Papers

Assessment of independent effect of olanzapine and risperidone on risk of diabetes among patients with schizophrenia: population based nested case-control study

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Abstract

Objective To quantify the association between olanzapine and diabetes.

Design Population based nested case-control study.

Setting United Kingdom based General Practice Research Database comprising 3.5 million patients followed between 1987 and 2000.

Participants 19 637 patients who had been diagnosed as having and treated for schizophrenia. 451 incident cases of diabetes were matched with 2696 controls.

Main outcome measures Diagnosis and treatment of diabetes.

Results Patients taking olanzapine had a significantly increased risk of developing diabetes than non-users of antipsychotics (odds ratio 5.8, 95% confidence interval 2.0 to 16.7) and those taking conventional antipsychotics (4.2, 1.5 to 12.2). Patients taking risperidone had a non-significant increased risk of developing diabetes than non-users of antipsychotics (2.2, 0.9 to 5.2) and those taking conventional antipsychotics (1.6, 0.7 to 3.8).

Conclusion Olanzapine is associated with a clinically important and significant increased risk of diabetes.

Introduction

Since the late 1980s new antipsychotic agents with different mechanisms of action from conventional antipsychotics have been developed and widely adopted in the treatment of schizophrenia. The main advantage of these newer antipsychotics is a reduction of extrapyramidal side effects[1]; however, they are associated with a different spectrum of side effects, including weight gain, alterations in glucose metabolism, increased concentrations of blood cholesterol and lipids, myocarditis, and cardiomyopathy.[2–5] These metabolic effects may pose a burden as serious as the extrapyramidal effects.[6]

Recent evidence has shown an association between olanzapine and diabetes.[7–14] Most of the articles were case reports documenting the incidence of diabetes or hyperglycaemia with olanzapine. No such case reports exist for risperidone, despite this drug being introduced three years before olanzapine and having a similar share of the market. Hyperglycaemia is listed as an "infrequent" side effect of both olanzapine and risperidone and diabetes mellitus as an "infrequent" metabolic and nutritional side effect of risperidone. The degree to which these drugs are associated with the incidence of diabetes has not, however, been established.

Drugs known to affect the risk of diabetes include α adrenergic blockers, β adrenergic blockers, thiazide diuretics, corticosteroids, phenytoin, oral contraceptives containing norgesterol, and valproate.[15–17] We used data from the United Kingdom based General Practice Research Database to quantify the risk of diabetes associated with conventional and newer generation antipsychotics, specifically olanzapine and risperidone. We aimed to assess the independent effect of these drugs on the risk of diabetes in patients with schizophrenia.

Methods

Study population

Our study population comprised patients with a recorded doctor diagnosis of and drug treatment for schizophrenia registered with medical practices in the General Practice Research Database between June 1987 and September 2000. The database is described elsewhere.[18] Briefly, it contains data from around 400 general practices, dealing with 3.5 million patients in England and Wales. Continuous information has been collected for over 10 years, providing more than 30 million patient years of observation.[19] We derived our data from patient registration records, medical records, and prescription records stored in the database. The source of the database in our study is the Epidemiology and Pharmacology Information Core. Our study protocol was approved by the Scientific and Ethical Advisory Group of the database.

Cohort

Patients were eligible from the time that up to standard data were provided for them in the database—that is, the data recording had reached a standard appropriate for research use. In addition, all previous diagnoses and treatments are recorded in the medical records. Eligibility criteria for our study included a diagnosis of and treatment for schizophrenia recorded at any time. We defined the study period for patients identified as

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schizophrenic before the inclusion of up to standard data as the date when the practice began submitting up to standard data for the patient to the date when the patient changed practice, died, or had had final data submitted to the database. For all other patients the start of the study period is defined as the earliest date of diagnosis with schizophrenia. To be eligible for our study, patients needed at least three months of up to standard data.

For the cohort analysis we calculated the incidence rates from the number of patients who developed diabetes within three months of using the drug of interest divided by the person time use for the drug of interest. We calculated the person time use from the number of prescriptions divided by 12 (the typical prescription in the General Practice Research Database is written for one month).

