Incident Diabetes Associated With Antipsychotic Use in the United Kingdom General Practice Research Database

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Background: Recent reports suggest an association between antipsychotic use and development or exacerbation of diabetes. This study evaluated the risk of incident diabetes associated with the use of atypical and conventional antipsychotics.

Method: This nested case-control study included all patients in the U.K. General Practice Research Database treated with antipsychotic drugs between January 1994 and December 1998. The main outcome measures were the odds ratios of current (within prior 6 months) or recent (7 to 12 months) antipsychotic exposure among those with (N = 424) compared with those without incident diabetes (N = 1522).

Results: The adjusted odds ratio for current use of any antipsychotic drug compared with no use in the past year among those with diabetes was 1.7 (95% confidence interval [CI] = 1.3 to 2.3). The adjusted odds ratio for current use of atypical and conventional antipsychotic drugs compared with no use in the past year among those with diabetes was 4.7 (95% CI = 1.5 to 14.9) and 1.7 (95% CI = 1.2 to 2.3), respectively. The adjusted odds ratio for recent use of conventional antipsychotic drugs compared with no use in the past year among those with diabetes was 1.0 (95% CI = 0.6 to 1.6). The odds ratio for recent atypical antipsychotic drug use could not be calculated because no study subjects had this exposure.

Conclusion: This study showed an increased risk of incident diabetes among current users of atypical and conventional antipsychotic medications. These results were independent of other established risk factors. The larger association observed for atypical antipsychotic users should be regarded as preliminary given the small number of incident diabetes cases in this group.

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Case reports and observational studies suggest the possibility of an association between onset of diabetes mellitus and use of conventional and atypical antipsychotics. The literature includes reports of both new-onset diabetes[1–11] and exacerbation of existing disease[1,8] in antipsychotic-treated individuals with and without a family history or risk factors for development of diabetes. These cases were unusual in that development of diabetes occurred shortly after the antipsychotic was started and that the symptoms usually disappeared when the antipsychotic was discontinued. In cases in which the diabetes did not resolve completely, antihyperglycemic medication was greatly reduced on discontinuation of the antipsychotic agent.[5,8,11] In some instances, there was evidence of redevelopment of diabetes when the antipsychotic regimen was restarted.[8–10] All cases involved atypical antipsychotics, with a variety of strengths and dosing regimens.

Diabetes is a major public health concern. In the general population, the increasing economic and medical burden of treating diabetes, and its rank as the seventh most common cause of mortality, have made this condition a focus of intense public health effort.[12] In the psychiatric population, there is an increased prevalence of diagnosed medical illnesses as compared with the general population, as well as a high percentage of underreporting of physical conditions.[13] Diabetes mellitus may have a

higher prevalence in schizophrenic patients than in the general population in industrialized countries.[14]

We found no published, population-based, epidemiologic study of incident diabetes associated with antipsychotic use. We conducted a large, nested case-control investigation using the U.K.-based General Practice Research Database (GPRD) to investigate the risk of incident diabetes associated with the use of atypical and conventional antipsychotics. We hypothesized that among current users of antipsychotic medication, there is an increased risk of developing diabetes mellitus as compared with past users of antipsychotics.

METHOD

Data Resource

The GPRD began in 1987 and is now a 15-year longitudinal database of approximately 3 million patients from selected practices in the U.K. General practitioners were provided with computers and were extensively trained in providing standardized medical information. In exchange, they agreed to provide anonymous, computerized, continuous medical information for researchers, including clinical diagnoses and prescription drug data. The database has been extensively described and validated elsewhere[15–19] and is broadly representative of the general U.K. population in terms of age, sex, and geography.[20]

