Relationship Between Antipsychotic Medication Treatment and New Cases of Diabetes Among Psychiatric Inpatients

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Objective: **This study examined data on patients with serious and persistent mental illness in a large state hospital system to determine whether patients who took second-generation antipsychotics were more likely to develop diabetes mellitus than patients who took first-generation antipsychotics.** ***Methods:*** **A case-control study design was used. A new prescription of an antidiabetic medication was used to identify new cases of diabetes mellitus. Odds ratios were calculated for exposure to second-generation antipsychotics (clozapine, risperidone, olanzapine, quetiapine, and multiple second-generation antipsychotics) compared with exposure to first-generation antipsychotics. Cases and controls were identified by using a database that contained drug prescription information from the inpatient facilities that were operated by the New York State Office of Mental Health. Data from January 1, 2000, to December 31, 2002, were examined. Among 13,611 unique patients who received antipsychotics, 8,461 met entry criteria of being hospitalized for at least 60 days and not having an antidiabetic medication prescribed in the past. A total of 181 of these inpatients received prescriptions for an antidiabetic medication at least 30 days after their admission. Eight controls (N=1,448) for each case (N=181) were matched by calendar year, length of observation period, race, age group, and diagnosis, giving a total sample of 1,629 patients.** ***Results:*** **Statistically significant elevations in risk were seen among patients who received more than one second-generation antipsychotic or clozapine or quetiapine, compared with patients who received first-generation antipsychotics alone. Although not statistically significant, odds ratios for olanzapine and risperidone were also elevated. Conditional logistic regression adjusting for gender and age did not change the results.** ***Conclusions:*** **Exposure to multiple second-generation antipsychotics or clozapine or quetiapine significantly increased the risk of treatment-emergent diabetes mellitus. (*Psychiatric Services* 55: 1006–1013, 2004)**

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Second-generation antipsychotics are widely used in the treatment of psychotic disorders. Koller and colleagues (1–4) have reported data from the U.S. Food and Drug Administration's MedWatch surveillance program that implicated clozapine, olanzapine, risperidone, and quetiapine in new-onset diabetes mellitus, including diabetic ketoacidosis. Several pharmacoepidemiologic studies have supported the notion that second-generation antipsychotics may raise the risk of diabetes (5–15), and several mechanisms of action have been suggested for this association, including weight gain and development of insulin resistance (16,17). However, the existing pharmacoepidemiologic literature is inconsistent about the magnitude of risk of diabetes that is attributable to different antipsychotics (18). Much of this inconsistency may result from differences in study design and population or sample selection. Previous work was done mainly with outpatients in a variety of health care systems, did not control for any differences in how frequently and by what methods diabetes mellitus was screened for, and has often included patients who did not receive antipsychotics. A complete discussion of this topic can be found elsewhere (18).

We performed a case-control study among patients with serious and persistent mental illness in a large state hospital system to determine whether patients who took second-generation

antipsychotics were more likely to develop diabetes mellitus than patients who took first-generation antipsychotics. A new prescription for an antidiabetic medication was used as a proxy for treatment-emergent diabetes mellitus. All the patients who were included in our study were given antipsychotics. Because the intensity of surveillance for diabetes may also affect the identification of cases, we assessed the rate at which plasma glucose tests were ordered for patients in the control group, by type of antipsychotic prescribed.

Methods

Database

Data were collected by using the Integrated Research Database that was created by the information sciences division of the Nathan S. Kline Institute for Psychiatric Research. The database contains patient information—demographic characteristics and diagnostic information as well as dates of admission, transfer, and discharge—and drug prescription information for every inpatient within the 17 adult civil facilities of the New York State psychiatric hospital system. These psychiatric centers provide intermediate and long-term care to patients with severe and persistent mental illness. The database can produce records that can be cross-referenced with other relevant databases, including those that are related to the ordering of laboratory tests.

