Antipsychotic Medication Treatment and

New Prescriptions for Insulin and Oral Hypoglycemics

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Word Count (excluding title, abstract, references, tables, and figures): 2350

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ACKNOWLEDGEMENTS

Partial support for the maintenance of the Integrated Research Database has been provided by unrestricted grants from Eli Lilly & Co., the Janssen Research Foundation, and Pfizer, Inc. The design and conduct of the study, the collection, analysis, and interpretation of the data, and the preparation, review, and approval of the manuscript was done independently by the authors, with no input from any of the pharmaceutical companies.

ABSTRACT

Context: Uncontrolled studies and case reports have linked atypical antipsychotic use to the development of diabetes mellitus. Current epidemiological evidence is limited and conflicting.

Objective: To detect the increase in risk of diabetes mellitus from exposure to atypical antipsychotics (clozapine, risperidone, olanzapine, quetiapine).

Design, Setting, and Participants: Using a retrospective case-control study design, odds ratios were calculated regarding exposure to different antipsychotics. Cases (patients receiving a new prescription of insulin or an oral hypoglycemic as a proxy for diabetes mellitus) and controls were identified for calendar years 1997 and 2000 using a database containing drug prescription information from the in-patient facilities operated by the New York State Office of Mental Health. Ten controls for each case were matched by length of observation period, age group, and ethnicity. Among 11,579 patients in 1997 and 9,622 patients in 2000, 5,751 and 4,923, respectively, met our entry criteria of being hospitalized at least 60 days, prescribed antipsychotic medication, and not prescribed anti-diabetic medication during the three prior calendar years.

Main Outcome Measure: Prescription of an anti-diabetic medication.

Results: Incident cases increased from 39 out of 5751 (0.68%) in 1997 to 58 out of 4923 (1.18%) in 2000. In the year 1997, there were no statistically significant

associations observed between antipsychotic prescriptions and new prescriptions for an anti-diabetic agent. In the year 2000, statistically significant elevations in risk were observed for patients receiving atypical antipsychotics as a group (OR=3.15, 95% CI=1.12-8.91), but for individual antipsychotics, statistically significant elevations were observed only for clozapine (OR=7.61, 95% CI=2.36-24.55), and olanzapine (OR=3.22, 95% CI=1.07-9.74). Patients prescribed clozapine received plasma glucose tests more frequently than patients prescribed other antipsychotics.

Conclusions: In 2000, exposure to atypical antipsychotics as a group increased the risk of developing diabetes mellitus, as defined by receiving a new prescription for an anti-diabetic agent. Risk was highest with clozapine and may have been related to increased surveillance for diabetes mellitus. Not as elevated, but statistically significant, was the increased risk observed for olanzapine.

Key Words/Medical Subject Headings

Antipsychotics, Insulin, Oral Hypoglycemics, Diabetes Mellitus, Clozapine, Olanzapine, Risperidone

Introduction

Atypical antipsychotics (for example, clozapine, risperidone, olanzapine, quetiapine) are widely used in the treatment of psychotic disorders. However, several reports have raised the concern that atypical antipsychotic medication may cause or exacerbate problems with glucose regulation (1,2,3). In a double blind randomized controlled study comparing clozapine, risperidone, olanzapine, and haloperidol, 14% of 101 subjects developed hyperglycemia (defined by a fasting plasma glucose greater than 125 mg/dL) within 14 weeks (3). Of these cases, six of the patients had been randomized to clozapine, four to olanzapine, three to risperidone, and one to haloperidol. However, there have not been any definitive studies that have established a true cause and effect relationship for this observation, although several mechanisms of action have been suggested, including weight gain and the development of insulin resistance (4,5).

The existing pharmacoepidemiological literature is inconsistent regarding the magnitude of the diabetes risk attributable to different antipsychotics (6-18). Prior work has been done mainly with outpatients in a variety of different healthcare systems, without accounting for different surveillance rates for detecting diabetes mellitus, and has often included patients not receiving antipsychotics.

