The Incidence and Determinants of Primary Nonadherence With Prescribed Medication in Primary Care

A Cohort Study

Robyn Tamblyn, PhD; Tewodros Eguale, MD, PhD; Allen Huang, MD; Nancy Winslade, PharmD; and Pamela Doran, MSc

Background: Primary nonadherence is probably an important contributor to suboptimal disease management, but methodological challenges have limited investigation of it.

Objective: To estimate the incidence of primary nonadherence in primary care and the drug, patient, and physician characteristics that are associated with nonadherence.

Design: A prospective cohort of patients and all their incident prescriptions from primary care electronic health records between 2006 and 2009 linked to provincial drug insurer data on all drugs dispensed from community-based pharmacies were assembled.

Setting: Quebec, Canada.

Patients: 15 961 patients in a primary care network of 131 physicians.

Measurements: Primary nonadherence was defined as not filling an incident prescription within 9 months. Multivariate alternating logistic regression was used to estimate predictors of nonadherence and account for patient and physician clustering.

Results: Overall, 31.3% of the 37 506 incident prescriptions written for the 15 961 patients were not filled. Drugs in the upper quartile of cost were least likely to be filled (odds ratio [OR], 1.11 [95% CI, 1.07 to 1.17]), as were skin agents, gastrointestinal drugs, and autonomic drugs, compared with anti-infectives. Reduced odds of nonadherence were associated with increasing patient age (OR per 10 years, 0.89 [CI, 0.85 to 0.92]), elimination of prescription copayments for low-income groups (OR, 0.37 [CI, 0.32 to 0.41]), and a greater proportion of all physician visits with the prescribing physician (OR per 0.5 increase, 0.77 [CI, 0.70 to 0.85]).

Limitation: Patients' rationale for choosing not to fill their prescriptions could not be measured.

Conclusion: Primary nonadherence is common and may be reduced by lower drug costs and copayments, as well as increased follow-up care with prescribing physicians for patients with chronic conditions.

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For author affiliations, see end of text.

Chronic diseases account for most health care expenditures and are responsible for more than one half of all deaths worldwide (1, 2). Many chronic conditions can be successfully managed with pharmaceutical interventions, but 2 common treatment barriers hinder optimal disease management (3, 4). First, there is a high prevalence of nonadherence with long-term therapy, a problem that is associated with an increase in emergency department (ED) visits and health care costs (5, 6). Second, there is an underuse of preventive therapies, such as inhaled steroids for preventing asthma exacerbations (7), which has been attributed to health professionals' failure to follow evidence-based guidelines. However, underuse may also be due to a patient not filling his or her initial prescription—a problem of primary nonadherence. If primary nonadherence is an important contributor to the underuse of therapy, a different set of patient and drug policy interventions will need to be developed (8).

One of the biggest challenges in investigating primary nonadherence is that there are considerable barriers to its measurement (8). Unlike secondary adherence, which assesses the extent to which a person who fills a prescription uses therapy as prescribed, in primary nonadherence patients not using medication need to be classified as having been prescribed therapy but never filling the initial prescription, primary nonadherence, or never having been prescribed therapy because of failure to adhere to guidelines. It has only been in recent years, with the advent of integrated electronic prescribing and dispensing data, that primary nonadherence studies are feasible. To date, there are only 11 studies of primary nonadherence, most conducted in subpopulations of patients with diabetes, hypertension, dermatologic problems, and acute cardiovascular events (9–19). Primary nonadherence varies between 2.4% to 30.7%. Newly started therapy (incident treatment) seems to be associated with a much higher rate of primary nonadherence (13), but only 2 studies differentiated between new therapy and switches within pharmacologic class among patients who were already being treated (10, 13). To address the problem of underuse of recommended treatment of chronic conditions, the contribution of primary nonadherence needs to be understood, particularly in primary care, where most treatment is initiated.

The purpose of this study was to estimate the incidence of primary nonadherence in primary care and the drug, patient, and physician characteristics that are associated with a greater risk for nonadherence.

METHODS

Setting

This study was conducted in Quebec, Canada, where the provincial insurance agency (Régie de l'Assurance Maladie du Québec) provides health insurance for all pro-

Context

Failure to fill an initial drug prescription may be important in determining clinical outcomes.

Contribution

This study found that nearly one third of all initial drug prescriptions were not filled within 9 months. Lower prescription copayments and a greater proportion of all care visits with the prescribing physician were among the factors associated with filling the prescription.

Caution

The study could not assess all clinical variables that may influence whether a prescription is filled, nor how or whether it is used.