Study Population

The current study population consisted of adults aged 18 to 64 years in December 1998 who had received at least 1 prescription for an antipsychotic drug between January 1994 and December 1998. (January 1994 was chosen as the start date because that was when the atypical antipsychotics became available in the U.K.) The majority of patients had few prescriptions and therefore had large periods of time when they were not receiving antipsychotic prescriptions. Participants were required to have at least 1 year of recorded clinic visits prior to the first diabetes mellitus diagnosis. Participants were excluded from the study if they had a diagnosis of diabetes mellitus prior to January 1994 or if they had a medical condition that might increase their risk or likelihood of detection of diabetes mellitus, such as cancer, human immunodeficiency virus/acquired immunodeficiency syndrome, acute or chronic pancreatitis, acute or chronic liver disease, or pregnancy. Those diagnosed with hyperglycemia but without a subsequent diagnosis of diabetes were excluded from the study population.

Case Ascertainment

Potential cases were identified from the computer record without knowledge of time of exposure to antipsychotic drugs. The case group consisted of all individuals diagnosed with incident diabetes after January 1, 1994, and prior to December 31, 1998, in the eligible study population. An "incident" case was defined as a case involving someone with a new diagnosis of diabetes without prior evidence of the disease or treatment anywhere in the computer record. All potential cases were evaluated for confirmation of a diabetes diagnosis by reviewing the entire computerized medical record. We excluded cases that did not confirm the diagnosis by detailing follow-up information consistent with a diagnosis of diabetes (e.g., treatment with diet, a prescription for an oral hypoglycemic [Table 1], insulin, or referral to a diabetic clinic followed by progress notes from the clinic).

Table 1. Hypoglycemics Included in Outcome Ascertainment and Antipsychotics Included in Exposure Assessment

Hypoglycemics	Antipsychotics	
	Atypical	Conventional
Acarbose	Clozapine	Benperidol
Glibenclamide	Olanzapine	Chlorpromazine
Gliclazide	Risperidone	Flupenthixol
Glimepride	Quetiapine	Fluphenazine
Glipizide		Haloperidol
Gliquidone		Loxapine
Glyburide		Mesoridazine
Metformin		Methotrimeprazine
Repaglinide		Pericyazine
Tolazamide		Perphenazine
Tolbutamide		Pimozide
		Pipothiazine
		Promazine
		Sulpiride
		Thioridazine
		Thiothixene
		Trifluoperazine
		Zuclopenthixol

Controls

For comparison with the case group, up to 4 randomly selected controls, matched to cases on age, gender, and practice, were derived from the base study population. The index date from which exposure was ascertained for the controls is the date of the first diabetes diagnosis in their matched case. The same exclusion criteria applied to cases were applied to the controls. Controls were also individually reviewed for eligibility criteria without knowledge of time of exposure to antipsychotics.

Exposure Assessment

Exposure information was derived from the computer record. Exposure was categorized on the basis of the index date for case subjects and controls as either current use (antipsychotic use in the 6 months prior to the index date), recent use (use within the past 7 to 12 months prior to the index date), or past use (no use in the past year). Antipsychotic drugs were divided into conventional and atypical antipsychotic classes. Table 1 contains a list of all antipsychotics included in the study.

Covariates

In addition to the matching variables, information on the covariates proximal to diagnosis was obtained: body mass index (BMI; kg/m^2); smoking status (current, former, never); current systemic steroid use; current lithium use; current thiazide use; current oral contraceptive use; alcoholism; hypertension; a history of myocardial infarction (MI), stroke, or angina; number of past antipsychotic prescriptions; multiple antipsychotic use; and primary psychiatric diagnostic category (schizophrenia, psychosis, neurosis, bipolar disorder, stress disorder).