This retrospective case-control study examines the risk of receiving a new prescription of insulin or oral hypoglycemic medication, depending on the antipsychotic(s) being prescribed among psychiatric in-patients hospitalized in facilities

operated by the New York State Office of Mental Health. All the patients included were prescribed antipsychotics. Additionally, two calendar years are compared: 1997 and 2000. The former was selected because it predates the widespread dissemination of information relating to the possibility that atypical antipsychotics may lead to glucose dysregulation. Because the intensity of surveillance for diabetes may also affect the identification of cases, we quantified surveillance by assessing the rate at which plasma glucose tests were ordered for patients depending on the calendar year and antipsychotic prescribed.

Methods

This is a retrospective case-control study whose objective is to determine whether exposure to atypical antipsychotic medication increases a person's risk for treatment-emergent diabetes mellitus. A new prescription for an anti-diabetic medication is used as a proxy for treatment-emergent diabetes mellitus.

Data was collected using the Integrated Research Database (IRDB) created by the Information Sciences Division of the Nathan S. Kline Institute for Psychiatric Research. The IRDB contains patient information (demographic characteristics, dates of admission/transfer/discharge, and diagnosis), and drug prescription information for every in-patient within the adult civil facilities of the New York State psychiatric hospital system. These psychiatric centers provide intermediate and long-term care to patients

who are severely and persistently mentally ill. The IRDB can produce records that can be cross-referenced with other relevant databases, including those related to the ordering of laboratory tests. The IRDB has been successfully used to examine the extent, pattern of use, and effectiveness, of depot neuroleptics (19, 20), extent of prescribing or co-prescribing of antipsychotics (21,22), effectiveness of newer atypical antipsychotics (23), and of the use of valproate (24, 25) and other mood stabilizers (26).

Inclusion Criteria, Case and Control Definitions: Cases and controls were included in the study if they 1) were in-patients during calendar years 1997 or 2000; 2) had a length of stay at least 60 days; and 3) were prescribed at least one dose of antipsychotic medication. We excluded those patients who were prescribed an anti-diabetic medication during the three prior calendar years.

Cases were defined as those who received new prescriptions of anti-diabetic medication (insulin, glyburide, glipizide, glimepiride, tolbutamide, chlorpropamide, tolazamide, repaglinide, metformin, troglitazone, acetohexamide, acarbose, miglitol, rosiglitazone maleate, pioglitazone hydrochloride, nateglinide). Non-psychiatric physicians generally wrote these new prescriptions after clinical and laboratory evidence indicated a need for this intervention.

In order to control for potentially confounding variables, controls were matched to cases first on length of stay during the calendar year (within 45 days), then on ethnicity (white vs. non-white), and then on age group (under 40 years, or 40 and older).

Selection of these matching variables was done after an evaluation of cases for the years 1998-1999 and finding an association between the prescription of anti-diabetic medication and length of stay during the calendar year, ethnicity and age. The preliminary analysis found no significant association with gender, diagnosis, or total length of stay that includes other calendar years. Multiple rounds of matching occurred, resulting in ten controls found for each case.

Definition of antipsychotic exposure: Atypical antipsychotic medications examined were clozapine (commercially available in the USA since 1989), risperidone (available since 1994), olanzapine (available since 1996), and quetiapine (available since 1997). Typical antipsychotic medications examined were chlorpromazine, fluphenazine, haloperidol, loxapine, mesoridazine, molindone, perphenazine, thioridazine, thiothixene, and trifluoperazine. Antipsychotic exposure was determined for cases and controls by examining a forty-five day period prior to the new prescription for anti-diabetic medication (for cases), or to an equivalent index date (for controls). Since this forty-five day period does not necessarily equate to actual extent of exposure to the antipsychotic of interest, the amount of time on the identified antipsychotic was also determined going back to a maximum of 180 days.

Odds ratios (O.R.) for receiving a new prescription of anti-diabetic agent were calculated as an estimate of relative risk, and 95% confidence intervals were determined.