Implication

Failure to fill an initial prescription is common and requires more study to identify ways to improve adherence.

—The Editors

vincial residents and drug insurance to approximately 50% of all residents, including seniors, social assistance recipients, and those without private drug insurance. All other provincial residents are covered by private drug insurance purchased through their employers. Beneficiary, medical billing, and pharmacy claims data have been validated and are frequently used for health services and epidemiologic research (20, 21). In 2003, the Medical Office of the 21st Century (MOXXI), an experimental community-based electronic health record, was the first to link to these databases and integrate this information into electronic health record systems to support clinical decision making (20). The MOXXI electronic health record includes a drug profile that shows prescribed and dispensed drugs, ED visits and hospitalizations in the past 12 months, and an electronic prescribing tool that requires mandatory entry of treatment indication (from a list of on- and off-label indications) and documentation of the reason for drug withdrawals and dose changes. Data generated by MOXXI have been validated and used in many studies (22–25). The MOXXI system provided us with the opportunity to systematically investigate primary nonadherence to newly prescribed medication in primary care.

Design and Patients

A prospective cohort of patients and their incident prescriptions for new treatment was assembled to estimate the incidence and determinants of primary nonadherence in primary care. The cohort was identified from a population of approximately 70 000 patients who were in the practices of 131 physicians who had consented to be in the MOXXI primary care research network. Potentially eligible physicians were identified from the provincial roster of active primary care physicians and were invited to participate. To be eligible, physicians needed to practice in a community setting and use MOXXI to write a minimum of 10 patient prescriptions per week (25, 26).

Patients were eligible for inclusion if they had received a prescription for a new drug from their primary care physician between 1 January 2006 and 31 December 2009. New drugs, defined by generic ingredient code, were those that had not been prescribed or dispensed in the past 12 months. To determine whether a prescription was filled, only patients with public drug insurance were eligible because the public insurer provided daily updates for each beneficiary on all drugs dispensed from any pharmacy in the province. Only drugs covered through the public plan were included, representing most of the drugs approved for marketing in Canada.

Primary Nonadherence

Primary nonadherence was defined as failing to fill a new-incident prescription within 9 months. Prescription was the unit of analysis, and each eligible beneficiary could have 1 or more new prescriptions, for which adherence was measured. For each new prescription, we used the generic drug code, date the prescription was issued, and beneficiary health insurance number to inspect all claims records of dispensed prescriptions in the 9 months after the prescription issue date. If a matching generic drug code was found in the dispensed medication records, the beneficiary was classified as adherent for the respective prescription. A 9-month window was selected to enable patients who were given prescriptions on a "take-as-needed basis" ample time to fill a prescription before it expired.

Factors Potentially Associated With Nonadherence

By using multilevel modeling and prescription as the unit of analysis, we measured and differentiated attributes of the prescription, patient, and prescribing physician that may influence primary nonadherence.

Prescription-Related Characteristics

First, we assessed whether a prescription for therapy for a new indication versus a switch in therapy to a new drug within a pharmacologic class was related to adherence. Switches may be associated with a higher probability of adherence because a person has already committed to taking medication for a given indication. Second, we evaluated whether the pharmacologic class or the therapeutic indication for which the drug was being used was associated with adherence, suspecting that drugs prescribed for symptomatic conditions would more likely be filled. The pharmacologic class of a prescribed drug was classified using the American Hospital Formulary Service (27). The therapeutic indication, which is documented by the physician at the time of prescribing in a mandatory field, was classified using the International Statistical Classification of Diseases and Related Health Problems (28). Third, we evaluated the relationship between the cost of the prescribed drug (in Canadian dollars) and primary adherence

because cost has been associated with secondary nonadherence (29).

Patient-Related Characteristics

Patient age and sex were measured because of their association with the use of medications and secondary adherence (11, 13, 30), and household income was assessed because of its association with the capacity to pay for medications (31). The copayment plan was retrieved for each patient from Quebec because copayments have been shown to influence medication use (32, 33). The level of copayment required in the public drug insurance plan is indexed to income, and Quebec assigns each resident to 1 of 3 types of plans: no copayment (free medication), partial copayment (25% per prescription to a maximum of $45 per month), and full copayment (25% per prescription to a maximum of $80 per month). Because access to income information to index prescription copayments was not permitted, we used the average census value for residents in the same postal code area to approximate household income (34). Because some studies have also found that comorbid conditions and severity of illness are associated with primary adherence, we used the Charlson Comorbidity Index (25, 35), number of concurrent medications used at the time of the prescription, and occurrence of a hospitalization or ED visit in the 6 months before the prescription date to measure these characteristics. We also measured the proportion of visits that a respective patient made in the past year to the prescribing physician because measures of greater continuity of care may be associated with better follow-up and support for medication adherence (36).

