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The Association between Depression and Medication Nonpersistence in New Users of Antidiabetic Drugs

Carlotta Lunghi, MSc, PhD[1,2,3], *Jocelyne Moisan, PhD*[1,2,3], *Jean-Pierre Grégoire, MPH, PhD*[1,2,3], *Line Guénette, BPharm, MSc, PhD*[1,2,3,*]

[1]*Faculty of Pharmacy, Laval University, Quebec, Quebec, Canada;* [2]*Chair on Adherence to Treatments, Laval University, Quebec, Quebec, Canada;* [3]*Population Health and Optimal Health Practices Research Unit, CHU de Québec Research Center, Laval University, Quebec, Quebec, Canada*

ABSTRACT

Objectives: To measure the association between depression and nonpersistence with antidiabetic drugs (ADs) among new users of oral ADs and to estimate factors associated with nonpersistence among these new users with depression. **Methods:** We used administrative claims data to identify an adult cohort (≥18 years) of new oral AD users who were free of depression. We followed the patients from AD initiation until either discontinuation, ineligibility for the public drug plan, death, or the end of the study. A proportional hazard Cox regression model with depression as a time-dependent variable was used to compute the adjusted hazard ratio of nonpersistence. A proportional hazard Cox regression model was also used to identify factors associated with nonpersistence in the subcohort of patients with depression. **Results:** We identified 114,366 new oral AD users, of whom 4,808 were diagnosed with depression during the follow-up. A greater proportion (55.4%) of patients with depression (vs. 42.5% without depression) discontinued their treatment during the follow-up. The adjusted hazard ratio of nonpersistence with ADs was 1.52 (95% confidence interval 1.41–1.63). Among patients with depression, independent factors associated with nonpersistence included younger age at oral AD initiation (<45 years) and starting treatment with drugs other than metformin (especially polytherapy with insulin). **Conclusions:** Patients with depression are more likely to discontinue their treatment. Health care professionals should pay attention to patients on AD therapy who also suffer from depression, especially if the patients are young or are using insulin because these patients are at an increased risk of nonpersistence.

Keywords: claims data, depression, medication persistence, type 2 diabetes mellitus.

Introduction

Type 2 diabetes is a common chronic condition expected to affect about 552 million people or nearly 10% of the global population by 2030 [1]. When lifestyle management, such as diet and exercise, fails to achieve glycemic control, an oral antidiabetic drug (AD) is recommended for patients with diabetes; if hyperglycemia is severe, a combination of ADs is recommended [2]. Adherence to recommended AD treatment is a crucial issue in diabetes management. Evidence suggests that medication adherence largely contributes to the achievement and maintenance of long-term glycemic control and to the prevention of complications [3,4]. Nevertheless, medication adherence in type 2 diabetes is less than optimal, and depression, along with other factors, represents a potentially modifiable predictor for medication nonadherence [5].

Depression is one of the leading causes of disability worldwide [6]. Patients with diabetes are at an increased risk of developing depression [7,8], and the comorbidity of diabetes and depression increases the risk of diabetes complications and mortality [9,10]. This increased risk could be mediated by the negative influence of depression on adherence to diabetes self-care recommendations, such as diet, physical activity, and drug therapy [11]. Persistence is a main component of medication adherence and refers to the act of continuously refilling prescriptions for the recommended length of time [12]. Persistence with recommended medications is a crucial factor in determining the success of long-term management, especially for chronic diseases such as type 2 diabetes. Nevertheless, few studies on the effect of depression on medication adherence have focused on persistence [5,13]. Only two authors reported on the effect of depression on persistence with AD therapy [14,15]. Kalsekar et al. [15] found a significantly higher proportion of nondepressed (67%) versus depressed (61%) patients persisting with their AD treatment 12 months after initiation, although this association was

Conflicts of interest: The authors declare that they have no conflicts of interest to disclose for this study.

* *Address correspondence to:* Line Guénette, Faculty of Pharmacy, Laval University, Centre de recherche du CHU de Québec, Hôpital du St-Sacrement, J1-08, 1050 Chemin Ste-Foy, Quebec, Quebec, Canada G1S 4L8.

E-mail: Line.Guenette@pha.ulaval.ca.

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not statistically significant in the adjusted logistic regression. In that study, the diagnosis of depression was assessed in the year before oral AD initiation, the follow-up was only 12 months, and the cohort was restricted to patients younger than 65 years. Caughey et al. [14] observed that patients using antidepressant drugs were 42% more likely to discontinue their antidiabetic medication. This study, however, was limited by its assessment of depression. All patients using antidepressant drugs were considered to be suffering from depression, although a large proportion of antidepressants are prescribed for reasons other than depression. In addition, less than 30% of patients having depression are treated with antidepressant drugs [16]. To our knowledge, the effect of depression occurring after the initiation of oral AD treatment on persistence with AD treatment has never been evaluated. Our study then aimed to 1) measure the association between depression and nonpersistence with AD treatment among patients newly treated with oral ADs in the Canadian province of Quebec and 2) identify factors associated with AD treatment nonpersistence in the subcohort of patients having both depression and diabetes.