Approval was obtained from the institutional review board of the Nathan S. Kline Institute for Psychiatric Research and Rockland Psychiatric Center, along with a waiver for written informed consent. Patient-identifying information was removed from the data. Because the study was a retrospective review of existing data, it was found to present no more than minimal risk to the participants. The Integrated Research Database has been successfully used to examine the extent, pattern of use, and effectiveness of depot neuroleptics (19,20); the extent of prescribing or coprescribing antipsychotics (21,22); the effectiveness of newer antipsychotics (23); and the extent of the use of valproate (24,25) and other mood stabilizers (26).

Sample selection

Patients for the case group and the control group were included in the study if they were inpatients during the period of January 1, 2000, through December 31, 2002; had a length of stay of at least 60 days; and were given at least one dose of antipsychotic medication. For patients who were hospitalized in the New York State Office of Mental Health system before January 1, 2000, we also examined information in the database back to January 1, 1994, and excluded any patients who were found to have received a prescription for antidiabetic medication.

This study demonstrated an association between second-generation antipsychotics and the development of diabetes mellitus among severely and persistently ill hospitalized patients.

Case and control groups

Patients in the case group were those who received new prescriptions of antidiabetic medication—insulin, glyburide, glipizide, glimepiride, tolbutamide, chlorpropamide, tolazamide, repaglinide, metformin, troglitazone, acetohexamide, acarbose, miglitol, rosiglitazone maleate, pioglitazone hydrochloride, and nateglinide. To reduce the possibility that a prescription of an antidiabetic medication was a renewal of a medication that was received before hospitalization, patients in the case group were required to have at least a 30-day period of hospitalization before the start of the prescription of the antidiabetic medication. Nonpsychiatric physicians generally wrote these new prescriptions after clinical and laboratory evidence indicated a need for this intervention.

To control for potentially confounding variables, patients in the control group were matched to those in the case group first on calendar year, then on length of stay during the calendar year (within 45 days), then on race (white versus nonwhite), then on age group (younger than 40 years versus 40 years or older), and then on diagnosis (given a *DSM-IV* diagnosis of schizophrenia or schizoaffective disorder versus any other diagnosis). Matching on gender or total length of stay that included other calendar years was not done, because a preliminary analysis of cases for the years 1998 through 1999 did not indicate a significant association between these variables and the likelihood of receiving antidiabetic medication. Multiple rounds of matching occurred until eight controls were found for each case.

Antipsychotic exposure

The second-generation antipsychotic medications that were examined were clozapine (commercially available in the United States since 1989), risperidone (available since 1994), olanzapine (available since 1996), and quetiapine (available since 1997). Ziprasidone and aripiprazole were excluded because they were not commercially available during the entire study period. Patients who received ziprasidone or aripiprazole were excluded from being considered for either the case or control group. First-generation antipsychotic medications examined were chlorpromazine, fluphenazine, haloperidol, loxapine, mesoridazine, molindone, perphenazine, thioridazine, thiothixene, and trifluoperazine. Emergency or stat use of intramuscular antipsychotics was not considered. Antipsychotic exposure was classified by examining a 45-day period before the new prescription for

Table 1

Demographic characteristics of inpatients taking antipsychotic medication who received (cases) or who did not receive (controls) a new prescription for an antidiabetic medication[a]

Characteristic	Controls (N=1,448)		Cases (N=181)	
	N	%	N	%
White	464	32	58	32
Age (mean±SD years)	43.7±12.8		43.3±11.4	
Men	1,030	71	110	61
Diagnosis of schizophrenia or schizoaffective disorder	1,200	83	150	83
Length of stay (mean±SD days)	1,481±2,189		1,169±1,556	
Length of stay during the calendar year when a new antidiabetic medication was prescribed or the equivalent index date for the controls (mean±SD days)	288.7±102.3		290.7±100	

[a] Patients were matched on year of stay, length of stay during the study year (observation period), race, age, and diagnosis.

antidiabetic medication for case patients or to an equivalent index date for control patients. Six exposure categories were created a priori: patients who received first-generation antipsychotics but did not receive any second-generation antipsychotics, patients who received only clozapine, patients who received only risperidone, patients who received only olanzapine, patients who received only quetiapine, and patients who received more than one second-generation antipsychotic, either simultaneously or consecutively. For all the second-generation antipsychotic categories, patients may have also been given first-generation antipsychotics. The category of patients who received more than one second-generation antipsychotic was necessary because exposure to more than one agent is not uncommon. The many possible combinations made it unfeasible to break this category down into smaller categories for statistical analysis; however, the combinations are qualitatively described in the results section. Because this 45-day period does not equate to actual extent of exposure to the antipsychotic of interest, the amount of time that the patient was given the identified antipsychotic for the six months before the index date was also determined.

