ORIGINAL ARTICLE

Clozapine Use in Patients With Schizophrenia and the Risk of Diabetes, Hyperlipidemia, and Hypertension

A Claims-Based Approach

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Background: Numerous case reports have linked clozapine to the development of diabetes mellitus and hyperlipidemia in patients with schizophrenia. However, investigators have been unable to clearly demonstrate this association when compared with a control group receiving conventional antipsychotics.

Methods: Medical and pharmacy claims from the Iowa Medicaid program were used to compare incidence rates for diabetes, hyperlipidemia, and hypertension in 552 patients receiving clozapine and 2461 patients receiving conventional antipsychotics (eg, haloperidol, chlorpromazine hydrochloride), with the use of a retrospective cohort design. Logistic regression was used to compare incidence rates adjusting for age, sex, and duration of available follow-up.

Results: No significant differences in overall incidence rates for diabetes, hyperlipidemia, or hypertension were observed in patients receiving clozapine vs conventional antipsychotics. However, among younger patients (aged 20-34 years), clozapine administration was associated with a significantly increased relative risk of diabetes (2.5 [95% confidence interval, 1.2-5.4]) and hyperlipidemia (2.4 [95% confidence interval, 1.1-5.2]), but not hypertension (0.9 [95% confidence interval, 0.4-2.0]).

Conclusions: These data suggest that clozapine may not be an independent cause of diabetes or hyperlipidemia, but instead acts as an effect modifier in susceptible populations by increasing weight or affecting insulin secretion and resistance. This finding requires confirmation in other settings and patient populations and with the other atypical antipsychotics (risperidone, olanzapine, and quetiapine fumarate). The potential long-term medical and economic implications of the early induction of diabetes and hyperlipidemia in patients with schizophrenia warrant further study.

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SINCE 1994, several case reports and uncontrolled studies have linked the atypical antipsychotic clozapine with the development of diabetes mellitus.[1-5] Similar reports have been published with the atypical agents olanzapine[6,7] and quetiapine fumarate.[8] One hypothesis proposes that diabetes may occur secondary to weight gain associated with the atypical antipsychotics.[9] Some investigators propose more direct physiological mechanisms, including effects on glucose regulation and insulin secretion and resistance.[3,10] Further complicating this relationship is the observation that patients with schizophrenia have a higher rate of diabetes than does the general population.[11,12]

While evidence continues to mount, investigators have been unable to clearly demonstrate that clozapine leads to a significantly increased rate of diabetes in patients with schizophrenia when compared with conventional antipsychotics.[13] Therefore, the primary objective of this study was to compare the incidence rates of diabetes in patients with schizophrenia receiving clozapine vs conventional antipsychotics, with the use of Medicaid claims data. As clozapine has also been associated with hyperlipidemia,[14,15] incidence rates for the additional weight-related outcomes of hyperlipidemia and hypertension were compared as secondary objectives.

RESULTS

POPULATION CHARACTERISTICS

A total of 4770 patients with at least 1 medical claim for schizophrenia were identified. Of these, 3013 (63.2%) satisfied entry criteria for the analysis. The conventional antipsychotic group included 2461 patients and the clozapine group included 552

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SUBJECTS AND METHODS

DATA SOURCE AND CASE SELECTION

The study was approved by the University of Iowa, Iowa City, institutional review board. Claims data for the Iowa Medicaid program were obtained through the Iowa Department of Human Services. Data from both medical and pharmacy claims were used, and patient identifiers were encrypted to protect patient confidentiality. Each Medicaid medical claim identifies a service provided, gives the date the service was provided, and includes up to 4 *International Classification of Diseases, Ninth Revision* (*ICD-9*) diagnosis codes. Pharmacy claims were used to identify the drug products dispensed and the date of fill. An associated data set containing Medicaid eligibility information was used to obtain demographic information such as sex and date of birth.