Physician-Related Characteristics

Physician sex and years of practice were measured because these characteristics have previously been shown to influence prescribing decisions as well as physician–patient communication (10, 13, 30, 37).

Statistical Analysis

Descriptive statistics were used to summarize characteristics of the study population and assess the incidence of primary nonadherence by treatment indication and pharmacologic class of the drug prescribed and for the most frequently prescribed drugs. Multivariate alternating logistic regression (ALR) was used to estimate the association among prescription, patient, and physician characteristics and primary nonadherence, with prescription as the unit of analysis, and was implemented with PROC GENMOD in SAS, version 9.3 (SAS Institute, Cary, North Carolina). Alternating logistic regression permits nonindependence of observations with more than 1 level of clustering to be managed in the context of a dichotomous outcome (38–40). Alternating logistic regression first measures the extent of clustering of nonadherence among multiple prescriptions for the same patient and among multiple patients with the same physician by estimating cluster-level odds ratios (ORs) for patients and physicians. The magnitude of the OR reflects the extent of clustering. Drug, patient, and physician factors that explain variance in primary nonadherence will reduce the respective cluster ORs. The final cluster-level ORs represent the extent of unmeasured factors at the patient and physician level that affect primary nonadherence.

We conducted a sensitivity analysis to determine whether education, which is associated with income and copayment level, could modify the results. The percentage of persons not completing high school in the census tract of each participant was included in the multivariate analysis to assess whether education modified the estimate for copayment, and various levels of misclassification of education were assessed. We also evaluated whether unmeasured physician characteristics may bias estimates by fitting physicians as fixed effects in a logistic-regression analysis using generalized estimating equations (**Appendix**, available at www.annals.org).

This study was approved by the McGill University Institutional Review Board.

Role of the Funding Source

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RESULTS

Overall, 15 961 patients were prescribed 37 506 new incident prescriptions, of which 4992 (13.3%) represented a switch in treatment from 1 drug to another in the same pharmacologic class, and 32 514 (86.7%) represented incident treatment. The mean age of the study population was 61.55 years, 62.3% were female, and 25.0% had a household income less than $34 749 (**Table 1**). Nearly one third of patients had visited an ED in the past 6 months, 15.3% had been hospitalized, and 5.9% had a Charlson Comorbidity Index score greater than 2. The mean number of medications used was 6.25, and 51% of all physician visits were made to the prescribing physician.

Overall, 31.3% of incident prescriptions were not filled within 9 months after the date of issue (**Table 2**). In relation to therapeutic indication, the incidence of primary nonadherence was highest for drugs prescribed for headache (51.0%), ischemic heart disease (51.3%), and depression (36.8%). The lowest incidence of primary nonadherence was for diseases of the genitourinary system (26.2%), with the most common therapeutic indication being urinary tract infection (21.0%). Primary nonadherence was lower for new drugs that represented a switch in pharmacologic class for the same indication (11.6%) than for drugs prescribed as new therapies for a treatment indication (34.3%).

Table 1. **Characteristics of Patients and Their Physicians Included in the Primary Adherence Cohort**

Characteristic	Persons*
Patients	15 961
Age	
<18 y	173 (1.1)
18–64 y	7242 (45.4)
≥65 y	8546 (53.5)
Mean age (SD), *y*	61.55 (16.51)
Sex	
Male	6023 (37.7)
Female	9938 (62.3)
Household income† (quartiles)	
<$34 749	3987 (25.0)
$34 749–$45 868	3995 (25.0)
$45 869–$58 330	4023 (25.2)
>$58 330	3956 (24.8)
Comorbid conditions and health care use (6 mo before first prescription)	
Charlson Comorbidity Index	
0	10 096 (63.3)
1	3638 (22.8)
2	1278 (8.0)
≥3	949 (5.9)
Any hospital visit	2442 (15.3)
Any ED visit	4318 (27.1)
Mean drugs (SD), *n*	6.25 (5.6)
Mean continuity of care (12 mo before first prescription) (SD), *n*	0.51 (0.2)
Median new prescriptions per patient (IQR), *n*	2.0 (1.0–3.0)
Physicians	131
Sex	
Male	66 (50.4)
Female	65 (49.6)
Years in practice	
<15 y	33 (25.2)
16–22 y	35 (26.7)
23–28 y	32 (24.4)
>28 y	31 (23.7)
Median new patient prescriptions per physician (IQR), *n*	105 (18–416)

ED = emergency department; IQR = interquartile range.
* Values are numbers (percentages) unless otherwise indicated.
† In Canadian dollars.

