Risk of Hospitalization for Hypoglycemia in Older Patients with Diabetes Using Antipsychotic Drugs

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Objective: *Antipsychotics may disrupt metabolic regulation in patients with diabetes mellitus. The risk of hypoglycemia in older users of antipsychotics with diabetes is largely unknown. Therefore, we investigated the association between the use of antipsychotic drugs and hypoglycemia requiring hospital admission in older patients with diabetes.* **Methods:** *In a nested case-control study using community pharmacy records linked to hospital admission data in the Netherlands (1998–2008), a cohort of 68,314 patients at least 65 years with diabetes was studied. Cases were patients from the study cohort with a first hospital admission for hypoglycemia; up to five comparison subjects were selected for each case. Exposure to antipsychotic drugs was the primary determinant of interest. Logistic regression analysis was performed to estimate the strength of the association between antipsychotic drug use and hypoglycemia, taking into account potential confounders.* **Results:** *Eight hundred fifteen patients were admitted to hospital for hypoglycemia. Current use of antipsychotic drugs was associated with an increased risk of hypoglycemia compared with non-use (adjusted OR: 2.26; 95% CI: 1.45–3.52; Wald $\chi^2 = 13.08$, $df = 1$, $p \leq 0.001$), especially in the first 30 days of treatment (adjusted OR: 7.65; 95% CI: 2.50–23.41; Wald $\chi^2 = 12.72$, $df = 1$, $p \leq 0.001$) and with higher doses (adjusted OR: 8.20; 95% CI: 3.09–21.75; Wald $\chi^2 = 17.90$, $df = 1$, $p \leq 0.001$).* **Conclusion:** *Use of antipsychotic drugs by older patients with diabetes mellitus was associated with an increased risk of hospitalization for hypoglycemia. Our findings suggest that glucose levels should be monitored closely after initiation of antipsychotic drugs.* (Am J Geriatr Psychiatry 2015; 23:1144–1153)

Key Words: Older patients, diabetes mellitus, hypoglycemia, antipsychotic drugs

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INTRODUCTION

Antipsychotics are increasingly prescribed to older patients to relieve psychotic or behavioral symptoms of dementia, schizophrenia, or delirium.[1–3] Their use is hampered by side effects, such as adverse cardiovascular and metabolic effects, and it has been suggested that cardiovascular problems underlie the increased mortality seen in older patients using antipsychotics.[4,5] Metabolic adverse effects, especially during atypical antipsychotic use, include insulin resistance and impaired glucose tolerance, which may result in an increased risk of new-onset diabetes mellitus (DM).[6] Antipsychotic treatment among patients with schizophrenia and type 2 DM is associated with the initiation of insulin therapy, which is indicative of worsening of the disease, especially in the first 2 years of antidiabetic therapy.[7]

Available studies involving older patients have tended to investigate the risk of new-onset DM during antipsychotic use, but the results are inconsistent.[8–14] Although one study reported that atypical antipsychotics do not affect glucose levels,[15] another study suggested that fasting glucose levels are abnormal in more than 10% of older users of atypical antipsychotics.[16] Lipscombe et al.[17] found an increased risk of hospital admission for the treatment of hyperglycemia during antipsychotic therapy in older patients without DM. The effect of antipsychotic drugs on glycemic regulation in older patients with DM has hardly been investigated. The limited evidence available indicates that the use of antipsychotics by older patients with DM is associated with an increased risk of hospital admission for hyperglycemia.[18,19] Some case reports have been published about the incidence of hypoglycemia, the counter effect of hyperglycemia during antipsychotic use.[20–27] Only three of these reports concerned older patients, one of which described a younger patient with DM.

This potential adverse effect during antipsychotic use is at least as important in clinical practice as hyperglycemia, but large retrospective studies are lacking. In the frail older population hypoglycemia has been associated with an increased risk of falls and fractures,[28] cognitive impairment, and acceleration of dementia.[29] Furthermore, it has been reported that in-hospital hypoglycemia may increase the risk on inpatient mortality and length of hospital stay.[30] Given that DM is a major public health concern, particularly in the older population, and the prevalence of antipsychotic drug use is high among older patients, it is surprising that so little is known about hypoglycemic manifestations during antipsychotic use in older patients with DM. Therefore, the objective of this study was to assess the effect of antipsychotic use on the risk of hypoglycemia requiring hospitalization in older patients with DM.

