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

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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.

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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

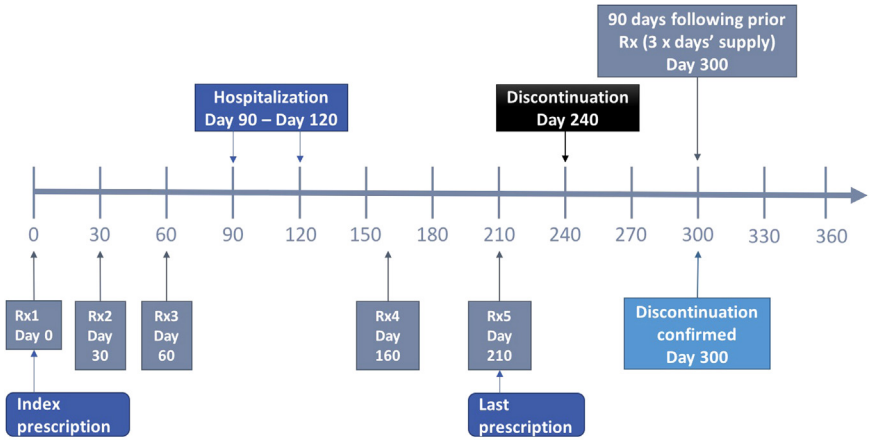

Fig. 1 – Representation of a hypothetical patient for the calculation of AD treatment discontinuation. The hypothetical patient started his treatment at day 0 with the index prescription claimed (Rx1) supplied for 30 days. The patient had claims on day 30 (Rx2) and on day 60 (Rx3). He or she was then 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.

the days' supply. Hospitalization days were excluded from the calculation because there is no information available on drug use during hospital stays in the RAMQ databases. Figure 1 represents a hypothetical patient who discontinued AD treatment and was considered nonpersistent after 240 days.

Independent variables

The presence of depression was assessed using a validated algorithm [21]. An individual was considered to have depression if we found 1) one inpatient or psychiatric (inpatient or outpatient) claim with an *ICD-9* or *ICD-10* code for depression, 2) two outpatient physician claims with depression codes within 2 years, or 3) one outpatient claim with a depression code and a 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) within 2 years. For the last two criteria of this algorithm, the date of the first claim with a depression code was set as the date on which depression was diagnosed. Sociodemographic variables, such as sex, age, region of residence (urban/rural), socioeconomic status (high: no GIS; medium: partial GIS; low: maximum GIS or welfare), and information regarding initial oral AD treatment and the initial prescriber's specialty, were measured at the time of oral AD initiation. We assessed the number of physician visits, the number of different physicians visited, the number of different medications claimed, the number of hospitalizations (excluding those for diabetes and depression), and the occurrence of anxiety disorders and brain diseases (Alzheimer's disease or dementia) in the 1-year period before oral AD initiation.

Statistical Analysis

Patients were followed from oral AD treatment initiation until oral AD discontinuation, loss of eligibility for the drug plan, death or the end date of the study (i.e., December 31, 2008), whichever came first. To estimate the adjusted effect of depression on the time to AD discontinuation and to avoid immortal time bias [22], we used multivariate Cox proportional hazard models, adjusting for potential confounders, with depression as a time-dependent binary covariate. This variable value changes from 0 to 1 at the date of depression diagnosis and allows for the consideration of patients in the nondepressive group until this date. The assumption of the proportionality of the hazards was verified by plotting the graph of the ln[−ln(survival)], and no violation was detected [23]. We identified the factors associated with nonpersistence in a subcohort of all patients who had a diagnosis of depression (according to our earlier definition) during their follow-up. We calculated unadjusted and adjusted hazard ratios (HRs) in the subcohort of patients with depression along with their 95% confidence intervals (CIs) using univariate and multivariate Cox regression analyses, respectively. Variables were selected using a backward procedure with a *P* value of more than 0.05 for their removal from the model. To describe the time from initiation to discontinuation of AD treatment, we performed survival analyses using Kaplan-Meier survival plots, with all differences compared with log rank tests.

