

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 effects¹; 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

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 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. This database contains data from around 400 general practices dealing with 3.5 million patients in England and Wales, providing more than 30 million patient years of observation.^{7 8}

Cohort

Eligibility criteria for our study included a diagnosis of and treatment for schizophrenia recorded at any time and at least three months of up to standard data. 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.

Selection of participants

Cases

Incident cases of diabetes were defined as the earliest date of a diagnosis of or treatment for diabetes (index date), occurring at least three months after the beginning of the study period. 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.

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 from patients who had been diagnosed as having or treated for schizophrenia but not diagnosed as having or treated for diabetes at any time.

Drug use

We classified antipsychotics as conventionals (depot or non-depot; see bmj.com), olanzapine, risperidone, and other newer drugs, including 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. 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

Our main study comprised a nested case-control analysis. We modelled the effect of drug use on the risk of diabetes development using conditional logistic regression.⁹ 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,

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Table 1 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.

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 (see bmj.com). Overall, 17 320 (88.2%) had at least one prescription 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 prevalence of conventional antipsychotic use differed among the cases and controls and among olanzapine users but not among risperidone users (table 1).

Compared with no antipsychotic use olanzapine significantly increased the risk of diabetes (adjusted odds ratio 5.8, 2.0 to 16.7; table 2), 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 2).

Discussion

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 kg for patients taking olanzapine and 2 kg for those taking risperidone.² Type 2 diabetes seems to be strongly and consistently associated with obesity and weight gain.^{10 11} Antagonism of histamine is also known to cause weight gain.¹² It is possible that serotonin antagonism plays a part in the weight gain associated with the newer drugs.^{13 14} Weight gain can also be due to increased leptin secretion, which in turn leads to a disturbance of insulin secretion and diabetes mellitus.¹⁵ Lastly, dopamine has been shown to stimulate insulin secretion by a β adrenergic mediated mechanism.^{16 17}

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.¹⁸ 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

Table 2 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.

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.

The General Practice Research Database is compliant with the Data Protection Act, 1998.

Contributors: See bmj.com

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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

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When I use a word

When I use a mocking bird

Of all types of slang, perhaps the best known is Cockney rhyming slang. It developed in London during the first half of the 19th century, at about the same time as Robert Peel was inaugurating his police force, perhaps to be used by criminals as a secret language that the slops (back slang, from ecilop) would not understand. Later, it spread with the convicts who were deported to Australia, and then to America, where it became known as Australian slang.

Several now familiar words in the English language had their origins in rhyming slang. For example, a dicky is a shirt because it is the shortened form of "dicky dirt," and perhaps there is an association with the German Decke, a cover. "Dickey" on the other hand means unwell, from "Uncle Dick," sick. To rabbit (rabbit and pork) is to talk. The brass tacks that people get down to are facts. The rude noise known as a raspberry is actually a raspberry tart. And who among us would call someone a silly berk if they knew that the word originates from rhyming slang "Berkshire Hunt"?

The best rhyming slang uses expressions that themselves reflect the meaning of the original word. For example, of the several

expressions for syphilis, the best is bang and biff, which not only rhymes with "syph" but also carries a suggestion of how you might catch it. Then there is a "snake's hiss," meaning an act of urination (oh, all right, a piss), which conveys its meaning through the sound that it suggests, not to mention the suggestive shape of the snake. Occasionally the meaning is subverted, as in "do me good", a Wood (Woodbine cigarette). Humour is important too. For instance, the Jim-brits or Jimmy Britts, shortened to "the jimmies," is Australian rhyming slang for diarrhoea; "Jimmy" (or "Jimmy Grant") is an immigrant, so not only is this a deft expression, it is also a neat insult of the Australians' traditional enemy.

So the next time you're feeling a bit Tom, Harry, and Dick or get frock and frill with a bout of threepenny bits or a dose of the horse and trap, and you think you're going to crack-a-cry, go to see the King's Proctor and ask him for some Jenny Hills to make you feel all harbour light. Under-cum-stumble?

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