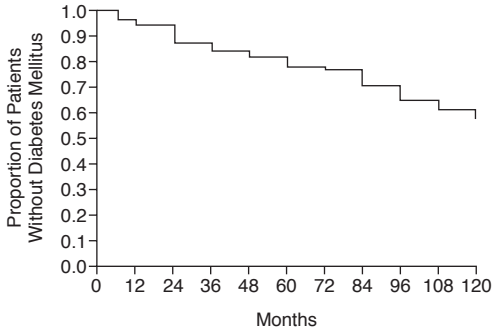
Clozapine appears to increase the rates of several medical disorders, including obesity, hyperlipidemia, hypertension, and diabetes mellitus. Long-term clozapine treatment resulted in an increase in number of risk factors for diabetes and cardiovascular disease. As expected, the increase in risk factors for diabetes and cardiovascular disease escalated over time. The cardiovascular deaths are most concerning, as 2 occurred in patients below the age of 30 years. Additionally, nonfatal cardiovascular events also occurred in this patient cohort. Risk factors such as ethnicity and BMI may increase the risks for

Table 3. The Cox Proportional Odds Model for Cardiovascular Disease–Related Death and for Diabetes Mellitus in Clozapine-Treated Patients With Schizophrenia Over a 10-Year Period

	Cardiovascular Disease–Related Death		Diabetes Mellitus	
Variable	Odds Ratio (95% CI)	p Value	Odds Ratio (95% CI)	p Value
Age	1.0 (0.868 to 1.124)	.85	1.02 (0.97 to 1.07)	.47
Ethnicity				
African American to White	7.2 (0.7 to 69.9)	.09	11.5 (3.59 to 36.88)	.0001
Hispanic American to White	11.3 (1.1 to 118.1)	.04	4.3 (1.19 to 15.55)	.027
Body mass index	1.2 (1.059 to 1.40)	.0058	1.11 (1.04 to 1.17)	.0006
Total cholesterol level	1.0 (0.97 to 1.01)	.028	1.006 (1.00 to 1.01)	.04
Serum triglyceride level	1.0 (0.995 to 1.004)	.84	1.002 (1.00 to 1.003)	.04
Systolic blood pressure	1.02 (0.96 to 1.09)	.55	1.0 (0.99 to 1.04)	.28
Diastolic blood pressure	1.1 (0.99 to 1.20)	.08	1.01 (0.975 to 1.05)	.57
Smoking[a]	1.4 (0.23 to 8.49)	.7	NA	NA
Diabetes mellitus	2.95 (0.42 to 20.83)	.28	…	…

[a]Smoking was not in the model for risk factors for developing diabetes mellitus.
Abbreviation: NA = not applicable.

Figure 3. Kaplan-Meier Estimates for 10-Year Development of Diabetes Mellitus in Clozapine-Treated Schizophrenia Patients



death from cardiovascular disease for patients treated with long-term clozapine therapy.[10] Our findings are consistent with year 2000 mortality data from the Massachusetts Department of Mental Health (DMH), which found elevated relative risk (RR) of cardiovascular death in DMH patients compared to the general Massachusetts population across several age groups (ages 25–34 years, RR = 11.5; ages 35–44 years, RR = 4.4; ages 45–54 years, RR = 3.9).[18] Additionally, United States vital statistics from the Centers for Disease Control and Prevention estimate that the number of myocardial infarction–related deaths for the 35-to-44-year-old age group was 3176 per 100,000.[19] The rates in our clozapine cohort greatly exceed both the United States and Massachusetts cardiovascular disease–related death rates. This finding also suggests that the gains in life expectancy made by clozapine's reduction in suicide rates in schizophrenia patients may be lost secondary to cardiovascular disease–related deaths.

Dyslipidemia represents one of the most important risk factors for cardiovascular morbidity and mortality.[20] High total cholesterol and low-density lipoprotein cholesterol levels are strong independent risk factors for coronary heart disease.[21] Hypertriglyceridemia is also an independent risk factor for coronary artery disease and insulin resistance.[22,23] Among lipid parameters in our study, only serum triglyceride level was shown to increase significantly over time.

Weight gain and obesity contribute markedly to the risk for a number of diseases, including diabetes mellitus, coronary artery disease, hypertension, gallbladder disease, osteoarthritis, and colon, breast, and uterine cancers.[24] Abdominal (visceral) adiposity, in particular, increases the risk for diabetes mellitus and cardiovascular disease. The risk for diabetes has been reported to be approximately 2-fold in mildly obese, 5-fold in moderately obese, and 10-fold in severely obese persons.[25] Weight gain leading to obesity is a significant problem with clozapine and is often difficult to reverse.[26,27] Finally, some patients experienced a second period of weight gain that occurred when they improved enough to leave structured environments, such as residential settings, to move to independent apartments. While clozapine may lead to an increase in functioning resulting in more independent living, this may also place patients at higher risk for weight gain, obesity, and metabolic deterioration.

Clozapine also appears to increase the rate of hypertension in patients with chronic schizophrenia.[28] Hypertension markedly increases the risk for myocardial infarction, congestive heart disease, stroke, and renal failure. It is increasingly evident that high blood pressure is a relatively late developing component of a cluster of pathologic changes that may include loss of vascular elasticity, obesity, abnormal lipid metabolism, insulin resistance, and renal disease and that these changes reflect complex genetic and environmental factors.

African Americans and Hispanic Americans in this study, as well as in the general population,[29] appear to be at greater risk for developing diabetes mellitus, and in this study, for death from cardiovascular disease following clozapine treatment. Hypervigilance in these populations should be undertaken with screening, assessment and

monitoring of risk factors, and aggressive interventions. Increased monitoring, such as for weight and blood pressure at every visit, along with an increase in the monitoring of glucose (every 6 months) and lipids (once a year) should be considered.

There are several limitations to this current study. First, it is possible that other unknown factors affected the rates of diabetes and cardiovascular disease–related deaths. While we identified African American and Hispanic American patients as having the greatest risk, it is possible that other risk factors or predispositions, including family history, contributed to the outcomes. Finally, although medical records, autopsy reports, and emergency department records were reviewed, it is possible that undetected cardiomyopathy or myocarditis contributed to the cardiovascular deaths. However, our results support the findings of Fontaine et al.,[4] which suggested that the lives saved via clozapine's reduction in suicide may essentially be offset by the deaths due to weight gain. Additionally, many patients participated in interventions to reduce risk factors for diabetes and cardiovascular disease, and these efforts may have reduced the overall incidence of new-onset diabetes mellitus or cardiovascular death in this patient cohort. It is possible that, without these interventions, many more patients would have developed diabetes mellitus and experienced cardiovascular events.

Long-term treatment with clozapine may significantly increase the risk of death from cardiovascular disease, with an estimate of up to 9% of clozapine-treated patients dying from cardiovascular disease over a 10-year period. Cardiovascular symptoms must be taken seriously in this population. Monitoring and assessing risks for diabetes and cardiovascular disease should be undertaken routinely, and interventions to reverse or prevent such occurrences should be instituted. While reasonable monitoring guidelines have recently been published by the American Diabetes Association,[30] high-risk populations such as African American and Hispanic American patients must be monitored even more closely.

Drug names: atenolol (Tenormin and others), clozapine (Clozaril, FazaClo, and others), haloperidol (Haldol and others), ipratropium (Atrovent), lithium (Lithobid, Eskalith, and others), lorazepam (Ativan and others), olanzapine (Zyprexa), risperidone (Risperdal), sertraline (Zoloft).

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