We conducted four different sensitivity analyses to verify the robustness of our results. First, we used different durations for the refill gap period (4 times, 2 times, and 1.5 times the days' supply for oral ADs, and 120, 60, and 45 days for insulin). Second, the time-dependent variable was changed to "depression" 30 days before the diagnosis date because people might start suffering from depression before the condition is diagnosed. Third, because death and loss of eligibility for the public drug plan are competing risks that could preclude the onset of the outcome (nonpersistence with AD treatment), we conducted a competing risk regression analysis using the Fine and Gray approach [24]. Finally, because almost all patients enrolled in the public drug plan were 65 years and older, we performed separate Cox analyses for those younger than 65 years and for those 65 years and older. Analyses were carried out using SAS version 9.4 (SAS Institute, Cary, NC).

Results

We identified 114,366 new users of oral ADs without depression before oral AD initiation (Fig. 2). These patients were followed for a total of 334,839.67 person-years. During the follow-up, 4,808 patients (4.2%) were diagnosed with depression, and 49,264 patients (43.1%) discontinued their AD treatment. For patients with and without depression, there were 14,308.92 and 320,530.75 person-years of follow-up, respectively. The baseline characteristics of the study population, according to the presence of depression, are presented in Table 1.

Among the patients with depression, 55.4% discontinued their AD treatment versus 42.4% of patients without depression. The multivariate Cox regression analysis showed a greater likelihood of discontinuation of AD treatment in patients with depression compared with patients with diabetes alone with a crude HR of 1.63 (CI 1.52–1.75) and an adjusted HR of 1.52 (CI 1.41–1.63). One year after oral AD treatment initiation, 33.2% of patients with a diagnosis of depression had discontinued their AD treatment compared with 28.6% of patients without depression. Within 2 years of AD treatment initiation, 41.7% of patients with depression and 35.4% of patients without depression had discontinued their treatment (see Fig. 3).

In the cohort of 4808 patients with depression, six variables were associated with nonpersistence with AD treatment (Table 2). Younger age (<45 years), having visited more than 2 different physicians in the year before oral AD initiation, being prescribed the initial oral AD treatment by an endocrinologist or another specialist rather than a general practitioner, having received a drug other than metformin, or polytherapy with insulin as initial treatment were all associated with a higher likelihood of nonpersistence. Having a low socioeconomic status and having been prescribed four or more different drugs in the year before oral AD initiation were associated with a lower likelihood of nonpersistence.

In the first sensitivity analysis, the adjusted HRs of nonpersistence were of the same magnitude as those observed in our main analysis. We, however, observed a trend suggesting that depression is more strongly associated with nonpersistence when the refill gap period defining nonpersistence is longer

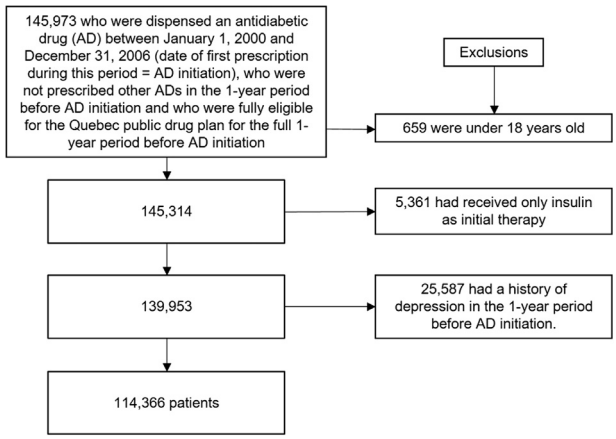

Fig. 2 – Selection of the study population.

Table 1 – Characteristics of patients (n = 114,366) according to the presence or absence of depression in the follow-up period.

