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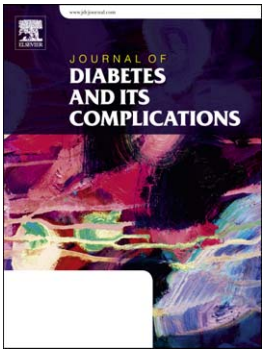

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Title: Factors associated with antidiabetic medication non-adherence in patients with incident comorbid depression

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Key words
Medication Adherence, Type 2 diabetes, Depression, Associated factors.

Conflict of Interest statement
The authors declare that they have no conflicts of interest to disclose related to this study.

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Abstract

Aim: To identify factors associated with antidiabetic drug (AD) non-adherence among patients with type 2 diabetes and depression.

Study Design and Settings: We conducted a population-based retrospective cohort study among new AD users with a diagnosis of depression following AD initiation. We used public health insurance data from Quebec. The dependent variable was non-adherence (i.e., <90% of days covered by ≥1 AD) in the year after a depression diagnosis. Different sociodemographic, clinical and medication-related variables were assessed as potential factors of non-adherence to AD treatment. We performed univariate and multivariate logistic regressions.

Results: We identified 3106 new users of ADs with a diagnosis of depression between 2000 and 2006. Of these individuals, 52% were considered non-adherent to their ADs. Baseline non-adherence, younger age, the addition of another AD to the initial treatment, <4 drug claims, visits with several different physicians, high socioeconomic status, and a small number of diabetes complications were associated with AD non-adherence.

Conclusions: The factors identified in the present study may help clinicians recognize patients with type 2 diabetes and incident depression at increased risk for non-adherence. In these patients, close follow-up and targeted interventions could help improve adherence to AD treatment, improve glycaemic control and reduce complications.

Keywords

Medication adherence; Depression; Type 2 diabetes mellitus; Healthcare Administrative Claims; Determinants.

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1. Introduction

In type 2 diabetes patients, when lifestyle modifications fail to control glycemic levels, a pharmacological treatment with oral antidiabetic drugs (ADs) and/or insulin is recommended [1]. Pharmacological treatment of type 2 diabetes has shown benefits in the prevention of microvascular and macrovascular complications, which characterize the advanced stages of the disease [2-4]. Despite the well-established efficacy of ADs, the degree of benefits due to this treatment may be reduced by suboptimal medication adherence. Medication adherence is defined as the extent to which patients observe physicians' recommendations for prescribed medications, with reference to timing, dosage, and frequency [5]. In patients with type 2 diabetes, better adherence to ADs largely contributes to improved glycemic control [6] and lower healthcare resource utilization in terms of lower incidence of diabetes complications [7] and reduction of diabetes-related hospitalizations [6]. A better adherence to ADs has also been associated with lower healthcare costs [8], improved patients' quality of life [9] and lower risk of death [7]. Nevertheless, in patients with type 2 diabetes, medication adherence is less than optimal [10, 11].

Depression is an independent risk factor for non-adherence to medications for different chronic conditions [12], including type 2 diabetes [13]. A recent meta-analysis showed that diabetes is a risk factor for incident depressive symptoms, with a 25% increased risk of incident depression in patients with diabetes compared to those without diabetes [14]. Moreover, depression has been associated with poor diabetes self-care, such as glucose monitoring [13, 15], diet [13, 16], physical activity [13, 16] and adherence to AD treatment [13, 15, 16]. Thus, it becomes important to identify patients at higher risk for non-adherence who may benefit from close medical follow-up and adherence-improving interventions.

Some studies have identified factors associated with non-adherence to AD treatment in patients with type 2 diabetes [11, 17-20], but none have assessed the factors associated with non-adherence measured in the post-depression diagnosis period in patients with both diabetes and depression. As patients with both

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diabetes and depression may present unique characteristics, different from those of people with diabetes alone, we conducted this study aiming to identify factors associated with AD treatment non-adherence among patients newly treated with oral ADs with incident comorbid depression.

