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Association of Antidepressant Prescription Filling With Treatment Indication and Prior Prescription Filling Behaviors and Medication Experiences

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Background: Given the wide range of uses for antidepressants, understanding indication-specific patterns of prescription filling for antidepressants provide valuable insights into how patients use these medications in real-world settings.

Objective: The objective of this study was to determine the association of antidepressant prescription filling with treatment indication, as well as prior prescription filling behaviors and medication experiences.

Design: This retrospective cohort study took place in Quebec, Canada.

Participants: Adults with public drug insurance prescribed antidepressants using MOXXI (Medical Office of the XXIst Century)—an electronic prescribing system requiring primary care physicians to document treatment indications and reasons for prescription stops or changes.

Measures: MOXXI provided information on treatment indications, past prescriptions, and prior medication experiences (treatment ineffectiveness and adverse drug reactions). Linked claims data provided information on dispensed medications and other patient-related factors. Multivariable logistic regression models estimated the independent association of not filling an antidepressant prescription (within 90 d) with treatment indication and patients' prior prescription filling behaviors and medication experiences.

Results: Among 38,751 prescriptions, the prevalence of unfilled prescriptions for new and ongoing antidepressant therapy was 34.2% and 4.1%, respectively. Compared with depression, odds of not filling an antidepressant prescription varied from 0.74 to 1.57 by indication and therapy status. The odds of not filling an antidepressant prescription was higher among adults filling < 50% of their medication prescriptions in the past year and adults with an antidepressant prescription stopped or changed in the past year due to treatment ineffectiveness.

Conclusion: Antidepressant prescription filling behaviors differed by treatment indication and were lower among patients with a history of poor prescription filling or ineffective treatment with antidepressants.

Key Words: antidepressants, treatment indications, prescriptions, dispensing data, primary care, pharmacoepidemiology, administrative data

Antidepressants are the most frequently prescribed class of psychotropic drugs[1–3] used by clinicians to treat not only depression but also a wide range of other indications, including anxiety, insomnia, and pain.[4] Despite their popular use, meta-analyses of clinical trials evaluating antidepressant use for depression have not found clear evidence of a meaningful benefit of antidepressants compared with placebo, with many efficacy trials being susceptible to numerous biases.[5–7] Antidepressant use for indications besides depression is also controversial due to these other indications oftentimes being not approved (off-label) for many antidepressants and insufficiently evaluated in clinical trials.[8]

In light of these concerns, pharmacoepidemiologic studies evaluating the real-world effectiveness and safety of antidepressant use for different indications could provide valuable insights into the actual benefits and risks of antidepressant use at the population level. To this end, it is important to understand patterns of antidepressant use in real-world settings, including patients' prescription filling behaviors and how they relate to clinicians' intentions for prescribing antidepressants—namely, the indication. Among naive antidepressant users, measuring levels of prescription filling helps estimate the proportion of antidepressant prescriptions leading to the actual initiation of use, which could differ across indications. Among prevalent antidepressant users, levels of prescription filling could also vary across

indications due to a variety of factors, including differences in treatment directives, effectiveness, or adverse drug events by indication, the latter of which is more likely when off-label drug use is not backed by strong scientific evidence.[9]

To date, no studies have measured *indication-specific* levels of prescription filling for antidepressants using a validated measure of treatment indication. In addition, few studies have measured the impact of patients' prior prescription filling behaviors and medication experiences on future prescription filling behaviors for antidepressants. To address these knowledge gaps, we used data from a unique electronic prescribing system linked to dispensing data to measure the prevalence of antidepressant prescription filling by indication and evaluate the association of prescription filling with the indication for antidepressant treatment and patients' prior prescription filling behaviors and experiences with medications, independent of other drug and patient factors. We also evaluated whether the relationship of antidepressant prescription filling with treatment indication differed between naive and non-naive users.

METHODS

Study Design and Setting

This cohort study took place in the Canadian province of Quebec, where the provincial health insurance agency—the Régie de l'Assurance Maladie du Québec (RAMQ)—covers the cost of essential medical services for all residents. By law, all residents must have drug insurance through either a private plan (ie, group or employee benefit plan) or the public drug insurance plan administered by the RAMQ.[10] Approximately 50% of Quebec residents are registered in the public drug insurance plan, including the elderly, welfare recipients, and persons not insured through an employer.