Characteristics	Total (n = 114,366)	Depression		P value
		Yes (n = 4,808)	No (n = 109,558)	
Discontinued AD treatment during follow-up				<0.001
Yes	49,264 (43.08)	2,665 (55.43)	46,599 (42.53)	
No	65,102 (56.92)	2,143 (44.57)	62,959 (57.47)	
Age (y) at oral AD treatment initiation, mean ± SD	65.01 ± 13.19	63.79 ± 14.45	65.07 ± 13.13	
Age (y)				<0.001
18–44	9,377 (8.20)	564 (11.73)	8,813 (8.04)	
45–54	13,658 (11.94)	677 (14.08)	12,981 (11.85)	
55–64	23,793 (20.80)	878 (18.26)	22,915 (20.92)	
65–74	40,226 (35.17)	1,502 (31.24)	38,724 (35.35)	
75–84	22,756 (19.90)	983 (20.45)	21,773 (19.87)	
85+	4,556 (3.98)	204 (4.24)	4,352 (3.97)	
Sex*				<0.001
Male	59,003 (51.59)	2,146 (44.63)	56,857 (51.90)	
Female	55,363 (48.41)	2,662 (55.37)	52,701 (48.10)	
Region*				<0.001
Urban	90,120 (78.80)	3,909 (81.30)	86,211 (78.69)	
Rural	23,986 (20.97)	889 (18.49)	23,097 (21.08)	
Missing	260 (0.23)	10 (0.21)	250 (0.23)	
Socioeconomic status				<0.001
High (no GIS)	64,683 (56.56)	2,453 (51.02)	62,230 (56.80)	
Medium (partial GIS)	29,103 (25.45)	1,221 (25.40)	27,882 (25.45)	
Low (maximum GIS or welfare)	20,580 (17.99)	1,134 (23.59)	19,446 (17.75)	
No. of physician visits†,‡				
0	38,115 (33.33)	1,245 (25.89)	36,870 (33.65)	
1–3	37,883 (33.12)	1,509 (31.39)	36,374 (33.20)	
≥4	38,368 (33.55)	2,054 (42.72)	36,314 (33.15)	
No. of different physicians visited†,‡				<0.001
0	36,196 (31.65)	1,177 (24.48)	35,019 (31.96)	
1–2	37,217 (32.54)	1,471 (30.59)	35,746 (32.63)	
≥3	40,953 (35.81)	2,160 (44.93)	38,793 (35.41)	
No. of different medications claimed†,‡				<0.001
0–3	36,734 (31.12)	1,211 (25.19)	35,523 (32.42)	
4–7	38,778 (33.91)	1,477 (30.72)	37,301 (34.05)	
≥8	38,854 (33.97)	2,120 (44.09)	36,734 (33.53)	
Hospitalized†,‡				<0.001
No	89,391 (78.16)	3,461 (71.98)	85,930 (78.43)	
Yes	24,975 (21.84)	1,347 (28.02)	23,628 (21.57)	
Anxiety disorders†				<0.001
No	108,007 (94.44)	4,223 (87.83)	103,784 (94.73)	
Yes	6,359 (5.56)	585 (12.17)	5,774 (5.27)	
Cognitive disorders†				0.5069
No	112,710 (98.55)	4,733 (98.44)	107,977 (98.56)	
Yes	1,656 (1.45)	75 (1.56)	1,581 (1.44)	
Specialty of initial oral AD prescriber*				0.2608
General practitioner	97,830 (85.54)	4,102 (85.32)	93,728 (85.55)	
Endocrinologist	5,445 (4.76)	236 (4.91)	5,209 (4.75)	
Internist	5,507 (4.82)	222 (4.62)	5,285 (4.82)	
Other specialty	5,218 (4.56)	239 (4.97)	4,979 (4.54)	
Undisclosed	366 (0.32)	9 (0.19)	357 (0.33)	
Initial oral AD treatment*				<0.001
Metformin	87,572 (76.57)	3,498 (72.75)	84,074 (76.74)	
Other monotherapy	20,497 (17.92)	1,023 (21.28)	19,474 (17.78)	
Polytherapy without insulin	5,860 (5.12)	275 (5.72)	5,585 (5.10)	
Polytherapy with insulin	437 (0.38)	12 (0.25)	425 (0.39)	