Surveillance for diabetes mellitus was measured by calculating the monthly rate of plasma glucose testing performed for control subjects during the relevant calendar year.

Institutional Review Board approval was obtained, along with a waiver for written informed consent as the data was anonymized and the study (retrospective review of a database) presented no more than minimal risk to the subjects.

Results

Description of Sample

The prevalence of anti-diabetic medication use within the civil hospitals operated by the State of New York increased from 5.86% among all patients hospitalized in 1997 (N=11,579) to 8.28% in 2000 (N=9,622). Among all patients eligible for inclusion in our study, patients receiving new prescriptions for anti-diabetic agents (i.e., cases) increased from 39 out of 5751 (0.68%) in 1997 to 58 out of 4923 (1.18%) in 2000. Demographic information regarding the cases and their respective controls are given in Table 1. There were no statistically significant differences between cases and controls on these demographic characteristics. Although the matching process guarantees that cases and controls are comparable overall, this may not hold when examining sub-groups of cases and controls exposed to a specific antipsychotic medication. For this reason we also compared cases and controls for age, length of stay during the calendar year, total length

of stay, and ethnicity when the sample is restricted to: typical-exposed vs clozapine-exposed; typical-exposed vs olanzapine-exposed; typical-exposed vs. risperidone-exposed; and typical-exposed vs. quetiapine-exposed (for 2000) (see Tables 2 and 3). There were no statistically significant differences between cases and controls for any of these subgroups.

Although we used a forty-five day window to classify patients by most proximate exposure to antipsychotic, most patients were prescribed the antipsychotic in question for a longer period of time. Going back in time to a maximum of 180 days, for cases in 1997, the average length of time (±standard deviation) on the atypical antipsychotic of interest was 106±69 days, and for 2000 it was 126±62 days.

Odds Ratios and 95% Confidence Intervals

In 1997 (Table 2) there was no statistically significant increase in the risk of being prescribed an anti-diabetic agent associated with exposure to any of the atypical antipsychotic medications.

In 2000 (Table 3), the odds ratio was statistically higher for patients receiving atypical antipsychotics as a group (OR=3.15, 95% CI=1.12-8.91), with clozapine exposure having the highest odds ratio (OR=7.61, 95% CI=2.36-24.55), followed by olanzapine (OR=3.22, 95% CI=1.07-9.74). Although not statistically significant, odds ratios for risperidone (OR=2.04) and quetiapine (OR=1.45) were also elevated. The actual number of available cases was small. This is reflected in the power analysis

provided in Tables 2 and 3, where we list the number of cases that would have been required to detect an odds ratio of 3.00, with an alpha (probability) of 0.05 and a beta (power) of 0.80. Figure 1 illustrates the overlapping confidence intervals for the odds ratios of the individual atypical antipsychotics.

Frequency of Plasma Glucose Determinations (Table 4)

A count of the number of plasma glucose tests obtained among the controls (this information was available for 70% of the controls for 1997 and 82% in 2000) revealed no significant differences in surveillance of glucose among the antipsychotics in 1997 (F=0.662, p=0.576). However, in 2000 there were significant differences (F=3.46, p=0.008). This was attributable to a two-fold increase in plasma glucose determinations for patients receiving clozapine. Comparing the exposure groups in 2000, patients receiving clozapine had a significantly higher rate of plasma glucose tests compared to those receiving typical antipsychotics (p=0.017, Bonferroni corrected).

Comment

In this study, exposure to atypical antipsychotics was associated with an increased risk of developing diabetes mellitus (as defined by receiving a new prescription of an anti-diabetic agent) in one of the two years studied. Our study is the first to show that there is differential surveillance for diabetes mellitus in patients receiving different

antipsychotics. This is also the first study to contrast two calendar years: 1997 when atypicals were utilized but the notion of increased risk for diabetes mellitus was not as well known, and 2000, after reports became generally available (27).