Statistical analysis

Crude odds ratios (ORs) for receiving a new prescription of an antidiabetic agent were calculated, and 95 percent confidence intervals (CIs) were determined. For the exposure variable, patients who received first-generation antipsychotics only were considered as the reference category. Conditional logistic regression analysis was used to adjust the ORs for age and gender. The use of conditional logistic regression allows data for cases to be compared directly with that of their respective controls, thus maximizing the benefit of the matched design. The analysis was performed with the Cox regression module of SPSS version 10, using syntax that stratified the data according to each case and its respective group of eight controls (27). Syntax is available from the authors on request.

Power calculations indicate that to detect at 80 percent power a crude OR of 3, with 95 percent certainty that the result is not caused by chance, a minimum sample size of 29 to 39 cases would be required for each of the categories of second-generation antipsychotics. The sample size is the sum of the number of patients in the case group who were exposed to first-generation antipsychotics only plus the number who were exposed to second-generation antipsychotics. In all exposure categories, the sample size was sufficient to detect the target OR of 3. An OR of 3 was selected for the power calculation because statistically a risk ratio of 2 is rather low and could be accounted for by many factors other than a causal connection between the suspect agent and disease (28). A risk ratio that exceeds 3—a threefold increase in risk—would indicate a strong association between the risk factor and disease (28). The actual limit of detection achieved in our study ranged from 2.3 to 2.65 for the various exposure categories.

Because the frequency of monitoring for diabetes mellitus with plasma glucose tests may vary depending on the type of antipsychotic medication prescribed, we measured this frequency among patients in the control group. The average monthly rate for plasma glucose testing was calculated by counting all plasma glucose tests that were performed for each patient in the control group during the relevant calendar year and dividing it by the number of months of observation. Information for this calculation was gathered from the administrative records that were maintained by the central laboratory that processes these tests for ten of the 17 hospitals that are operated by the New York State Office of Mental Health. Data were available for 1,154 patients in the control group (79.7 percent).

Results

Sample

Among the 13,611 unique hospitalized patients who received antipsychotic medication from January 1, 2000, to December 31, 2002, a total of 8,461 patients met our entry criteria of being hospitalized for at least 60 days and not being given antidiabetic medication in the past. Within the hospital system during this period, 1,539 patients (841 out of 8,876 men and 698 out of 4,735 women) received antidiabetic medications, for a prevalence rate of 11.31 percent among all inpatients who received antipsychotic medications (9.5 percent for men and 14.7 percent for women; χ^2=85.4, df=1, p<.001). A total of 181 patients received a new prescription for an antidiabetic agent at least 30 days after their admittance, 62 received this prescription in 2000 (out of 4,908 patients who met entry criteria), 68 received this prescription in

Table 2

Risk of developing diabetes mellitus among inpatients taking antipsychotic medication who received (cases) or who did not receive (controls) a new prescription for an antidiabetic medication[a]

Exposure	Cases	Controls	Crude OR	95% CI for crude OR	OR[b]	95% CI[b]	p for OR[b]
First-generation antipsychotics only	17	250	1	—	1	—	—
Clozapine only[c]	24	171	2.06	1.08–3.96	2.06	1.07–3.99	.031
Olanzapine only[c]	43	402	1.57	.88–2.82	1.57	.87–2.82	.132
Quetiapine only[c]	24	112	3.15	1.63–6.09	3.09	1.59–6.03	<.001
Risperidone only[c]	31	305	1.49	.81-2.76	1.5	.81–2.79	.196
More than one second-generation antipsychotic[c,d]	42	208	2.97	1.64–5.37	2.86	1.57–5.2	<.001