Note. Unless otherwise indicated, values are numbers and proportions (in %).
AD, antidiabetic drug; GIS, guaranteed income supplement.
* Measured at initiation of oral AD treatment.
† In the 1-y period before oral AD treatment initiation.
‡ For reasons other than diabetes or depression.

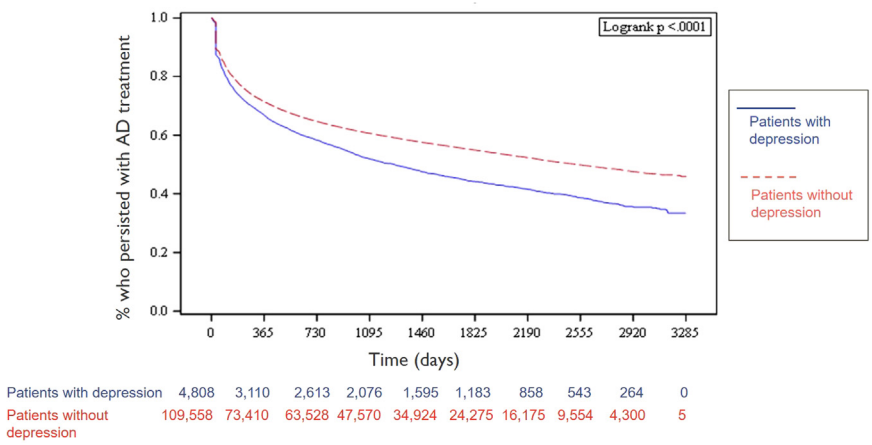

Fig. 3 – Probability of persisting with AD treatment according to the presence of depression diagnosis. AD, antidiabetic drug.

(see Appendix Table 2 in Supplemental Materials found at http://dx.doi.org/10.1016/j.jval.2016.09.2399). Moving the date of depression diagnosis 30 days earlier in the second sensitivity analysis revealed no differences in the adjusted HR (1.53; CI 1.42–1.64). Considering death and loss of eligibility for the public drug plan as competing risks did not show any significant changes in the adjusted HR (1.49; CI 1.39–1.61). Finally, in the subgroup analysis, adjusted HRs were similar for both patients younger than 65 years (1.52; CI 1.37–1.68) and those 65 years and older (1.63; CI 1.47–1.80).

Conclusions

The main finding of our study was that depression is associated with a 52% increased likelihood of nonpersistence with AD treatment. This result is consistent with the results of the two studies that examined the effect of depression on persistence with AD treatment in patients with diabetes [14,15]. Kalsekar et al. [15] found that at the end of a 12-month follow-up period, patients not suffering from depression were 30% more likely to be persistent than depressed patients, although this result was not statistically significant. In their cohort of 29,710 new users of metformin or sulfonylureas, Caughey et al. [14] found that using an antidepressant during the 6-month period before AD initiation was associated with a 42% increased risk of nonpersistence.

In our study, six factors were associated with nonpersistence with AD treatment among the 4808 patients with depression. All those factors have been previously associated with nonpersistence with AD treatment in the diabetic population of Quebec, irrespective of depression status [19,25].

We found that patients 45 years and older were more likely to persist with their AD treatment than patients aged between 18 and 44 years. This finding is consistent with the findings of earlier studies in which increased age has been negatively associated with discontinuation [15,19,25,26]. Patients with a low rather than a high socioeconomic status were more likely to be persistent. Other studies conducted in the province of Quebec found a similar association between nonpersistence and socioeconomic status [19,25,26]. This association is possibly due to the public drug plan co-payment modalities. The co-payment is lower for people with a low socioeconomic status. It has previously been reported that lower co-payment costs are associated with better adherence [27,28].