RESULTS

There were 73,428 subjects with at least 1 prescription for an antipsychotic in the study population who filled 19,102 and 958,453 prescriptions for atypical and conventional antipsychotic drugs, respectively. After review of the entire computerized patient record for each potential case, we found 424 cases of incident diabetes. These case subjects were matched, approximately 4:1, to 1522 controls by age, gender, general practice, and index date, and the subsequent analyses were done on this group. The majority of the case subjects (N = 238) and controls (N = 996) were categorized as having past exposure to antipsychotic drugs (no use in the year before the index date). One hundred sixty case subjects and 419 controls were currently exposed, and 26 case subjects and 107 controls were recently exposed. Of those subjects currently exposed, 8 case subjects and 8 controls were exposed to an atypical antipsychotic, while 152 case subjects and 411 controls were exposed to a conventional antipsychotic. Among the subjects currently exposed to an atypical antipsychotic drug, 5 case subjects and 5 controls were exposed to risperidone and 3 case subjects and 3 controls were exposed to olanzapine. Among those recently exposed, no case subjects or controls were exposed to an atypical antipsychotic, while 26 case subjects and 107 controls were exposed to a conventional antipsychotic.

The characteristics of case subjects and controls are listed in Table 2. Among the case subjects, 41% were male and the mean age was 51.4 years. The case subjects and controls were similar in relation to many of the variables assessed, except for BMI, diagnosis of hypertension, history of MI or angina, current systemic steroid use, and history of stroke. The mean BMI for case subjects was 32.0 kg/m^2 compared with 26.2 kg/m^2 for controls. Case subjects were more likely to have a diagnosis of hypertension, a history of MI or angina, or a history of stroke than controls. None of the individual psychiatric diagnoses was independently associated with incident diabetes.

Conditional logistic regression was used to calculate relative odds ratios of current or recent antipsychotic use among subjects with incident diabetes compared with those who did not develop diabetes (Table 3). The unadjusted odds ratio was 1.6 (95% confidence interval [CI] = 1.2 to 2.0) for current users of all antipsychotics combined and 0.9 (95% CI = 0.6 to 1.5) for recent users. We adjusted for alcoholism; current lithium use; current systemic steroid use; multiple antipsychotic use; current oral contraceptive use; current thiazide use; BMI; diagnosis of hypertension; history of MI, angina, or stroke; smoking status; and psychiatric diagnostic category. After adjustment, the odds ratio for current users of all antipsychotics was 1.7 (95% CI = 1.3 to 2.3) and for recent users was 0.9 (95% CI = 0.6 to 1.6).

We further categorized the exposure groups into those exposed to conventional and atypical antipsychotic drugs (Table 4). The past exposure group was again used as the reference. The unadjusted odds ratio was 4.0 (95% CI = 1.5 to 10.9) for current users of atypical antipsychotics and 1.5 (95% CI = 1.2 to 1.9) for current users of conventional antipsychotics. The odds ratio was 0.9 (95% CI = 0.6 to 1.5) for recent users of conventional antipsychotics, but the odds ratio for recent users of atypical antipsychotics could not be calculated because there were no subjects with this exposure. After adjustment for

Table 2. Characteristics of Case Subjects With Newly Diagnosed Diabetes and Controls, and Independent Effects of Confounders[a]

Variable	Case Subjects (N = 424) N	%	Controls (N = 1522) N	%	Odds Ratio (95% CI)
BMI					
< 30	155	37	916	60	Reference
30–34	86	20	151	10	3.1 (2.2 to 4.4)
35+	92	22	60	4	7.8 (5.2 to 11.7)
Unknown	91	21	395	26	1.2 (0.8 to 1.8)
Hypertension diagnosis	114	27	183	12	2.0 (1.4 to 2.9)
History of MI/angina	51	12	82	5	2.0 (1.3 to 3.1)
History of stroke	15	4	27	2	1.5 (0.7 to 3.2)
Smoking status					
Nonsmoker	192	45	625	41	Reference
Current smoker	139	33	523	34	0.9 (0.7 to 1.2)
Ex-smoker	38	9	156	10	0.6 (0.4 to 1.0)
Unknown smoking status	55	13	218	14	0.9 (0.6 to 1.5)
Alcoholism	34	8	96	6	1.3 (0.8 to 2.1)
Epilepsy	14	3	47	3	1.1 (0.6 to 2.2)
Current systemic steroid use	3	1	4	0.3	2.6 (0.5 to 14.2)
Schizophrenia	52	12	156	10	0.8 (0.5 to 1.4)
Bipolar disorder	33	8	98	6	1.3 (0.7 to 2.3)
Other psychoses	24	6	70	5	0.9 (0.5 to 1.8)
Neurosis	245	58	907	60	0.9 (0.7 to 1.3)
Stress disorder	2	0.5	21	1	0.5 (0.1 to 2.4)
Other mental disorder	68	16	270	18	Reference
Current lithium use	19	4	59	4	1.0 (0.5 to 2.0)
Use of multiple antipsychotics	107	25	112	7	1.1 (0.8 to 1.5)
Current OC use	48	11	183	12	0.9 (0.6 to 1.4)
Current thiazide use	103	24	202	13	1.3 (0.9 to 1.9)

