Published in final edited form as:

Ann Pharmacother. 2017 August ; 51(8): 640–648. doi:10.1177/1060028017705393.

Provider and Patient Determinants of Generic Levothyroxine Prescribing: An Electronic Health Records-Based Study

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Abstract

Background—Despite the availability of generic levothyroxine products for more than a decade, uptake of these products is poor.

Objective—We sought to evaluate determinants of generic prescribing of levothyroxine.

Methods—In a cross-sectional analysis of electronic health records data between 2010 and 2013, we identified adult patients with a levothyroxine prescription from a primary-care physician (PCP) or endocrinologist. We used mixed-effect logistic regression models with random intercepts for prescribing provider to examine predictors of generic levothyroxine prescribing. Models include patient, prescription, and provider fixed-effect covariates. Odds ratios (ORs) and 95% CIs were generated. Between-provider random variation was quantified by the intraclass correlation coefficient (ICC).

Results—Study patients (n = 63 838) were clustered among 941 prescribing providers within 25 ambulatory care clinics. The overall prevalence of generic prescribing of levothyroxine was 73%. In the multivariable mixed-effect model, patients were significantly less likely to receive generic levothyroxine from an endocrinologist than a PCP (OR = 0.43; 95% CI = 0.33–0.55; $P < 0.001$). Women were less likely to receive generic levothyroxine than men from endocrinologists (OR = 0.68; 95% CI = 0.59–0.78; $P < 0.001$) but not from PCPs. Between-provider variation in generic prescribing was 18.3% in the absence of fixed-effect covariates and could be explained marginally by patient, prescription, and provider factors (ICC = 15.9%).

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Authors' Note

Sarah Dutcher and Xia Pu are employees of the United States Food and Drug Administration, Office of Generic Drugs. Views expressed in this publication do not necessarily reflect the official policies of the Department of Health and Human Services, nor does any mention of trade names, commercial practices, or organization imply endorsement by the United States Government. Robert Romanelli has previously received research support from Pfizer, Inc, and Janssen Scientific Affairs.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Supplemental Material

The supplementary material is available at <http://journals.sagepub.com/doi/suppl/10.1177/1060028017705393>.

Conclusions—Generic levothyroxine prescribing differed by PCPs and endocrinologists. Residual variation in generic prescribing, after accounting for measurable factors, indicates the need for provider interventions or patient education aimed at improving levothyroxine generic uptake.

Keywords

generic prescribing; levothyroxine; electronic health records

Introduction

Levothyroxine sodium is a synthetic thyroxine hormone, and is the mainstay of treatment for hypothyroidism and the suppression of thyroid stimulating hormone (TSH) in patients with thyroid cancer or after thyroidectomy.¹ Two main properties of levothyroxine have contributed to a turbulent regulatory history. First, levothyroxine targets a narrow therapeutic range of thyroxine and requires careful titration to a safe and effective dose.² Second, levothyroxine is relatively unstable and its degradation is accelerated by environmental factors and the presence of some inert product ingredients.^{3,4} Between 1991 and 1997 there were 10 recalls of different levothyroxine products mostly as a result of subpotency or uncertain potency.⁵

Although major regulatory changes were implemented to improve the quality and safety of levothyroxine products in 1997 and again in 2007,^{5–7} concerns persist among some health care providers and patients about bioequivalence and variation in levothyroxine product potency.⁸ Previously, using a nationally representative commercial claims data, we found that generic use of thyroid agents, mostly comprising levothyroxine, was 61% in 2013,⁹ despite the availability of generic preparations for more than a decade. This utilization rate is markedly low given that overall generic uptake is approaching 90% in the United States.¹⁰

To encourage use of generic levothyroxine, more information is needed about barriers to the use of generic preparations among health care providers and patients. We used a large electronic health record (EHR) database from a health care delivery system to evaluate measurable determinants of, and unexplained variation in, outpatient generic prescribing of levothyroxine. We hypothesized that both health care provider and patient factors contribute to generic levothyroxine prescribing and that residual variation in providers' generic prescribing would persist after accounting for measurable factors.