METHODS

Data Source

A population-based cohort study was carried out using the Dutch PHARMO Record Linkage System (RLS) (see http://www.pharmo.nl), a population-based, patient-centric data network for the whole country. This network contains high-quality and complete information about, among other things, patient demographics, drug-dispensing records from community pharmacies, and hospital discharge records of more than 4 million individuals (approximately 24% of the Dutch population).[31,32]

The drug-dispensing records consist of data on the drug dispensed, the type of prescriber, the dispensing date, the amount dispensed, and the written dose instructions. Hospital records were obtained from the Dutch National Medical Register, which includes data on all hospital admissions in the Netherlands. The hospital records provided information about hospital admission and discharge, together with primary and secondary diagnoses coded according to the *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM). Drugs were coded according to the Anatomical Therapeutic Chemical (ATC) codes (see http://www.whocc.no/atc_ddd_index). Information has been collected since 1986 and has been used in many pharmacoepidemiologic and outcome studies.[31,32] Hospital diagnoses and drug exposure data retrieved from the prescription records in the PHARMO RLS have been validated in several studies.[33–35]

Study Design and Sample

A nested case-control design was used to study the association between the use of antipsychotics and

TABLE 1. Characteristics of Older Patients with DM Who Were or Were Not Hospitalized for Hypoglycemia

Characteristics	Cases (N = 815)	Comparison Subjects (N = 3,917)	p
Mean age, y (SD)	79.4 (6.5)	76.9 (6.4)	<0.001[a]
Age, N (%)			<0.001[b]
65–74 y	196 (24.0)	1,563 (39.9)	
75–84 y	438 (53.7)	1,823 (46.5)	
≥85 y	181 (22.2)	531 (13.6)	
Sex, N (%)			<0.413[b]
Female	510 (62.6)	2,391 (61.0)	
DM medication,[c] N (%)			<0.001[b]
OAD	357(43.8)	2,565 (65.5)	
Insulin	306 (37.5)	833 (21.3)	
OAD + insulin	152 (18.7)	519 (13.2)	
Number of glucose-influencing comedication,[d] mean (SD)	2.9 (1.7)	2.2 (1.6)	<0.001[a]
Number of glucose-influencing comedication,[d] N (%)			<0.001[b]
None	59 (7.2)	610 (15.6)	
1–3	468 (57.4)	2,507 (64.0)	
≥4	288 (35.3)	800 (20.4)	
Use of antibiotic drugs,[e] N (%)	126 (15.5)	112 (2.9)	<0.001[b]
Number of hospital admissions,[c] mean (SD)	1.0 (1.7)	0.5 (1.2)	<0.001[a]
Number of hospital admissions,[f] N (%)			<0.001[b]
None	402 (49.3)	2,858 (73.0)	
1–2	327 (40.1)	856 (21.9)	
≥3	86 (10.6)	203 (5.2)	
Discharge diagnoses for cardiovascular diseases,[f] N (%)			<0.001[b]
None	727 (89.2)	3,735 (95.4)	
1–2	88 (12.1)	182 (4.6)	
Chronic disease score,[c] N (%)			<0.001[b]
≤3	58 (7.1)	626 (16.0)	
4–6	193 (23.7)	1,274 (32.5)	
≥7	564 (69.2)	2,017 (51.5)	

[a]Student independent sample t test. t = 9.90, df = 1,167 for mean age; t = 11.4, df = 4,730 for mean number of glucose-influencing comedication; t = 8.43, df = 992.2 for mean number of hospital admissions.

[b]Chi-square test. $\chi^2_{(2)} = 86.50$ for age; $\chi^2_{(1)} = 0.670$ for sex; $\chi^2_{(2)} = 139.5$ for DM medication; $\chi^2_{(2)} = 103.0$ for number of glucose-influencing comedication; $\chi^2_{(1)} = 224.3$ for treatment with antibiotic drugs; $\chi^2_{(2)} = 176.6$ for number of hospital admissions; $\chi^2_{(1)} = 47.44$ for discharge diagnoses for cardiovascular diseases hospital admissions; $\chi^2_{(2)} = 92.49$ for chronic disease score.

