The Risk of Diabetes During Olanzapine Use Compared With Risperidone Use: A Retrospective Database Analysis

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Background: The relative risk of diabetes among patients undergoing risperidone treatment was compared with that of patients receiving olanzapine.

Method: A cohort was formed of 33,946 patients with at least 1 prescription for either olanzapine (N = 19,153) or risperidone (N = 14,793) between January 1, 1997, and December 31, 1999, recorded in the Régie de l'Assurance Maladie du Québec database. Patients were excluded if clozapine was dispensed to them during the study period or if they were diagnosed with diabetes before beginning antipsychotic therapy. New diabetes diagnoses made after the first antipsychotic prescription during the period were tabulated until December 31, 1999; censoring occurred at this date or at the last service date, if there was no record of using services during the last 6 months of follow-up. Crude hazard ratio and proportional hazard analyses were carried out.

Results: 319 patients developed diabetes on olanzapine treatment, and 217 developed diabetes on risperidone treatment; a crude hazard ratio of 1.08 (95% CI = 0.89 to 1.31, p = .43) was determined. When age, gender, and haloperidol use were controlled for using proportional hazard analysis, there was a 20% increased risk of diabetes with olanzapine relative to risperidone (95% CI = 0% to 43%, p = .05). Proportional hazard analyses adjusted for duration of olanzapine exposure indicated that the first 3 months of olanzapine treatment was associated with an increased risk of diabetes of 90% (95% CI = 40% to 157%, p < .0001), after adjusting for age, gender, and haloperidol use.

Conclusion: Compared with risperidone, olanzapine was associated with an increased risk of developing diabetes. More studies are required to further investigate this association.

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Atypical antipsychotic agents such as risperidone, olanzapine, quetiapine, and clozapine have been a major development in the long-term treatment of psychotic disorders. One major advantage is the lower incidence and severity of extrapyramidal symptoms and tardive dyskinesia compared with conventional antipsychotic agents such as haloperidol.[1] Recently, there have been many case reports associating the atypical antipsychotic agents, especially olanzapine and clozapine, with the development of diabetes.[2–25] Apparent remission of diabetes after discontinuing olanzapine has also been observed in 9 of the published cases,[3–6,8,17,19,24] and 1 patient exhibited a return of hyperglycemia after rechallenge with olanzapine.[3] It is unclear whether these cases reflect an incidence of olanzapine-related diabetes in excess of that expected.

Retrospective database analyses have also provided evidence that atypical antipsychotic agents may be associated with development of diabetes by comparison with a general population not receiving any antipsychotic agent.[26–28] In addition, a study of patients diagnosed with schizophrenia indicated a higher prevalence of diabetes among patients prescribed atypical antipsychotics than among those receiving conventional agents, especially in patients less than 40 years old.[29] The studies published have not directly compared the risk of diabetes after initiating olanzapine with that associated with each of the other atypical antipsychotic agents. This study was, therefore, designed to estimate the risk of developing diabetes among patients undergoing treatment with olanzapine compared with risperidone.

METHOD

Data Source

The health care databases managed by the Régie de l'Assurance Maladie du Québec (RAMQ) were used to obtain data for patients who were treated with either olanzapine or risperidone. RAMQ is a provincial government department overseeing health care claims, including those for approximately 3.5 million patients eligible for the drug insurance program. This program covers all residents of Quebec, Canada, aged 65 years and older, welfare recipients, and patients without private insurance. The databases contain outpatient prescription claims (including drug code and service date), the primary diagnosis recorded at each outpatient physician visit, dates of service, age, and gender. These databases were linked using unique patient identifiers. Each patient in the database has a unique identification number that is encrypted to protect confidentiality when the files are released for research.

Cohort and Outcome Definition

Patients who received at least 1 prescription for olanzapine or risperidone between January 1, 1997, and December 31, 1999, were identified. The date of the first prescription for one of these drugs was identified as the start date for each patient. Subjects were excluded if a prescription for clozapine was dispensed during the study period, if records were not available for at least 1 year before their start date, or if diabetes had been diagnosed or they were receiving medication for diabetes during the year prior to their start date. The cohort of olanzapine and risperidone users was then divided into 2 groups depending on whether they were dispensed a prescription for olanzapine.

The outcome of interest was whether or not patients received a primary diagnosis of diabetes at a physician visit (4-digit codes 250.0–250.9 in the *International Classification of Diseases*, Ninth Revision [ICD-9])[30] or had a first medication claim for insulin or an oral hypoglycemic agent. The date of onset of diabetes was defined as the first date on which the outcome was noted. Patients diagnosed with schizophrenia were identified using ICD-9 codes 295.0 to 295.9.[30]

The end of follow-up was defined as the date of onset of diabetes; or December 31, 1999; or, among patients with no recorded physician visit or medication claims in the last 6 months of the study, the last service date. For each patient, the observation time was calculated as the number of days between the start and end dates. The duration of exposure to each drug was determined as the time from the first prescription to the end of follow-up, and the total potential exposure time was divided into 4 categories: less than 3 months from index date of prescription, 3 to < 6 months, 6 to < 12 months, and 1 year or more.