Selection of participants

Cases

Incident cases of diabetes were defined as the earliest date of a diagnosis of or treatment for diabetes, occurring at least three months after the beginning of the study period. We define the date for diagnosis as the index date. To ensure that the patients with diabetes were incident cases, we checked the medical and prescription records for any diagnosis of or treatment for diabetes before the study began. Patients identified as cases should not have had a prescription for insulin or oral antidiabetic agents within three months of the index date. The use of a three month window avoided the exclusion of patients with diabetes who contributed no more than three months of data. However, 97% of the cases were free of diabetes for six months or more.

Controls

For each case we matched six controls with study periods at least as long as that of the case by age at index date (SD 5 years), sex, and index date. Controls that met the matching criteria were selected at random with SAS software. Controls were selected from patients who had been diagnosed as having or treated for schizophrenia but not diagnosed as having or treated for diabetes at any time. Controls were assigned the

same index date as the cases to which they were matched. Therefore the calendar time distributions of the index date were the same for both cases and controls.

Drug use

We classified antipsychotics as conventionals (depot or non-depot), olanzapine, risperidone, and other newer drugs. Non-depot conventional antipsychotics included benperidol, chlorpromazine, droperidol, flupenthixol, fluphenazine, haloperidol, loxapine, methotrimeprazine, oxypertine, pericyazine, perphenazine, pimozide, prochlorperazine promazine, sulpiride, thioridazine, trifluoperazine, trifluperidol, and zuclopenthixol. Depot conventional antipsychotics included flupenthixol decanoate, fluphenazine decanoate, fluphenazine enanthate, fluspirilene, haloperidol decanoate, and pipothiazine palmitate. Other newer antipsychotics included amisulpiride, remoxipride, and sertindole.

We abstracted all prescriptions written by the doctor for the treatment of schizophrenia and diabetes between the start of the study period and the index date. We defined drug use as the receipt of at least one prescription for an antipsychotic within three months of the index date. The selection of a three month window was based on a review of the case reports suggesting a mean time to onset of glucose dysregulation of three months after starting olanzapine.[7-14] Patients not taking the drugs of interest were those who did not have a prescription for an antipsychotic within three months of the index date.

Statistical analysis

We conducted all analyses with SAS version 7.0. Our main study comprised a nested case-control analysis. To account for the matched study design, we modelled the effect of drug use on the risk of diabetes development using conditional logistic regression.[20]

We used different referent groups to compare the risk of diabetes developing among users of the different antipsychotics. The first group included all patients except those receiving the drug of interest. The second group included patients taking conventional antipsychotics. The third group included patients with no prescription for an antipsychotic within three months of the index date. In addition to the matching variables, we adjusted the analysis for use of other drugs known to affect the risk of diabetes, such as α blockers, β blockers, thiazide diuretics, corticosteroids, phenytoin, oral contraceptives containing norgesterol, and valproate.

Results

Cohort analysis

Between 1 June 1987 and 24 September 2000, 21 145 patients were diagnosed as having and treated for schizophrenia. We excluded 916 of these with less than three months' follow up, 582 diagnosed as having or treated for diabetes before the start of their follow up period, and 10 with no information on diabetes diagnosis or treatment dates. This left 19 637 patients for study.

Males and females were equally represented in the study population, with a mean age of 51 (SD 20) years (table 1). Overall, 17 320 (88.2%) had at least one pre-

Table 1 Characteristics of study population and incident cases of diabetes. Values are numbers (percentages)

	Study population (n=19 637)	Incident cases of diabetes (n=451)
Age (years)		
<20	487 (2.5)	2 (0.4)
20-44	7 854 (40.0)	74 (16.4)
45-64	5 693 (29.0)	191 (42.4)
≥65	5 603 (28.5)	184 (40.8)
Sex		
Male	9 522 (48.5)	169 (37.5)
Female	10 115 (51.5)	282 (62.5)
Ever use of antipsychotics*		
Conventional antipsychotics:	18 443 (93.9)	382 (84.7)
Non-depot	17 320 (88.2)	339 (75.2)
Depot	4 421 (22.5)	95 (21.1)
Olanzapine	970 (4.9)	9 (2.0)
Risperidone	1 683 (8.6)	23 (5.1)
Other newer agents	578 (2.9)	6 (1.3)

*Categories not mutually exclusive. Ever use is at least one prescription for drug of interest, with prescription date any time during study period.

scription for non-depot conventional antipsychotics, 4421 (22.5%) for depot conventional antipsychotics, 970 (4.9%) for olanzapine, 1683 (8.6%) for risperidone, and 578 (2.9%) for other newer antipsychotics.