2. Materials and Methods

2.1 Data and Population Sources

We performed this population-based retrospective cohort study using administrative data from health insurance board of Quebec (RAMQ), the *Institut de la Statistique du Québec* (ISQ) and the Quebec registry of hospitalizations. In the Canadian province of Quebec, the RAMQ manages all medical services for Canadian citizens and permanent residents and the public drug insurance plan for citizens without private drug insurance, those aged 65 years and above and recipients of welfare or the guaranteed income supplement (GIS). The RAMQ databases have been validated for research use and are considered accurate. [21]. The Ethics Review Board of the *CHU de Québec* Research Centre approved this study.

From the RAMQ, we collected information on every citizen and permanent resident who claimed at least one AD in the period from January 1, 2000 to December 31, 2006. To include only new users of ADs, patients who received an AD in the year before AD initiation were excluded, along with those who had not been eligible for the Quebec drug plan during the full 1-year period prior to AD initiation. To focus on type 2 diabetes, we also excluded patients who were under 18 years old and those who did not receive an oral AD as their initial AD therapy. We also excluded prevalent cases of depression, namely all subjects with ≥1 inpatient or outpatient medical claim with a code for depression or a claim for an antidepressant drug in the full 1-year period before AD initiation. The codes for depression were the International Classification of Diseases (ICD) ninth revision (ICD-9) codes 311 and 300.4 and the tenth revision (ICD-10) codes F32, F33, F34.1, and F41.2. Additionally, we excluded subjects who were not enrolled in the public drug plan during the 120-day period prior to the 1-year period after receiving a diagnosis of depression in order to measure

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adherence before and after the diagnosis of depression. To select patients with depression after AD treatment initiation, we used an algorithm validated in a Canadian setting [22]. A patient with depression was someone who had (1) one inpatient or psychiatric (inpatient or outpatient) claim with a depression code or (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 within 2 years. The date of the first outpatient, inpatient or antidepressant drug claim coded for depression was considered the date of the depression diagnosis.

2.2 Definition of variables

2.2.1 Dependent variable

Non-adherence to ADs in the year after the diagnosis of depression was the dependent variable. Non-adherence was defined as having a proportion of days covered (PDC) by one or more ADs below 90%. To compute the PDC, we used drug claims data. The cut-off of 90% to define non-adherence was based on studies that assessed the cut-offs of adherence measures derived from drug claims data [23, 24]. Because of the lack of information on drug use during hospital stays in the RAMQ database, we excluded the days of hospitalization from both the numerator and denominator in the calculation of PDC. Figure 1 shows the timeline of the study through an example of the calculation of PDC for a hypothetical patient.

2.2.2 Independent Variables (potential factors of non-adherence)

At different points in time, we assessed variables related to sociodemographic, clinical and medication-related factors potentially associated with non-adherence among patients with diabetes and depression, as visualized in Figure 1. We assessed the type of initial oral AD at the time of AD treatment initiation and the specialty of the physician who prescribed it. We assessed variables on the utilization of healthcare resources, such as the number of physician visits, different physicians visited, different medications claimed, and hospitalizations during the 1-year period before the diagnosis of depression. We also

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assessed variables related to the presence of comorbidities, namely anxiety disorders, brain diseases (Alzheimer's disease or dementia), and other mental disorders (bipolar disorder or schizophrenia), and we assessed variables related to the severity of diabetes, namely changes (switching or adding ADs) to the initial treatment (only oral ADs, only insulin, or insulin and oral ADs) and the presence of diabetes complications. For the latter variable, having a complication of diabetes was defined as the presence of at least 1 claim for a main complication of diabetes (see Supplemental Table 1 for details). We assessed the baseline adherence with the PDC during a 90-day period. This period went from the 120th day up to the 31th day before the depression diagnosis (see Figure 1). We excluded from the PDC calculation period, the 30 days preceding the diagnosis of depression since in this period symptoms of depression perceived by patients may have influenced their treatment adherence. (see Figure 1). At the time of the depression diagnosis, we assessed sociodemographic variables (sex, age, region of residence, socioeconomic status as high=no GIS, medium=partial GIS, low=maximum GIS or welfare).

2.3 Statistical Analysis

To identify factors associated with non-adherence among patients with type 2 diabetes and depression, we performed univariate and multivariate logistic regression analyses. For the selection of the variables, we used a backward procedure: starting from the full adjusted model (the model containing all the variables) we removed one by one all those variables having a P-value >0.05, starting from those having the higher P-value to those having the lower P-value. Because the cut-off point of 80% is widely used to define adherence, we performed a sensitivity analysis using this threshold. According to this new definition of adherence, non-adherent patients were those having a PDC by one or more ADs below 80%. We carried out all of the analyses using SAS version 9.4 (SAS Institute, Cary, NC, USA).