When primary adherence was assessed by pharmacologic class, the highest incidence of nonadherence was for hormones and synthetics (36.3%), particularly for thyroid agents (49.4%), followed by ear, nose, and throat preparations (34.2%) and cardiovascular drugs (34.7%) (**Table 3**). The lowest incidence of nonadherence was for anti-infectives (24.2%). For the 20 most frequently prescribed drugs, the highest incidence of nonadherence was treatment for a new indication with L-thyroxine (49.4%), fluticasone (40.5%), and atorvastatin (36.8%).

The estimated cluster OR for drugs within a patient was 50.5 (95% CI, 39.9 to 63.9) and for patients with the same physician was 1.22 (CI, 1.12 to 1.34), indicating that factors explaining differences between patients were more important than differences between physicians. The multivariate model reduced the unexplained cluster OR to 28.0 (CI, 23.1 to 34.0) for patients and 1.13 (CI, 1.07 to 1.21) for physicians. Among the drug characteristics measured, we found that primary nonadherence was significantly greater for ear, nose, and throat preparations; skin and mucous membrane agents; autonomic drugs; and gastrointestinal drugs than for anti-infectives (**Table 4**). There was a significant dose–response relationship between drug cost and nonadherence. Compared with the bottom quartile, the odds of nonadherence in the second, third, and upper quartile of cost increased by 4%, 6%, and 11%, respectively. Patients who were newly started on therapy were more likely to be nonadherent than those switching from 1 drug to another within a pharmacologic class.

Older patients were less likely to be nonadherent; the odds of nonadherence were reduced by 11% per 10-year increase in age (OR, 0.89 [CI, 0.85 to 0.92]) (**Table 4**). Drug plan type had a strong association with nonadherence. Compared with those who had the maximum copayment, there was a 63% reduction in the odds of nonadherence among patients with free prescription medication. Patients using a greater number of medications were also more likely to be adherent, with a 17% reduction in the odds of nonadherence per additional medication. In contrast, evidence of significant comorbid conditions, including hospitalizations or ED visits in the 6 months before being prescribed the medication, as well as a positive Charlson Comorbidity Index score, was associated with increased odds of nonadherence. In addition, patients who had a greater proportion of physician visits with the prescribing physician had lower odds of nonadherence, and the odds of primary nonadherence were 17% more for female physicians ($P = 0.056$). Sensitivity analyses did not appreciably alter the observed associations (**Appendix**).

DISCUSSION

This large-scale study of primary nonadherence in primary care practice used a multilevel modeling approach to investigate the associations of drug, patient, and physician characteristics with the likelihood of nonadherence (13). We found that 31.3% of first-time prescriptions were not filled, a rate that was greater for new users (34.3%) than for those who were switching treatment from 1 drug to another within a pharmacologic class (11.6%). The risk for primary nonadherence was greater for higher-cost drugs and most chronic preventive therapies compared with antibiotics. Patients with higher drug copayments, recent hospitalization, and more severe comorbid conditions were also at a greater risk for primary nonadherence, whereas older age and a greater proportion of physician visits with the prescribing physicians were associated with a lower risk.

This study provided new insights into policy-relevant factors that were associated with primary nonadherence: elimination of copayments for the poor and an increased proportion of physician visits with the prescribing physician, a measure that may reflect better continuity of care. Although primary nonadherence rates for chronic preven-

tive therapies is consistent with the only other 2 large-scale studies conducted in primary care (13, 14), to our knowledge, this was the first study to characterize the rates of primary nonadherence by actual treatment indication. This is relevant because primary nonadherence rates by pharmacologic class likely reflects differences in the reasons for treatment, expected length of therapy, and extent to which symptoms will be relieved by treatment.

Of interest, we found that patients with previous hospitalization or ED visits and more severe comorbid conditions were more likely to be nonadherent, whereas those already using a greater number of drugs were less likely. These observations fuel speculations that high rates of primary nonadherence may contribute to potentially preventable complications and more severe comorbid conditions in the population (13, 14). Ko and colleagues' study (12) of primary nonadherence to thienopyridine therapy after percutaneous coronary interventions with stents supports this hypothesis because patients who did not fill the initial prescriptions had a 2-fold increase in the risk for death in the following year than did adherent patients. The seemingly protective effect of using more medications, also noted by Shin and colleagues (16), may simply reflect the tendency to fill new preventive therapy prescriptions, possibly because of better education about the need for therapy or stronger beliefs about the benefits of medication.