Methods

Study Setting

Sutter Health is a health care delivery system in Northern California, serving approximately 3 million patients annually. The organization is a mixed-payer system, with no single drug formulary. Thus, it is an appropriate setting to evaluate variation in drug prescribing/use. Drugs are prescribed electronically in the EpicCare EHR, and generic prescribing is the default option. California has a permissive, rather than mandatory, generic substitution policy, requiring that pharmacists notify the patient when substituting a generic drug.¹¹

The Sutter Health Institutional Review Board and the FDA's Research in Human Subjects Committee approved this study. All data were stripped of protected health information according to Health Insurance Portability and Accountability Act standards.

Study Design

This was a cross-sectional study of patients, aged 18 years, who received a prescription for an oral levothyroxine product in the outpatient setting between 2010 and 2013. We included patients with a levothyroxine prescription from a primary-care physician (PCP) or endocrinologist because they are the most prevalent prescribers. The first levothyroxine prescription during the study period was considered the index prescription. Each person contributed 1 observation to the analysis. We required patients to have 12 months of EHR activity prior to the index prescription to collect sufficient disease and medication history. We excluded patients with prescriptions for liothyronine, a T₃ hormone replacement therapy.

Data Collection

Primary Outcome—The primary outcome was generic prescribing of levothyroxine. We classified the index prescription as brand or generic based on the name of the ordered medication (ie, active ingredient or brand name) and whether or not “dispense as written” was requested in the EHR.¹² When brand levothyroxine (ie, Synthroid, Levothyroid, Levoxyl, Tirosent, Unithyroid) was ordered, but “dispensed as written” was not requested, we assumed that a generic product was dispensed.

Predictors—We extracted information from the EHR on patient demographics, including age, gender, and race/ethnicity. Race and ethnicity were as reported by the patient during clinical care and recorded in accordance with US Census standards.¹³ We identified TSH laboratory results for each patient in the 12 months prior to the index prescription. In the case of multiple measurements, we chose the one closest to (but not after) the date that the prescription was ordered. When TSH was unavailable in the EHR, it was set to missing. We also extracted information on other patient characteristics, including use of concomitant medications active at the time of the index levothyroxine prescription, insurance type, and clinical diagnoses. Insurance type was categorized as fee-for-service or preferred provider organization (FFS/PPO), health maintenance organization (HMO; including Medicare Advantage), Medicare, Medicaid, and unknown (including self-pay). For each patient, we calculated a Charlson Comorbidity Index (CCI) score based on diagnoses-coded encounters and diagnoses documented in problem lists in the 12 months prior to the index prescription.¹⁴ We used 2010 US Census information to determine regional median household income as a proxy for socioeconomic status.

Similarly, we used information from the EHR database to characterize the index levothyroxine prescription. We classified the encounter at which the index prescription was ordered as an office visit or an online/telephone encounter. The index prescription was classified as “incident” if there were no active prescriptions or pharmacy claims for levothyroxine in the 12 months prior; otherwise, it was classified as a renewal. For each patient, we quantified the duration of the prescription as determined by the prescribed daily dose, quantity dispensed, and number of refills.

Providers were classified as a PCP or endocrinologist based on their clinical department. We defined health care providers' prescribing volume of levothyroxine as the average number of levothyroxine prescriptions written per week in the 3 months prior to the index prescription for each patient. We defined health care providers' total patient volume as the average number of office encounters per week in the 3 months prior to the index prescription per patient.

Statistical Methods

Continuous variables were categorized based on their observed distributions. We calculated prevalence of levothyroxine generic prescribing for index prescriptions overall, by year, and by provider type.

We used mixed-effects multivariable logistic regression to assess the relationship between generic prescribing of levothyroxine (dependent variable) and patient factors (see Table 1) as well as prescription and provider factors (see Table 2). All covariates were level-1 variables (vary at the patient level), with the exception of providers' department, which was a level-2 variable (varies at the provider level). We assumed that patients with prescriptions from the same prescriber were more alike in their propensity to receive a generic product than patients from different providers. Accordingly, we included random intercepts in our models for each prescribing health care provider of the index levothyroxine prescription ($n = 941$). To quantify between-provider variation, we calculated the intraclass correlation coefficient (ICC) in the absence of covariates (variance-components model) and in the presence of patient, prescription, and provider fixed-effect covariates (mixed-effects multivariable models). Odds ratios (ORs) and 95% CIs were calculated for fixed-effect covariates. These models were also fit separately by provider type (PCP and endocrinologist) to further examine between-provider variation and effect modification.