3. Results

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Of the 145,793 patients who claimed at least one AD between 2000 and 2006 and after applying our exclusion criteria (see Figure 2), our study included 3,106 patients who started antidiabetic treatment with ≥1 oral AD and had a diagnosis of depression thereafter during follow-up (from 2000 to 2007). As summarized in Table 1, the majority of patients (57.5%) were female, and the average age at the time of the diagnosis of depression was 67 years (median 68, range 19-94). Metformin was the most common AD used as initial treatment (72.9%). Additionally, 63.8% of patients had no changes in their initial AD treatment. The median PDC by ≥ 1 AD before the diagnosis of depression (baseline adherence) was 91.1% (range 0-100), and the median PDC in the 1-year period after the depression diagnosis was 89.1% (range 0-100). When adherence was dichotomized, 52.0% of patients were considered non-adherent to their AD treatment after their depression diagnosis, as they had a PDC by ≥ 1 AD less than 90%. In the period before the diagnosis of depression this proportion was 46.7%. In the sensitivity analysis, when adherence was dichotomized with a cut-off point of 80%, patients considered non-adherent to their AD treatment in the year after and in the three-month period before the diagnosis of depression were 38.4% and 37.1%, respectively.

In the multivariate logistic regression model, baseline non-adherence to AD treatment was strongly and positively associated with post-depression diagnosis non-adherence to AD with an OR of 7.86. Other factors that were independently and positively associated with non-adherence included being prescribed the initial oral AD treatment by a specialist other than an endocrinologist or internist, rather than by a general practitioner, visiting a large number of different physicians and changing the initial therapy to a combination of another oral AD plus insulin. Conversely, older age (> 44 years), low socioeconomic status, more than seven different drug claims in the year preceding the depression diagnosis, diabetes complications, mental disorders other than depression (such as bipolar disorder or schizophrenia) and changes of the initial therapy to another oral AD added to or replacing the initial therapy were all associated with a lower likelihood of non-adherence. When we used a cut-off point of 80% to define adherence, seven of the ten variables associated with adherence when using the 90% cut-off point remained statistically associated with

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adherence (see Supplemental Table 2). However, having had a mental disorder other than depression, the number of diabetes complications and the number of different drugs claimed in the year before depression diagnosis, were not statistically associated with non-adherence. On the contrary, the initial antidiabetic drug treatment was statistically associated with non-adherence with the 80% cut-off point.

4. Discussion

In this population of adult patients newly treated with ADs and with comorbid depression, only 48.0% were adherent to their AD treatment. Since diabetes is a highly prevalent disease and depression is a common comorbid condition in diabetes patients [14], this relationship has become a public health concern driving efforts to improve patients' medication adherence. In our study, nine factors were associated with non-adherence to AD treatment. Some of them, namely age, socioeconomic status, the number of distinct drugs claimed, and the specialty of the physician who prescribed the initial oral AD, have been previously shown to be associated with non-adherence to AD treatment, independent of the presence of depression, in the general diabetic population of Quebec [11, 17]. In line with results from studies based on behavioural theories that suggest that past behaviour is a strong predictor of future behaviour [25], we observed that past non-adherence to AD treatment strongly predicted post-depression diagnosis non-adherence.

We found that increased age was associated with better adherence. Individuals in all age groups over 45 years were 39% to 71% more likely to be adherent to their AD treatment. Many other studies conducted among patients with diabetes have found that increased age is associated with better medication adherence [11, 17, 19, 20, 26-28]. Older patients may have greater acceptance of their chronic condition and perception of the usefulness of ADs possibly due to the presence of comorbidities or diabetes complications, which could lead them to be more reliant and adherent to their ADs. We also found that a greater number of diabetes complications was associated with a higher likelihood of adherence. Moreover, patients with eight or more claims of different drugs in the year preceding depression diagnosis were more

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likely to be adherent. Claiming a large number of different drugs may indicate concurrent illnesses or diabetes complications.[29] This result related to drugs claims was consistent with what has previously been reported for the general diabetic population [11, 17, 19, 20, 28]. In contrast, data on diabetes complications and adherence are limited. In a recent claims-based study on factors associated with persistence and adherence to oral ADs, the authors did not find any significant associations with either microvascular or macrovascular diabetes complications [17]. In a sample of Irish patients with diabetes, it was indeed reported that the presence of at least one chronic condition concordant with diabetes, such as cardiovascular conditions, was associated with better adherence to ADs [30]. In another study on factors affecting medication adherence in geriatric diabetes patients, the authors found that a higher perception of the severity of diabetes complications was associated with better medication adherence [18]. Nevertheless, the effect of comorbidities, including diabetes complications, on adherence to AD remains controversial [17, 30].