[a] Patients were matched on year of stay, length of stay during study year (observation period), race, age, and diagnosis.
[b] Calculated by logistic regression, adjusting for gender and age
[c] Patients may have also been exposed to first-generation antipsychotics.
[d] Simultaneously or consecutively within the 45-day window before the new prescription of an antidiabetic agent

2001 (out of 4,525 who met entry criteria), and 51 received this prescription in 2002 (out of 4,159 who met entry criteria), yielding percentage annual incident rates of 1.26, 1.5, and 1.27 for each respective year. Eight controls (N=1,448) for each case (N=181) were matched by calendar year, length of observation period, race, age group, and diagnosis, which gave a sample size of 1,629 patients.

Demographic information for cases and their respective controls is given in Table 1. With the exception of gender, no statistically significant differences were found between cases and controls on these demographic characteristics. A lower percentage of men were in the case group than the control group (χ^2=8.22, df=1, p=.004). This difference arose because we did not match control patients on the basis of their gender; consequently, the percentage of men in the control group is the same as the percentage of men in the inpatient population that is served by the New York State Office of Mental Health—approximately 70 percent. To adjust for this difference, gender was included in the conditional logistic regression model.

Although we used a 45-day window before the index date to classify patients by their most proximate exposure to an antipsychotic, most patients were given the antipsychotic in question for a longer period. Therefore, we also measured the amount of time that the identified antipsychotic was prescribed for the patient for the six months before the index date. The mean±SD number of days that patients received a single second-generation antipsychotic was 121±60.9 days for patients in the case group and 133.7±55 days for patients in the control group. Although the minimum length of stay that was required for study inclusion was 60 days, the sample was composed of patients with much longer stays, as can be seen in Table 1. Overall, the longer stay was associated with much longer exposure to antipsychotic medication treatment. Within the New York State psychiatric hospital system, approximately one-quarter of all inpatients have a length of stay that ranges from one to five years, and one-fourth have a length of stay that exceeds five years.

Odds ratios and 95 percent confidence intervals

Table 2 shows that when crude ORs were calculated and when the analyses used logistic regression and adjusted for gender and age, statistically significant elevations in risk were observed for patients who received more than one second-generation antipsychotic (OR=2.86, CI=1.57 to 5.2), clozapine (OR=2.06, CI=1.07 to 3.99), or quetiapine (OR=3.09, CI=1.59 to 6.03), compared with patients who received first-generation antipsychotics alone. ORs for olanza-

Table 3

Age-adjusted risk of developing diabetes mellitus among inpatients taking antipsychotic medication who received (cases) or who did not receive (controls) a new prescription for an antidiabetic medication, by gender

	Men (N=1,140)			Women (N=489)	
Exposure	OR	95% CI	p	OR	95% CI
First-generation antipsychotics only	1	—		1	—
Clozapine only[a]	2.52	1.04–6.13	.041	.92	.29–2.89
Olanzapine only[a]	2.09	.93–4.7		.79	.29–2.15
Quetiapine only[a]	3.89	1.54–9.81	.004	1.99	.6–6.56
Risperidone only[a]	1.85	.81–4.21		.73	.23–2.35
More than one second-generation antipsychotic[a,b]	3.72	1.61–8.57	.002	1.28	.46–3.58

[a] Patients may have also been exposed to first-generation antipsychotics.
[b] Simultaneously or consecutively within the 45-day window before the new prescription of an antidiabetic agent

Table 4

Monthly frequency of plasma glucose tests among inpatients taking an antipsychotic medication who did not receive a new prescription for an antidiabetic medication (N=1,154)

Exposure	N	Mean number of plasma glucose tests per month	SD
First-generation antipsychotics only	206	.241	.454
Clozapine only[a,c]	134	.36	.538
Olanzapine only[a,c]	312	.346	.58
Quetiapine only[a]	88	.334	.454
Risperidone only[a]	253	.258	.422
More than one second-generation antipsychotic[a,b,c]	161	.424	.739
Any antipsychotic (all controls)	1,154	.32	.543

[a] Patients may have also been exposed to first-generation antipsychotics.

