CHAPTER 7

Antipsychotic Drugs May Worsen Metabolic Control in Type 2 Diabetes Mellitus Patients
Abstract

Aim - Several studies have indicated that type 2 diabetes mellitus is more common among schizophrenic patients than in the general population. Purpose of the present study was to assess the association between the use of antipsychotic drugs and alterations of glycemic control.

Methods - In this cohort study, newly diagnosed patients with type 2 diabetes were selected from the PHARMO Record Linkage System, comprising pharmacy records for all 320,000 residents of six Dutch cities. In total, 2,585 patients with type 2 diabetes were identified as incident oral hypoglycemic agents users between 1991-1997 and had at least two years medication history after diagnosis. Switching from oral hypoglycemic agents to insulin therapy was considered a proxy for deterioration of beta-cell function. We compared the incidence of switching between users of antipsychotic drugs and non-users by performing a Cox’s proportional hazards model analysis.

Results - Two years after diagnosis we found an increased risk for switching to insulin therapy for users of antipsychotics compared to non-users; the relative hazard (hazard ratio, HR) was 2.0 (CI95%: 1.2 – 3.3), which did not change after adjustment for potential confounders. The risk decreased in the subsequent years after diagnosis.

Conclusion - It seems that use of antipsychotics in type 2 diabetes mellitus is associated with switching to insulin therapy (i.e. ‘secondary failure’), especially in the first two years of the disease.
**Introduction**

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. As type 2 diabetes advances, secondary failure of oral hypoglycemic therapy develops as a consequence of progressive loss of beta-cell function and worsening of insulin resistance caused by persistent hyperglycemia and possible development of drug resistance.

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. Those ‘novel’ antipsychotics are called atypical for their relative lack of the extrapyramidal side effects typical of older, mostly higher dosed antipsychotics. Furthermore, already decades ago it has been reported that conventional neuroleptics, chlorpromazine in particular, may also alter glucose-insulin homeostasis and lead to new cases of diabetes mellitus.

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. Switching from oral hypoglycemic agents to insulin therapy is considered a proxy for deterioration of metabolic control. Therefore, we compared ‘switchers’ and ‘non-switchers’ with respect to antipsychotic drug use during a period following diagnosis of type 2 diabetes mellitus.
Patients and Methods

Data source
The PHARMO Record Linkage System (PHARMO RLS) was used as data source for this study, comprising pharmacy dispensing records of all community-dwelling residents of six Dutch cities, counting for more than 450,000 patients histories, from 1985 to present.\textsuperscript{16, 17} Drugs were coded according to the \textit{Anatomical Therapeutic Chemical (ATC) Classification}.\textsuperscript{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, incident patients with 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 180 days (half a year) preceding the date of starting oral hypoglycemic agent use. Furthermore, patients were only included if they were dispensed at least two consecutive prescriptions of oral hypoglycemic agents. Subsequently, we excluded subjects who switched to insulin 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 who had at least two years (730 days) of medication history after diagnosis, i.e. first prescription of an oral hypoglycemic agent. Exposure was defined as the usage of antipsychotic drugs (i.e. ‘any use’), ATC group N05A (excluding lithium, N05AN), in the two years after the first use of an oral hypoglycemic agent. The event of interest was defined
by switching from oral hypoglycemic agents to insulin therapy (ATC code A10A) with or without continuation of oral hypoglycemic medication. We compared the incidences of switching to insulin therapy between users of antipsychotic drugs and non-users. Atypical antipsychotic drugs included risperidone, clozapine, olanzapine, and quetiapine.\textsuperscript{19}

\section*{Data analysis}
For the comparison of continuous variables and categorical variables between users of antipsychotics and non-users, we used the Student’s $t$-test and $\chi^2$ test, respectively.
We performed a Cox’s proportional hazards model analysis (variable follow-up) in the cohort of all incident type 2 diabetic patients who had at least two years of follow-up. Survival time was from date of first prescription of oral hypoglycemic agents to the day of switching to insulin therapy. Patients who did not switch were censored at the date of leaving the pharmacy (i.e. loss to follow-up) or end of study (July 1999). Use of antipsychotics (dichotomous), age at date of first prescription of oral hypoglycemic agents (years), gender, and calendar year of diagnosis, were time-independent variables.