Low rather than high socioeconomic status was associated with a higher likelihood of adherence in our study. Similar associations were found in past studies in the Quebec diabetic population [11, 17]. Nonetheless, contradictory findings have been reported for the association between low socioeconomic status and adherence, with some studies reporting a positive association [18], others reporting a negative association [28], and still others reporting no association [27]. However, this result should be interpreted considering the drug plan co-payment system. In fact, for the Quebec population, co-pays are lower for people with low socioeconomic status, and lower co-payment costs have previously been associated with better adherence [31, 32].

We found that among patients with depression, the number of different physicians visited in the year before the depression diagnosis was positively associated with the likelihood of non-adherence to their AD treatment, with a 3% increase for every different physician visited. Bice et al. [33] reported that a large number of different physicians visited may reflect a lower level of interpersonal continuity of care. A study

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conducted in Taiwan among patients newly diagnosed with type 2 diabetes found that patients with high scores of continuity of care were more likely to be adherent to their AD treatment than those with low scores [34]. This finding has been recently confirmed in a population with type 2 diabetes in Quebec. Patients with low and medium interpersonal continuity of care constituted 23% and 11%, respectively, and were less likely to be compliant to their AD when compared to those with a high continuity of care [35].

We observed that having a mental disorder other than depression, such as bipolar disorder or schizophrenia, was associated with a lower likelihood of non-adherence. Two studies comparing medication adherence in patients with and without schizophrenia showed a lower likelihood of poor adherence in patients with both diabetes and schizophrenia compared to patients with diabetes alone [36, 37]. Authors of those studies explained this result by the fact that having a serious mental illness could improve patients' ability to self-manage their other chronic conditions [36]. However, the observed lower likelihood of poor adherence in patients with both diabetes and schizophrenia could be the result of a bias due to the use of administrative data to measure medication adherence, which is based on claims and not actual use. In fact, people with serious mental illnesses may be more closely supported by informal caregivers who could actually be responsible for their drug claims and be helping them manage their treatment.

Finally, we did not find an association between the initial AD and non-adherence, but we found that changes to the initial therapy during follow-up were associated with non-adherence. In particular, changing to a combination of another AD plus insulin, rather than remaining on the initial AD, was associated with an increased likelihood of non-adherence. Yurgin et al. [38] reported that in their population of type 2 diabetes patients who were assessed with the self-administered Morisky-Green questionnaire, the lowest proportion of patients reporting good compliance were those treated with insulin in combination with oral ADs. On the contrary, we found that changing to another oral AD was associated with a lower likelihood of non-adherence. This result is difficult to interpret and could be biased because of the definition of adherence that we used in our study. As we calculated the PDC by ≥ 1 AD, adding a new drug increased the likelihood of

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having days covered by drugs and therefore being considered adherent. Additionally, since the reason for prescribing a new drug is not recorded in the RAMQ database, we could not differentiate patients who added an oral AD from those who switched to a different oral AD. Patients switching to a different oral AD because of adverse reactions or a lack of efficacy of the initial AD treatment might become more adherent to the new AD as a result of better tolerance or reliance on the treatment.

In the sensitivity analysis, when we used a cut-off point of 80%, we found a percentage of non-adherent patients (38.4%) higher than that reported in a past study carried on the diabetic population of Quebec (20.7%) [11]. The difference could be explained by the fact that our cohort is composed of patients having had a diagnosis of depression and, in the study by Guénette et al., adherence was assessed only among the patients who were persistent to their antidiabetic treatment at the end of the 1-year study period. We also found that the initial antidiabetic drug treatment was associated with non-adherence. In particular, starting the antidiabetic treatment with a monotherapy other than metformin was associated with a higher likelihood of non-adherence. This result is consistent with other studies [11, 17, 39] and might be due to a lower number of side effects for metformin, which is the first-line drug according to the Canadian clinical practice guidelines for diabetes management [1].

