Antipsychotic Drugs May Worsen Metabolic Control in Type 2 Diabetes Mellitus

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This study was supported by an unrestricted fellowship from Novo Nordisk, Alphen aan de Rijn, the Netherlands.

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Background: Several studies have indicated that type 2 diabetes mellitus is more common among schizophrenic patients than in the general population. In this study, we investigated whether the use of antipsychotic drugs in patients with diabetes leads to worsening of glycemic control.

Method: In this cohort study, patients with newly diagnosed type 2 diabetes were selected from the PHARMO Record Linkage System, which comprises pharmacy records for all 320,000 residents of 6 Dutch cities. In total, we identified 2585 patients with incident cases of type 2 diabetes who began treatment with oral hypoglycemic agents between 1991 and 1997 and had a medication history of at least 2 years after diagnosis of diabetes. A change in treatment from oral hypoglycemic agents alone to insulin therapy (with or without continuation of oral hypoglycemic agents) was considered a proxy for deterioration of β-cell function. We compared the incidence of initiation of insulin therapy between users and nonusers of antipsychotic drugs by performing a Cox proportional hazards model analysis.

Results: We found an increased risk for initiation of insulin therapy at 2 years after diagnosis of diabetes in users of antipsychotics compared with nonusers; the relative hazard (hazard ratio) was 2.0 (95% CI = 1.2 to 3.3), which did not change after adjustment for potential confounders. The risk decreased in the years after diagnosis of diabetes.

Conclusion: It seems that use of antipsychotics by patients with type 2 diabetes mellitus is associated with initiation of insulin therapy (i.e., "secondary failure"), especially in the first 2 years of the disease.

(J Clin Psychiatry 2004;65:674–678)

Several studies indicate that type 2 diabetes mellitus, impaired glucose tolerance, and insulin resistance are more common among patients with psychiatric disorders such as major mood disorders and schizophrenia than among the general population.[1–3] As type 2 diabetes advances, secondary failure of oral hypoglycemic therapy develops as a consequence of progressive loss of β-cell function and worsening of insulin resistance caused by persistent hyperglycemia and possible development of drug resistance.[4]

In recent years, case reports have been published describing the emergence of de novo onset of diabetes or worsening of previously well-controlled diabetes after the start of treatment with atypical antipsychotics.[5–10] Those "novel" antipsychotics are termed *atypical* for their relative lack of the extrapyramidal side effects typical of older, mostly higher-dosed antipsychotics.[11,12] Furthermore, for decades it has been reported that conventional neuroleptics, chlorpromazine in particular, may also alter glucose-insulin homeostasis[13,14] and lead to new cases of diabetes mellitus.[15]

The present study deals with the possible relationship between the use of antipsychotic drugs and worsening of glycemic control in patients with type 2 diabetes mellitus. Initiation of insulin therapy after failure of oral hypoglycemic treatment is considered a proxy for deterioration of metabolic control. Therefore, we compared those who did and did not begin insulin therapy with respect to antipsychotic drug use during a period following diagnosis of type 2 diabetes mellitus.

METHOD

Data Source

The PHARMO Record Linkage System was used as the data source for this study. It provided pharmacy dispensing records of all community-dwelling residents of 6 Dutch cities, totaling more than 450,000 patient histories, from 1985 to present.[16,17] Drugs were coded according to the Anatomical Therapeutic Chemical (ATC) Classification.[18] Because in the Dutch health care system ambulatory patients are usually designated a single pharmacy to fill their prescriptions independent of prescriber, virtually complete data are available for each subject. These data include sex, date of birth, drug names with ATC codes, dispensing date, total supply, prescribed dosage regimen, and prescriber. Pharmacy data from January 1991 to June 1999 were obtained for this study, comprising about 320,000 patient histories.

Study Subjects

In this cohort study, patients with incident type 2 diabetes mellitus were defined as subjects starting their first oral hypoglycemic treatment (ATC code A10B) between 1991 and 1997. Patients were eligible for inclusion if they received no hypoglycemic medication (tablets or insulin) during the 180 days preceding the date of starting oral hypoglycemic agent use. Furthermore, patients were included only if they were dispensed at least 2 consecutive prescriptions of oral hypoglycemic agents. We excluded subjects who began insulin treatment within 3 months (90 days) after their first prescription of a hypoglycemic agent ("primary failure").

