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Original article

The impact of incident depression on medication adherence in patients with type 2 diabetes

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ABSTRACT

Background. – Depression has been correlated with suboptimal adherence to antidiabetic drugs (ADs). Most studies on this topic were cross-sectional; thus, the directionality of this relationship could not be established. The objective of this study was to measure the association between incident depression and AD nonadherence among newly treated patients with diabetes.
Methods. – We performed a population-based cohort study among new AD users using the Quebec public health insurance data. To avoid immortal time bias, we carried out depression diagnosis-time distribution matching by assigning a date of depression diagnosis to individuals without depression. Nonadherence (i.e., $< 90\%$ of days covered by ≥ 1 AD) during the year following depression diagnosis (real or assigned date) was the outcome. Multivariate logistic regression analyses that adjusted for baseline adherence and other confounders were used to estimate the adjusted effect of depression on AD nonadherence.
Results. – Between 2000 and 2006, we identified 3,106 new AD users with a subsequent diagnosis of depression and 70,633 without depression, of which 52% and 49% became non-adherent to AD treatment, respectively. Among patients with depression, 52.0% were considered AD non-adherent in the year after depression diagnosis compared with 49.0% of matched patients without depression. Depression was associated with AD nonadherence after accounting for baseline adherence and other confounders with an adjusted odds ratio of 1.24 (95% confidence interval: 1.13–1.37).
Conclusions. – The results suggest that depression is an independent risk factor for AD nonadherence. Patients with type 2 diabetes and depression might benefit from adherence-enhancing interventions.

Introduction

Type 2 diabetes is a highly prevalent chronic condition [1]. Because glucose levels likely worsen over time and lifestyle modifications may fail to achieve glycemic control, pharmacological treatment with oral antidiabetic drugs (ADs) and insulin, when appropriate, is necessary to optimize the management of type 2 diabetes [2]. Thus, adherence to pharmacological treatment is a key point in the management of type 2 diabetes. Medication adherence is defined as the act of observing a physician's recommendations on medication use in terms of timing, dosage, and frequency [3]. Evidence shows that medication adherence is an important contributory factor in the successful management of type 2 diabetes because AD treatment improves glycemic control and decreases the risk of related complications [4].

The risk of depression is higher among patients with type 2 diabetes [5]. Studies conducted among patients with type 2 diabetes suggest that depression is associated with suboptimal adherence to recommendations regarding healthy diet, physical activity and prescribed medications [6,7]. However, among the many studies [6–13] that assessed the association between depression and adherence to diabetes medication, only six [6,8–12] used a longitudinal design and only one [6] accounted for baseline adherence (i.e., adherence before depression), providing some evidence of a causal relationship. In the one longitudinal study that accounted for baseline adherence [6], adherence was assessed with a self-reported scale; therefore, the results could be subject to memory and social desirability biases.

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According to behavioral theories, past behavior may predict future behavior, such as adherence [14]. That is why we measured baseline adherence and we investigated the impact of an incident diagnosis of depression after the initiation of an AD treatment on adherence to ADs. The lack of robust longitudinal studies to assess the directionality and possible causal nature of the relationship between depression and medication nonadherence justified this study, which aimed to measure the association between incident depression and subsequent nonadherence to AD treatment among patients starting an oral AD treatment.

Methods

Data and population sources

Administrative data from the Quebec Health Insurance Board (RAMQ), the Institut de la Statistique du Québec (ISQ) and the Quebec registry of hospitalizations were used. The RAMQ runs medical services for all permanent residents and the public drug insurance plan for people aged 65 years and older, recipients of guaranteed income supplement (GIS) or welfare, and people without a private drug insurance plan. The public drug insurance plan enrolls over 40% of the Quebec population [15], and the data for pharmaceutical services are considered to be accurate [16]. The RAMQ database contains demographic information on beneficiaries, information on drug insurance plan coverage, medical services billed and pharmacy dispensed drugs that were reimbursed by the public drug plan. The hospitalization registry contains information on hospitalizations, and the ISQ database provides vital statistics. This study was approved by the Ethics Review Board of the CHU de Québec Research Centre.