This study has some limitations. First, when selecting the population, we could have missed some cases of depression because we used a claims-based algorithm [22]; despite the validity of this approach, the claims-based algorithm identified only diagnosed patients rather than all patients with clinical signs of depression. Some evidence also suggests that underdiagnosis of depression is not uncommon, especially among older subjects [40, 41]. We could also have overestimated the actual adherence to ADs. Indeed, we assumed that all the ADs claimed were actually taken by patients. Moreover, patients treated with a combination of two ADs were considered adherent if $\geq$ 90% of days were covered by at least one of those ADs. Additionally, some factors that were potentially associated with non-adherence to AD treatment were

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unable to be assessed in the RAMQ database. In particular, we were unable to assess the presence and magnitude of side effects of ADs (such as hypoglycaemia, weight gain, or nausea) [1], which could have influenced adherence [42, 43], or the perception of health status [44, 45], medication efficacy, and need for medications [42, 46]. Finally, the generalization of the results to the population of type 2 diabetes patients not covered by drug insurance or covered by drug plans with different characteristics than the Quebec drug plan should be done with caution.

This study also has strengths. First, this was the first study to assess factors associated with AD non-adherence in patients newly treated with oral ADs with incident depression. Second, we measured adherence to ADs in a real world setting, where physicians adjusted and changed the treatment according to their patients' needs [47]. In fact, we measured adherence to AD or insulin, allowing patients to switch from one AD to another over time. Third, we used objective measures of adherence and depression. Those measures were not affected by recall bias or biases that are typical of self-reported information [48, 49]. Fourth, by using medico-administrative data, we were able to build a large cohort of patients with type 2 diabetes newly treated for diabetes who received a diagnosis of depression during a follow-up period of up to eight years. Finally, because people who just turned 65 years old were automatically registered in the RAMQ drug plan despite their previous plan, our study was population-based for patients aged 65 years and above.

We observed that lower AD treatment adherence before a depression diagnosis, younger age, a large number of different physicians visited and, especially, the addition of insulin or other oral ADs to the initial therapy were risk factors for future non-adherence in patients with both diabetes and depression. Our results suggest that efforts to help these patients better manage their AD treatment should particularly target patients with prior suboptimal adherence to medications and those who need adjustments to their AD therapy. Such individuals could benefit from closer medical attention and interventions aiming to improve adherence.