[b] Simultaneously or consecutively within the 45-day window preceding the new prescription of an antidiabetic agent

c Statistically significant when compared with controls who received only first-generation antipsychotics (p=.046 for clozapine, p=.03 for olanzapine, p=.001 for more than one second-generation antipsychotic) or with controls who received risperidone as the only second-generation antipsychotic (p=.002 for more than one second-generation antipsychotic)

pine and risperidone were also elevated, although the elevations were not statistically significant.

There were 42 cases of treatment-emergent diabetes mellitus among the patients who were exposed to more than one second-generation antipsychotic. The combinations of second-generation antipsychotics were risperidone and quetiapine (12 patients, or 29 percent), risperidone and olanzapine (nine patients, or 21 percent), risperidone and clozapine (eight patients, or 19 percent), olanzapine and quetiapine (five patients, or 12 percent), olanzapine and clozapine (four patients, or 10 percent), quetiapine and clozapine (three patients, or 7 percent), and risperidone, olanzapine, and clozapine (one patient, or 2 percent).

As shown in Table 3, when the analysis was stratified by gender, ORs differed for men and women. Although men and women did not differ significantly on treatment assignment, ORs for men were statistically significant among those who received more than one second-generation antipsychotic (OR=3.72, CI=1.61 to 8.57), clozapine (OR=2.52, CI=1.04 to 6.13), or quetiapine (OR=3.89, CI=1.54 to 9.81). Statistical significance was not reached for any of the ORs for women, even after controlling for any differences in age or observation days.

Plasma glucose tests

As shown in Table 4, a comparison of the rate of plasma glucose testing that was obtained for patients in the control group revealed significant differences in surveillance rates among the exposure groups (F=3.049, df=5, 1,148, p=.01). Patients in the control group who received clozapine, olanzapine, or more than one second-generation antipsychotic were more likely to have a plasma glucose test (mean number of tests per month: .360±.538, .346±.58, or .424±.739, respectively) than control patients who received first-generation antipsychotics alone (.241±.454 tests per month; p=.046, p=.03, or p=.001, respectively, Bonferroni-corrected comparison). Patients in the control group who received more than one second-generation antipsychotic were more likely to have a plasma glucose test than those who received only risperidone (.258±.422 tests per month, p=.002 Bonferroni-corrected comparison).

Discussion

This study demonstrated an association between second-generation antipsychotics and the development of diabetes mellitus among severely and persistently ill hospitalized patients. None of the previous studies that examined this relationship included patients who were in state hospitals (5–15), and several studies included patients who were not exposed to antipsychotic medication as controls (8–10,12–14).

Both the diagnostic distribution and the choice of exposure groups for comparison may have a significant impact on the outcome of pharmacoepidemiologic studies in this area. For example, evidence exists that patients with schizophrenia may be at higher risk of developing diabetes, independent of antipsychotic use (29). In addition, second-generation antipsychotics are being used increasingly for indications outside the treatment of schizophrenia, such as for mania, dementia, and severe anxiety. Thus antipsychotic exposure groups among diagnostically heterogeneous populations are likely to differ in many patient characteristics besides the medication exposures under study. As a consequence, our restriction of the patient population to persons who were hospitalized and severely and persistently mentally ill and matching on diagnosis (schizophrenia or schizoaffective disorder versus other) may have certain methodologic advantages.