Table 2. **Frequency of Incident Prescriptions and Primary Nonadherence Rate, by Therapeutic Indication**

Therapeutic Indication	Primary Nonadherence Rate, *n* (%)		
	Overall	Switch to New Drug in Pharmacologic Class	New Indication
Circulatory system disease	5395 (34.8)	966 (5.9)	4429 (41.1)
Hypertensive diseases	4768 (33.2)	905 (5.4)	3863 (39.8)
Ischemic heart diseases	261 (51.3)	27 (11.1)	234 (56.0)
Respiratory system disease	5351 (28.5)	687 (16.0)	4664 (30.3)
Acute bronchitis	1299 (20.4)	97 (9.3)	1202 (21.3)
Rhinitis	1010 (37.8)	113 (27.4)	897 (39.1)
Endocrine and metabolic disease	4509 (33.9)	628 (7.8)	3881 (38.1)
Dyslipidemia	2656 (33.4)	570 (7.5)	2086 (40.4)
Diabetes/complications	1019 (28.8)	33 (12.5)	986 (29.6)
Musculoskeletal system disease	3968 (28.2)	503 (13.5)	3465 (30.3)
Dorsopathies	1303 (27.9)	238 (12.2)	1065 (31.5)
Osteopathies and chondropathies	975 (33.1)	88 (13.6)	887 (35.1)
Mental and behavioral disorders	3870 (31.6)	451 (7.5)	3419 (34.8)
Depression	1110 (36.8)	71 (14.1)	1039 (38.3)
Anxiety	971 (32.1)	97 (7.2)	874 (34.9)
Skin disease	2381 (27.8)	444 (18.7)	1937 (29.9)
Inflammation/pruritus	996 (25.2)	240 (19.2)	756 (27.1)
Dermatitis/eczema	725 (30.1)	161 (19.9)	564 (33.0)
Digestive system disease	2211 (32.3)	400 (10.8)	1811 (37.1)
GERD/esophageal reflux	971 (33.9)	219 (7.3)	752 (41.6)
Gastritis/hyperacidity	879 (33.0)	152 (15.8)	727 (36.6)
Genitourinary system disease	1653 (26.2)	147 (10.9)	1506 (27.7)
Urinary tract infection	808 (21.0)	65 (10.8)	743 (21.9)
Benign prostatic hypertrophy	504 (29.2)	51 (7.8)	453 (31.6)
Infectious and parasitic disease	1400 (27.4)	40 (30.0)	1360 (27.4)
Other fungal infections	437 (24.9)	1 (100.0)	436 (24.8)
Candidiasis	325 (27.4)	6 (0)	319 (27.4)
Nervous system disease	487 (40.5)	38 (15.8)	449 (42.5)
Headache and migraine	253 (51.0)	20 (20.0)	233 (53.6)
Symptoms and signs	448 (28.1)	58 (15.5)	390 (30.0)
Pain	238 (28.2)	44 (13.6)	194 (31.4)
Other	5833 (33.2)	630 (14.8)	5203 (35.4)
Total	37 506 (31.3)	4992 (11.6)	32 514 (34.3)

GERD = gastroesophageal reflux disease.

Table 3. **Frequency of Incident Prescriptions and Primary Nonadherence Rate, by Pharmacologic Class**

Prescriptions	Primary Nonadherence Rate, *n (%)*		
	Overall	Switch to New Drug in Pharmacologic Class	New Indication
Central nervous system agents	9035 (30.1)	1082 (10.2)	7953 (32.8)
Analgesics and antipyretics	3248 (27.8)	444 (14.0)	2804 (30.0)
Psychotherapeutic agents	2762 (32.5)	168 (11.3)	2594 (33.9)
Cardiovascular drugs	7718 (34.7)	1567 (6.8)	6151 (41.8)
Hypotensive agents	3108 (32.2)	862 (5.9)	2246 (42.3)
Antilipemic	2794 (33.6)	590 (8.0)	2204 (40.5)
Anti-infectives	5087 (24.2)	361 (11.9)	4726 (25.1)
Antibacterials	4179 (23.3)	344 (10.8)	3835 (24.5)
Antivirals	271 (35.4)	13 (46.2)	258 (34.9)
Hormones and synthetics	3919 (36.3)	376 (17.3)	3543 (38.3)
Antidiabetic agents	979 (29.1)	7 (42.9)	972 (29.0)
Thyroid/antithyroid agents	614 (49.4)	0 (NA)	614 (49.4)
Skin and mucous membrane drugs	3221 (27.6)	523 (18.2)	2698 (29.4)
Anti-inflammatory agents	1046 (27.4)	500 (18.2)	546 (30.2)
Gastrointestinal drugs	2410 (33.1)	434 (12.0)	1976 (37.7)
Antiulcer agents	2244 (33.0)	428 (12.2)	1816 (37.9)
Ear, nose, and throat preparations	1752 (34.2)	185 (20.9)	1567 (35.9)
Anti-inflammatory agents	1442 (36.3)	161 (21.7)	1281 (38.1)
Autonomic drugs	1311 (27.1)	276 (15.2)	1035 (30.2)
Diuretics	981 (33.4)	7 (28.6)	974 (33.5)
Other pharmacologic classes	2072 (34.3)	181 (12.2)	1891 (36.4)
Total	37 506 (31.3)	4992 (11.6)	32 514 (34.3)