Data Source and Study Population

The Medical Office of the XXIst Century (MOXXI) is an indication-based electronic prescribing and drug management system used by consenting primary care physicians in 2 major urban centers in Quebec, Canada.[11] Since 2003, ~200 physicians (25% of eligible) and over 100,000 patients (26% of all who visited a MOXXI physician) have consented to participate in the MOXXI program. In general, MOXXI physicians are younger than nonparticipating physicians, while MOXXI patients are older and have more health problems than nonconsenting patients.[12]

MOXXI features numerous functionalities for enhancing drug safety and coordination of care for patients.[11] The MOXXI prescribing tool requires physicians to document at least 1 treatment indication per prescription by using a drop-down menu containing on-label and off-label indications without distinction or by typing the indication(s) into a free-text field. These physician-documented indications were previously validated and had excellent sensitivity (98.5%) and positive predictive value (97.0%).[13] The MOXXI prescribing tool also requires physicians to document the reasons for prescription stops or changes using a drop-down menu listing options related to safety (eg, adverse drug reaction) or effectiveness (eg, ineffective treatment), which have also been validated.[14]

Administrative health data for MOXXI patients were obtained by linking individuals via their unique health care number to provincial health administrative databases, which provided dispensing data from the public drug insurance plan, as well as information on demographics, diagnoses, hospitalizations, and medical services received. These databases are valid and reliable sources of data for pharmacoepidemiologic and health services research.[15,16]

This study was approved by the McGill Institutional Review Board.

Inclusion and Exclusion Criteria

The unit of analysis was the antidepressant prescription, which represented a physician's authorization to dispense medication to a patient for a given regimen and duration (including any subsequent refills over the valid period of the prescription) for either new or modified treatment.[17] Prescriptions were included if they were issued between January 1, 2003, and December 31, 2012, for a medication approved to treat depression (Supplement 1, Supplemental Digital Content 1, http://links.lww.com/MLR/C346) and if the patient was at least 18 years old, was enrolled in the public drug insurance plan and had at least 1 year of historical dispensing data available in the public drug insurance database on the prescription date to distinguish new from continued antidepressant users. Prescriptions were excluded if they were for antidepressants not covered under the public drug insurance plan (escitalopram, desvenlafaxine, and duloxetine) or monoamine oxidase inhibitors, which were rarely prescribed (Fig. 1).

Antidepressant Prescription Filling

The study outcome of interest was not filling an antidepressant prescription within 90 days of its issuance, reflecting the concept of nonadherence for indications with a more chronic nature, like depression and anxiety, where not filling an antidepressant prescription may represent a deviation from the planned treatment. Filled prescriptions were tracked using linked dispensing data from the public drug insurance plan, where prescriptions were considered filled if any brand of the prescribed drug was dispensed to the patient within 90 days. As only a negligible proportion (0.1%) of patients both did not fill the index prescription and died or became ineligible for the public drug insurance plan within 90 days, we treated all patients as if they were followed for the complete period.

Potential Determinants of Antidepressant Prescription Filling

Treatment Indication

Treatment indications for antidepressant prescriptions were retrieved from the MOXXI system and classified using the clinical definitions under the *International Statistical Classification of Diseases and Related Health Problems, 10th Revision* (ICD-10) coding into the following categories: (1) depressive disorders; (2) anxiety-related disorders, including panic disorders, phobias, and stress disorders; (3) insomnia; (4) pain, including chronic pain, neurogenic pain, and dorsalgia; or (5) miscellaneous indications, including migraine, fibromyalgia,
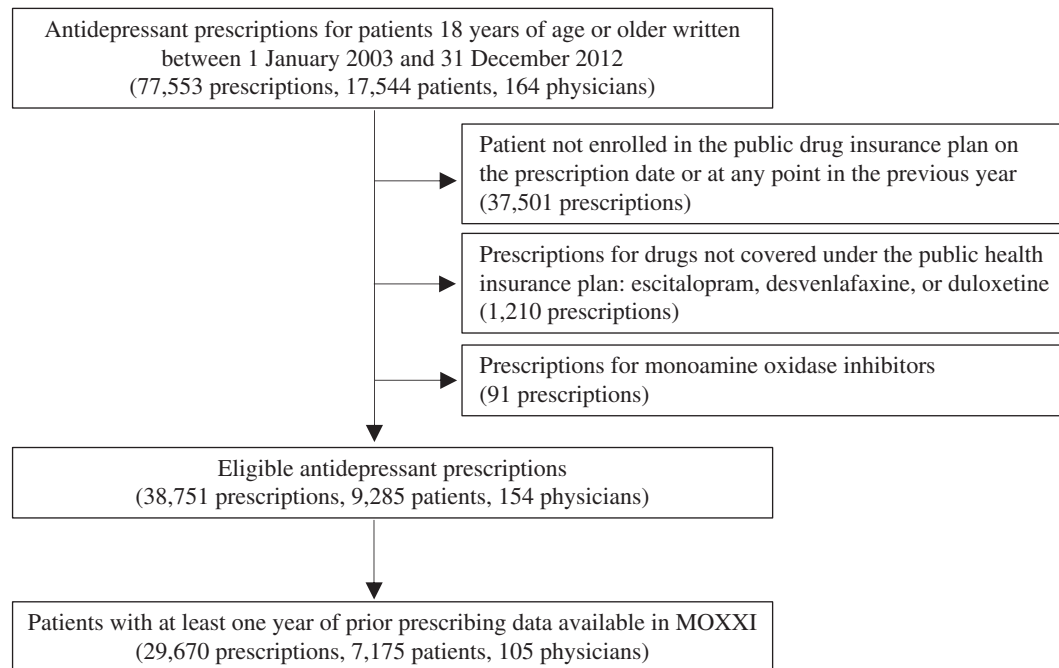
Antidepressant prescriptions for patients 18 years of age or older written between 1 January 2003 and 31 December 2012
(77,553 prescriptions, 17,544 patients, 164 physicians)