Our study is the first published case-control study to report a statistically significant increase in the risk of developing diabetes mellitus with quetiapine, compared with exposure to first-generation antipsychotics alone. This result is consistent with case reports (30–32), the "pharmacovigilance" report by Koller and colleagues (4), and the prevalence study by Sernyak and colleagues (6), in which an OR of 1.31 (CI=1.11 to 1.55) for quetiapine was reported. These results are also consistent with two presentations given at scientific meetings and whose abstracts were published (33,34). Although Buse and colleagues (12) found a hazard ratio of 1.7 (CI 1.2 to 2.4) for persons who took quetiapine, compared with persons who did not take antipsychotics, they also found a hazard ratio of .67 (CI .46 to .97) for persons who took quetiapine, compared with persons who took haloperidol, which sig-

nified a decreased risk. This result may be related to diagnostic and dosage issues. The database that was used by that study did not have information about diagnosis, and the mean dosage of quetiapine was low (79.9 mg per day). In contrast, during our study period of 2000 through 2002, within the adult civil inpatient facilities that are operated by the state of New York, 83 percent of the patients had a diagnosis of either schizophrenia or schizoaffective disorder, and the mean daily dosage of quetiapine ranged from 409 mg (first quarter of 2000, N=481) to 570 mg (fourth quarter of 2002, N=992). Similar to Buse and colleagues (12), Gianfrancesco and colleagues (14) found that patients who were given quetiapine did not have an increased risk of receiving treatment for diabetes. Although the authors stated that antipsychotic dosages did not affect their findings, they did not report on the actual dosages used. This lack of information on dosing is a particular issue for quetiapine, because it is not uncommon to see quetiapine being used as an adjunctive agent at lower doses for sedation or sleep than what is needed for a full antipsychotic effect. Moreover, in the study by Gianfrancesco and colleagues (14) only 10 percent of the patients who received quetiapine had a diagnosis of schizophrenia.

Our findings for clozapine generally confirm those of earlier published pharmacoepidemiologic studies. Reported relative risk or ORs for persons who took clozapine have been as high as 2.5 (CI=1.2 to 5.4), compared with patients who took first-generation antipsychotics (5), and 7.44 (CI=1.60 to 34.75), compared with persons who did not have any exposure to antipsychotics (10). However, one study found no difference in risk of developing diabetes mellitus among patients who were taking clozapine compared with patients who were not taking clozapine (7). In that study an almost exclusively older population was examined—the mean age of patients in the case group was 63.6 years and the mean age of patients in the control group was 61.9 years (7).

Although elevated, the OR for olanzapine in our study was not statistically significant. Our results were consistent with those of Buse and colleagues (12)—who found an elevated risk ratio of 3 for persons who took olanzapine (CI 2.6 to 3.5), compared with persons who did not take antipsychotics, but no difference when compared with persons who took haloperidol. However, our results differ from those of six published studies (8,10,11,13–15), which found relative risk or ORs for olanzapine as high as 4.2 (CI=1.5 to 12.2), compared with exposure to first-generation antipsychotics (8), and 5.8 (CI=2 to 16.7), compared with no exposure to antipsychotics (8).

Antipsychotics may put men at greater risk of developing diabetes mellitus than women, and the effect of antipsychotics on developing diabetes may be harder to detect among women because women have a higher base rate of diabetes.

Our finding that olanzapine was not associated with an increased risk of diabetes may in part be because of the period that we examined. Our study was the first to examine a period—2000 through 2002—in which information was readily available about the suspicion that second-generation antipsychotics—olanzapine and clozapine in particular, because they were the subject of some of the earliest reports—may be associated with diabetes. Thus clinicians may have deliberately avoided prescribing olanzapine to patients who would have otherwise been at higher risk of developing diabetes. We did observe that the monitoring rates for plasma glucose differed among the controls and that patients who received clozapine, olanzapine, or more than one second-generation antipsychotic had significantly higher rates of glucose testing than patients who received only first-generation antipsychotics. If clinicians altered their prescribing behavior, it may have attenuated the signal for clozapine and olanzapine and amplified the signal for the antipsychotics chosen instead, such as quetiapine or risperidone. However, although we observed an elevated OR for quetiapine that was statistically significant, we did not see this result for risperidone.