Study Design

We performed a follow-up study in a subcohort of patients for whom there was at least 2 years (730 days) of medication history after diagnosis, i.e., first prescription of an oral hypoglycemic agent. Exposure was defined as the use of antipsychotic drugs (i.e., any use), ATC group N05A (excluding lithium, N05AN), during the first use of an oral hypoglycemic agent or in the 2 years thereafter to include long-term users. The event of interest was initiation of insulin therapy (ATC code A10A) with or without continuation of oral hypoglycemic medication. We compared the incidence of beginning insulin therapy between users of antipsychotic drugs and nonusers. Atypical antipsychotic drugs included risperidone, clozapine, olanzapine, and quetiapine.[19]

Data Analysis

For the comparison of continuous and categorical variables between users and nonusers of antipsychotics, we used the Student t test and chi-square test, respectively.

We performed a Cox proportional hazards model analysis (variable follow-up) in the cohort of all incident type 2 diabetic patients with at least 2 years of follow-up. Survival time was measured from the date of the first prescription of oral hypoglycemic agents to the date on which the patient began insulin therapy. Patients who did not receive insulin therapy were censored at the date of leaving the pharmacy (i.e., loss to follow-up) or at the end of the study (July 1999). Use of antipsychotics (dichotomous), age (in years) at date of first prescription of oral hypoglycemic agents, gender, and calendar year of diagnosis were time-independent variables.

We adjusted for the use of anticholinergic antiparkinsonian medication (ATC group N04A) because a higher rate of insulin treatment might be expected in patients suffering from extrapyramidal side effects. With regard to other potential confounders, we took into account the use of medication with known side effects on glucose metabolism: corticosteroids for systemic use (H02), β-blocking agents (C07), and thiazides and loop diuretics (C03, except C03D). Because of the known positive association between the prevalence of depressive disorders and type 2 diabetes,[20] we also investigated the potential association or interaction between use of antipsychotics, initiation of insulin therapy, and use of antidepressants.

Subsequently, we calculated crude and adjusted relative hazards (hazard ratios [HRs]) with the corresponding 95% confidence intervals (CIs) for initiation of insulin therapy in users of antipsychotic drugs at several time intervals of follow-up (2, 3, 4, and 5 years after diagnosis of diabetes mellitus).