We derived the predicted probabilities of generic levothyroxine prescribing for each fixed-effect covariate from post hoc estimation of adjusted means, holding all other variables constant.¹⁵ Because of multiple comparisons within models, a P value < 0.01 was considered statistically significant to mitigate type-1 statistical errors.

We also explored between-clinic variation in generic prescribing of levothyroxine by fitting variance-components models with random intercepts for each clinic in which providers practiced ($n = 25$), alone and in the presence of random effects for each provider. All analyses were conducted in Stata 13 (Stata Corp, College Station, TX).

Results

Description of the Study Cohort

Between 2010 and 2013, 96 034 patients received a prescription for an oral levothyroxine product; of these, 19 824 patients were excluded because of insufficient EHR history, 1710 were excluded because of a prescription for liothyroxine, and 10 662 were excluded because levothyroxine was prescribed by a prescriber from a department other than primary care or endocrinology. The excluded prescribers were from more than 50 unique departments or service lines. The final study cohort of 63 838 patients were clustered among 941 health care

providers (mean = 68 patients/provider) within 25 clinics throughout the health care organization (means = 2554 patients/clinic and 38 providers/clinic). Most of the prescribers were PCPs (95%).

The prevalence of generic prescribing of levothyroxine over the study period was 73%. Approximately 38% of patients were 65 years or older, 81% were female, and 63% were non-Hispanic white (Table 1). Approximately half of levothyroxine prescriptions were renewals (53%; Table 2). Incident prescriptions were more likely to have been prescribed at an office encounter than renewals (38% vs 18%, respectively). Among patients with a renewal, 84% had a prior prescription for generic levothyroxine; of those with a prior generic, 92% had a generic levothyroxine index prescription. Overall, 79% of patients received generic levothyroxine when prescribed by a PCP versus 38% when prescribed by an endocrinologist (Table 3). Annual prevalence of levothyroxine generic prescribing was consistently lower for endocrinologists than for PCPs. The proportion of patients receiving generic levothyroxine from an endocrinologist increased 2-fold between 2010 and 2013 (30% to 63%; Figure 1).

Determinants of Levothyroxine Generic Prescribing

In the mixed-effect multivariable model, older patients, those with more concomitant medications, Hispanic patients, and men had lower odds of receiving generic levothyroxine than their reference groups (Table 4). Patients with higher TSH levels had greater odds of receiving generic levothyroxine (>5.0 vs <5.0 mU/L), as did patients residing in regions with higher household incomes ($>\$100K$ vs $\leq \$55K$). Levothyroxine generic prescribing was less common for incident prescriptions than for renewals, prescriptions of shorter duration, and those ordered during office encounters versus online/telephone encounters. Patients had greater odds of receiving generic levothyroxine from a PCP than an endocrinologist (predicted probabilities: 81% vs 64%, respectively; Table 5).

Provider type was an effect modifier of the relationship between gender and generic levothyroxine prescribing. Women had lower odds than men of receiving generic levothyroxine from an endocrinologist (predicted probabilities: 63% vs 71%; OR = 0.68; 95% CI = 0.59, 0.78; $P < 0.001$) but not a PCP (80.1% each; OR = 0.98; 95% CI = 0.93, 1.04; $P = 0.603$).

Between-Provider Variation in Levothyroxine Generic Prescribing

In the absence of covariates, nearly 20% of the variation in generic prescribing of levothyroxine was a result of differences between prescribers (Supplemental Table, available at <http://aop.sagepub.com/supplemental>). Some of the variation was explained by measurable differences among patients, characteristics of the prescription, and providers; however, residual variation between providers persisted (15.9%). Similar results were observed in stratified analyses by PCPs and endocrinologists; yet, endocrinologists had larger variation in generic prescribing in the absence or presence of predictor variables compared with PCPs. Overall, patient, prescription, and provider predictor variables could explain approximately 14% of the between-provider variation among PCPs and 43% of the variation among endocrinologists. Variation between clinics was relatively small (between-

clinic ICC = 5.9%), much of which could be explained by between-prescriber variation (between-clinic ICC = 2.4%), after adjusting for random differences between providers.

Discussion

In this cross-sectional analysis, the prevalence of levothyroxine generic prescribing in an outpatient setting was lower among endocrinologists than PCPs even after controlling for differences among patients, and prescription and provider characteristics. Measurable factors could explain a larger proportion of the between-provider variation in generic prescribing for endocrinologists than PCPs. Nevertheless, residual variation after accounting for these factors was still larger among endocrinologists (ICC = 22% vs 12% for PCPs).