Table 1. Patient Demographic Data and Clinical Characteristics[a]

Characteristic	Olanzapine	Risperidone	p Value
Subjects, N (person-years)	19,153 (18,765)	14,793 (13,563)	
Female	9637 (50.3)	8287 (56.0)	< .001
Age			
All patients			< .001
< 45 years	10,967 (57.3)	6096 (41.2)	
45–64 years	4778 (25.0)	2938 (19.9)	
≥ 65 years	3408 (17.8)	5759 (38.9)	
Schizophrenia patients			< .001
< 45 years	7785 (66.0)	3202 (56.0)	
45–64 years	3088 (26.2)	1613 (28.2)	
≥ 65 years	928 (7.9)	905 (15.8)	
Concomitant haloperidol	7293 (38.1)	4832 (32.6)	< .001

[a]Values shown as N (%) unless otherwise noted.

Analyses

The hazard of diabetes was estimated as the number of cases of diabetes divided by the total observation time. Crude hazard ratios and 95% confidence intervals (CIs) were estimated. Comparisons stratified by age, gender, and treatment exposure duration were also carried out.[31] A p value ≤ .05 was considered statistically significant. Cox proportional hazard analyses[32] were used to adjust for age, gender, diagnosis of schizophrenia, haloperidol use, use of other antipsychotic agents, and duration of exposure.

RESULTS

A total of 34,692 patients had at least 1 prescription for olanzapine or risperidone between January 1, 1997, and December 31, 1999. Clozapine was dispensed to 746 patients (2.2%), who were excluded from the study. The patients receiving either olanzapine or risperidone accumulated 32,328 person-years of follow-up between January 1, 1997, and December 31, 1999. Overall, 4775 (14.1%) of the patients had no evidence of service use in the last 6 months of the study and were censored at their last visit date. Olanzapine was dispensed more than once to 17,142 (89.5%) of the patients in the olanzapine group, and risperidone was dispensed more than once to 12,259 (82.9%) of the patients in the risperidone group.

Patients in the olanzapine group tended to be younger and more frequently male (Table 1). More of the olanzapine users were diagnosed with schizophrenia; 62% compared with 39% of the risperidone patients. Olanzapine users were also more likely to be prescribed haloperidol (see Table 1).

Overall, 319 patients developed diabetes after being prescribed olanzapine, and 217, after being prescribed risperidone; a crude hazard ratio of diabetes was 1.08 (95% CI = 0.89 to 1.31, p = .43) (Table 2). These crude rates may be misleading, because they do not take the imbalances of age, gender, and other characteristics into account.

Table 2. Diabetes Event Rates in Olanzapine Versus Risperidone Users and Crude Relative Risk, According to Gender, Age, and Duration of Treatment

Characteristic	Olanzapine		Risperidone		Relative Risk (95% CI)	p Value
	No. of Diabetes Cases	Rate[a]	No. of Diabetes Cases	Rate[a]		
All patients	319	17	217	16	1.08 (0.89 to 1.31)	.43
Gender						
Male	118	12	85	14	0.86 (0.60 to 1.23)	.41
Female	201	23	132	18	1.28 (1.05 to 1.67)	.02[b]
Age group						
< 45 years	147	13	70	11	1.14 (0.79 to 1.65)	.49
45–64 years	113	24	56	19	1.26 (0.89 to 1.90)	.22
≥ 65 years	59	24	91	20	1.19 (0.94 to 1.51)	.16
Treatment duration						
< 3 months	60	26	51	21	1.21 (0.84 to 1.75)	.31
3 < 6 months	24	17	16	13	1.23 (0.62 to 2.44)	.56
6 < 12 months	53	17	31	14	1.20 (0.72 to 2.01)	.49
≥ 12 months	182	16	119	15	1.04 (0.76 to 1.42)	.80

[a]Rates per 1000 person-years.
[b]Significant p value.

Table 3. Relative Risk of Developing Diabetes in Olanzapine Versus Risperidone Users (adjusted for age, gender, and haloperidol use)

Model	Adjusted Relative Risk (95% CI)	p Value
All patients	1.20 (1.00 to 1.43)	.05
Women	1.30 (1.05 to 1.65)	.02
Drug exposure time		
< 3 months	1.90 (1.40 to 2.57)	< .0001
3 < 6 months	1.16 (0.75 to 1.78)	.50
6 < 12 months	1.11 (0.81 to 1.51)	.51
≥ 12 months	1.06 (0.86 to 1.31)	.58

When age, gender, and haloperidol use were controlled for using proportional hazard analysis, the relative risk of diabetes was increased 20% (95% CI = 0% to 43%, p = .05) for olanzapine compared with risperidone (Table 3). This analysis also revealed significant interaction between olanzapine use and gender. Consequently, the proportional hazard analyses were also stratified by gender. Among women, the relative risk of diabetes was increased 30% (95% CI = 5% to 65%, p = .02) comparing olanzapine with risperidone, after adjusting for age, schizophrenia diagnosis, and haloperidol use (see Table 3). Adjusting for use of other antipsychotic medications did not change our findings.