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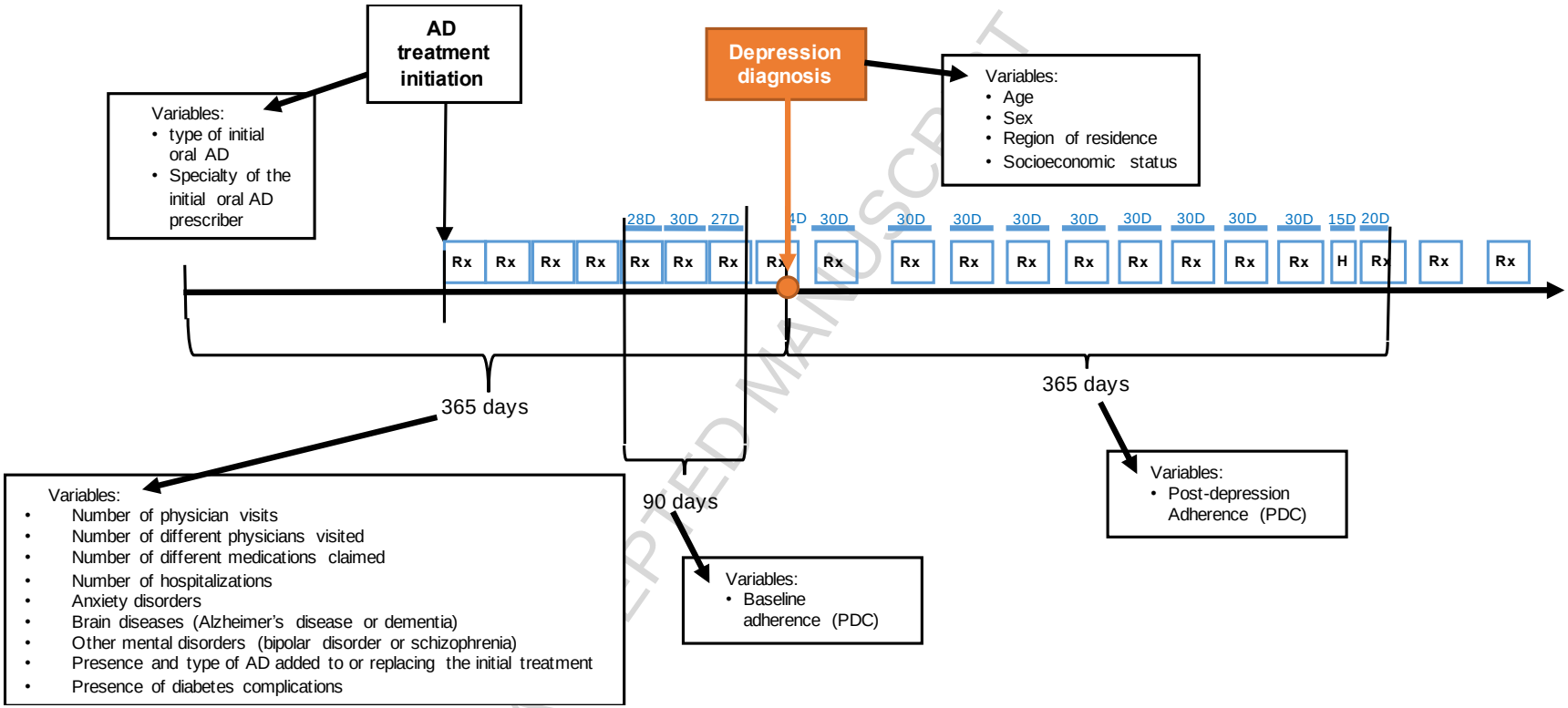

Figure 1 Example of the calculation of adherence for a hypothetical patient.

AD= antidiabetic drug. D= days. H= hospitalization. PDC= proportion of days covered by ≥1 AD

Baseline adherence for the hypothetical patient: PDC= [(28+30+27)/90]*100=94.4%

Post-depression diagnosis adherence for the hypothetical patient: PDC=[(4+30+30+30+30+30+30+30+30+30+20-15)/(365-15)]*100=79.7%

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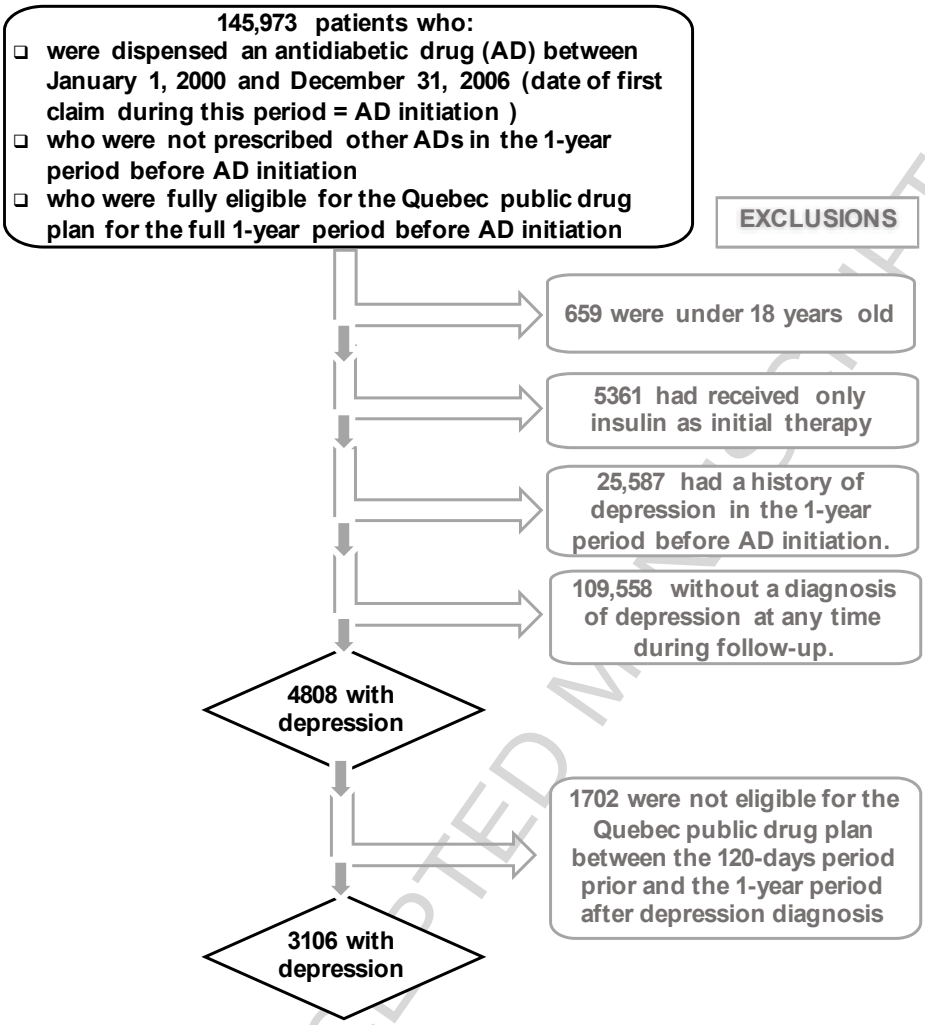