In total, 451 patients developed diabetes during a mean follow up of 5.2 (SD 3) years. The incidence rate of diabetes among all patients with schizophrenia treated with antipsychotics was 4.4/1000 person years. Women exhibited a higher incidence rate than men (5.3 v 3.5/1000 person years). The incidence rate within three months of a prescription was 10.0/1000 person years for olanzapine (95% confidence interval 5.2 to 19.2), 5.4/1000 person years for risperidone (3.0 to 9.8), and 5.1/1000 person years for conventional antipsychotics (4.5 to 5.8).

Case-control analyses

We matched 451 cases of diabetes with 2696 controls. Three patients had fewer than six controls per case, totalling 10 missing controls. The age and sex of the cases and controls were similar (table 2). The prevalence of conventional antipsychotic use differed among the cases and controls and among olanzapine users but not among risperidone users (table 2).

The risk of diabetes was greatest among olanzapine users (odds ratio 4.4, 1.8 to 11.0; table 3); use of conventional antipsychotics slightly increased the risk (1.3, 1.1 to 1.6). Use of risperidone was also associated with a slightly increased risk of diabetes (1.6, 0.8 to 3.3), but this was not significant (table 3).

Compared with no antipsychotic use olanzapine significantly increased the risk of diabetes (adjusted odds ratio 5.8, 2.0 to 16.7; table 4), followed by risperidone (2.2, 0.9 to 5.2) and conventional antipsychotics (1.4, 1.1 to 1.7). Olanzapine was associated with a significantly increased risk of diabetes (4.2, 1.5 to 12.2)

compared with conventional antipsychotics, unlike risperidone (1.6, 0.7 to 3.8; table 4).

Discussion

After adjustment for personal risk factors and concomitant drug use, patients taking conventional or newer antipsychotics for schizophrenia have an increased risk of diabetes. The risk was significantly increased with the newer antipsychotic olanzapine but not with the other newer antipsychotic, risperidone. Our study is the first to show these associations in a large cohort of patients with schizophrenia.

Several mechanisms are proposed for the observed association between diabetes and antipsychotic use, including weight gain and disruption of glucose metabolism. A meta-analysis showed a mean increase in weight of 4.15 kg for patients taking olanzapine and 2.10 kg for those taking risperidone.[2] Type 2 diabetes

Table 2 Characteristics of cases and controls. Values are numbers (percentages)

Characteristics	Cases (n=451)	Controls (n=2696)
Age (years):		
<20	2 (0.4)	14 (0.5)
20-44	74 (16.4)	440 (16.3)
45-64	191 (42.4)	1158 (43.0)
≥65	184 (40.8)	1084 (40.2)
Sex:		
Female	282 (62.5)	1687 (62.6)
Male	169 (37.5)	1009 (37.4)
Use of antipsychotic within 3 months of index date*:		
Conventional antipsychotics	268 (59.4)	1428 (53.0)
Olanzapine	9 (2.0)	15 (0.6)
Risperidone	11 (2.4)	42 (1.6)
Other newer agents	1 (0.2)	7 (0.3)

*Categories not mutually exclusive.

Table 3 Exposure odds ratios and 95% confidence intervals for development of diabetes in patients using different classes of antipsychotics within 3 months of index date compared with patients not taking drug of interest. Values are numbers (percentages) unless stated otherwise

Antipsychotic	Cases (n=451)	Controls (n=2696)	Unadjusted odds ratio (95% CI)	P value	Adjusted odds ratio (95% CI)*	P value
Conventional antipsychotics:	268 (59.4)	1428 (52.9)	1.3 (1.1 to 1.6)	0.009	1.3 (1.1 to 1.6)	0.013
Non-depot	235 (52.1)	1269 (47.1)	1.2 (1.0 to 1.5)	0.043	1.2 (1.0 to 1.5)	0.051
Depot	48 (10.6)	281 (10.4)	1.0 (0.7 to 1.4)	0.881	1.0 (0.7 to 1.4)	0.855
Olanzapine	9 (1.9)	15 (0.6)	4.0 (1.7 to 9.5)	0.002	4.4 (1.8 to 11.0)	0.002
Risperidone	11 (2.4)	42 (1.6)	1.6 (0.8 to 3.1)	0.177	1.6 (0.8 to 3.3)	0.160
Other newer antipsychotics	1 (0.2)	7 (0.3)	0.9 (0.1 to 7.0)	0.885	0.7 (0.1 to 5.8)	0.723