We found that depressed patients who visited three or more different physicians in the year before oral AD treatment initiation were slightly more likely to discontinue their treatment. As proposed by Bice and Boxerman [29], the large number of different physicians visited might also reflect that patients have a low level of interpersonal continuity of care. Continuity of care has recently been associated with an increased likelihood of persistence among diabetic patients initiating an AD treatment [30].

Consistent with what has been previously reported for diabetic patients, we found that patients having claimed a large number of different drugs (four or more drugs) in the year before oral AD initiation were more likely to be persistent with their AD treatment [15,25,26,31].

Finally, we found that the initial AD treatment was associated with nonpersistence. In particular, initiating treatment with metformin rather than with another oral AD was associated with an increased likelihood of persistence, a result consistent with other studies [19,25,26]. This finding might be due to a lower number of side effects for metformin, the first-line choice in diabetes management [2]. Initiating AD treatment with a combination of oral ADs and insulin was associated with a higher likelihood of nonpersistence. We, however, did not observe the same result for combinations without insulin, suggesting that starting treatment with insulin could negatively influence persistence with any AD. Drawing up insulin and treatment complexity, in general, are known barriers to adherence with AD treatment [32,33]. Starting AD treatment with a combination of drugs that includes insulin might also indicate that those patients had severe hyperglycemia at diagnosis and required intensive treatment because this regimen is recommended by clinical guidelines. These patients could have possibly consulted a physician late because they are less careful about their health and less adherent to lifestyle recommendations.

This study has several strengths. First, by using the RAMQ databases and the hospitalization registry, we were able to build a large cohort of subjects treated for diabetes in the province of Quebec for up to 9 years of follow-up. In addition, we measured persistence using drug claims, avoiding recall biases typical of surveys based on self-report information. Furthermore, in our study, we took into account AD treatment switches over time, which might be due to a proper therapeutic management, and followed patients even if they switched from an oral AD to another oral AD or to insulin.This approach, rather than studying persistence with the initial AD treatment, gives a better representation of real-life practices, in which treatment switches are common, concerning approximately 10% of patients in the first year [34]. In addition, this study could be considered population-based for patients 65 years and older because in the province of Quebec, almost all these patients are enrolled in the public drug plan. Finally, we used a time-dependent analysis, which provided

Table 2 – Factors associated with nonpersistence with AD treatment among patients with depression (n = 4808).