Figure 2 Selection of the study population

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Table 1 Characteristics of patients diagnosed with depression during follow-up (N =3106)

Characteristics		N	(%)
Adherence to antidiabetic drug treatment*	Yes (PDC ≥ 90%)	1492	(48.04)
	No (PDC <90%)	1614	(51.96)
Baseline adherence (PDC2) ‡, median (range)		89.1%	(0-100)
Baseline adherence to antidiabetic treatment‡	Yes (PDC2 ≥90%)	1656	(53.32)
	No (PDC2 <90%)	1450	(46.68)
Age£, mean (SD)		64.00	(14.33)
Age£ in years:	18-44	344	(11.08)
	45-54	457	(14.71)
	55-64	584	(18.80)
	65-74	905	(29.14)
	75-84	690	(22.22)
	85+	126	(4.06)
Sex£:	Male	1319	(42.47)
	Female	1787	(57.53)
Region£:	Urban	2534	(81.58)
	Rural	568	(18.29)
	Missing	4	(0.13)
Socioeconomic status£:	High (No GIS)	1388	(44.69)
	Medium (Partial GIS)	847	(27.27)
	Low (Maximum GIS or welfare)	871	(28.04)
No. of physician visits#&, mean (SD)		7.05	(10.56)
No. of different physicians visited #&		4.81	(5.38)
No. of different medications claimed #&	0-4	421	(13.55)
	5-7	658	(21.18)
	≥8	2027	(65.26)
No. of hospitalizations#&, mean (SD)		0.59	(1.14)
No. of diabetes complications#, mean (SD)		0.22	(0.62)
Anxiety disorders#	No	2410	(77.59)
	Yes	696	(22.41)
Brain diseases#	No	2975	(95.78)
	Yes	131	(4.22)
Other mental disorders#	No	2852	(91.82)
	Yes	254	(8.18)
Specialty of initial oral AD prescriber†	General practitioner	2682	(86.35)
	Endocrinologist	150	(4.83)
	Internist	136	(4.38)
	Other specialty	131	(4.22)
	Undisclosed	7	(0.23)
Initial oral AD treatment†	Metformin	2263	(72.86)
	Other monotherapy	672	(21.64)
	Polytherapy	171	(5.51)
No. of classes of ADs†, mean (SD)		1.06	(0.24)
Initial AD treatment changes#	No changes	1982	(63.81)
	Another oral AD	1008	(32.45)
	Insulin	35	(1.13)
	Combination of insulin plus oral AD	81	(2.61)

Unless otherwise indicated, values are numbers and proportions (in %). AD: antidiabetic drug; GIS: Guaranteed Income Supplement. SD: Standard deviation. *In the 1-year period after depression diagnosis. ‡PDC2: Proportion of days covered by ≥1 AD in the 3-month period before depression diagnosis. £ Measured at depression diagnosis. #In the

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period from AD treatment initiation to depression diagnosis. [&]For reasons other than diabetes or depression. [†]Measured at initiation of oral AD treatment.