A major question is whether or not more cases of diabetes mellitus are found among the different antipsychotics independent of how frequently diabetes mellitus is being tested for. Among the controls, surveillance for diabetes mellitus did indeed increase from 1997 to 2000, but only for clozapine, which saw a two-fold increase in the rate of plasma glucose tests obtained, was this finding statistically significant. This bias towards clozapine may be related to increased concern about a link between clozapine and diabetes, but may also be partly attributable to the ease to which plasma glucose can be obtained. Because patients receiving clozapine are required to have frequent white blood cell count monitoring, it is not inconvenient for the patient to have a plasma glucose taken on the same blood draw. Regardless of the reason, the higher rate of blood glucose surveillance for clozapine patients may have contributed to the observation that risk of diabetes mellitus appeared highest with clozapine in 2000, and showed the largest changed between 1997 and 2000. This explanation cannot, however, explain the change in observed risk for the patients in other exposure groups, who did not show a marked increase in blood glucose surveillance.

It is notable that in the hospital system we examined, incident rates for anti-diabetic medication use has almost doubled from 0.68% of patients in 1997 to 1.18% in

2000. Parallel to this increase in new anti-diabetic medication use was an increase in the use of atypical antipsychotics. As a percentage of total antipsychotic use, atypical antipsychotic utilization increased from 55% of prescriptions in 1997 (4th quarter) to 79% in 2000 (4th quarter) as measured by prescriptions of at least 7 days in duration (21, 22). One possible explanation for the increase in incidence of new prescriptions for anti-diabetic medication may be the increase in exposure to atypical antipsychotics.

Limitations of study

The most significant limitation is the small number of cases observed, leading to a lack of sufficient power to make definitive conclusions among the individual atypical antipsychotics. Identification of cases was limited by utilizing prescription of an anti-diabetic agent as a proxy for the diagnosis of diabetes mellitus, with the rationale that the use of a pharmacological intervention is indicative of severe disease that is readily identifiable. It is unknown what the prevalence of untreated or undiagnosed diabetes mellitus is in this population. Our procedure for case finding also misses those patients with diabetes mellitus controlled by diet alone. This could have also led to the inclusion of such patients as controls. As a consequence of these factors, we are probably underestimating the true numbers of patients with problems of glycemic dyscontrol.

Another limitation of this study is the lack of information on weight, and Body Mass Index. It is known that obesity is a risk factor for the development of diabetes mellitus, and that atypical antipsychotics have a greater propensity towards causing

weight gain than typical agents (28). We do note that clozapine and olanzapine, the two atypical antipsychotics with statistically significantly increased odds, are also associated with a greater degree of weight gain (28).

Comparison with the Literature

From other published pharmacoepidemiological reports (6-11), and from posters presented at scientific meetings (12-18), hyperglycemia and new-onset diabetes mellitus appears to be associated with antipsychotic exposure. The published studies are inconsistent, with one suggesting no increased risk of diabetes mellitus with clozapine (8), while others finding otherwise (6,7,11). A possible explanation for this discrepancy is the different populations studied. The negative report (10) utilized Medicare records, representing a significantly older population (mean patient age = 63 years). Supporting our finding of increased diabetes risk associated with olanzapine are two published reports (9,11). The first uses the United Kingdom based General Practice Research Database (GPRD) (9), and the other, a United States based database consisting of patients covered by one of two health insurance plans (11). Neither of these studies included patients found in state hospitals, and utilized as controls patients who were not exposed to antipsychotic medication, suggesting that these two studies may represent a less severely ill population than those hospitalized in state institutions in New York.

Conclusion

This study lends support to the hypothesis that there is an association between atypical antipsychotic use and the development of diabetes mellitus. It also highlights the important role of blood glucose surveillance in identifying cases of glycemic dyscontrol among patients receiving antipsychotics – a fact with implication both for clinical management and for future epidemiological research in this area. Long-term prospective epidemiological cohort studies, as well as randomized clinical trials, will be needed to ascertain whether or not there is a true cause-effect relationship between exposure to atypical antipsychotic medication and diabetes mellitus. 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 fasting plasma glucose levels with all antipsychotics, especially when weight gain or obesity is present. An increase in surveillance would likely capture more cases as we have seen with clozapine.