Characteristics	Unadjusted HR	95% CI	P value	Adjusted HR*	95% CI	P value
Age† (y)						
18–44	1			1		
45–54	0.59	0.52–0.68	<0.0001	0.61	0.53–0.70	<0.0001
55–64	0.52	0.45–0.59	<0.0001	0.52	0.45–0.59	<0.0001
65–74	0.55	0.49–0.62	<0.0001	0.52	0.46–0.60	<0.0001
75–84	0.60	0.53–0.68	<0.0001	0.57	0.49–0.67	<0.0001
85+	0.56	0.44–0.70	<0.0001	0.53	0.41–0.67	<0.0001
Socioeconomic status†						
High (no GIS)	1			1		
Medium (partial GIS)	0.95	0.86 1.04	0.2625	1.02	0.92–1.13	0.7140
Low (maximum GIS or welfare)	1.00	0.91–1.10	0.9439	0.88	0.79–0.97	0.0136
Sex†						
Male	1					
Female	0.97	0.90–1.05	0.4625	NA	NA	NA
Region†						
Urban	1					
Rural	0.90	0.82–1.00	0.0452	NA	NA	NA
Missing	0.49	0.16–1.53	0.2212	NA	NA	NA
No. of physician visits‡						
0	1					
1–3	0.99	0.89–1.09	0.7905	NA	NA	NA
≥4	1.11	1.01–1.22	0.0266	NA	NA	NA
No. of different physicians visited‡						
0	1			1		
1–2	1.01	0.91–1.12	0.8927	1.01	0.90–1.12	0.9316
≥3	1.14	1.03–1.25	0.0093	1.15	1.04–1.27	0.0090
No. of different medications prescribed‡						
0–3	1			1		
4–7	0.82	0.74–0.90	<0.0001	0.87	0.79–0.97	0.0090
≥8	0.83	0.76–0.91	<0.0001	0.88	0.80–0.96	0.0047
Hospitalized‡						
No	1					
Yes	1.13	1.04–1.23	0.0048	NA	NA	NA
Anxiety disorders‡						
No	1					
Yes	1.04	0.93–1.17	0.4712	NA	NA	NA
Cognitive disorders‡						
No	1					
Yes	0.88	0.62–1.24	0.4536	NA	NA	NA
Specialty of initial oral AD prescriber†						
General practitioner	1			1		
Endocrinologist	1.31	1.12–1.55	0.0011	1.22	1.03–1.44	0.0206
Internist	1.21	1.02–1.44	0.0339	1.11	0.93–1.33	0.2346
Other specialty	1.54	1.31–1.81	<0.0001	1.40	1.19–1.65	<0.0001
Undisclosed	1.33	0.60–2.96	0.4891	1.02	0.46–2.27	0.9655
Initial oral AD treatment†						
Metformin	1			1		
Other monotherapy	1.32	1.21–1.45	<0.0001	1.32	1.20–1.44	<0.0001
Polytherapy without insulin	1.15	0.98–1.35	0.0885	1.07	0.91–1.25	0.4446
Polytherapy with insulin	4.72	2.61–8.55	<0.0001	3.34	1.84–6.05	<0.0001

AD, antidiabetic drug; CI, confidence interval; GIS, guaranteed income supply; HR, hazard ratio; NA, not applicable (variable not retained in adjusted model).

* For all variables with results presented in the table.

† Measured at initiation of oral AD treatment.

‡ In the 1-y period before oral AD treatment initiation.

us a more reliable assessment of the risk of nonpersistence with AD treatment after depression, avoiding immortal time bias [22].

Our study, as with any claim-based study, also has some limitations. We used an algorithm based on administrative databases, rather than a structured interview, to assess the presence of depression. This approach could have led to an underestimation of depression cases because the algorithm sensitivity is 78% [21], and depression is likely underdiagnosed

in primary care [35]. This misclassification of depression cases has probably caused an underestimation of the actual risk of nonpersistence. Although we adjusted for a number of possible confounders (e.g., the number of physician visits, the number of different physicians visited, the number of different medications claimed, and the number of hospitalizations), we did not take into account any variation that might have occurred during follow-up (especially after depression diagnosis). Consequently, residual confounding could still be present because of time-varying changes in health care utilization. Furthermore, in the RAMQ databases, there is no information about patients younger than 65 years who are covered by a private drug plan. This lack of information resulted in a cohort of patients in which employed patients are under-represented with an effect on the estimated likelihood of nonpersistence difficult to assess. We also assumed that drugs claimed were actually taken, and we considered that patients following a polytherapy regimen were persistent if they claimed at least one of their ADs. This assumption could have led to an overestimation of the real persistence. Finally, the RAMQ databases do not contain information about some factors that could be associated with persistence with AD treatment, such as clinical data (e.g., glycated hemoglobin) indicating the severity of diabetes, side effects of drugs [36,37], or self-perception of health status [38], and therefore these variables could not be assessed and accounted for in the analysis. Thus, the presence of residual confounding cannot be excluded.