[c]Based on the community pharmacy prescriptions in the 360 days before the index date.

[d]Based on the community pharmacy prescriptions in the 180 days before the index date. See Appendix 1 for detailed information.

[e]Based on the community pharmacy prescriptions for antibiotic drugs in the 14 days before the index date (ATC code J01) as a proxy for infection.

[f]Based on the discharge diagnoses in the 360 days before the index date.

hypoglycemia requiring hospitalization. The cohort comprised all patients 65 years and older with at least 1 year of valid medication history and at least three prescriptions for insulin and/or oral antidiabetic drugs (OADs; ATC code A10) filled in 1 year between January 1998 and December 2008 or a discharge diagnosis of DM (ICD-9-CM code 250). This cohort was followed up until the end of the data collection (December 2008), the patient's transfer out of the registry, or the patient's death, whichever occurred first.

Case Definition and Comparison Subjects

Cases were those patients from the cohort with a first hospital admission for hypoglycemia (ICD-9-CM codes 250.3 or 251.0–251.2). The date of hospitalization for hypoglycemia was taken as the index date. Patients were excluded if the index date was before the date of the first prescription for insulin and/or OADs or if there were no prescriptions for antidiabetic drugs in the year before the index date. Up to five comparison subjects from the cohort were sampled to each case.[36] Each comparison subject was assigned the index date and sampled by duration of DM treatment from cohort entry ± 30 days of the corresponding case. Comparison subjects had not been admitted to hospital for hypoglycemia before the index date. The date of the first prescription for an OAD or insulin was used to calculate the duration of DM up to the index date.

Exposure Assessment and Classification

Exposure to antipsychotic drugs (ATC code N05A, except lithium) before the index date was the primary determinant of interest. The duration of antipsychotic use was calculated as the length of the treatment episode, with treatment episodes defined as a series of prescription refills, regardless of changes to another type of drug or to the dosing regimen. A new treatment episode was considered to occur if there was an interval of 14 days or more between the theoretical end date of a prescription and the dispensing date of the next prescription for the same patient. Patients were classified as current users if the index date fell between the start and end dates of a

TABLE 2. Risk of Hospitalization for Hypoglycemia Related to Antipsychotic Drugs

	Cases (N = 815) N (%)	Comparison Subjects (N = 3,917) N (%)	OR Crude[a] (95% CI)	Wald χ^2	p	OR Adjusted[a,b] (95% CI)	Wald χ^2	p
Use of antipsychotic drugs								
No use	771 (94.6)	3,842 (95.9)	(reference)	(reference)	(reference)	(reference)	(reference)	(reference)
Current use	36 (4.4)	61 (1.6)	2.94 (1.93−4.47)	25.41	<0.001	2.26 (1.45−3.52)	13.08	<0.001
Past use	8 (1.0)	14 (0.4)	2.87 (1.20−6.86)	5.60	0.018	2.68 (1.08−6.63)	4.53	0.033
Duration of use[c]								
No use	771 (95.5)	3842 (98.4)	(reference)	(reference)	(reference)	(reference)	(reference)	(reference)
Up to 30 days	9 (1.1)	5 (0.1)	9.03 (3.02−27.03)	15.47	<0.001	7.65 (2.50−23.41)	12.72	<0.001
31−90 days	5 (0.6)	6 (0.2)	4.17 (1.27−13.70)	5.52	0.019	3.03 (0.85−10.80)	2.93	0.087
91−365 days	13 (1.6)	24 (0.6)	2.70 (1.37−5.32)	8.19	0.004	2.16 (1.06−4.42)	4.48	0.034
≥366 days	9 (1.1)	26 (0.7)	1.72 (0.80−3.68)	1.92	0.166	1.16 (0.51−2.63)	0.13	0.720
Daily dose[c]								
No use	771 (95.5)	3842 (98.4)	(reference)	(reference)	(reference)	(reference)	(reference)	(reference)
DDD ≤ 0.25	26 (3.2)	53 (1.4)	2.45 (1.52−3.93)	13.56	<0.001	1.67 (1.00−2.74)	3.90	0.048
DDD > 0.25	10 (1.2)	8 (0.2)	6.20 (2.44−15.67)	14.67	<0.001	8.20 (3.09−21.75)	17.90	<0.001
Type[c]								
No use	771 (95.5)	3842 (98.4)	(reference)	(reference)	(reference)	(reference)	(reference)	(reference)
Haloperidol	12 (1.5)	17 (0.4)	3.52 (1.67−7.39)	11.00	0.001	2.50 (1.15−5.44)	5.31	0.021
Pipamperone	13 (1.6)	15 (0.4)	4.37 (2.07−9.22)	14.93	<0.001	3.05 (1.38−6.72)	7.65	0.006
Risperidone	5 (0.6)	11 (0.3)	2.24 (0.77−6.47)	2.21	0.137	1.57 (0.51−4.89)	0.62	0.433
Other[d]	6 (0.7)	18 (0.5)	1.66 (0.65−4.16)	1.11	0.293	1.67 (0.64−4.35)	1.08	0.300