Patient not enrolled in the public drug insurance plan on the prescription date or at any point in the previous year
(37,501 prescriptions)

Prescriptions for drugs not covered under the public health insurance plan: escitalopram, desvenlafaxine, or duloxetine
(1,210 prescriptions)

Prescriptions for monoamine oxidase inhibitors
(91 prescriptions)

Eligible antidepressant prescriptions
(38,751 prescriptions, 9,285 patients, 154 physicians)

Patients with at least one year of prior prescribing data available in MOXXI
(29,670 prescriptions, 7,175 patients, 105 physicians)

FIGURE 1. Flow chart of antidepressant prescriptions used in the analysis. Eligible antidepressant prescriptions for the study were used to construct cumulative survival curves, stratified by treatment indication and therapy status, and estimate odds ratios for the association between treatment indication and antidepressant nonadherence at 90 days, adjusted for other drug and patient factors. A subset of eligible antidepressant prescriptions for which the patient had at least 1 year of historical prescribing data available in the MOXXI (Medical Office of the XXIst Century) system was used to estimate the association of antidepressant nonadherence with prior prescription filling behaviors and experience with medications (treatment ineffectiveness and adverse drug reactions in the past year), also adjusted for other drug and patient factors.

vasomotor symptoms of menopause, nicotine dependence, and pruritus, among others. If multiple indications were documented (1.7% of prescriptions), the indication entered first was used.

Therapy Status

Prescriptions were classified as being for new or ongoing antidepressant therapy, where prescriptions for new antidepressant therapy were those where the patient did not have any antidepressants dispensed in the previous year.

Prior Prescription Filling Behaviors and Experience With Medications

As patients' past prescription filling behaviors could be predictive of future prescription filling behaviors for antidepressants,[18] the proportion of prescriptions in the past year that were filled within 90 days was measured and analyzed separately for chronic disease-modifying medications and symptom-relieving medications[19] (Supplement 2, Supplemental Digital Content 2, http://links.lww.com/MLR/C347). To assess the potential impact of patients' prior experiences with medications on future prescription filling behaviors for antidepressants, the presence of any prescriptions in the past year that had been modified due to ineffective treatment or an adverse drug reaction was measured and analyzed separately for antidepressants and non-antidepressant medications. All these variables were measured only for the subset of prescriptions

where the patient had been enrolled in MOXXI for at least 1 year at the time of the prescription (Fig. 1).

Other Patient and Drug Factors Possibly Influencing Prescription Filling

Other patient and drug-related factors that could affect prescription filling behaviors for antidepressants were measured and treated as adjusting covariates, including patient age and sex,[18,20–25] copayment plan for medications (no copayment, partial copayment of 25% per prescription to a maximum of $600 annually, or maximum copayment of 25% per prescription to a maximum of $1000 annually),[25] comorbidities in the Charlson Comorbidity Index,[26] and health services use in the past year (number of outpatient visits, number of non-antidepressant drugs dispensed, any emergency department (ED) visit, any hospitalization, and continuity of care measured as the proportion of outpatient visits to the prescribing physician).[18,20,24,25] The pharmacological class of the prescribed antidepressant and whether the antidepressant had been prescribed on a "take-as-needed" basis was also measured from the MOXXI system.