We adjusted for the use of anticholinergic antiparkinson medication (ATC group N04A), because a higher rate of switching 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), beta-blocking agents (C07), and thiazides and loop diuretics (C03, except C03D). Because of the known positive relationship between the prevalence of depressive disorders and type 2 diabetes\textsuperscript{20}, we also investigated the potential association or interaction between antipsychotics, switching and antidepressants.

Subsequently, we calculated crude and adjusted relative hazards (hazard ratios, HR) with the corresponding 95\% confidence intervals (CI\textsubscript{95\%}) for switching to insulin in the users of antipsychotic drugs at several time intervals of follow-up (two, three, four and five years after diagnosis of diabetes mellitus).
Results

In total 3,001 patients with newly diagnosed type 2 diabetes mellitus were enrolled in the study, their demographic characteristics and some data on drug usage are given in Table 7.1.

Table 7.1   Basic characteristics of patients with type 2 DM

<table>
<thead>
<tr>
<th>Variable</th>
<th>N = 3,001</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex (%)</td>
<td>1472 (49.1%)</td>
</tr>
<tr>
<td>Age at index date* (yrs)</td>
<td>63.4 (0.24)</td>
</tr>
<tr>
<td>Duration of disease (yrs)</td>
<td>4.0 (0.04)</td>
</tr>
<tr>
<td>Total follow-up time (yrs)</td>
<td>9.9 (0.05)</td>
</tr>
<tr>
<td>Insulin therapy (%)</td>
<td>603 (20.1%)</td>
</tr>
<tr>
<td>Age at switching† (yrs)</td>
<td>62.2 (0.54)</td>
</tr>
<tr>
<td>Duration of disease at date of switching† (yrs)</td>
<td>2.8 (0.07)</td>
</tr>
<tr>
<td>Drug use during diabetes (%)</td>
<td></td>
</tr>
<tr>
<td>Cardiovascular drugs‡</td>
<td>2298 (76.6%)</td>
</tr>
<tr>
<td>Psycholeptic drugs§</td>
<td>1435 (47.8%)</td>
</tr>
<tr>
<td>Antipsychotics</td>
<td></td>
</tr>
<tr>
<td>Atypical antipsychotics¶</td>
<td>14 (0.5%)</td>
</tr>
<tr>
<td>Lithium</td>
<td>12 (0.4%)</td>
</tr>
<tr>
<td>Antidepressive agents</td>
<td>361 (12.0%)</td>
</tr>
</tbody>
</table>

Data are means with standard error of the mean between parentheses or numbers (with percentages, %)

* date of first prescription of oral hypoglycemic agents
† N = 603 (switchers)
‡ cardiovascular drugs are defined as antithrombotics, cardias, diuretics, β-blockers, calcium channel blockers, ACE inhibitors, other antihypertensive drugs, and lipid lowering agents (ATC codes B01, C01-C03, C07-C10)
§ ATC group N05
|| ATC group N05A (excluding lithium, N05AN)
¶ clozapine, risperidone, olanzapine, or quetiapine
Age at diagnosis varied between 18 and 98 years. Among antipsychotic drug users (‘ever use’), 99 (40%) received only one or two prescriptions, 68 (27%) received 3-9 prescriptions, 30 (12%) received 10-19 prescriptions, and 51 (21%) received 20 or more prescriptions. In the baseline cohort, within the total follow-up period only 14 (0.5%) used an atypical antipsychotic drug after the date of first prescribed oral hypoglycemic agent. Antipsychotic drugs most frequently used were haloperidol (Haldol®, 29%), pipamperone (Dipiperon®, 27%), levomepromazine (Nozinan®, 16%), and zuclopenthixol (Cisordinol®, 14%).