Proportional hazard analyses adjusting for the duration of olanzapine exposure indicated that, particularly in the first 3 months of olanzapine treatment, there was a 90% increase (95% CI = 40% to 157%, p < .0001) in the risk of developing diabetes when compared with risperidone (see Table 3).

DISCUSSION

In our study of a large population of patients, olanzapine use was associated with an increased risk of developing diabetes, especially during the first 3 months of treatment, when compared with risperidone. Other researchers have also noted that, in most cases, the onset of diabetes occurred within a year of initiating treatment.[16,28] In addition, significant increases in glucose levels have recently been observed among patients treated with olanzapine,[16,33] but not risperidone.[16] This study supports the suggestion that it is appropriate to consider periodic glucose monitoring in olanzapine-treated patients and, if hyperglycemia is observed, to consider withdrawal of olanzapine to see if the condition remits.[34]

Several features of our study must be considered in interpreting the findings. The study is a retrospective analysis based on RAMQ medication claims data. These data have been validated, however, and have been shown to be an accurate and comprehensive means of determining the medications dispensed.[35] The RAMQ data have also been used to study other adverse events.[36,37] The data are believed to accurately reflect services used, as underreporting is not in the provider's interest and claims are not processed with incomplete mandatory fields.

The RAMQ database includes information only from patients aged 65 years and older, welfare recipients, and those without private insurance. Consequently, the patient demographics and other characteristics, including known risk factors for developing diabetes, may not be representative of the broader population of patients receiving atypical antipsychotics.

This database did not include data on diagnoses recorded at admission to the hospital, so any patients admitted to the hospital for treatment of diabetes may have been missed. Also, any patients with hyperglycemia controlled by diet but without a primary diagnosis of diabetes being recorded at a visit to their physicians would not have been identified in these analyses. The recording of a primary diagnosis of diabetes or dispensing of an antidiabetic

medication was used to determine the occurrence of diabetes. On the basis of oral glucose tolerance testing, it is believed that, for every diagnosed case of diabetes, there may be about 1 undiagnosed case.[38] Some diabetic cases may not have been excluded from or counted during this study, as the physician may not have made a diagnosis of diabetes. So, this study design does not yield an accurate estimate of the total number of cases of diabetes.

Diabetes incidence rates are higher among women and increase with age.[38] Given that there were imbalances between treatment groups in both of these characteristics, this study adjusted the results for age and gender, with resulting increases in the relative risk. Data were not available on race, body mass index, or whether there was a family history of diabetes, which are characteristics also known to affect the risk of diabetes, so these could not be considered as covariates.

Patients who were prescribed olanzapine were also more frequently diagnosed with schizophrenia, and some research has indicated that patients with this disorder may have an increased prevalence of diabetes compared with the general population.[39–41] In our study, however, schizophrenia diagnosis was not a significant predictor of diabetes and did not change our finding of a higher risk of diabetes among patients prescribed olanzapine.

Clozapine has also been associated with an increased risk of diabetes,[42–45] so patients who received this drug were excluded from the study. Approximately one third of the patients prescribed olanzapine or risperidone also received haloperidol. In our study, haloperidol use was found to be a significant predictor of developing diabetes (relative risk = 1.24, 95% CI = 1.05 to 1.47), adjusting for age and gender. Controlling for haloperidol use, however, did not eliminate the association between olanzapine and a higher risk of developing diabetes. Although conventional antipsychotic agents have been associated with an increased risk of diabetes in some studies,[26,28] we did not exclude patients who were prescribed other antipsychotic products (except clozapine) concurrently with olanzapine or risperidone. In our study, the inclusion of use of other antipsychotic agents in the models did not eliminate the association between olanzapine and a higher risk of developing diabetes.

Other commonly prescribed medications may also be associated with diabetes. For example, diabetes or impaired glucose metabolism has been associated with oral contraceptives, β-blockers, thiazides, glucocorticoids, lithium, and valproic acid. Some of the diabetes cases observed could be due to these other products, and this could explain the increased relative risk of diabetes among patients receiving olanzapine, but only if these drugs were preferentially coadministered to the patients receiving olanzapine.

There are many limitations to the information currently available to assess the degree to which patients receiving atypical antipsychotic agents are at risk of developing diabetes. The information comprises case reports and 4 retrospective claims database analyses, but full details of the design are not available for 3 studies, as the main findings have been presented only in abstracts. Despite the limitations of this retrospective study, the design and sample size allowed us to quantify the additional risks associated with olanzapine compared with risperidone.

It is important for prescribers to be aware of the potential risk of developing diabetes with olanzapine treatment, so that they may assess each patient's risk profile and decide whether to monitor glucose levels regularly, as well as react swiftly to manage the diabetes and, should it arise, consider discontinuing olanzapine. Further research is required to confirm whether olanzapine is associated with a higher risk than risperidone of development of diabetes and to better understand the precise biological basis of this association in order to identify patients at higher risk.

Drug names: clozapine (Clozaril and others), haloperidol (Haldol and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal), valproic acid (Depakene and others).

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