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Table 2 Factors associated with non-adherence to antidiabetic drug treatment among patients with depression (n = 3,106)

Characteristics	Unadjusted OR	95% CI	P-value	Adjusted* OR	95% CI	P-value
Age£						
18-44	1			1		
45-54	0.43	0.32-0.58	<.0001	0.57	0.40-0.81	0.0021
55-64	0.33	0.24-0.44	<.0001	0.40	0.28-0.56	<.0001
65-74	0.31	0.24-0.41	<.0001	0.35	0.24-0.50	<.0001
75-84	0.33	0.25-0.44	<.0001	0.41	0.28-0.59	<.0001
85+	0.24	0.16-0.37	<.0001	0.31	0.18-0.53	<.0001
Socioeconomic status£						
High (No GIS)	1			1		
Medium (Partial GIS)	0.70	0.59-0.83	<.0001	0.96	0.77-1.20	0.7337
Low (Maximum GIS or welfare)	0.69	0.59-0.82	<.0001	0.62	0.50-0.78	<.0001
Sex£						
Male	1					
Female	0.89	0.77-1.02	0.1009	N/A	N/A	N/A
Region£						
Urban	1					
Rural	0.90	0.75-1.08	0.2512	N/A	N/A	N/A
Missing	0.30	0.03-2.91	0.3004	N/A	N/A	N/A
No. of physician visits#&	1.01	1.00-1.01	0.0450	N/A	N/A	N/A
No. of different physicians visited#&	1.02	1.01-1.03	0.0060	1.03	1.01-1.05	0.0004
No. of different medications claimed#&						
0-4	1			1		
5-7	0.57	0.44-0.74	<.0001	0.86	0.64-1.17	0.3357
≥8	0.38	0.31-0.48	<.0001	0.64	0.49-0.84	0.0014
No. of hospitalizations#&	1.04	0.98-1.11	0.1747	N/A	N/A	N/A
No. of diabetes complications#	0.88	0.78-0.98	0.0239	0.83	0.72-0.95	0.0082
Anxiety disorders#						
No	1					
Yes	1.17	0.99-1.39	0.0663	N/A	N/A	N/A
Brain diseases#						
No	1					
Yes	0.77	0.54-1.10	0.1502	N/A	N/A	N/A
Other mental disorders#						

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No	1					
Yes	0.65	0.50-0.84	0.0011	0.63	0.46-0.87	0.0046
Specialty of initial oral AD prescriber†						
General practitioner	1			1		
Endocrinologist or internist	1.40	1.10-1.80	0.0073	1.22	0.91-1.63	0.1866
Other specialty or undisclosed	2.18	1.51-3.14	<.0001	1.76	1.13-2.72	0.0121
Initial oral AD treatment†						
Metformin	1					
Other monotherapy	1.25	1.05-1.49	0.0107	N/A	N/A	N/A
Polytherapy	1.08	0.79-1.48	0.6157	N/A	N/A	N/A
No. of classes of ADs†	1.05	0.78-1.40	0.7623	N/A	N/A	N/A
Initial AD treatment changes#						
No changes	1			1		
Another oral AD	0.49	0.42-0.58	<.0001	0.61	0.51-0.73	<.0001
Insulin	1.62	0.79-3.33	0.1861	1.58	0.68-3.65	0.2841
Combination of insulin plus oral AD	1.34	0.84-2.21	0.2208	1.78	1.03-3.07	0.0393
Baseline adherence to an AD†						
Adherent (PDC ≥ 90%)	1			1		
Non-adherent (PDC < 90%)	9.17	7.78-10.81	<.0001	7.86	6.63-9.33	<.0001

AD: Antidiabetic drug. CI: Confidence interval. GIS: Guaranteed Income Supply. N/A: Not applicable, the variable was not retained in the multivariate model as the P-value was > 0.05). OR: Odds ratio. PDC: Proportion of days covered. *Adjusted for all of the variables listed in the table. £ Measured at depression diagnosis. #In the period from AD treatment initiation to depression diagnosis. &For reasons other than diabetes or depression. & For reasons other than diabetes or depression. #In the period from AD treatment initiation to depression diagnosis. † Measured at initiation of oral AD treatment. ‡ Proportion of days covered by ≥1 AD in the 3-month period before depression diagnosis.