Table 1. Characteristics of 3001 Patients With Type 2 Diabetes Mellitus

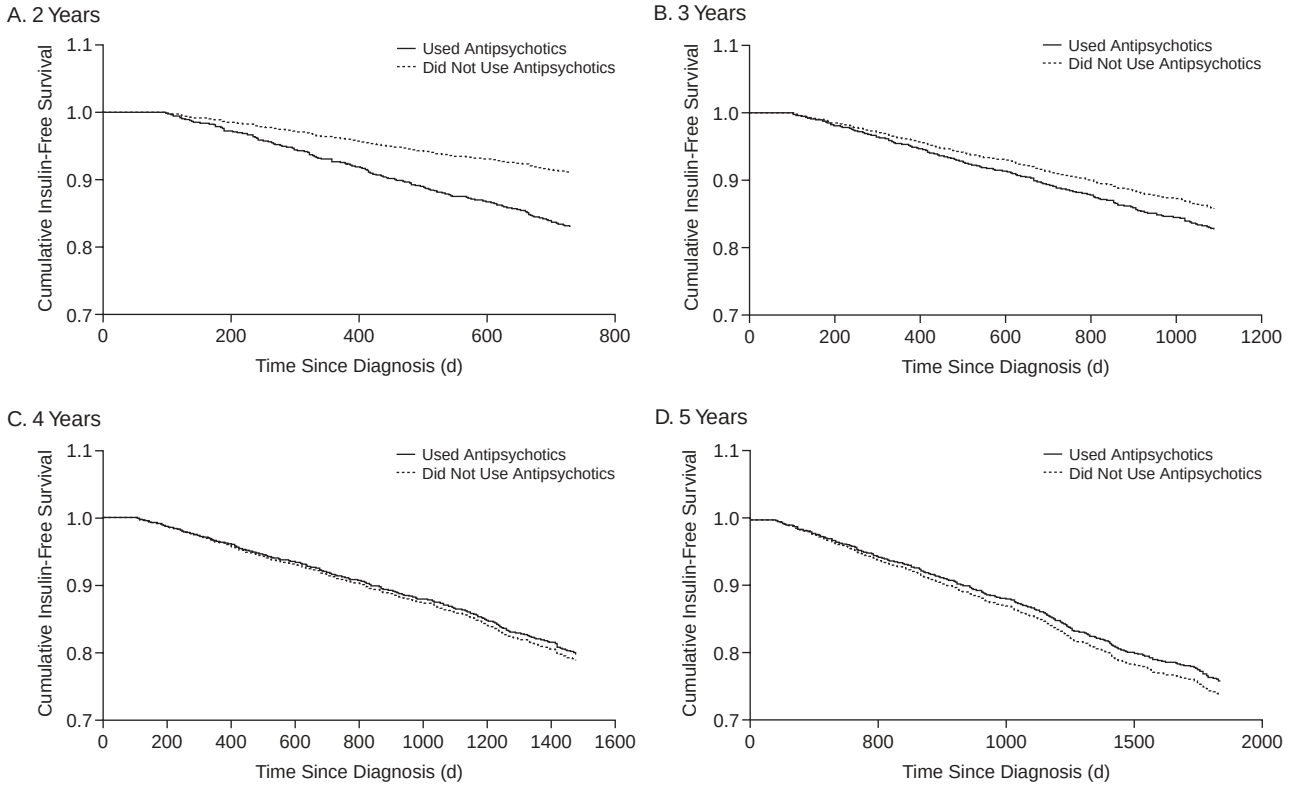
Variable	Value
Male, N (%)	1472 (49.1)
Age at index date, mean (SEM), y[a]	63.4 (0.24)
Duration of disease, mean (SEM), y	4.0 (0.04)
Total follow-up time, mean (SEM), y	9.9 (0.05)
Insulin therapy, N (%)	603 (20.1)
Age at initiation of insulin therapy, mean (SEM), y[b]	62.2 (0.54)
Duration of disease at initiation of insulin therapy, mean (SEM), y[b]	2.8 (0.07)
Psychiatric drug use during diabetes, N (%)	
Psycholeptic drugs[c]	1435 (47.8)
Antipsychotics[d]	248 (8.3)
Atypical antipsychotics[e]	14 (0.5)
Lithium	12 (0.4)
Antidepressive agents	361 (12.0)

[a]Date of first prescription of oral hypoglycemic agents.
[b]N = 603 (patients who began insulin therapy).
[c]Anatomical Therapeutic Chemical (ATC) group N05.
[d]ATC group N05A (excluding lithium, N05AN).
[e]Clozapine, risperidone, olanzapine, or quetiapine.

RESULTS

A total of 3001 patients with newly diagnosed type 2 diabetes mellitus were enrolled in the study; their demographic characteristics and data on drug use are given in Table 1.

Figure 1. Rate of Initiation of Insulin Therapy 2, 3, 4, and 5 Years After Diagnosis of Type 2 Diabetes Mellitus, by Antipsychotic Drug Use



Age at diagnosis varied between 18 and 98 years. Among the 248 patients who had ever used an antipsychotic drug, 99 (40%) received only 1 or 2 prescriptions, 68 (27%) received 3 to 9 prescriptions, 30 (12%) received 10 to 19 prescriptions, and 51 (21%) received 20 or more prescriptions. Within the total follow-up period, only 14 (0.5%) of patients in the baseline cohort used an atypical antipsychotic drug after the date of the first prescription of an oral hypoglycemic agent; therefore, these patients were not analyzed separately. The antipsychotic drugs most frequently used were haloperidol (29%), pipamperone (27%), levomepromazine (16%), and zuclopenthixol (14%).