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Table 1: Cases and Controls – Demographic Characteristics, 1997 and 2000

	1997		2000	
Characteristic	**Controls**	**Cases**	**Controls**	**Cases**
N	390	39	580	58
Mean Length of Observation (SD) (days)	188 (100)	180 (105)	176 (94)	172 (96)
Percent White Ethnicity	39	39	33	33
Mean Age (SD) (years)	43 (14)	41 (11)	43 (13)	44 (12)
Percent Male Gender	61	51	66	60
Percent with Diagnosis of Schizophrenia or Schizoaffective Disorder	77	77	79	72
Mean Length of Stay (SD) (days)	1029 (2397)	1521 (2494)	815 (1633)	1192 (1517)

Table 2: Risk of Developing Diabetes Mellitus Depending on Exposure to Antipsychotic Medication: 1997 Odds Ratios and 95% Confidence Intervals; Power Analysis

Exposure	Cases	Controls	OR (CI)	N of exposed cases needed to detect OR of 3 at standard alpha/beta of .05/.20	Power to detect OR of 3 at current N
Only typical AP(s)	17	187	1		
At least one atypical AP*	22	203	1.19 (0.61-2.31)	29	83%
CLO (but not RIS or OLZ)*	3	36	0.92 (0.26-3.29)	13	62%
RIS (but not CLO or OLZ)*	8	87	1.01 (0.42-2.43)	11	76%
OLZ (but not CLO or RIS)*	8	72	1.22 (0.50-2.96)	10	76%

*** Patients may have also been exposed to typical AP(s)**

AP=antipsychotic, CLO=clozapine, RIS=risperidone, OLZ=olanzapine

Table 3: Risk of Developing Diabetes Mellitus Depending on Exposure to Antipsychotic Medication: 2000 Odds Ratios and 95% Confidence Intervals; Power Analysis

Exposure	Cases	Controls	OR (CI)	N of exposed cases needed to detect OR of 3 at standard alpha/beta of .05/.20	Power to detect OR of 3 at current N
Only typical AP(s)	4	110	1		
At least one atypical AP*	54	470	3.15 (1.12-8.91)	88	60%
CLO (but not RIS or OLZ or QUE)*	13	47	7.61 (2.36-24.55)	23	60%
RIS (but not CLO or OLZ or QUE)*	11	148	2.04 (0.63-6.59)	36	40%
OLZ (but not CLO or RIS or QUE)*	19	162	3.22 (1.07-9.74)	38	54%
QUE (but not CLO or RIS or OLZ)*	2	38	1.45 (0.25-8.22)	23	26%

*** Patients may have also been exposed to typical AP(s)**

AP=antipsychotic, CLO=clozapine, RIS=risperidone, OLZ=olanzapine, QUE=quetiapine

Table 4: Monthly Frequency of Plasma Glucose Tests Done Among the Controls, 1997 and 2000

Exposure	1997	2000
Only typical AP(s)	0.23	0.22
CLO (but not RIS or OLZ or QUE)*	0.28	0.53
RIS (but not CLO or OLZ or QUE)*	0.22	0.27
OLZ (but not CLO or RIS or QUE)*	0.32	0.30
QUE (but not CLO or RIS or OLZ)*	N/A	0.43
Any AP (All Controls)	0.25	0.31

*** Patients may have also been exposed to typical AP(s)**

AP=antipsychotic, CLO=clozapine, RIS=risperidone, OLZ=olanzapine, QUE=quetiapine

Figure 1: Risk of Developing Diabetes Mellitus Depending on Exposure to Antipsychotic Medication: 2000 Odds Ratios and 95% Confidence Intervals by Atypical Antipsychotic