Statistical Analysis

Cumulative survival curves showing the percentage of unfilled prescriptions on days 0–90 after the prescription date were constructed, stratified by treatment indication and therapy status. The reported 95% confidence intervals (CIs)
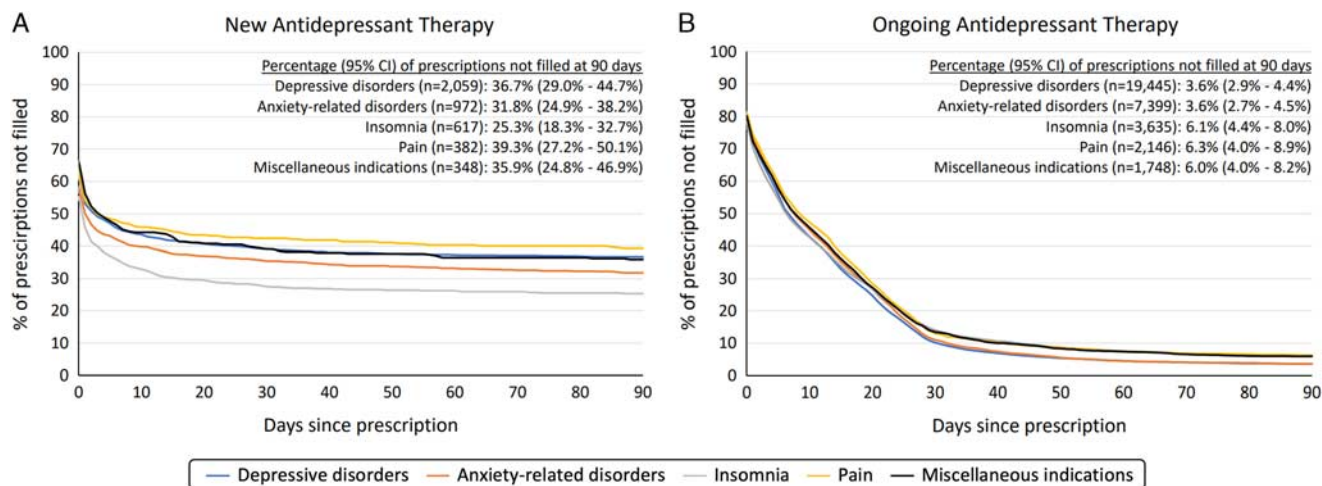
FIGURE 2. Percentage of antidepressant prescriptions not filled at 0–90 days, by treatment indication and therapy status. The cumulative survival curves show the percentage of antidepressant prescriptions for new (Panel A) or ongoing (Panel B) antidepressant therapy that were not dispensed to the patient over 90 days, stratified by treatment indication. Prescriptions for new antidepressant therapy were defined as those where the patient did not have an antidepressant dispensed in the previous year. Prescriptions for ongoing therapy were defined as those were the patient had an antidepressant dispensed in the previous year and were issued for reasons such as switching to a different antidepressant, modifying the dosage, or renewing the prescription.

around the percentage of unfilled prescriptions at 90 days corresponded to the values at the 2.5th and 97.5th percentiles of the distribution across 1000 bootstrap resamples of the study data using a 2-stage cluster bootstrap[27] to account for multilevel clustering of prescriptions within patients, who in turn were nested within physicians.

Multivariable alternating logistic regression was used to estimate the association of treatment indication with failing to fill an antidepressant prescription within 90 days, independent of other patient and drug factors. Alternating logistic regression, implemented using PROC GENMOD in SAS, was used to adjust the main effect estimates for multilevel clustering of prescriptions in the context of a dichotomous outcome.[28] To determine if the association of treatment indication was modified by therapy status, a 2-way interaction term was included in the model. The independent association of failing to fill an antidepressant prescription with prior prescription filling behaviors and experience with medications was assessed in a separate multivariable model that included only the subset of patients with at least 1 year of prior prescribing data in MOXXI (Fig. 1).

All statistical analyses were performed using SAS (SAS Institute Inc., Cary, NC) software, version 9.4.

RESULTS

A total of 38,751 antidepressant prescriptions written by 154 physicians for 9284 patients met the study inclusion criteria; 29,670 (76.6%) of these prescriptions had 1 year of historical MOXXI prescribing data available for the patient (Fig. 1). Antidepressant prescriptions were most commonly prescribed for depressive disorders (55.5%), anxiety-related disorders (21.6%), insomnia (11.0%), and pain (6.5%). Depressive disorders accounted for a lower proportion of

prescriptions for new (47.0%) compared with ongoing (56.6%) antidepressant therapy.

Treatment Indication and Therapy Status

Prescriptions for new antidepressant therapy were filled faster than those for ongoing antidepressant therapy (Fig. 2), with a median time-to-fill of 2 and 7 days, respectively. By indication, the median time-to-fill for new therapy prescriptions was shortest for insomnia (1 d) and longest for miscellaneous indications (4 d), while for ongoing therapy, was shortest for depression and insomnia (7 d) and longest for pain (9 d). Rates of prescription filling among new and ongoing therapy prescriptions reached a plateau after ~15 and 30 days, respectively.

Among new antidepressant therapy prescriptions, the proportion of unfilled prescriptions was highest for pain (39.3%) and lowest for insomnia (25.3%) (Fig. 2). Among ongoing antidepressant therapy prescriptions, the proportion of unfilled prescriptions was also highest for pain (6.3%), while depressive disorders and anxiety-related disorders tied for the lowest percentage of unfilled prescriptions at 3.6%.