A total of 2,585 (86%) patients completed two 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 versus 69.0 years (P< 0.001), they did not significantly differ with respect to gender distribution. These patients were included in the Cox’s regression analysis.

Figures 1a – 1d show the ‘insulin free survival’ in antipsychotic users and non-users during the course of time (exposure definition at two, three, four and five years after diagnosis, respectively). For instance, after four years of disease, well over 20% switched to insulin therapy in both groups. Because primary failure was an exclusion criterion, the figures show straight regression lines in both groups during the first three months (i.e. no events). Crude and adjusted HRs are shown in Table 7.2. Two years after diagnosis we found an significantly increased risk for switching to insulin therapy for users of antipsychotics compared to non-users; the hazards were 18.4% and 9.3% respectively, and the crude relative hazard (hazard ratio, HR) was 2.0 (CI_{95%}: 1.2 – 3.3). In this two-year period, 236 patients (9.1%) switched to insulin therapy. Adjusted for age at onset and calendar year of first prescription of an oral hypoglycemic agent, the HR was 2.0 (CI_{95%}: 1.2 – 3.3). Additionally, we controlled for concomitant medication (see table comments). Adjustment for differences in gender distribution did not change the results.
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Figure 7.1a Cut-off point at 2 years

Figure 7.1b Cut-off point at 3 years

Figure 1a-1d Switching to insulin therapy by use of antipsychotic drugs after 2, 3, 4, and 5 years respectively
Figure 7.1 c Cut-off point at 4 years

Figure 7.1 d Cut-off point at 5 years
**First two years after diagnosis**

Subsequently, we singled out the two-year period after diagnosis. We investigated the degree of continuation of oral hypoglycemic medication after the start of insulin therapy (i.e. combination therapy) in both groups. In non-users of antipsychotics, the oral therapy was continued in about half of the patients (49%), while in users of antipsychotics only 4 out of 16 switchers (25%) were on combined medication regimen. The odds ratio for continuation of oral therapy after switch was 0.4 (CI\textsubscript{95%}: 0.1 – 1.1), thus borderline significant (p= 0.06).

Of the 236 switchers, 14 (7.0%) used antipsychotics during the last two years, compared to 77 (3.3%) of the patients who continued oral hypoglycemic therapy (OR 2.2, CI\textsubscript{95%}: 1.2 – 4.0). No switch to insulin therapy was seen in any of the 6 patients who used atypical antipsychotic drugs.

Use of antipsychotics was strongly associated with use of antidepressants, in users of antipsychotics the prevalence of antidepressant use was 34% versus 7% in non-users (OR 7.5, CI\textsubscript{95%}: 4.8 – 11.9). After additional adjustment for use of antidepressants, the relationship was still statistically significant (*Table 7.2*).

<table>
<thead>
<tr>
<th>Time since diagnosis</th>
<th>( \text{HR}_{\text{crude}} )</th>
<th>( \text{HR}_{\text{adj}^*} )</th>
<th>( \text{HR}_{\text{adj}^†} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 years</td>
<td>2.0 [1.2-3.3]</td>
<td>2.0 [1.2-3.3]</td>
<td>1.7 [1.0-3.0]</td>
</tr>
<tr>
<td>3 years</td>
<td>1.2 [0.8-2.0]</td>
<td>1.3 [0.8-2.1]</td>
<td>1.2 [0.8-2.0]</td>
</tr>
<tr>
<td>4 years</td>
<td>0.9 [0.6-1.4]</td>
<td>1.0 [0.7-1.6]</td>
<td>1.0 [0.7-1.6]</td>
</tr>
<tr>
<td>5 years</td>
<td>0.9 [0.6-1.3]</td>
<td>1.0 [0.7-1.4]</td>
<td>1.0 [0.7-1.6]</td>
</tr>
</tbody>
</table>

95% Confidence intervals between square brackets

* Adjusted for age at onset and calendar of diagnosis

† Additional adjustment for use of β-blocking agents, diuretics (thiazides and loop-), antiparkinson drugs, antidepressants, and corticosteroids for systemic use
Finally, when we compared the risk of switching to insulin therapy over the total follow-up period between users and non-users of antipsychotics in the first two years after the onset of diabetes, the HR was 1.6 (CI\textsubscript{95%}: 1.1 – 2.4).