Methods

Data Sources and Subjects

We conducted a population-based inception cohort study using administrative data from the Quebec health insurance board (RAMQ), the Quebec registry of hospitalizations, and the Institut de la Statistique du Québec. In Quebec, the RAMQ manages medical services for all permanent residents. The RAMQ also manages the public drug insurance plan, which covers people aged 65 years and older, recipients of guaranteed income supplement (GIS) or welfare, and individuals without a private insurance group plan. In 2014, the public drug insurance plan enrolled approximately 3.5 million people (over 40% of the Quebec population) [17]. The RAMQ data file for pharmaceutical services has been considered accurate [18]. The RAMQ databases contain information on beneficiary demographic characteristics, drug insurance plan coverage, medical services billed by physicians, and pharmacy-dispensed drugs reimbursed by RAMQ. The hospitalization registry includes information on hospitalizations, and the Institut de la Statistique du Québec database provides vital statistics (date and reason of death). The Quebec information access commissioner authorized the transfer of data to this group. The Ethics Review Board of the CHU de QuébecResearch Center approved this study.

We asked the RAMQ to send us information on all beneficiaries who claimed at least one AD between January 1, 2000, and December 31, 2006. To ensure that we included only new users and that we had complete information regarding the use of physician and pharmaceutical services, we further asked RAMQ to exclude patients who received an AD in the year before AD initiation, as well as those who had not been eligible for the Quebec drug plan for the full 1-year period before AD initiation. We then excluded patients younger than 18 years. To focus on type 2 diabetes, we further excluded patients whose initial therapy was only insulin. We then also excluded all patients with a history of depression, namely, all those who had at least one inpatient or outpatient claim with an *International Classification of Diseases, Ninth or Tenth Revision* (ICD-9/ICD-10) code for depression (*ICD-9* codes: 311 and 300.4; ICD-10 codes: F32, F33, F34.1, and F41.2) or a prescription claim for an antidepressant drug (see Appendix Table 1 in Supplemental Materials found at http://dx.doi.org/10.1016/j.jval.2016.09.2399) in the 1-year period before AD initiation. The date of inclusion in the study was the date of the first claim for any oral AD.

Definition of Variables

Main outcome

The main outcome was *nonpersistence*, defined as the failure to refill any AD within an allowed gap period. To take into account switches over time from an oral AD to another oral AD or to insulin, we calculated the allowed gap as follows: 3 times the number of days supplied for the last prescription claimed, if the last prescription claimed was an oral AD supplied for 10 days or more; 30 days, if the last prescription claimed was an oral AD supplied for less than 10 days [19]; and 90 days, if the last prescription claimed was insulin, because the use of insulin might vary from day to day and the count of the days' supply in the RAMQ database could be imprecise [20]. Treatment discontinuation was set at the date corresponding to the last prescription claimed (oral AD or insulin) for which we added

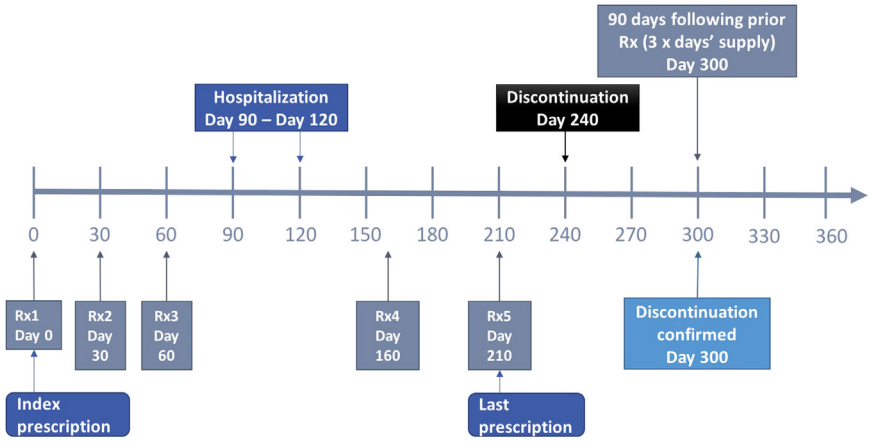

Fig. 1 – Representation of a hypothetical patient for the calculation of AD treatment discontinuation. The hypothetical patient started his treatment at day 0 with the index prescription claimed (Rx1) supplied for 30 days. The patient had claims on day 30 (Rx2) and on day 60 (Rx3). He or she was then hospitalized from day 90 to day 120, and thus 30 days were excluded from the calculation of the permissible gap. There were two additional claims, one on day 160 (Rx4) and the last one on day 210(Rx5). Because no prescriptions were claimed by day 300, the patient was considered nonpersistent. Day 240 was set as the date of discontinuation because this was the date on which the patient would have run out of medication after the last prescription filled (Rx5). AD, antidiabetic drug.