Notes: Each p value was based on a Wald χ^2 with df = 1. DDD: daily defined dose.

[a]The unconditional logistic regression model includes the index date and the duration of diabetes treatment.

[b]Adjusted for age, glucose-influencing comedication, and number of discharge diagnoses for cardiovascular diseases.

[c]Among current users (N = 97).

[d]Other antipsychotic drugs include bromperidol, fluphenazine, levomepromazine, olanzepine, penfluridol, perphenazine, pimozide, quetiapine, thioridazine, tiapride, and zuclopenthixol.

TABLE 3. Risk of Hospitalization for Hypoglycemia Related to Antipsychotic Drugs Stratified for Sex

	Cases N (%)	Comparison Subjects N (%)	OR Crude[a] (95% CI)	Wald χ^2	p	OR Adjusted[a,b] (95% CI)	Wald χ^2	p
Male	305	1,526						
Use of antipsychotic drugs								
No use	285 (93.4)	1,513 (99.1)	(reference)	(reference)	(reference)	(reference)	(reference)	(reference)
Current use	17 (5.6)	8 (0.5)	11.26 (4.81–26.36)	31.15	<0.001	9.74 (4.03–23.51)	25.62	<0.001
Past use	3 (1.0)	5 (0.3)	3.18 (0.75–13.39)	2.48	0.115	2.96 (0.67–13.07)	2.04	0.153
Female	510	2,391						
Use of antipsychotic drugs								
No use	486 (95.3)	2,329 (97.4)	(reference)	(reference)	(reference)	(reference)	(reference)	(reference)
Current use	19 (3.7)	53 (2.2)	1.71 (1.00–2.91)	3.86	0.049	1.27 (0.72–2.24)	0.70	0.402
Past use	5 (1.0)	9 (0.4)	2.69 (0.90–8.06)	3.11	0.078	2.45 (0.78–7.71)	2.34	0.126

[a]The unconditional logistic regression model includes index date and the duration of diabetes treatment.
[b]Adjusted for age, glucose-influencing comedication, and number of discharge diagnoses for cardiovascular diseases.

treatment episode. Past users were defined as patients who were not current users at the index date but who had a history of antipsychotic drug use in a 90-day period before the index date. Patients who had no prescriptions for an antipsychotic drug or in whom a treatment episode ended more than 90 days before the index date were classified as non-users.

The duration of antipsychotic treatment was defined for current users as the number of days between the start of the prescription period and the index date (up to 30 days, 31–90 days, 91–365 days, ≥366 days). The daily antipsychotic exposure was calculated for current users at the index date by expressing the daily dose divided in daily defined doses during the last prescription period. Antipsychotic treatment of current users was divided in individual antipsychotic drugs based on the highest numbers of users.