In the multivariable analysis, the odds of not filling an antidepressant prescription was 28% higher when antidepressants were newly prescribed for anxiety-related disorders [odds ratio (OR),1.28; 95% CI, 1.05–1.57] compared with depressive disorders, but 26% lower when antidepressants were newly prescribed for insomnia (OR, 0.74; 95% CI, 0.56–0.98) (Table 1). Conversely, for ongoing antidepressant therapy, the odds of not filling an antidepressant prescription was 57% higher when antidepressants were prescribed for insomnia (OR, 1.57; 95% CI, 1.24–2.00) and 54% higher when prescribed for miscellaneous indications (OR, 1.54; 95% CI, 1.20–1.97), compared with depressive disorders. For all indications except insomnia, prescriptions for new antidepressant therapy were associated with a statistically significant higher odds of not being

TABLE 1. Association of Treatment Indication With Not Filling an Antidepressant Prescription Within 90 Days, by Antidepressant Therapy Status

Variables	No. of Prescriptions (N = 38,751)	% Unfilled at 90 d	Adjusted OR[†] (95% CI) for Not Filling the Prescription Within 90 d
Treatment indication, by antidepressant therapy status*			
New therapy			
Depressive disorders	2059	36.7	1.00 (reference)
Anxiety-related disorders	972	31.8	1.28 (1.05–1.57)
Insomnia	617	25.3	0.74 (0.56–0.98)
Pain	382	39.3	0.93 (0.62–1.40)
Miscellaneous indications	348	35.9	1.10 (0.82–1.48)
Ongoing therapy			
Depressive disorders	19,445	3.6	1.00 (reference)
Anxiety-related disorders	7399	3.6	1.02 (0.89–1.17)
Insomnia	3635	6.1	1.57 (1.24–2.00)
Pain	2146	6.3	1.27 (0.95–1.70)
Miscellaneous indications	1748	6.0	1.54 (1.20–1.97)
Antidepressant therapy status,* by treatment indication			
Depressive disorders			
Ongoing therapy	19,445	3.6	1.00 (reference)
New therapy	2059	36.7	2.53 (1.98–3.24)
Anxiety-related disorders			
Ongoing therapy	7399	3.6	1.00 (reference)
New therapy	972	31.8	3.18 (2.53–4.00)
Insomnia			
Ongoing therapy	3635	6.1	1.00 (reference)
New therapy	617	25.3	1.19 (0.89–1.59)
Pain			
Ongoing therapy	2146	6.3	1.00 (reference)
New therapy	382	39.3	1.85 (1.12–3.05)
Miscellaneous indications			
Ongoing therapy	1748	6.0	1.00 (reference)
New therapy	348	35.9	1.82 (1.28–2.58)

*Therapy status was classified as new antidepressant therapy if the patient did not have any antidepressants dispensed from any prescriber in the past year.
[†]From a multivariable model that additionally included all drug and patient factors shown in Table 3.
CI indicates confidence interval; OR, odds ratio.

filled within 90 days compared with prescriptions for ongoing antidepressant therapy.

Prior Prescription Filling Behaviors and Experience With Medications

Poor prescription filling behaviors in the past year were associated with increased odds of not filling an antidepressant prescription (Table 2). Compared with patients who filled ≥ 75% of their prescriptions for chronic disease-modifying medications in the past year, the odds of not filling a new or continuing antidepressant prescription was over 2.5 times higher among patients who filled < 50% of their chronic disease prescriptions in the past year (OR, 2.57; 95% CI, 1.85–3.57). Patients with no prescriptions for chronic disease-modifying medications in the past year also had a statistically significant higher odds of not filling their antidepressant prescriptions (OR, 1.16; 95% CI, 1.02–1.31). A similar, albeit attenuated association was observed for symptom-relieving medications.

Patients who had an antidepressant prescription stopped or changed in the past year due to treatment ineffectiveness had 21% higher odds of not filling the index antidepressant prescription (OR, 1.21; 95% CI, 1.02–1.43) (Table 2). However, this association was not observed among patients who had prescriptions for non-antidepressant medications stopped or changed in the past year due to treatment ineffectiveness (OR, 1.02; 95% CI, 0.92–1.14). Adverse drug reactions in the past year to antidepressants and non-antidepressant medications were not associated with not filling antidepressant prescriptions.