Gender may act as a moderator variable. Adjusted ORs were higher among men than women. This observed gender difference may have been due solely to chance, because the CIs for the men and the women overlap substantially for each drug. However, the differences could also be explained in other ways: antipsychotics may put men at greater risk of developing diabetes mellitus than women, and the effect of antipsychotics on developing diabetes may be harder to detect among women because women have a higher base rate of diabetes (35). In the population we studied, the prevalence of antidiabetic medication use among patients who received antipsychotics in 2000 through 2002 was 9.5 percent for men and 14.7 percent for women. This problem of detection of antipsychotic effect on diabetes mellitus has also been seen among older patients in other studies (5–7).

The study design was naturalistic. Treatment assignment was not randomized. Factors associated with the choice of medication and the risk of diabetes mellitus may have confounded our results. Our methodology shares this limitation with other large-scale pharmacoepidemiologic studies that have been previously published (18). Double-blind randomized clini-

cal trials avoid this limitation and may ultimately be needed to answer the question of how strong the association is between exposure to a second-generation antipsychotic and treatment-emergent diabetes mellitus.

Identification of cases was limited by using prescription of an antidiabetic agent as a proxy for the diagnosis of diabetes mellitus, with the rationale that the use of a pharmacologic intervention is indicative of severe disease that is readily identifiable. The Integrated Research Database does not consistently record medical diagnoses, nor does it contain information on care that is received outside the New York State psychiatric hospital system. However, hospital stays within the system can be very long. It is unknown what the prevalence of untreated or undiagnosed diabetes mellitus is in this population. Our procedure for case finding also missed patients who had a diagnosis of diabetes mellitus but who controlled their disorder by diet alone, which could have led to the inclusion of such patients as controls. As a consequence of these factors, we are probably underestimating the true number of patients with problems of glycemic dyscontrol. In addition, patients with elevated plasma glucose may have had their antipsychotic medications switched or stopped, which may have improved their hyperglycemic state. Not being able to include these patients as cases could also have resulted in an underestimation of risk.

Although we attempted to include only new cases by examining records in the Integrated Research Database back to January 1, 1994, and excluding patients who had received a prescription of an antidiabetic medication before January 1, 2000, it is possible that some patients received antidiabetic medication before January 1, 1994, or at any time in other health-care systems.

Another limitation of our study was the lack of information on weight and body mass index. It is known that obesity is a risk factor in the development of diabetes mellitus and that second-generation antipsychotics have a greater propensity for causing weight gain than first-generation antipsychotics (36). Other risk factors that were not controlled for include elevated insulin levels, family history of diabetes mellitus, lack of engagement in physical activity, and hepatitis C infection—all of which have been strongly associated with diabetes mellitus (37).

Although the risk of treatment-emergent diabetes with second-generation antipsychotics appears greater than with first-generation antipsychotics, the study design does not permit us to quantify differences between the second-generation antipsychotics in terms of risk for emergent diabetes. Generalizability of our results is limited to similar chronically mentally ill inpatient populations. Outpatient psychiatric populations may differ significantly on parameters such as diet, level of activity, and disease severity.

Conclusions

This study lends support to the hypothesis that an association exists between second-generation antipsychotic use and the development of diabetes mellitus. This association was demonstrated to be statistically significant for clozapine, quetiapine, and multiple second-generation antipsychotics. ORs were also elevated for olanzapine and risperidone, although the results were not statistically significant. Long-term prospective epidemiologic cohort studies, as well as randomized clinical trials, will be needed to ascertain whether or not there is a true cause-and-effect relationship between exposure to second-generation antipsychotics and diabetes mellitus. Future pharmacoepidemiologic studies need to be particularly mindful of the possibility of treatment assignment bias—that is, when physicians avoid prescribing agents that are believed to cause an increase in risk of diabetes among patients who are at a higher perceived baseline risk.

Actual incidence rates for emergent diabetes mellitus in this patient population appear small. However, given the long duration of illness, the prevalence of diabetes in this group of patients was not inconsiderable. At present, a reasonable clinical strategy would be to manage risk of onset of diabetes mellitus with careful medical monitoring, including baseline and regular monitoring of plasma glucose levels for all patients who are given antipsychotics, especially when risk factors such as weight gain, lack of physical activity, family history of diabetes, or advancing age are present. ♦

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