Medical claims from the years 1990 to 1994 were used to identify all patients with a diagnosis of schizophrenia (identified by *ICD-9* code 295.xx, excluding 295.7x). For these patients, the additional codes for schizoaffective disorder (*ICD-9* code 295.7x) and bipolar affective disorder (*ICD-9* code 296.xx, excluding 296.2x and 296.3x) were identified. From these diagnostic codes, the number of months the patient was diagnosed as having schizophrenia, schizoaffective disorder, or bipolar affective disorder were summed. Entry into the analysis required at least two thirds of these months to be coded for schizophrenia. The goal of this restriction was to isolate patients with schizophrenia by eliminating patients who were longitudinally considered schizoaffective or bipolar, because these populations might have a different intrinsic risk for diabetes than do patients with schizophrenia. Medical claims for psychiatric diagnoses were limited to the years 1990 to 1994, because the processing of psychiatric claims was changed in 1995 and the claims were unavailable after this point. Pharmacy claims and nonpsychiatric medical claims were unaffected by this change and were available for the years 1990 to 1998. Pharmacy claims were used to create a longitudinal drug history for each patient, beginning with the first observed medical claim for schizophrenia. Individual antipsychotic agents were identified from the pharmacy claims by means of both the National Drug Code field and the drug name text field. Antipsychotic agents classified as conventional agents were chlorpromazine hydrochloride, fluphenazine hydrochloride, haloperidol, loxapine, mesoridazine besylate, molindone hydrochloride, perphenazine, pimozide, prochlorperazine edisylate, thioridazine hydrochloride, thiothixene, trifluoperazine hydrochloride, and triflupromazine hydrochloride. Risperidone, olanzapine, and quetiapine were considered atypical antipsychotics.

RATES OF DIABETES, HYPERLIPIDEMIA, AND HYPERTENSION

The outcomes of interest were the development of diabetes, hyperlipidemia, or hypertension. A diabetes outcome was defined as either a medical claim with an *ICD-9* code for diabetes (*ICD-9* code 250.xx) or a pharmacy claim for a glucose-reducing agent (ie, insulin, sulfonylurea, etc). Similarly, the occurrence of hyperlipidemia was identified

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patients. Among patients receiving conventional antipsychotics, 77.5% received monotherapy with an oral agent during the index month. These included haloperidol (19.8%), thiothixene (14.8%), thioridazine (14.7%), trifluoperazine (7.2%), fluphenazine (6.8%), chlorpromazine (5.3%), and other oral monotherapy (8.9%). The remaining 22.5% of the conventional antipsychotic group received monotherapy with a long-acting injectable antipsychotic (11.5%) or some combination regimen of conventional antipsychotics (11.0%) during the index month.

The mean (±SD) age during the index month was 42.9±17.1 years in the conventional antipsychotic group compared with 37.4±12.1 years in the clozapine group (Mann-Whitney, $z=-6.18$, n=3013, $P<.001$). The clozapine group had a significantly larger proportion of men than the conventional antipsychotic group (61.4% vs 49.5%; $\chi^2_1=25.48$, $P<.001$).

INCIDENCE RATES OF DIABETES, HYPERLIPIDEMIA, AND HYPERTENSION

The mean (±SD) duration of available follow-up was 24.5±26.9 months for the conventional antipsychotic group and 25.5±24.4 months for the clozapine group (Mann-Whitney, $z=2.45$, n=3013, $P=.01$). The overall cumulative incidence rates of diabetes, hyperlipidemia, and hypertension are presented in **Table 1**. There were no significant differences in the overall incidence rates for diabetes, hyperlipidemia, or hypertension between patients receiving clozapine vs conventional antipsychotics. These differences remained nonsignificant after adjusting for index age, sex, and duration of follow-up by logistic regression.

While the overall incidence rate of diabetes was similar between groups, the effect of clozapine was significant in younger patients (**Table 2**). In patients 20 to 34 years of age, the incidence rate for diabetes was 5.0% in the clozapine group and 2.0% in the conventional antipsychotic group, representing a relative risk of 2.5 (95% confidence interval, 1.2-5.4). Diabetes incidence rates were not significantly different between antipsychotic groups among other age strata. A similar age effect was observed with hyperlipidemia (Table 2). Among patients 20 to 34 years old, the hyperlipidemia incidence rate was 4.6% in the clozapine group and 2.0% in the conventional antipsychotic group, representing a relative risk of 2.4 (95% confidence interval, 1.1-5.2). In contrast, no age effect was observed for hypertension (Table 2).

COMMENT

In recent years, clozapine has been linked to the development of diabetes in a number of individual cases, but the general scope of the effect has not been characterized. A recent naturalistic follow-up study of 82 patients starting clozapine treatment reported an alarming diabetes rate of 36.6% (30/82) within 5 years.[4] While this rate appears el-

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by either an appropriate *ICD-9*–coded medical claim (*ICD-9* code 272.xx) or a pharmacy claim for a lipid-lowering medication. For both diabetes and hyperlipidemia, the occurrence of drug therapy was considered sufficient to identify an outcome because these drugs are almost exclusively used for the primary indication. In contrast, the occurrence of hypertension was identified only through medical claims coded for hypertension (*ICD-9* codes 401.xx, 402.xx, 403.xx, 404.xx, and 405.xx). A pharmacy claim for a primary antihypertensive drug was not considered a reliable indicator for hypertension because of the large number of secondary indications for these agents, particularly in psychiatry (eg, β-blockers for antipsychotic-induced akathisia).