*Adjusted for age, sex, index year, duration of follow up, and use of either α blocker, β blocker, β blocker and thiazide diuretic, corticosteroid, thiazide diuretic, lithium, oral contraceptives containing norgesterol, or valproate.

Table 4 Comparison of patients using olanzapine and risperidone within three months of index date with patients not using antipsychotics or those using conventional antipsychotics

Antipsychotic*	Cases (n=451)	Controls (n=2696)	Adjusted odds ratio (95% CI)†	P value
No antipsychotics (reference)	168	1228		
Conventional antipsychotics	263	1404	1.4 (1.1 to 1.7)	0.004
Olanzapine	7	11	5.8 (2.0 to 16.7)	0.001
Risperidone	7	26	2.2 (0.9 to 5.2)	0.079
Other newer agents	1	3	1.6 (0.2 to 17.1)	0.699
Conventional antipsychotics (reference)	263	1404		
Olanzapine	7	11	4.2 (1.5 to 12.2)	0.008
Risperidone	7	26	1.6 (0.7 to 3.8)	0.290
Other newer agents	1	3	1.2 (0.1 to 12.4)	0.900

*Categories mutually exclusive. Results not shown for patients using more than one antipsychotic, included in model.
†Adjusted for age, sex, index year, duration of follow up, and use of either α blocker, β blocker, β blocker and thiazide diuretic, corticosteroid, thiazide diuretic, lithium, oral contraceptives containing norgesterol, or valproate.

What is already known on this topic

Recent evidence has suggested an association between the newer class of antipsychotics and diabetes

Most of these studies were case reports

The association has not been confirmed in epidemiological studies, with the relation adjusted for comorbid factors

What this study adds

Olanzapine is associated with a clinically important increased risk of diabetes

After adjustment for relevant risk factors this association is significant

The metabolic consequences of olanzapine should be considered by doctors giving treatment

seems to be strongly and consistently associated with obesity and weight gain.[21][22] Antagonism of histamine is also known to cause weight gain.[23] It is possible that serotonin antagonism plays a part in the weight gain associated with the newer drugs.[24][25] Weight gain can also be due to increased leptin secretion, which in turn leads to a disturbance of insulin secretion and diabetes mellitus.[12] Lastly, dopamine has been shown to stimulate insulin secretion by a β adrenergic mediated mechanism.[26][27]

Limitations of study

Our study has several limitations. Drug use was inferred from automated prescribing data. Also, patient specific data were limited to that recorded in the database. However, one study showed that 95% of prescriptions and 74% of consultations in the General Practice Research Database were recorded on computer compared with 42% and 75% in written records.[28] In addition, there was no direct information on the severity of schizophrenia, race, social class, or weight gain. We were thus unable to adjust for these variables. Confounding by indication remains a concern in observational pharmacoepidemiological studies. Clinicians may have prescribed one drug over the other based on the severity of the schizophrenia. We attempted to reduce this confounding by adjusting for known risk factors for diabetes. However, since confounders must be associated with both the use of the drug and the disease, we believe it is unlikely that the severity of schizophrenia would be linked to the incidence of diabetes. It was not possible to study the association between an important newer antipsychotic, clozapine, and diabetes as clozapine therapy must be started when patients are in hospital, and these patients are not included in the General Practice Research Database. Another limitation of our analysis was that we ignored the use of antipsychotics before the three month exposure period, therefore patients may have used different antipsychotics during the study period. Lastly, our analysis lacked power to compare the odds ratios between olanzapine and risperidone users.

Olanzapine use is consistently associated with a clinically important increased risk of diabetes, and this association, after adjustment for relevant risk factors, is significant. The metabolic consequences of antipsychotic therapy should be considered by treating doctors.

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