A total of 2585 patients (86%) completed 2 years of follow-up after the index date (first prescription of oral hypoglycemic agent). They were younger at diagnosis than the remaining 416 subjects (62.6 vs. 69.0 years, $p < .001$), but they did not significantly differ with respect to gender distribution. These patients were included in the Cox regression analysis.

Figures 1A through 1D show "insulin-free survival" in antipsychotic users and nonusers over the course of time (exposure definition at 2, 3, 4, and 5 years after diagnosis of diabetes). For instance, 4 years after diagnosis, well over 20% of the patients in both groups had begun receiving insulin therapy. Because primary failure was an exclusion criterion, Figure 1 shows straight regression lines in both groups during the first 3 months (i.e., no events). Excluding patients with a single antipsychotic prescription resulted in similar results, but due to the smaller number of patients, the results were not statistically significant. Crude and adjusted HRs are shown in Table 2. Two years after diagnosis, we found a significantly increased risk for initiation of insulin therapy in users of antipsychotics compared with nonusers; the hazards were 18.4% and 9.3% respectively, and the crude relative hazard (HR) was 2.0 (95% CI = 1.2 to 3.3). In this 2-year period, 236 patients (9.1%) began insulin therapy. Adjusted for age at onset and calendar year of first prescription of an oral hypoglycemic agent, the HR was 2.0 (95% CI = 1.2 to 3.3). Additionally, we controlled for concomitant medication use (see Table 2). Adjustment for differences in gender distribution did not change the results.

Subsequently, we analyzed the 2-year period after diagnosis. We investigated the continuation of oral hypoglycemic medication after the start of insulin therapy (i.e., combination therapy) in both groups. In nonusers of antipsychotics, oral therapy was continued in about half (49%) of the patients, while in users of antipsychotics,

Table 2. Crude and Adjusted Hazard Ratios (HRs) for Initiation of Insulin Therapy in Antipsychotic Users (vs. nonusers) at Different Time Intervals Since Diagnosis of Type 2 Diabetes Mellitus

No. of Years Since Diagnosis	Crude		Adjusted for Age at Onset and Calendar Year of Diagnosis		Adjusted for Medication Use[a]	
	HR	95% CI	HR	95% CI	HR	95% CI
2	2.0	1.2 to 3.3	2.0	1.2 to 3.3	1.7	1.0 to 3.0
3	1.2	0.8 to 2.0	1.3	0.8 to 2.1	1.2	0.8 to 2.0
4	0.9	0.6 to 1.4	1.0	0.7 to 1.6	1.0	0.7 to 1.6
5	0.9	0.6 to 1.3	1.0	0.7 to 1.4	1.0	0.7 to 1.6

[a]Adjustment for use of β-blocking agents, diuretics (thiazides and loop diuretics), antiparkinsonian drugs, antidepressants, and corticosteroids for systemic use.

only 4 (25%) of 16 patients who began insulin therapy were on a combined medication regimen. The odds ratio (OR) for continuation of oral therapy after initiation of insulin treatment was 0.4 (95% CI = 0.1 to 1.1) and thus of borderline significance (p = .06).

Of the 236 patients who began insulin therapy, 14 (6.0%) used antipsychotics during the last 2 years, compared with 77 (3.3%) of the patients who continued oral hypoglycemic therapy (OR = 2.2, 95% CI = 1.2 to 4.0).

Use of antipsychotics was strongly associated with use of antidepressants. In users of antipsychotics, the prevalence of antidepressant use was 34% versus 7% in nonusers (OR = 7.5, 95% CI = 4.8 to 11.9). After additional adjustment for use of antidepressants, the relationship between antipsychotic use and initiation of insulin therapy was still statistically significant (Table 2).

Finally, when we compared the risk of initiation of insulin therapy over the total follow-up period between users and nonusers of antipsychotics in the first 2 years after the onset of diabetes, the HR was 1.6 (95% CI = 1.1 to 2.4).