Patients who met entry criteria for a diagnosis of schizophrenia were separated into either the clozapine or conventional antipsychotic group, on the basis of observed treatments. The clozapine treatment group consisted of patients who had at least 1 pharmacy claim for clozapine during the observation period (1990-1998). The first month of clozapine treatment was defined as the index month. Beginning with this index month, treatment was followed up until an end point occurred. End points for the clozapine group were the end of available follow-up data, clozapine discontinuation, the addition of an atypical antipsychotic, or the occurrence of an outcome (ie, diabetes, etc). Patients in whom an outcome was observed before the index month were considered to have a preexisting condition and excluded from the determination of the incidence rate for that outcome. For example, a patient with a pharmacy claim for insulin before starting clozapine treatment was excluded from the outcome analysis for diabetes, but not for hyperlipidemia or hypertension.

The conventional antipsychotic group consisted of all patients who received conventional antipsychotics, with 2 exclusions. First, all patients who qualified for the clozapine group were excluded from the conventional group. Second, patients who received an atypical antipsychotic before the first observed month of treatment with conventional antipsychotics were excluded. The first month of conventional antipsychotic treatment was defined as the index month. As in the clozapine group, patients were followed up from the index month until an end point occurred. The end points for the conventional antipsychotic group were identical to those for the clozapine group except that patients were allowed to change antipsychotic regimens, provided only conventional antipsychotics were involved.

STATISTICAL ANALYSES

The sex distribution between treatment groups was compared by a χ^2 test. Inspection of the distribution of duration of follow-up and age indicated distinctly skewed data, violating the assumptions for standard parametric tests. Consequently, we used nonparametric tests, as necessary.[16,17] Unadjusted comparisons of cumulative incidence rates for diabetes, hyperlipidemia, and hypertension between groups were performed with Fisher exact test. Logistic regression was used for the multivariate comparison of incidence rates adjusting for index age, sex, and duration of follow-up. All statistical analyses and database manipulations were performed with the SAS system version 6.12.[18] All *P* values are 2-tailed at the significance level of .05.

evated, there was no comparison group available to directly test for the effect of clozapine. The only study that has incorporated a control group contrasted rates of diabetes and glucose intolerance in a series of 63 clozapine-treated patients and 67 patients receiving depot injections of high-potency conventional antipsychotics.[13] The authors reported an increased rate of diabetes or impaired glucose tolerance among clozapine-treated patients, but the difference did not reach statistical significance ($P=.06$). As the sample size was somewhat limited, the study may have lacked sufficient power to detect an effect of clozapine on the occurrence of diabetes.

The present study, however, involved data from more than 3000 patients with schizophrenia and more than 550 patients taking clozapine. While this sample size provided a greater than 99% power to detect a small effect size (Cohen $W=0.1$),[19] we were unable to demonstrate a significantly increased risk for diabetes, hyperlipidemia, or hypertension among clozapine users when compared with a control group treated with conventional antipsychotics. However, the age-stratified results suggested that age was a significant factor in the relationship between clozapine and diabetes.

There are numerous potential hypotheses for the influence of age on clozapine-induced diabetes and hyperlipidemia. The fact that the overall incidence rates were not increased suggests that clozapine may not be an independent risk factor for diabetes and hyperlipidemia but may modify other risk factors in younger patients. In the case of diabetes, family history, advancing age, obesity, and lack of physical activity are the strongest known risk factors.[20] As clozapine can produce substantial weight gain, increased diabetes risk may occur through the modification of this risk factor, particularly in younger, genetically susceptible patients. Alternatively, clozapine may promote hyperglycemia through inhibition of insulin secretion or promoting peripheral insulin resistance, as can be observed with other drugs.[10,21] This hypothesis is supported by the observation that not all cases of clozapine-related diabetes have involved weight gain.[5] Thus, for younger patients with schizophrenia who have not developed diabetes or hyperlipidemia, but are predisposed, clozapine may provide a sufficient insult through weight gain or some direct physiological mechanism to produce a clinically evident syndrome. Of course, this hypothesis requires confirmation in other settings and patient populations. If confirmed, the medical and economic implications of the early induction of diabetes and hyperlipidemia demand further study. It is unknown whether this effect is unique to clozapine or can be generalized to other atypical antipsychotics.