**Discussion**

In our study, the use of antipsychotic drugs in type 2 diabetes mellitus was associated with a higher rate of switching to insulin therapy (i.e. ‘secondary failure’), especially in the first two years of the disease. This present study strongly indicates that antipsychotic drugs can not only induce diabetes but also cause worsening of glycemic control in patients with already known type 2 diabetes.

In type 2 diabetes the primary underlying defect 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.\textsuperscript{1-3, 9, 21} For instance, Mukherjee and colleagues found a 15.8% overall prevalence of diabetes among schizophrenic patients, this prevalence is considerably higher than reported from epidemiological surveys in the general population.\textsuperscript{3} Therefore, the possibility remains that diabetes in schizophrenia may result from the use of neuroleptics, rather than the psychiatric disorder itself.\textsuperscript{22} Although the exact mechanism of antipsychotic induced diabetes remains obscure, studies by Ardizzone et al suggest that atypical drugs may block glucose accumulation directly at the level of the glucose transporter protein in cells derived both from peripheral and brain tissue.\textsuperscript{23}

Some limitations of this study need to be addressed, notably the lack of information on important patient factors that predict severity or prognosis of disease, like body mass index, lipids, smoking habits, HbA\textsubscript{1c}, prevalence of diabetic complications, and blood pressure. So the results could be confounded by one of these factors, without the possibility to correct for it. Therefore, differences in switching to insulin therapy may to some extent be explained by metabolic...
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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\textsuperscript{24, 25}, so maybe the weight gain is partly responsible for the worsening of metabolic control rather than the drug itself.\textsuperscript{26} Although we cannot examine the possible etiologic causal explanations, this 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, for instance: (nocturnal) agitation, the beginnings of dementia, acute psychosis, delirium, bipolar disorder, or schizophrenia. Unfortunately, we had no information on the indication for which the antipsychotic drugs were prescribed. So, we could not link psychiatric diagnoses to switching to insulin therapy directly.

Antipsychotic drugs can be classified, based on their liabilities to induce extrapyramidal side effects (EPS), into two main categories: typical antipsychotics, which are often associated with EPS of both acute and chronic nature and atypical antipsychotics, which cause a significant lower incidence of EPS.\textsuperscript{11} In contrast to current belief, we found no difference between atypical and conventional antipsychotic drugs with regard to worsening of glycemic control, but the ‘novel’ drugs were rarely prescribed and no event of interest was observed in the group of atypical antipsychotic drug users.

We propose that the observed worsening of metabolic control is probably due to pancreatic beta-cell toxicity of antipsychotic drugs. First, the deterioration appears in an early stage of the disease, which suggests that antipsychotic drugs have a quite immediate effect in susceptible subjects. The fact that two, three, four, and five years after the diagnosis of diabetes the corresponding risk for switching in users of antipsychotics compared to non-users changed from 2.0 through 1.2 into 0.9, indicates an acute effect that diminishes in the course of time. This is
strongly in favor of beta-cell toxicity rather than deterioration of insulin resistance, which would cause a more gradual decline in beta-cell function.

Secondly, after the switch to insulin therapy only 25% of the antipsychotic users continued their oral hypoglycemic therapy, which is half the prevalence of combination therapy in non-users. Since the mechanism of action of all oral hypoglycemic agents to a great extent depends on the residual activity of the beta-cell, oral therapy will be ineffective if beta-cell toxicity is the case.

In conclusion, our study suggests that antipsychotics, besides already known diabetogenic effects, can lead to fast deterioration of glycemic control, probably due to beta-cell toxicity. Although many aspects of this relation remain unclear and uncertain, we believe that glycemic control should be monitored more closely in these patients.
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References