Lower levothyroxine generic prescribing among endocrinologists was not unexpected. In 2004, when the FDA approved generic levothyroxine products as therapeutically equivalent to branded reference listed drugs, several endocrinology medical societies challenged this decision.¹⁶ Chiefly, they were concerned with the methods used to establish bioequivalence and that allowable differences in between-lot product potency could have clinically significant implications for this narrow-therapeutic-index drug, particularly when switching between products from different manufacturers.^{16,17} Although the FDA defended the bioequivalence methodology, in 2007, the agency announced that it would narrow the required assay range specifications of levothyroxine from 90% to 110%, to 95% to 105% to address potential inconsistencies in between-lot potency.^{6,7} Nevertheless, these medical societies still caution against switching between levothyroxine products.^{18–20}

The debate regarding bioequivalence of generic and branded levothyroxine is ongoing. A recent crossover randomized study of 31 children with congenital hypothyroidism in 2013 showed that generic levothyroxine is not bioequivalent to brand levothyroxine.²¹ Conversely, a retrospective study of 27 children with congenital hypothyroidism published at the same time showed similar or better control of TSH variance with generic versus branded levothyroxine.²² These studies reached contradictory conclusions; however, comparisons across studies are complicated by different study designs and distinct approaches to testing bioequivalence.

Although annual levothyroxine generic prescribing in our study was consistently lower among endocrinologists than PCPs, we found that generic prescribing increased for endocrinologists each year between 2010 and 2013. These results suggest improved acceptance of generic levothyroxine among endocrinologists in recent years. Notably, there was a decrease in generic prescribing of levothyroxine among PCPs in 2011 compared with 2010. The reason for this is uncertain, but it may be a result of enhanced advertising or coupon distribution by brand manufacturers targeted to PCPs during that time. We cannot rule out the possibility that this observation is a result of factors intrinsic to this health care organization; however, if this were the case, we would expect both PCPs and endocrinologists in the organization to be equally affected.

Despite variation in generic prescribing of levothyroxine between physicians, we found little variation between clinics, especially after controlling for between-provider variation. This is

not surprising given that there are no clinic-level policies or distinct formularies that would restrict prescribing within this health system.

Several patient, prescription, and provider factors were associated with receiving generic levothyroxine. For most covariates, effect sizes were small and should be interpreted cautiously. We note larger effects for several prescription characteristics. For example, the predicted probability of receiving generic levothyroxine was higher for prescriptions of longer duration (85% for prescriptions >220 days vs 74% for prescriptions ≤60 days). Patients and providers may have been more accepting of generic levothyroxine when it would be taken for longer periods of time, reflecting lower cumulative out-of-pocket drug cost. The predicted probability of receiving generic levothyroxine was also higher for renewals than incident prescriptions (83 vs 73%) and for online/telephone encounters versus office encounters (81% vs 72%). These factors are related because patients with a renewal more frequently receive levothyroxine during an online/telephone encounter than those with an incident prescription, yet they remained independent predictors of generic prescribing in the multivariable model. Among patients with a renewal, 84% received generic levothyroxine prior to the index prescription; of those with a prior prescription for generic levothyroxine, the vast majority (92%) received a renewal for a generic levothyroxine product. It follows that patients were less likely to have been prescribed brand levothyroxine if they were previously prescribed a generic.

In a study of 36 832 older adults (≥65 years) in the United States initiating narrow therapeutic index drugs, of which warfarin (48%) and levothyroxine (29%) were the most prevalent, predictors of higher generic drug initiation included older age, male sex, higher comorbidity, lower census block median household income, and prior generic use. These findings from a Medicare population are overall consistent with our results.²³ In our study, bivariate analyses showed that HMO and Medicare beneficiaries were more likely to receive generic levothyroxine than FFS/PPO beneficiaries; however, this association was mitigated in the presence of other predictors in multivariable analyses.