As this study has important clinical implications, the estimated incidence rates for diabetes, hyperlipidemia, and hypertension must be carefully scrutinized. A common criticism of claims-based research is that disease states are inadequately coded in medical claims and, therefore, important outcomes may go unreported. While this may cause the outcome rates to be artificially low, the

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Table 1. Cumulative Incidence Rates for Patients Receiving Conventional Antipsychotics vs Clozapine*

	Conventional Antipsychotic		Clozapine		*P*	
	Rate, No. (%)	95% CI	Rate, No. (%)	95% CI	χ^2_1	LR
Diabetes	78/2296 (3.4)	2.7-4.1	21/531 (4.0)	2.3-5.6	.62	.16
Hyperlipidemia	93/2373 (3.9)	3.1-4.7	26/518 (5.0)	3.1-6.9	.31	.06
Hypertension	124/2333 (5.3)	4.4-6.2	21/513 (4.1)	2.4-5.8	.30	.61

*CI indicates confidence interval; LR, logistic regression adjusting for index age, sex, and duration of follow-up.

Table 2. Cumulative Incidence Rates Among Patients Aged 20 to 34 Years*

	Conventional Antipsychotic		Clozapine		
	Rate, No. (%)	95% CI	Rate, No. (%)	95% CI	Relative Risk (95% CI)
Diabetes	15/768 (2.0)	1.0-2.9	11/222 (5.0)	2.1-7.8	2.5 (1.2-5.4)
Hyperlipidemia	15/768 (2.0)	1.0-2.9	10/216 (4.6)	2.5-8.6	2.4 (1.1-5.2)
Hypertension	25/766 (3.3)	2.0-5.6	6/216 (2.8)	0.6-5.0	0.9 (0.4-2.0)

*CI indicates confidence interval.

bias is likely to be similar between the clozapine and conventional groups and therefore not affect comparisons between treatment groups. Also, the age-stratified prevalence of diabetes in this population (data not presented) was slightly higher than rates previously reported from clinical data,[12] suggesting a reasonable sensitivity in detecting the occurrence of diabetes from Medicaid data. An exception may be the hypertension rates, which are likely underestimated because pharmacy claims could not be used to maximize detection. It should also be noted that the incidence rates reported in this study were not strictly defined temporally, such as a 1-year incidence rate. Therefore, it is difficult to directly compare the incidence rates with those reported in other studies. However, among the nonschizophrenic Iowa Medicaid recipients aged 20 to 34 years, the incidence rate of diabetes by similar methods and time periods was 1.7% (95% confidence interval, 1.6%-1.9%).

Another potential difficulty is the lack of important patient characteristics that can be controlled for as independent risk factors for developing an outcome, such as family history, weight gain, etc. One such factor that was available was age during the index month of antipsychotic treatment. The patients in the conventional group were significantly older, which could have artificially inflated the overall outcome rates for this group. However, the differences in incidence rates remained nonsignificant after controlling for index age and duration of follow-up with logistic regression.

Another issue is related to the potential for monitoring bias in patients treated with clozapine. As a result of the frequent hematologic monitoring required for clozapine, clinicians may have more interaction with these patients and be more likely to order other tests, including glucose and lipids. This bias could elevate the observed incidence rates of diabetes and hyperlipidemia among patients treated with clozapine. While this is a potential limitation of our study design, the lack of increased risk for hypertension argues against a strong monitoring bias. Also related to monitoring bias, as reports of clozapine-induced diabetes increased over time, clinicians may have been more likely to screen for this condition. However, there was not an increase in the rate of diabetes diagnoses over time in our study.

An additional criticism is the validity of considering all conventional antipsychotics together. Of particular concern is the reported difference in weight gain reported with low-potency vs high-potency conventional antipsychotics.[9] However, a within-class analysis in this study population actually suggested a trend toward lower incidence rates with low-potency conventional antipsychotics, particularly with hypertension.

It is apparent from the available literature that screening for diabetes and hyperlipidemia should be considered in the routine monitoring of patients receiving clozapine. This study specifically observed that younger patients treated with clozapine were at greater risk than were their counterparts receiving conventional antipsychotics. We concur with other investigators in recommending a fasting glucose and lipid panel every 6 months.[4] In addition to laboratory monitoring, weight and blood pressure should be recorded at each visit. A tendency to ignore hyperglycemia in patients receiving clozapine has been reported, and it should be emphasized that appropriate action must be taken in response to abnormal screening results.[4] Unfortunately, it is unknown whether diabetes and hyperlipidemia may be prevented or delayed in this population through lifestyle interventions to control weight. With vigilant monitoring and the institution of appropriate interventions, we may be able to reduce the medical morbidity and mortality in patients treated with clozapine.

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