NA = not applicable.

An important policy-relevant aspect of this research is the association between higher drug costs and copayments and the likelihood of primary nonadherence. Quebec is the first Canadian province to aggressively establish a policy to address access to medications for chronic conditions by passing legislation for universal requirements for public and private drug coverage in 1996, followed by antipoverty policies that made prescription drugs free for all persons receiving social assistance (41). This policy may have had a positive effect on primary adherence. Our findings are consistent with other studies of primary nonadherence that show that waivers of copayments for persons with low income (12) or low copayments (42) are associated with a lower risk for primary nonadherence. Consistent with this trend, higher copayments (15) and lower income are associated with a higher rate of primary nonadherence (14, 15). It is not known whether Quebec's antipoverty policy will have the intended effect of reversing the negative socioeconomic gradient in chronic disease that is evident in Canada (43, 44) and elsewhere (45–47). More ED visits and hospitalizations for chronic conditions, such as asthma, are common in socially disadvantaged groups, even in Canada where all residents have comprehensive health insurance (48, 49). A recent national survey reported a notable reduction in chronic disease incidence in very poor persons in Quebec in comparison with temporal trends in other Canadian provinces (41); however, the possible causal association between the introduction of antipoverty drug policies and illness has not been investigated.

A greater proportion of physician visits with the prescribing physician was associated with increased primary adherence. Although this has not been investigated previously, it has been assumed that the primary care health reforms that are taking place in many countries will enable better management of chronic conditions, including medication adherence (50–52). The introduction of policy and funding initiatives to support more comprehensive health care strategies, such as medical homes and case managers, should improve continuity of care (53, 54).

Our study has important limitations. First, there were substantial unmeasured patient effects that influenced primary nonadherence. Patients' attitudes and beliefs about medication are likely some of the most important factors that may influence primary nonadherence (55). This would be an important but challenging area to tackle in future research because persons who do not fill prescrip-

Table 4. **Drug, Patient, and Physician Characteristics Associated With Primary Nonadherence***