We found that in multivariable models, provider type was an effect modifier for the relationship between patient gender and generic prescribing of levothyroxine. In stratified analyses, whereas the predicted prevalence of receiving a generic levothyroxine prescription from a PCP was similar among women and men (81%, each), the prevalence of receiving a generic prescription from an endocrinologist was disproportionately lower for women (63% vs 71% for men). Because gender differences in prescribing of generic levothyroxine were observed for endocrinologists but not PCPs, this phenomenon is likely driven by provider rather than patient preferences. Future studies are warranted to better understand these gender differences in prescribing practices. One explanation is that endocrinologists likely see more high-risk patients, for whom they may prefer branded levothyroxine, such as pregnant women with thyroid disease. Anecdotally, we know that endocrinologists are more cautious in titrating levothyroxine in pregnant women and may have a preference for brand in these situations. Women composed 81% of the total cohort in our study, which is not surprising given that thyroid disease is more common among women than^{24,25} men.

This study has several limitations. The retrospective, observational nature of this study limits causal inferences. Furthermore, prevalence of generic prescribing of levothyroxine may overestimate generic use of this drug because some patients may not consent to generic substitution at the pharmacy. Although California has a permissive generic substitution law, patients can still refuse a substitution. In the absence of pharmacy claims, we cannot know whether a generic or branded product was actually dispensed. Nevertheless, in a previous study, we showed that an algorithm used to determine brand versus generic prescribing measured by EHR data performs well in predicting actual dispensing patterns.¹² Whereas we lost a large number of patients because of the exclusion of health care providers who were not PCPs or endocrinologists, this other group of providers comprised more than 50 specialties or service lines and would introduce much heterogeneity to the analysis. Thus, we focused on PCPs and endocrinologists to improve generalizability of study findings to these common prescribers of levothyroxine. The study setting is a health care delivery system in Northern California, and we cannot know if our findings are generalizable to other parts of the United States; however, the organization is a mixed-payer system and operates much like other provider-based delivery systems in the nation, without a single drug formulary. As such, our findings are likely relevant to other similar health systems in the United States.

Despite limitations, this study has several strengths. We used a relatively large cohort of patients from a mixed-payer health care delivery system over a 4-year period to examine patterns in and determinants of generic prescribing of levothyroxine. We leveraged extensive information from the health system's EHR database, including disease and medication history, TSH levels, and providers' levothyroxine prescribing and patient volume. To our knowledge, this is the first study to quantify variation in generic prescribing of levothyroxine between health care providers.

Conclusions

In an outpatient setting, generic levothyroxine prescribing differed by PCPs and endocrinologists as well as by other patient, prescription, and provider characteristics. The presence of residual variation between providers in generic prescribing of levothyroxine, after controlling for important measurable confounders, indicates potential unwarranted variation caused by prescribing preferences. Such variation, which may also be influenced by patient beliefs and preferences, can be the target of interventions directed at providers or patient education aimed at improving levothyroxine generic uptake.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This study was funded by a United States Food and Drug Administration cooperative agreement with

the Johns Hopkins School of Medicine and the Palo Alto Medical Foundation Research Institute (1U01FD005267-01; PI: Segal).

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Figure 1. Levothyroxine generic prescribing by year and provider type: unadjusted proportions of index levothyroxine prescriptions written for generic products are shown. Error bars represent binomial 95% CIs.

Table 1.**Patient Demographics and Characteristics.**

Patient Covariates, n (%)	Study Patients, n = 63 838
Age, Years	
18 To 45	13 652 (21.4)
45 To <65	25 726 (40.3)
65 To <75	11 053 (17.3)
75 Or older	13 407 (21.0)
Sex, Female	51 817 (81.2)
Race/Ethnicity	
Non-Hispanic White	40 483 (63.4)
African American	950 (1.5)
Asian American	5840 (9.2)
Hispanic	10 322 (16.2)
Other	3013 (4.7)
Unknown	3230 (5.1)
TSH, mU/L	
<1.0	11 785 (18.5)
1.0 To <2.0	9326 (14.6)
2.0 To <5.0	14 417 (22.6)
5.0 Or higher	12 267 (19.2)
Missing	16 043 (25.1)
CCI score	
0	54 557 (85.5)
1	9281 (14.5)
Concomitant medications	
0	22 241 (34.8)
1	14 457 (22.6)
2	9289 (14.6)
3 Or more	17 851 (28.0)
Insurance type	
PPO/FFS	21 790 (34.1)
HMO	6188 (9.7)
Medicare	23 052 (36.1)
Medicaid	923 (1.4)
Other/Unknown	11 885 (18.6)
Median household income	
<\$55K	14 821 (23.2)
\$55K To \$75K	13 903 (21.8)
>\$75K To \$100K	13 375 (21.0)
>\$100K	15 804 (24.8)
Unknown	5935 (9.3)

Abbreviations: CCI, Charlson comorbidity index; FFS, fee-for-service; HMO, health maintenance organization; PPO, preferred provider organization; TSH, thyroid-stimulating hormone.