Potential Confounding Factors

The following covariates were studied as potential confounding factors: age at index date, sex, type of DM medication, current use of glucose-influencing comedication, use of antibiotic drugs, number of hospital admissions in the year before the index date, discharge diagnoses for cardiovascular diseases, and extent of chronic comorbidity, measured with the chronic disease score (CDS). The type of DM medication was subdivided into three groups: OADs, insulin, or a combination of OADs and insulin. Patients with at least one prescription for an OAD in the 360 days before the index date but without a prescription for insulin were categorized as being treated with OADs. Patients with at least one prescription for insulin in the 360 days before the index date without a prescription for an OAD were categorized as being treated with insulin, and patients with at least one prescription for insulin and also at least one prescription for an OAD in the 360 days before the index date were categorized as being treated with OADs and insulin. Patients were classified as current users of glucose-influencing comedication[37–39] if a drug was dispensed in a 180-day period before the index date. The use of an antibiotic drug (ATC code J01) in the 14 days before the index date was used as a proxy for the occurrence of an infection. The CDS was used to evaluate the chronic disease status of people who used prescribed drugs. This measure can be

considered an indicator of an individual's morbidity and overall health status. The CDS is calculated as the number of drugs dispensed in the year before the index date.[40]

Data Analysis

Patient characteristics are reported as numbers with percentages in the case of nominal data and as means with standard deviations (SDs) in the case of continuous data. Cases and comparison subjects were compared using the χ^2 test in the case of nominal data. Means were compared using Student independent sample t tests when the data satisfied assumptions for parametric analysis; otherwise, the Mann-Whitney U test was used.

Differences in baseline characteristics are expressed as p values. Unconditional logistic regression was performed to estimate the strength of the association between hypoglycemia and antipsychotic drug use in older patients with DM, always including the terms "index date" and "duration of DM treatment." All odds ratios (ORs) are expressed as point estimates with 95% confidence intervals (CIs).

The use of glucose-influencing comedication and number of discharge diagnoses for cardiovascular diseases were included in the final logistic regression model to correct for potential confounding and covariates that induced more than 10% change in the regression coefficient of the logistic regression model.[41] We studied potential effect modification of sex, age, use of antibiotic drugs, and DM medication by adding the interaction term with antipsychotic use in the regression model. The interaction term was considered as significant when $p < 0.05$. All statistical analyses were carried out with the SPSS statistical package (IBM Corp, Armonk, NY, version 19.0).

RESULTS

The cohort consisted of 68,314 patients with DM with an average follow-up of 4.5 years. From this cohort, 823 patients (1.2%) were hospitalized for hypoglycemia; 4,114 comparison subjects were selected. In the year before the index date, eight cases and 197 comparison subjects had no prescriptions for an antidiabetic drug and were excluded. The final study population therefore consisted of 815 cases and 3917 comparison subjects.

Table 1 describes the patient characteristics of cases and comparison subjects. The cases were older than the comparison subjects (79.4 versus 76.9 years), and 62% were women. Use of insulin or OADs and insulin was significantly higher among cases (37.5% and 18.7%, respectively) than among comparison subjects (21.3% and 13.2%, respectively). Glucose-influencing comedication, discharge diagnoses for cardiovascular diseases, and treatment with antibiotics were more common among cases (2.9 prescriptions versus 2.2 prescriptions, 1.0 hospital admissions versus 0.5 hospital admissions, and 15.5% versus 2.9% treatment with antibiotics, respectively), as were higher CDS scores (CDS $\geq$ 7: 69.2% versus 51.5%).

As shown in Table 2, current and past use of antipsychotic drugs was associated with an increased risk of hospitalization for hypoglycemia (adjusted OR: 2.26; 95% CI: 1.45–3.52; Wald $\chi^2 = 13.08$, df = 1, $p \leq 0.001$ and adjusted OR: 2.68; 95% CI: 1.08–6.63; Wald $\chi^2 = 4.53$, df = 1, p = 0.033, respectively). The risk of hospitalization for hypoglycemia was highest during the first 30 days after initiation of antipsychotic drug use and decreased with increasing duration of antipsychotic treatment. The risk was significantly higher with higher drug doses (daily defined dose > 0.25 adjusted OR: 8.20 compared with daily defined dose $\leq$ 0.25 adjusted OR: 1.67). Treatment with haloperidol and pipamperone was associated with an increased risk of hospitalization for hypoglycemia, whereas treatment with risperidone was not.