Characteristic	Prescriptions, *n*	Primary Nonadherence, %	Multivariate Alternating Logistic Regression	
			OR (95% CI)	*P* Value
Drugs				
Pharmacologic class				
Anti-infectives	5087	24.2	Reference	
Cardiovascular	7718	34.7	0.96 (0.85–1.08)	0.47
Central nervous system	9035	30.1	1.11 (0.98–1.25)	0.100
Gastrointestinal	2410	33.1	1.20 (1.05–1.38)	0.009
Hormone and synthetics	3919	36.3	1.11 (0.99–1.26)	0.078
Ear, nose, and throat preparations	1752	34.3	1.44 (1.26–1.66)	<0.001
Skin and mucous membrane	3221	27.6	1.29 (1.13–1.47)	<0.001
Diuretics	981	33.4	1.07 (0.92–1.26)	0.36
Autonomic	1311	27.1	1.25 (1.05–1.48)	0.011
Other	2072	34.3	1.01 (0.91–1.12)	0.85
Drug cost				
Bottom quartile (<$9.87)	9270	32.8	Reference	
Second quartile ($9.87–$23.58)	9270	29.9	1.04 (0.98–1.10)	0.20
Third quartile ($23.59–$36.52)	9915	32.6	1.06 (1.00–1.12)	0.057
Top quartile ($36.51–$913.95)	9051	29.6	1.11 (1.07–1.17)	<0.001
Odds per $20 increase in cost			1.05 (1.03–1.07)	<0.001
Therapy status				
New to therapy	32 514	34.3	1.25 (1.15–1.35)	<0.001
Switch to new drug in pharmacologic class	4992	11.6	Reference	
Patients				
Age				
<52 y	8944	41.0		
52–65 y	9120	25.2		
66–72 y	9867	32.3		
>72 y	9423	26.2		
Odds per 10-y increase			0.89 (0.85–0.92)	<0.001
Sex				
Male	13 610	33.6	Reference	
Female	23 896	30.0	0.95 (0.88–1.02)	0.124
Drug plan				
Maximum copayment ($80/mo)	24 519	41.2	Reference	
Partial copayment ($45/mo)	7008	12.6	0.56 (0.49–0.64)	<0.001
Free medication	5978	12.3	0.37 (0.32–0.41)	<0.001
Comorbid conditions and health care use				
Recent hospitalization/ED visit				
No	22 429	32.2	Reference	
Yes	15 077	29.9	1.20 (1.10–1.31)	<0.001
Charlson Comorbidity Index				
0	22 906	32.7	Reference	
≥1	14 600	29.1	1.11 (1.08–1.14)	<0.001
Number of drugs				
<5	17 486	51.9		
≥5	20 020	13.3		
Odds per 1-drug increase			0.83 (0.81–0.85)	<0.001
Continuity of care				
<0.4	18 730	33.3		
≥0.4	18 776	29.2		
Odds per 0.5 increase			0.77 (0.70–0.85)	<0.001
Physicians				
Sex				
Male	23 286	29.5	Reference	
Female	14 076	34.2	1.17 (1.00–1.37)	0.056
Years in practice				
<15 y	2172	31.8		
16–22 y	9260	35.8		
23–28 y	10 822	33.6		
>28 y	15 100	26.4		
Odds per 10 y in practice			0.91 (0.82–1.01)	0.088

ED = emergency department; OR = odds ratio.
* Overall, data were available for 99.2% of incident prescriptions. The 295 prescriptions with ≥1 missing value were excluded from multivariate analysis.

tions may be less likely to participate in research (56, 57). Second, we did not assess the need for prescribed therapy. It could be that patients were advised to fill prescriptions as needed, which may explain the greater rate of primary nonadherence for topical skin creams and ear, nose, and throat preparations. However, a substantial proportion of patients did not fill prescriptions for oral hypoglycemics, antihypertensives, and hypothyroid agents, which are unlikely to be prescribed on an as-needed basis. In addition, the consequences of not filling the first prescription are unknown. In the 1 study that assessed the outcome of primary nonadherence, patients had a 2-fold increase in the risk for death (12), but the consequences will likely vary by treatment indication.

Future research should estimate the contribution of medication attitudes and beliefs to the likelihood of primary nonadherence as well as the effect of nonadherence on subsequent illness, death, and health care use. If primary nonadherence is an important contributor to avoidable illness, then policy interventions to minimize risk for primary nonadherence for the most vulnerable groups, such as those implemented in Quebec, should be evaluated. The extent of health insurance coverage has been associated with rates of preventable illness in some but not all international comparisons (58–62). Despite the significance of these associations, there has been considerable debate about the value of comprehensive drug insurance coverage in many countries (63–67), as well as a paucity of international comparisons of the effect of variable drug insurance coverage on rates of adherence and illness (68–71). This is an important area for future research.

Physicians need to be aware that suboptimal treatment response may be due to a patient's decision not to fill prescribed therapy. This, in turn, may be more likely for higher-cost drugs and among lower-income groups, particularly if there are costly copayments. Efforts to improve follow-up care with prescribing physicians may reduce the risk for primary nonadherence.

From the Clinical and Health Informatics Research Group, McGill University, Montreal, Quebec, and University of Ottawa and The Ottawa Hospital, Ottawa, Ontario, Canada.

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Requests for Single Reprints: Robyn Tamblyn, PhD, McGill University, Morrice House, 1140 Pine Avenue West, Montreal, Quebec H3A 1A3, Canada; e-mail, robyn.tamblyn@mcgill.ca.

Current author addresses and author contributions are available at www.annals.org.

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Current Author Addresses: Drs. Tamblyn, Eguale, and Huang; Ms. Winslade; and Ms. Doran: McGill University, Morrice House, 1140 Pine Avenue West, Montreal, Quebec H3A 1A3, Canada.

