

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; ■:■–■)

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

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