We asked the RAMQ to send us information on all beneficiaries with a claim of at least one AD between January 1, 2000, and December 31, 2006, and to exclude those 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 prior to AD initiation. This ensured that we included only new users of ADs. We then excluded patients under 18 years old. In addition, we excluded patients whose initial therapy was insulin only to focus on type 2 diabetes. Since we wanted to isolate the effect of depression on adherence to AD treatment, we selected a population of patients without prior depression diagnosis, by excluding all patients who had at least one inpatient or outpatient medical claim with an International Classification of Diseases (ICD) code for depression (ICD-9 codes: 311, 300.4; ICD-10 codes: F32, F33, F34.1, F41.2) or a prescription claim for an antidepressant drug (Table S1; see supplementary data associated with this article on line) in the 1-year period before AD initiation. To measure AD adherence before and after the depression diagnosis, we further excluded patients who were not eligible for the public drug plan throughout the 120-day period preceding and the 1-year period following the depression diagnosis (Fig. 1). The date of inclusion in this study was the date of depression diagnosis for patients with depression and an assigned date of depression diagnosis for patients without depression (see the next section for details).

Study design

The following two sub-cohorts were created: a sub-cohort of patients who initiated an oral AD treatment and received a subsequent diagnosis of depression and a sub-cohort of patients who initiated an oral AD treatment and did not receive a subsequent diagnosis of depression during the study follow-up period. Because individuals in the depression cohort were already using an AD treatment before their depression diagnosis, the comparison of their AD-related outcome (i.e., AD adherence) with that of individuals without depression could be biased by "immortal time". Immortal time is a period of time in an observation period during which, according to the way exposure is being defined by design, the outcome of interest cannot occur. [17] Without taking into account immortal time with an adequate study design or statistical analysis, one could erroneously observe, for example, that Oscar winners live longer than non-winners. [18] It would be so because, by design, individuals "exposed" to an Oscar (Oscar winners) must have survived until exposure definition is fulfilled i.e. until they win an Oscar. Those who die before winning an Oscar, although they might be expected to win an Oscar in the future, will automatically be part of the "non-exposed" (Oscar non-winners) group. To correct this potential immortal time bias, we performed depression diagnosis-time matching, a method proposed by Suissa et al. [17]. This method consists of matching the two sub-cohorts using the overall depression diagnosis-time distribution (i.e., the time between oral AD initiation and depression diagnosis) among the patients with depression. With this method, immortal time bias is controlled by selecting patients with a similar survival pattern. [19] More specifically, for patients with a diagnosis of depression after oral AD treatment initiation, the number of days from oral AD treatment initiation to depression diagnosis was assessed. To ensure that everyone had a sufficient follow-up period to measure adherence, the period during which post-depression adherence was computed (i.e., 365 days) was added to the depression diagnosis-time. Finally, for each patient without depression, a matching time was randomly selected from the set of depression diagnosis-times, and a fictive date of depression diagnosis (i.e., the same date of depression diagnosis of an "individual" that was randomly selected from the other sub-cohort) was assigned to him/her. If the assigned matching time exceeded the length of his/her follow-up, the patient was excluded.

Definition of variables

Outcome

The outcome was AD nonadherence, which was defined as having a proportion of days covered (PDC) by at least one AD lower than 90% during the 365 days following a depression diagnosis or the assigned date of depression for patients without depression. The PDC was computed using drug claims data. The cut-off of 90% to define nonadherence was based on studies that assessed the cut-offs of adherence measures derived from drug claims data [20,21]. In our study, PDC was the proportion of days covered by at least one AD during the post-depression period, namely in the 1-year period after depression diagnosis (real or assigned date). Hospitalization days were excluded from both the numerator and denominator because there was no available information on drug use during hospital stays in our databases. Fig. 2 shows an example of the PDC calculation for a hypothetical patient.

Independent Variable

In this study, depression was the binary explanatory variable. An individual was considered to have depression based on an algorithm validated in a Canadian setting [22]:

- one inpatient or psychiatric (inpatient or outpatient) claim with an ICD-9 or ICD-10 code for depression;
- two outpatient physician claims with depression codes within 2 years;
- one outpatient claim with a depression code and a claim for an antidepressant drug (Table S1; see supplementary material associated with this article on line) within 2 years.

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