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Table 2.**Prescription and Provider Characteristics.**

Prescription Covariates, n (%)	Study Patients, n = 63 838
Prescription status	
Renewal	33 937 (53.2)
Incident	29 901 (46.8)
Prescription duration	
60 days	17 500 (27.4)
60 To 120 days	13 812 (21.6)
120 To 220 days	17 501 (27.4)
>220 days	15 025 (23.5)
Year prescribed	
2010	41 147 (64.5)
2011	9110 (14.3)
2012	6899 (10.8)
2013	6682 (10.5)
Encounter type	
Office encounter	17 747 (27.8)
Online/telephone	46 091 (72.2)
Average levothyroxine prescriptions per week by provider	
<2	8467 (13.3)
2 To 4	21 526 (33.7)
>4 To 6	15 430 (24.2)
6 Or more	18 415 (28.8)
Average total patient volume per week by provider	
<40	11 893 (18.6)
40 To 60	21 753 (34.1)
>60 To 75	16 012 (25.1)
>75	14 180 (22.2)
Provider Covariates, n (%)	Study Patients, n = 63 838
Provider type	
Primary care	54 838 (85.9)
Endocrinologist	9000 (14.1)

Table 3.
 Characteristics of Health Care Providers of Index Levothyroxine Prescriptions Overall and by Provider Type.

	All	Primary Care	Endocrinologist	<i>P</i> Value ^a
Patients receiving levothyroxine, n	63 838	54 838	9000	
Average patients per provider, n	68	62	173	
Patients prescribed generic levothyroxine, n (%)	46 588 (73.0)	43 142 (78.7)	3446 (38.3)	<0.001
Providers	n = 941	n = 889	n = 52	
Average levothyroxine prescriptions per week, n (%)				<0.001
<2	436 (46.3)	423 (47.6)	13 (25.0)	
2 To 4	296 (31.5)	292 (32.8)	4 (7.7)	
>4 To 6	123 (13.1)	119 (13.4)	4 (7.7)	
6 Or more	86 (9.1)	55 (6.2)	31 (59.6)	
Average total patient volume per week, n (%)				0.008
<40	370 (39.3)	338 (38.0)	32 (61.5)	
40 To 60	315 (33.5)	303 (34.1)	12 (23.1)	
>60 To 75	157 (16.7)	151 (17.0)	6 (11.5)	
>75	99 (10.5)	97 (10.9)	2 (3.8)	

^a *P*values derived from 2-sided *t* test for means or χ^2 tests of independence for categorical variables.

Table 4.

Mixed-Effects Logistic Regression Model Output for Levothyroxine Generic Prescribing: Patient Predictors.^a

Level-1 Patient Covariates	Multivariable Associations			P Value
	Bivariate Associations, Odds Ratio (95% CI)	Odds Ratio (95% CI)	Predicted Probability	
Age, years				
18 To 45 (reference)	1.00	1.00	77.1	—
45 To <65	1.23 (1.17, 1.30)	1.06 (1.00, 1.12)	78.0	0.053
65 To <75	1.48 (1.39, 1.58)	1.17 (1.07, 1.27)	79.7	<0.001
75 Or older	1.62 (1.51, 1.72)	1.24 (1.14, 1.35)	80.7	<0.001
Sex				
Male (reference)	1.00	1.00	79.7	—
Female	1.01 (0.96, 1.07)	0.93 (0.88, 0.98)	78.4	0.009
Race/Ethnicity				
Non-Hispanic White (reference)	1.00	1.00	78.3	—
African American	1.06 (0.90, 1.26)	1.10 (0.92, 1.31)	79.8	0.296
Asian American	0.87 (0.81, 0.94)	1.07 (0.98, 1.15)	79.4	0.117
Hispanic	1.06 (1.00, 1.12)	1.09 (1.03, 1.16)	79.7	0.006
Other	0.91 (0.83, 1.00)	1.01 (0.91, 1.11)	78.4	0.903
Unknown	0.99 (0.90, 1.08)	1.05 (0.96, 1.16)	79.2	0.291
TSH, mU/L				
<1.0 (reference)	1.00	1.00	76.9	—
1.0 To <2.0	1.36 (1.26, 1.46)	1.32 (1.22, 1.42)	81.5	<0.001
2.0 To <5.0	1.25 (1.17, 1.34)	1.32 (1.24, 1.41)	81.5	<0.001
5.0 Or higher	0.47 (0.44, 0.49)	0.65 (0.61, 0.70)	68.6	<0.001
Missing	1.18 (1.10, 1.25)	1.38 (1.29, 1.47)	82.1	<0.001
CCI score				
0 (reference)	1.00	1.00	78.8	—
1	1.01 (0.94, 1.06)	0.97 (0.92, 1.03)	78.3	0.378
Concomitant medications				
0 (reference)	1.00	1.00	77.0	—
1	1.08 (1.02, 1.13)	1.06 (1.00, 1.12)	77.9	0.051