Other Drug and Patient Factors

The odds of not filling an antidepressant prescription was lower for serotonin-norepinephrine reuptake inhibitors compared with every other pharmacological class of antidepressants, while the odds of not filling an antidepressant prescription was 49% higher when antidepressants were prescribed on a take-as-needed basis (OR, 1.49; 95% CI, 1.11–2.00) (Table 3). Compared with patients aged 18–50 years old, older patients were increasingly more likely to fill their antidepressant prescriptions. Compared with patients with no medication copayments, the odds of not filling an antidepressant prescription was 2- to 3-fold higher for patients with a partial copay (OR, 2.23; 95% CI, 1.73–2.89) or maximum copay (OR, 2.90; 95% CI, 2.42–3.47). The odds of not filling an antidepressant prescription decreased with greater numbers of non-antidepressant drugs dispensed in the past year but was greater

TABLE 2. Association of Prior Prescription Filling Behaviors and Medication Experiences With Not Filling an Antidepressant Prescription Within 90 Days

Variables	No. of Prescriptions* (N = 29,670)	% Unfilled at 90 d	Adjusted OR[†] (95% CI) for Not Filling the Prescription Within 90 d
Prescription filling behaviors in the past year			
Chronic disease-modifying medications			
75%–100% of prescriptions filled	20,992	3.8	1.00 (reference)
50% to <75% of prescriptions filled	690	18.6	1.40 (0.92–2.11)
0% to <50% of prescriptions filled	856	71.3	2.57 (1.85–3.57)
No essential medications prescribed	7132	8.5	1.16 (1.02–1.31)
Symptom-relieving medications			
75%–100% of prescriptions filled	13,315	3.6	1.00 (reference)
50% to <75% of prescriptions filled	1335	7.6	1.41 (1.10–1.80)
0% to <50% of prescriptions filled	1426	32.3	1.64 (1.34–2.00)
No symptom-relieving medications prescribed	13,594	8.1	1.09 (0.94–1.26)
Experiences with medications in the past year			
Antidepressants			
Prescription stopped or changed due to ineffective treatment			
No	25,731	7.1	1.00 (reference)
Yes	3939	7.8	1.21 (1.02–1.43)
Prescription stopped or changed due to an adverse drug reaction			
No	28,953	7.2	1.00 (reference)
Yes	717	7.1	0.81 (0.51–1.30)
Other medications besides antidepressants			
Prescription stopped or changed due to ineffective treatment			
No	23,784	7.3	1.00 (reference)
Yes	5886	6.9	1.02 (0.92–1.14)
Prescription stopped or changed due to an adverse drug reaction			
No	27,849	7.2	1.00 (reference)
Yes	1821	7.2	0.99 (0.81–1.20)

*Only antidepressant prescriptions where the patient had been enrolled in the MOXXI (Medical Office of the XXIst Century) program for at least 1 year were included in this analysis to ensure that patients had at least 1 year of prior prescribing data available

[†]From a multivariable model that additionally included all variables in Table 1 (treatment indication, therapy status, and a 2-way interaction between treatment indication and therapy status) and all drug and patient factors shown in Table 3.

CI indicates confidence interval; OR, odds ratio.

among patients who had visited the ED or had greater numbers of outpatient visits in the past year.

These trends were largely similar when estimated separately among prescriptions for new and ongoing antidepressant therapy, except for 3 patient factors (visiting the ED, number of outpatient visits, and number of non-antidepressant drugs dispensed in the past year), for which the observed association across all prescriptions was driven by the association among prescriptions for new antidepressant therapy (Supplement 3, Supplemental Digital Content 3, http://links.lww.com/MLR/C348).

DISCUSSION

To our knowledge, this study is the first to measure indication-specific prescription filling patterns for antidepressants using validated, physician-documented indications. The odds of antidepressant prescription filling differed by treatment indication, with the nature of these associations being distinct among naive and non-naive antidepressant users. Failing to fill previous prescriptions, especially for chronic disease-modifying medications, was also independently associated with not filling a future antidepressant prescription, as was having an antidepressant prescription stopped or changed in the past year because of treatment a

To date, most studies of antidepressant nonadherence and prescription filling behaviors have focused only on patients with depression, with many studies reporting a prevalence of ~30%–40%[29,30] for primary nonadherence, similar to the levels at which new antidepressant prescriptions for depression were not filled in this study. Two previous studies using the Dutch general practice and dispensing databases[31,32] attempted to investigate the association between treatment indication and antidepressant prescription filling, but visit-level diagnoses could not be linked directly to antidepressant prescriptions, and no approved indication could be identified for over half of patients filling only a single antidepressant prescription.[31] Nonspecific indications such as fatigue, weight loss, and sleeping problems were suspected as likely indications among these patients, who were more likely to present with these conditions. These findings are consistent with our observation that patients with at least 1 previous dispensing of an antidepressant were less likely to fill future antidepressant prescriptions indicated for insomnia or other miscellaneous indications (eg, migraine, hot flashes, chronic fatigue) compared with depression.