Medication persistence is a key point in the achievement and maintenance of long-term glycemic control, which is crucial in preventing diabetes complications. Nonpersistence was extremely common in our cohort, with 43.1% of patients discontinuing their AD treatment during the follow-up. The discontinuation rates that we observed could dramatically reduce treatment efficacy and might increase diabetes complications. The results of our study demonstrate the negative association of depression on medication persistence in patients with diabetes. The higher likelihood of nonpersistence observed in patients who had a diagnosis of depression could partly explain reports showing that diabetic patients with depression have a higher risk of diabetes complications than do patients without depression. Because depression negatively influences persistence with AD treatment, it appears important to recognize diabetic patients with depression and to closely follow their AD treatment. Physicians should also pay attention more closely to depressive patients at a higher risk for nonpersistence, in particular younger users of AD, to help them better manage their treatment.

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Supplemental Materials

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REFERENCES

[1] Whiting DR, Guariguata L, Weil C, Shaw J. IDF diabetes atlas: global estimates of the prevalence of diabetes for 2011 and 2030. Diabetes Res Clin Pract 2011;94:311–21.
[2] Harper W, Clement M, Goldenberg R, et al. Pharmacologic management of type 2 diabetes. Can J Diabetes 2013;37(Suppl. 1):S61–8.
[3] UK Prospective Diabetes Study (UKPDS) Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). Lancet 1998;352:854–65.
[4] Stratton IM, Adler AI, Neil HAW, et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. BMJ 2000;321:405–12.
[5] Krass I, Schieback P, Dhippayom T. Adherence to diabetes medication: a systematic review. Diabet Med 2015;32:725–37.
[6] World Health Organization. Depression fact sheet no. 3692012. Available from: http://www.who.int/mediacentre/factsheets/fs369/en/. [Accessed January 20, 2016].
[7] Nouwen A, Winkley K, Twisk J, et al. Type 2 diabetes mellitus as a risk factor for the onset of depression: a systematic review and meta-analysis. Diabetologia 2010;53:2480–6.
[8] Anderson RJ, Freedland KE, Clouse RE, Lustman PJ. The prevalence of comorbid depression in adults with diabetes: a meta-analysis. Diabetes Care 2001;24:1069–78.
[9] de Groot M, Anderson R, Freedland KE, et al. Association of depression and diabetes complications: a meta-analysis. Psychosom Med 2001;63:619–30.
[10] van Dooren FE, Nefs G, Schram MT, et al. Depression and risk of mortality in people with diabetes mellitus: a systematic review and meta-analysis. PLoS One 2013;8:e57058.
[11] Gonzalez JS, Safren SA, Delahanty LM, et al. Symptoms of depression prospectively predict poorer self-care in patients with type 2 diabetes. Diabet Med 2008;25:1102–7.
[12] Cramer JA, Roy A, Burrell A, et al. Medication compliance and persistence: terminology and definitions [Review]. Value Health 2008;11:44–7.
[13] Grenard JL, Munjas BA, Adams JL, et al. Depression and medication adherence in the treatment of chronic diseases in the United States: a meta-analysis. J Gen Intern Med 2011;26:1175–82.
[14] Caughey GE, Preiss AK, Vitry AI, et al. Does antidepressant medication use affect persistence with diabetes medicines? Pharmacoepidemiol Drug Saf 2013;22:615–22.
[15] Kalsekar ID, Madhavan SS, Amonkar MM, et al. Impact of depression on utilization patterns of oral hypoglycemic agents in patients newly diagnosed with type 2 diabetes mellitus: a retrospective cohort analysis. Clin Ther 2006;28:306–18.
[16] Olfson M, Marcus SC. National patterns in antidepressant medication treatment. Arch Gen Psychiatry 2009;66:848–56.
[17] Régie de l'Assurance Maladie du Québec. Rapport annuel de gestion 2013–2014. Available from: http://www.ramq.gouv.qc.ca/SiteCollectionDocuments/citoyens/fr/rapports/rappann1314.pdf. [Accessed: 2016-01-20].
[18] Tamblyn R, Lavoie G, Petrella L, Monette J. The use of prescription claims databases in pharmacoepidemiological research: the accuracy and comprehensiveness of the prescription claims database in Quebec. J Clin Epidemiol 1995;48:999–1009.
[19] Gregoire JP, Sirois C, Blanc G, et al. Persistence patterns with oral antidiabetes drug treatment in newly treated patients—a population-based study. Value Health 2010;13:820–8.
[20] Bonafede MM, Kalsekar A, Pawaskar M, et al. A retrospective database analysis of insulin use patterns in insulin-naive patients with type 2 diabetes initiating basal insulin or mixtures. Patient Prefer Adherence 2010;4:147–56.
[21] Alaghehbandan R, Macdonald D, Barrett B, et al. Using administrative databases in the surveillance of depressive disorders—case definitions. Popul Health Manag 2012;15:372–80.
[22] Suissa S. Immortal time bias in pharmaco-epidemiology. Am J Epidemiol 2008;167:492–9.