DISCUSSION

The use of antipsychotic drugs in type 2 diabetes mellitus was associated with a higher rate of initiation of insulin therapy (i.e., "secondary failure"), especially in the first 2 years of the disease. These results suggest that antipsychotic drugs can not only induce diabetes but also cause worsening of glycemic control in patients known to have type 2 diabetes.

The primary underlying defect in type 2 diabetes is probably insulin resistance, with an early phase of normal plasma glucose levels maintained by compensatory hyperinsulinemia. The failure to maintain this compensatory hyperinsulinemia eventually results in loss of glycemic control and development of clinical diabetes. Many studies have reported that diabetes, impaired glucose tolerance, and insulin resistance are more common among patients with schizophrenia and other mental illnesses than among the general population.[1–3,9,21] For instance, Mukherjee and colleagues[3] found a 15.8% overall prevalence of diabetes among schizophrenic patients, a prevalence considerably higher than those reported in epidemiologic surveys in the general population. Therefore, the possibility remains that diabetes in schizophrenia may result from the use of neuroleptics rather than from the psychiatric disorder itself.[22] Although the exact mechanism of antipsychotic-induced diabetes remains obscure, studies by Ardizzone et al.[23] suggest that atypical drugs may block glucose accumulation directly at the level of the glucose transporter protein in cells derived from both peripheral and brain tissue.

Some limitations of this observational study need to be addressed, notably the lack of information on important patient factors that predict severity or prognosis of disease, such as body mass index, lipid levels, smoking habits, hemoglobin A_{1c} level, prevalence of diabetic complications, and blood pressure. The results could be confounded by one of these factors without the possibility of correcting for it. Therefore, differences in initiation of insulin therapy may to some extent be explained by metabolic differences. For instance, type 2 diabetes mellitus is strongly and consistently associated with overweight and obesity. Moreover, weight gain is a well-known side effect of antipsychotic drug use,[24,25] so the weight gain, rather than the drug itself, may be partly responsible for the worsening of metabolic control.[26] Our inability to examine the possible etiologic explanations, however, does not weaken the found association between antipsychotic drug use and worsening of glycemic control.

Furthermore, it is important to mention that we studied an elderly population with type 2 diabetes in an outpatient setting. Data were obtained from community pharmacies, so patients living in nursing homes, psychiatric institutes, and mental clinics were not included. Elderly patients have various medical grounds for using antipsychotic drugs, including (nocturnal) agitation, the beginnings of dementia, acute psychosis, delirium, bipolar disorder, and schizophrenia. Unfortunately, since we had no information on the indication for which the antipsychotic drugs were prescribed, we could not directly link psychiatric diagnoses with initiation of insulin therapy.

We propose that the observed worsening of metabolic control is probably due to pancreatic β-cell toxicity of antipsychotic drugs. First, the deterioration appears in an early stage of the disease, which suggests that antipsychotic drugs have an immediate effect in susceptible subjects. The decrease in corresponding risk for initiation of insulin therapy among users of antipsychotics compared with nonusers from 2.0 at 2 years to 1.2 at 3 years to 0.9 at 4 and 5 years after diagnosis of diabetes indicates an acute effect that diminishes over time. In addition, the proportion of antipsychotic use diminished during follow-up; only a limited proportion of the study population received

more than 10 prescriptions. This finding strongly supports β-cell toxicity as an explanation rather than deterioration of insulin resistance, which would cause a more gradual decline in β-cell function.

Second, after beginning insulin therapy, only 25% of the antipsychotic users continued oral hypoglycemic therapy, which is half the prevalence of combination therapy in nonusers. Since the mechanism of action of all oral hypoglycemic agents depends to a great extent on the residual activity of the β-cell, oral therapy will be ineffective if β-cell toxicity is causing the deterioration of metabolic control.

In conclusion, our study may indicate that antipsychotics, besides having known diabetogenic effects, can lead to fast deterioration of glycemic control, probably due to β-cell toxicity. Although many aspects of this relationship remain unclear, we believe that glycemic control should be monitored more closely in these patients.

Drug names: chlorpromazine (Thorazine and others), clozapine (Clozaril and others), haloperidol (Haldol and others), lithium (Lithobid, Eskalith, and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal).

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