Author Contributions: Conception and design: R. Tamblyn, T. Eguale, A. Huang, N. Winslade.
Analysis and interpretation of the data: R. Tamblyn, T. Eguale, N. Winslade.
Drafting of the article: R. Tamblyn, T. Eguale, P. Doran.
Critical revision of the article for important intellectual content: R. Tamblyn, T. Eguale, A. Huang, P. Doran.
Final approval of the article: R. Tamblyn, T. Eguale, A. Huang, N. Winslade, P. Doran.
Provision of study materials or patients: R. Tamblyn.
Statistical expertise: R. Tamblyn, T. Eguale.
Obtaining of funding: R. Tamblyn.
Administrative, technical, or logistic support: R. Tamblyn, P. Doran.
Collection and assembly of data: R. Tamblyn, T. Eguale, A. Huang.

Appendix: Sensitivity Analysis

Addressing Bias With an Unmeasured Covariate

We elected to use the proportion of persons who did not complete secondary school residing in a 6-digit postal code as a proxy for education status for the sensitivity analysis.

First, we evaluated the correlation between education (proportion that did not complete secondary school) and the covariates included in the model. This education variable was negatively correlated with primary nonadherence and positively correlated with the insurance variables (that is, partial copayment and free medication).

We then included the education variable in the model as continuous and categorical variable (quartiles and dichotomous) to evaluate the effect in terms of the change in the OR estimates of the other risk factors (covariates), especially the insurance variable. There was no appreciable change in the ORs of the covariates when education was included in the ALR models. The ORs for the patients who got their drugs for free or had partial copayment changed by 0.01 (for example, OR of 0.56 became 0.57).

The education variable was also dichotomized to evaluate the effect of different levels of misclassification of education on free medication status. The median of the proportion of secondary school noncompletion was used as a cut-off to create the 2 groups (that is, 1 group with low secondary school noncompletion and another group with high secondary school noncompletion). The group with high secondary school noncompletion (compared with low secondary school noncompletion) was associated with primary nonadherence in unadjusted ALR (OR, 0.79 [CI, 0.72 to 0.89]). However, the association in multivariate ALR was borderline significant (OR, 0.91 [CI, 0.83 to 1.00]); $P = 0.055$). To investigate the strength of the association reported in the manuscript and verify the existence of a major confounding variable, we manipulated this variable by sequentially misclassifying 25%, 50%, and 75% of patients who did not fill their prescription and grouped to the high secondary school noncompletion. This misclassification created stronger associations between this dichotomous variable and primary nonadherence. The multivariate ORs for the group with high secondary school noncompletion with the 25% misclassification became 0.60 (CI, 0.53 to 0.68). For the 50% and 75% misclassifications, the ORs became 0.39 (CI, 0.34 to 0.45) and 0.23 (CI, 0.19 to 0.27), respectively. We then investigated the effect on the other covariates in the multivariate model. In the 25% misclassification, the OR for partial copay and free medication changed by 0.03 and 0.02, respectively. In the 50% misclassification, the OR for partial copay and free medication changed by 0.05 and 0.04, respectively. In the 75% misclassification, the ORs for partial copay and free medication changed by 0.07.

Overall, the sensitivity analyses showed that the increased misclassification that resulted in the creation of a strong association between the high secondary school noncompletion and primary nonadherence did not appreciably affect the association between the insurance variable and primary nonadherence.

Addressing Confounding by Unmeasured Physician Characteristics

To investigate the possibility of confounding by physician, we compared ORs obtained from the alternating logistic regression and generalized estimating equations logistic regression model where physician was considered fixed effects (72). Because there were 131 physicians with very different cluster sizes (interquartile range, 18 to 416), we were unable to fit each physician as a fixed effect; the logistic regression model using generalized estimating equations did not converge. To assess whether there was uncontrolled bias, we eliminated physicians who contributed less than 100 patient–drug pairs and reran the analysis with the remaining 64 physicians as fixed effects. The percentage of change in OR (difference in OR divided by the ALR OR) ranged from 0% to 11.9% with an interquartile range of 1.9% to 7.3%. In addition, we also aggregated the physicians who contributed less than 100 patient–drug pairs to 1 group and reran the fixed-effects model. The change in OR ranged from 0% to 12.9% with an interquartile range of 1.2% to 6.4%. Overall, there was no appreciable change in the estimated effects between ALR and generalized estimating equations with physicians as fixed effects. These findings are not surprising because the OR for clustering by physician in the full multivariate ALR model was only 1.13 (CI, 1.07 to 1.21), suggesting that there are very little unmeasured physician factors contributing to unexplained variance in primary nonadherence compared with patient-level factors where the OR was 28.0 (CI, 23.1 to 34.0).

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