Table 3 shows the risk of hospitalization for hypoglycemia among antipsychotic users compared with non-users stratified for sex. Sex was identified as an effect modifier (Wald $\chi^2 = 13.54$, df = 2, $p \leq 0.001$). The adjusted OR of current antipsychotic use for men was 9.74. No effect modification was found for age (Wald $\chi^2 = 7.89$, df = 4, p = 0.096), DM medication (Wald $\chi^2 = 0.84$, df = 4, p = 0.934), and the use of antibiotic treatment (Wald $\chi^2 = 3.18$, df = 2, p = 0.204). However, the risk seems to be slightly increased in current users of antipsychotic drugs in patients with DM without antibiotic treatment in the 14 days before the index date (adjusted OR: 2.32; 95% CI: 1.14–3.77; Wald $\chi^2 = 12.12$, df = 1, $p \leq 0.001$) compared with those with antibiotic treatment

(adjusted OR: 1.08; 95% CI: 0.30−3.85; Wald χ^2 = 0.01, df = 1, p = 0.912).

DISCUSSION

The results of this study show that compared with non-use, the current use of antipsychotic drugs by older patients with DM is associated with an approximately two times higher risk of hypoglycemia and that the risk is highest during the first 30 days of antipsychotic treatment compared with those diabetics not using antipsychotic therapy. Furthermore, the risk of hospitalization for hypoglycemia increased with drug dose, and the use of haloperidol or pipamperone would appear to be more harmful than risperidone. Men (adjusted OR: 9.74) were at highest risk.

To our knowledge, this is the first study to assess the association between antipsychotic drugs and hypoglycemia. The association with dose and time suggests a causal relation between antipsychotic drug use and hypoglycemia, although causality cannot be established in an observational study. Only three case reports were found on hypoglycemia during antipsychotic use in older patients,[20,23,27] and one case report was found in a younger patient with DM.[24]

We found no studies of hypoglycemia and antipsychotic treatment, but an earlier study reported that the risk of hyperglycemia, instead of hypoglycemia, in older patients with DM was highest early during therapy with atypical or conventional antipsychotics.[18] Our results and the results of Lipscombe et al.[19] indicate that although few people need to be hospitalized for glucose dysregulation, some individuals, especially those with existing DM, do.

The proposed mechanism by which antipsychotics may increase the risk of hypoglycemia include a direct drug effect, decreased food intake, or anorexia as a consequence of the underlying disease for which the patient is being treated with antipsychotics or the underlying disease itself. Atypical antipsychotics cause insulin resistance by antagonism of serotonin-2a receptors, increase food intake by antagonism of serotonin 1a receptors, cause weight gain by antagonism of histamine-1 receptors, and impair insulin secretion by antagonism of muscarinic-3 receptors and serotonin-2a receptors. However, it has been suggested that antipsychotic drugs may have the opposite effect on insulin regulation. Previous studies report that dopamine-2/3 blockade by raclopride, amisulpride, and sulpiride stimulates insulin secretion by pancreatic beta cells.[42−44] Furthermore, it has been reported that administration of serotonin in vivo can cause hyperglycemia[45] and hypoglycemia.[46]

It has been reported that conventional antipsychotics may elevate extracellular glutamate levels during hypoglycemic episodes, resulting in cognitive impairment that delays recovery from hypoglycemia, whereas atypical antipsychotics might be less neurotoxic because they inhibit glutamate release.[47] The increased risk of hypoglycemia among past users of antipsychotics was unexpected. It is possible that insulin resistance or hyperglycemia during (long-term) antipsychotic treatment may lead to changes in antidiabetic treatment,[48] such that if antipsychotic treatment is discontinued but antidiabetic treatment is not reassessed, the patient may receive too high a dose of antidiabetic treatment and thus be at risk of hypoglycemia. Another explanation for this finding is that patients were misclassified by exposure because we used a strict definition of current antipsychotic use.