[a]Abbreviations: BMI = body mass index, CI = confidence interval, MI = myocardial infarction, OC = oral contraceptive.

Table 3. Distribution of Case Subjects and Controls According to Current and Recent Exposure to Any Antipsychotic, Matched on Age, Gender, Calendar Time, and Practice[a]

Exposure	Case Subjects (N = 424)	Controls (N = 1522)	Unadjusted Odds Ratio	95% CI	Adjusted[b] Odds Ratio	95% CI
Past[c]	238	996	Reference	…	Reference	…
Current[d]	160	419	1.6	1.2 to 2.0	1.7	1.3 to 2.3
Recent[e]	26	107	0.9	0.6 to 1.5	0.9	0.6 to 1.6

[a]Abbreviation: CI = confidence interval.
[b]Adjusted for alcoholism; lithium use; use of systemic steroids; multiple antipsychotic use; body mass index; diagnosis of hypertension; current thiazide use; current oral contraceptive prescription; history of myocardial infarction, angina, or stroke; smoking status; and psychiatric diagnostic category.
[c]No antipsychotic use in the year before the index date.
[d]Antipsychotic use in the 6 months before the index date.
[e]Antipsychotic use in the past 7 to 12 months before the index date.

Table 4. Distribution of Case Subjects and Controls According to Current/Recent Exposure to and Receipt of Conventional/Atypical Antipsychotics, Matched on Age, Gender, Calendar Time, and Practice[a]

Variable	Case Subjects (N = 424)	Controls (N = 1522)	Unadjusted Odds Ratio	95% CI	Adjusted[b] Odds Ratio	95% CI
Past exposure[c]	238	996	Reference	…	Reference	…
Current[d] atypical	8	8	4.0	1.5 to 10.9	4.7	1.5 to 14.9
Current[d] conventional	152	411	1.5	1.2 to 1.9	1.7	1.2 to 2.3
Recent[e] atypical	0	0	…	…	…	…
Recent[e] conventional	26	107	0.9	0.6 to 1.5	1.0	0.6 to 1.6

[a]Abbreviation: CI = confidence interval.
[b]Adjusted for alcoholism; lithium use; use of systemic steroids; multiple antipsychotic use; body mass index; diagnosis of hypertension; current thiazide use; current oral contraceptive prescription; history of myocardial infarction, angina, or stroke; smoking status; and psychiatric diagnostic category.
[c]No antipsychotic use in the year before the index date.
[d]Antipsychotic use in the 6 months before the index date.
[e]Antipsychotic use in the past 7 to 12 months before the index date.

alcoholism; current lithium use; current systemic steroid use; multiple antipsychotic use; current oral contraceptive use; current thiazide use; BMI; diagnosis of hypertension; history of MI, angina, or stroke; smoking status; and psychiatric diagnostic category, the odds ratio was 4.7 (95% CI = 1.5 to 14.9) for current users of atypical antipsychotics, 1.7 (95% CI = 1.2 to 2.3) for current users of conventional antipsychotics, and 1.0 (95% CI = 0.6 to 1.6) for recent users of conventional antipsychotic drugs. The independent effects of potential confounders are listed in Table 2.