[23] Hess KR. Graphical methods for assessing violations of the proportional hazards assumption in Cox regression. Stat Med 1995;14:1707–23.
[24] Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. J Am Stat Assoc 1999;94:496–509.
[25] Guenette L, Moisan J, Breton MC, et al. Difficulty adhering to antidiabetic treatment: factors associated with persistence and compliance. Diabetes Metab 2013;39:250–7.
[26] Simard P, Presse N, Roy L, et al. Persistence and adherence to oral antidiabetics: a population-based cohort study. Acta Diabetol 2015;52:547–56.
[27] Hunt J, Rozenfeld Y, Shenolikar R. Effect of patient medication cost share on adherence and glycemic control. Manag Care 2009;18:47–53.
[28] Eaddy MT, Cook CL, O'Day K, et al. How patient cost-sharing trends affect adherence and outcomes: a literature review. Pharm Ther 2012;37:45–55.
[29] Bice TW, Boxerman SB. A quantitative measure of continuity of care. Med Care 1977;15:347–9.
[30] Dossa R, Grégoire J-P, Lauzier S, et al. Effect of continuity of care on antidiabetes drug adherence and use of guidelines-recommended drugs. Can J Diabetes 2014;38:S22.
[31] Hertz RP, Unger AN, Lustik MB. Adherence with pharmacotherapy for type 2 diabetes: a retrospective cohort study of adults with employer-sponsored health insurance. Clin Ther 2005;27:1064–73.
[32] de Vries ST, Keers JC, Visser R, et al. Medication beliefs, treatment complexity, and non-adherence to different drug classes in patients with type 2 diabetes. J Psychosom Res 2014;76:134–8.
[33] Odegard PS, Capoccia K. Medication taking and diabetes: a systematic review of the literature. Diabetes Educ 2007;33:1014–29; discussion 30–1.
[34] Boccuzzi SJ, Wogen J, Fox J, et al. Utilization of oral hypoglycemic agents in a drug-insured U.S. population. Diabetes Care 2001;24: 1411–5.
[35] Kahn LS, Fox CH, McIntyre RS, et al. Assessing the prevalence of depression among individuals with diabetes in a Medicaid managed-care program. Int J Psychiatry Med 2008;38:13–29.
[36] Chao J, Nau DP, Aikens JE, Taylor SD. The mediating role of health beliefs in the relationship between depressive symptoms and medication adherence in persons with diabetes. Res Social Adm Pharm 2005;1:508–25.
[37] Larkin AT, Hoffman C, Stevens A, et al. Determinants of adherence to diabetes treatment. J Diabetes 2015;7:864–71.
[38] Egede LE. Major depression in individuals with chronic medical disorders: prevalence, correlates and association with health resource utilization, lost productivity and functional disability. Gen Hosp Psychiatry 2007;29:409–16.