Male gender has previously been mentioned as a risk factor for hypoglycemia.[49−51] Blood glucose levels tend to be monitored more frequently in diabetics who are using antibiotics, and therefore glucose dysregulation may be detected earlier and prevent severe hypoglycemia. This may explain why older patients with DM treated without antibiotic drugs appeared to be more likely to develop hypoglycemia than patients who did use antibiotics.

This study involved a large cohort of older patients with DM with a long follow-up, which made it possible to distinguish between new and long-term antipsychotic use. However, it also had a number of limitations. First, hypoglycemia may have been underestimated because most patients with hypoglycemia are treated as outpatients,[52] and only patients with severe hypoglycemia or hypoglycemia complicated by additional conditions (such as falls or loss of consciousness) require hospitalization. Hypoglycemia may also have been underestimated as a result of ascertainment bias if comparison subjects had developed hypoglycemia but were not admitted to hospital. However, because this type of misclassification probably occurred at random among cases

and comparison subjects, it was not considered to be relevant. Second, drug exposure was based on drug dispensing data, but there was no information about whether dispensed drugs were actually used. However, this potential misclassification of exposure may have occurred at random among cases and comparison subjects and was not considered relevant.

Protopathic bias could also have occurred if an antipsychotic drug was initiated because a patient exhibited delirious symptoms or agitation as a result of hypoglycemia. However, we believe most doctors would measure blood glucose levels, to exclude hypoglycemia, in patients with DM and psychotic symptoms. Therefore, we do not consider this bias as relevant.

Unfortunately, we had no information about psychiatric diagnosis and indications for which the antipsychotic drug was initiated. Therefore, confounding by indication may have occurred if the hypoglycemia episode was a result of self-care impairment in dementia or another mental illness instead of a direct antipsychotic effect. Additionally, confounding by contraindication may have occurred and may be differential because the physician's decision for initiation and type of antipsychotic drug was influenced by the severity of the DM and the extent of the blood glucose control. Finally, residual confounding may have been present, because the PHARMO RLS does not provide information about risk factors, such as body mass index, renal and liver function, blood pressure, or smoking habit.[53]

We believe the risk of hypoglycemia was probably underestimated. Only community-dwelling older patients were included in our study, and patients living in long-term facilities have a higher estimated risk of hypoglycemia (because they are more vulnerable, with comorbidities) than older patients in the general population.

Despite these limitations, the results of this observational study suggest that older patients with DM on antipsychotics are at risk of hypoglycemia. We suggest this risk is probably additional to the risk of hypoglycemia due to their antidiabetic treatment. Further research is needed to confirm the association between antipsychotic drugs and hypoglycemia and to establish the underlying mechanism. Our findings suggest that in clinical practice glucose levels should be closely monitored in older patients with DM after the prescription or discontinuation of antipsychotic drugs to prevent the serious consequences of hypoglycemia.

In conclusion, the results of this study suggest that the use of antipsychotics increases the risk of hospitalization for hypoglycemia in older patients with DM, compared with diabetics without antipsychotic treatment, especially during the first 30 days of treatment and with higher antipsychotic doses. If confirmed, these findings should prompt the close monitoring of blood glucose levels in older patients with DM prescribed antipsychotics to facilitate the early detection of hypoglycemia.

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APPENDIX 1. MEDICATIONS INFLUENCING THE LEVEL OF BLOOD GLUCOSE

Acetaminophen, acetazolamide, angiotensin-converting enzyme inhibitors, beta agonists, beta blockers, calcium channel blockers, central alpha blockers, chlordiazepoxide, corticosteroids, cyclosporine, dapsone, diazoxide, disopyramide, fibric acid derivates, indomethacin, isoniazid, L-dopa, lithium, loop diuretics, mebendazole, monoamine oxidase inhibitors, morphine, nicotinic acid, octreotide, phenytoin, rifampicin, salicylates, selective serotonin reuptake inhibitors, tetracycline, theophylline, thiazide diuretics, thyroid hormones, tricyclic antidepressants, trimethoprim-sulfamethoxazole.