Antidepressants prescribed for insomnia had a distinct pattern of prescription filling: naive antidepressant users were more likely to fill new prescriptions for insomnia compared with other indications while continuing antidepressant users were less likely. The findings among naive antidepressant users suggest a

TABLE 3. Association of Other Drug and Patient Factors With Not Filling an Antidepressant Prescription Within 90 Days

Variables	No. Prescriptions (N = 38,751)	% Unfilled at 90 d	Adjusted OR* (95% CI) for Not Filling the Prescription Within 90 d
Drug factors			
Pharmacological class			
SSRI[†]	16,471	5.9	1.00 (reference)
SNRI[‡]	7690	7.1	1.24 (1.07–1.42)
TCA[§]	5095	10.5	1.77 (1.44–2.17)
Other[‖]	9495	9.0	1.48 (1.30–1.69)
Drug prescribed on a "take-as-needed" basis			
No	37,967	7.3	1.00 (reference)
Yes	784	17.0	1.49 (1.11–2.00)
Patient factors			
Sex			
Female	26,914	7.3	1.00 (reference)
Male	11,837	8.1	1.00 (0.88–1.14)
Age (y)			
18–50	9476	12.3	1.00 (reference)
51–62	9885	6.8	0.72 (0.60–0.87)
63–72	9425	6.5	0.62 (0.53–0.74)
73+	9965	4.7	0.50 (0.42–0.61)
Copayment plan for medications			
No copayment (free)	12,139	3.5	1.00 (reference)
Partial copayment (up to 600 CAD/year)	7323	9.0	2.23 (1.73–2.89)
Maximum copayment (up to 1000 CAD/year)	19,289	11.0	2.90 (2.42–3.47)
Chronic conditions in the Charlson Comorbidity Index			
Myocardial infarction			
No	38,124	7.6	1.00 (reference)
Yes	627	4.0	0.79 (0.56–1.11)
Congestive heart failure			
No	37,596	7.6	1.00 (reference)
Yes	1155	4.9	0.95 (0.67–1.37)
Peripheral vascular disease			
No	37,843	7.6	1.00 (reference)
Yes	908	5.3	1.10 (0.70–1.73)
Cerebrovascular disease			
No	37,840	7.6	1.00 (reference)
Yes	911	4.7	0.93 (0.71–1.24)
Dementia			
No	37,598	7.7	1.00 (reference)
Yes	1153	3.5	0.77 (0.58–1.04)
Chronic pulmonary disease			
No	31,011	7.9	1.00 (reference)
Yes	7740	5.9	1.00 (0.89–1.12)
Rheumatic disease			
No	37,950	7.6	1.00 (reference)
Yes	801	3.8	0.87 (0.63–1.21)
Peptic ulcer disease			
No	38,278	7.5	1.00 (reference)
Yes	473	7.8	1.17 (0.85–1.61)
Mild liver disease			
No	37,989	7.6	1.00 (reference)
Yes	762	6.0	1.10 (0.80–1.50)
Diabetes without chronic complication			
No	33,012	7.9	1.00 (reference)
Yes	5739	5.4	1.09 (0.94–1.25)
Diabetes with chronic complication			
No	38,498	7.5	1.00 (reference)
Yes	253	6.7	1.07 (0.65–1.76)
Hemiplegia or paraplegia			
No	38,521	7.5	1.00 (reference)
Yes	230	9.1	1.17 (0.75–1.84)
Renal disease			
No	37,866	7.6	1.00 (reference)
Yes	885	4.3	1.03 (0.78–1.35)
Any malignancy			
No	36,145	7.6	1.00 (reference)
Yes	2606	6.0	1.04 (0.88–1.24)

(Continued)

TABLE 3. Association of Other Drug and Patient Factors With Not Filling an Antidepressant Prescription Within 90 Days (*continued*)

Variables	No. Prescriptions (N = 38,751)	% Unfilled at 90 d	Adjusted OR* (95% CI) for Not Filling the Prescription Within 90 d
Moderate or severe liver disease			
No	38,709	7.5	1.00 (reference)
Yes	42	2.4	0.15 (0.03–0.79)
Metastatic solid tumor			
No	37,875	7.6	1.00 (reference)
Yes	876	4.2	0.72 (0.48–1.07)
AIDS/HIV			
No	38,588	7.5	1.00 (reference)
Yes	163	9.2	0.70 (0.43–1.14)
No. outpatient visits in the past year			
0–3	8574	9.3	1.00 (reference)
4–6	8828	6.9	1.13 (1.01–1.26)
7–11	10,414	6.7	1.20 (1.04–1.37)
12+	10,935	7.5	1.35 (1.15–1.58)
Hospitalized in the past year			
No	32,031	7.9	1.00 (reference)
Yes	6720	5.9	0.95 (0.86–1.06)
Visited the ED in the past year			
No	24,506	7.9	1.00 (reference)
Yes	14,245	6.9	1.16 (1.07–1.25)
Continuity of care with the prescribing physician¶			
< 0.33	9594	9.3	1.00 (reference)
0.33–0.55	9989	7.3	1.05 (0.96–1.15)
0.56–0.82	9458	6.8	1.09 (0.98–1.22)
0.83+	9710	6.7	1.02 (0.92–1.13)
No. non-antidepressant drugs dispensed in the past year			
0	1609	56.3	1.00 (reference)
1–4	7888	8.7	0.27 (0.23–0.33)
5–9	15,425	3.8	0.20 (0.16–0.24)
10+	13,829	5.3	0.15 (0.12–0.18)