DISCUSSION

In this study, the results showed elevated risk of incident diabetes associated with current exposure to atypical or conventional antipsychotic drugs, independent of the risk due to other established risk factors (adjusted odds ratio = 1.7, 95% CI = 1.3 to 2.3).

The results of this study are consistent with published case reports and case series reports of diabetes associated with conventional antipsychotics and with the growing number of reports of incident diabetes and increased severity of disease associated with the atypical agents.[1,2–4,7,9–11,21–24] Although these reports involved clozapine, olanzapine, quetiapine, and risperidone, to our knowledge only clozapine has been investigated in a more formal study. Both Hägg and colleagues[25] and Melkersson and colleagues[26] studied prevalent diabetes and glucose function in cohorts of schizophrenic patients taking clozapine or conventional antipsychotics and found that patients taking clozapine were more likely to be classified as having type 2 diabetes than those taking conventional antipsychotic medication, although this association was not statistically significant.

The current study has several strengths. First, it was done using the GPRD, a large and well-validated data resource.[15–17,19,20] The GPRD contains a large cohort of antipsychotic users, allowing for 4:1 matching between case subjects and controls. There was complete case ascertainment based on the GPRD medical record. Because the computer record in the GPRD is the patient's primary clinical medical record, it was possible to examine several other risk factors for diabetes mellitus in this population, such as systemic steroid and lithium use. In addition, we restricted the study population to subjects who had at least 1 prescription for an antipsychotic drug at some time. The use of this base population not only provides information on all users of antipsychotics but also increases the efficiency of the design and reduces the likelihood that selection bias related to the use of antipsychotic drugs would influence the results. Finally, case subjects and controls were matched on several important potential confounders—age, gender, practice, and index date—to minimize

potential confounding due to these variables. Most individuals had only a single prescription for an antipsychotic, so the majority of the cohort was not exposed to antipsychotics during the study period or at the time that diabetes was first diagnosed.

This study also had some limitations. Most importantly, although the base study group of antipsychotic users was quite large, there were a limited number of incident cases of diabetes among atypical antipsychotic users (N = 8). This could be due to the limited availability of the atypical antipsychotics as compared with conventional antipsychotic agents during the study period (January 1994 through December 1998). The general practitioners do not systematically record data on some potentially important confounders, such as education, socioeconomic status, and ethnicity. In addition, the general practitioners do not systematically collect either laboratory results or anthropometric measures (such as height, weight, or BMI). Thus, the results seen could be due to some of these other factors rather than antipsychotic medication. Because the clinical measures were not available, more accurate diagnostic measures of diabetes (such as blood glucose test results) could not be obtained. Finally, insight into possible mechanisms of how the antipsychotics contributed to the development of diabetes, or if a change in BMI during antipsychotic use affected diabetes risk, could not be explored.

The results of this analysis may be important in relation to the risk of diabetes among users of atypical antipsychotic medication. Nevertheless, the reported association should be regarded as preliminary and should be reexamined in additional independent studies. Specifically, due to the small numbers of users of atypical antipsychotics in the present study, it would be beneficial to replicate these results in a population with more atypical antipsychotic use and in a sample in which changes in weight could be more closely monitored. Examining the time to diabetes diagnosis for different antipsychotic agents and regimens would also be valuable in determining the risks and benefits of specific antipsychotic agents and in encouraging appropriate use of these substances.

Drug names: acarbose (Precose), chlorpromazine (Thorazine and others), clozapine (Clozaril and others), glimepride (Amaryl), glipizide (Glucotrol and others), glyburide (DiaBeta and others), haloperidol (Haldol and others), loxapine (Loxitane and others), mesoridazine (Serentil), metformin (Glucophage and others), olanzapine (Zyprexa), perphenazine (Trilafon and others), pimozide (Orap), quetiapine (Seroquel), repaglinide (Prandin), risperidone (Risperdal), thiothixene (Navane and others), tolbutamide (Orinase and others), trifluoperazine (Stelazine and others).

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