*From a multivariable model that additionally included all variables in Table 1 (treatment indication, therapy status, and a 2-way interaction between treatment indication and therapy status).
†Includes citalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline.
‡Includes venlafaxine.
§Includes amitriptyline, clomipramine, desipramine, doxepin, imipramine, nortriptyline, and trimipramine.
‖Includes trazodone, bupropion, mirtazapine, and maprotiline.
¶Measured as the proportion of all outpatient visits in the past year that were made to the prescribing physician.
AIDS/HIV indicates acquired immunodeficiency syndrome/human immunodeficiency virus; CAD, Canadian dollars; CI, confidence interval; ED, emergency department; OR, odds ratio; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

heightened sense of eagerness among patients with sleep disorders to acquire medication for their insomnia. This observation is noteworthy given that the most popular antidepressants used for sleep are neither approved nor recommended for insomnia due to the paucity of data supporting their efficacy and safety for this indication.[33] Among continuing antidepressant users, several mechanisms could play a role in the lower likelihood of prescription filling observed for insomnia than depression and anxiety. One likely explanation is that patients receiving an updated antidepressant prescription for insomnia (eg, to adjust the dose or simply renew the prescription) may still have some supply on hand at the time of the newer prescription, since antidepressants, when prescribed for insomnia, are often taken on an as-needed basis, unlike for depression and anxiety where antidepressants are taken daily and according to a scheduled regimen. Another possible reason could be a lack of treatment efficacy or poor balance of patient-perceived harms versus benefits among patients taking antidepressants for insomnia—a hypothesis that requires further investigation and highlights the importance of conducting more research on the safety and effectiveness of antidepressant use for insomnia.

This study contributes novel insights into the association of past adverse reactions to and failures with antidepressant treatment on future prescription filling behaviors. Although experiencing or fearing side effects has been identified as a reason for nonadherence in previous studies,[34–38] we did not find that prior experience of adverse drug reactions to antidepressants or other medications influenced the odds of not filling an antidepressant prescription. However, having a prior antidepressant prescription stopped or changed because of ineffective treatment increased the odds of not filling a subsequent antidepressant prescription. This effect appeared to be isolated to past experiences with antidepressants only, as similar prior experiences with other medications did not have the same effect on filling future antidepressant prescriptions. While no comparable data exist using physician-documented reasons for therapy changes, one Veterans Administration study of antidepressant use found that patients most commonly reported discontinuing new therapy because it was not effective.[38]

Our finding that antidepressant prescription filling was strongly associated with poor prescription filling for other

medications in the past year, especially chronic disease medications, is concordant with another study[39] that found patients with low adherence to chronic preventive medications in the past year were half as likely to adhere to statin therapy as patients with a history of high medication adherence. Similarly, our finding that not filling an antidepressant prescription was strongly associated with the level of cost-sharing for medications has been consistently reported in previous studies.[22,25,40]

As this study included patients with public drug insurance in primary care settings in Quebec, future studies should determine if the indication-specific patterns of antidepressant prescription filling reported in this study are similarly observed in other patient subgroups and geographic regions. This study also only tracked if the initial prescription issued by a physician for either new or modified antidepressant therapy was filled within 90 days; it did not measure if refills associated with the prescription were subsequently dispensed beyond the initial dispensing. Thus, this study did not measure persistence with antidepressants. Finally, it should also be noted that given the wide variety of indications for which antidepressants are used, failure to fill an antidepressant prescription may, in some cases, represent a suboptimal patient behavior (eg, as one component of medication nonadherence when used for chronic conditions like depression and anxiety), while in other cases, may not be a cause for concern (eg, when used as-needed for symptomatic conditions like insomnia and other miscellaneous indications). Thus, rates of prescription filling for antidepressants should be interpreted in light of the nature of the indication for which the antidepressant was prescribed and the treatment regimen according to which antidepressants are usually used for the indication.

CONCLUSIONS

Using data from a unique, indication-based electronic prescribing system linked to dispensing data, this study is the first to describe levels of prescription filling for antidepressants by treatment indication. Antidepressant prescription filling behaviors were found to differ by treatment indication, with the nature of these associations depending on whether or not the patient had previously used antidepressants. The findings from this study represent an important step toward better understanding patterns of antidepressant use for different indications among adult primary care populations in real-world settings.

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