Level-1 Patient Covariates	Multivariable Associations			P Value
	Bivariate Associations, Odds Ratio (95% CI)	Odds Ratio (95% CI)	Predicted Probability	
2	1.19 (1.12, 1.27)	1.13 (1.06, 1.20)	79.0	<0.001
3 Or more	1.40 (1.33, 1.48)	1.28 (1.21, 1.36)	81.1	<0.001
Insurance type				
PPO/FFS (reference)	1.00	1.00	78.3	—
HMO	1.08 (1.01, 1.16)	0.97 (0.90, 1.05)	77.8	0.439
Medicare	1.37 (1.31, 1.44)	1.04 (0.97, 1.11)	78.9	0.316
Medicaid	1.13 (0.967, 1.33)	1.15 (0.97, 1.37)	80.6	0.101
Other/Unknown	1.34 (1.26, 1.42)	1.05 (0.98, 1.12)	79.2	0.143
Median household income				
<\$55K (reference)	1.00	1.00	79.6	—
\$55K To \$75K	0.95 (0.90, 1.01)	0.97 (0.91, 1.04)	79.1	0.383
>\$75K To \$100K	0.93 (0.87, 0.99)	0.96 (0.90, 1.02)	78.8	0.176
>\$100K	0.85 (0.80, 0.91)	0.87 (0.82, 0.93)	77.3	<0.001
Unknown	0.96 (0.88, 1.03)	0.96 (0.88, 1.04)	78.8	0.273

Abbreviations: CCI, Charlson comorbidity index; FFS, fee-for-service; HMO, health maintenance organization; PPO, preferred provider organization; TSH, thyroid-stimulating hormone.

^aMultivariable models included all covariates shown as well as those covariates in Table 5. Predicted probability was derived from post hoc estimation of adjusted means, holding all other variables constant.

Table 5.

Mixed-Effects Logistic Regression Model Output for Levodopa Generic Prescribing: Prescription and Provider Predictors.^a

Level-1 Prescription Covariates	Bivariate Associations, Odds Ratio (95% CI)	Multivariable Associations		
		Odds Ratio (95% CI)	Predicted Probability	P Value
Prescription status				
Renewal (reference)	1.00	1.00	82.7	—
Incident	0.42 (0.40, 0.44)	0.58 (0.55, 0.61)	73.4	<0.001
Prescription duration				
60 Days (reference)	1.00	1.00	74.4	—
60 To 120 days	1.25 (0.19, 1.32)	1.34 (1.26, 1.41)	79.5	<0.001
120 To 220 days	1.16 (1.10, 1.22)	1.08 (1.02, 1.14)	78.9	0.005
>220 days	2.17 (2.04, 2.30)	1.93 (1.81, 2.05)	84.9	<0.001
Year prescribed				
2010 (reference)	1.00	1.00	79.0	—
2011	0.45 (0.43, 0.48)	0.70 (0.65, 0.74)	72.4	<0.001
2012	0.57 (0.53, 0.61)	1.03 (0.95, 1.11)	79.4	0.481
2013	0.70 (0.66, 0.76)	1.34 (1.23, 1.45)	83.4	<0.001
Encounter type				
Office encounter	1.00	1.00	71.8	—
Online/Telephone	1.87 (1.79, 1.96)	1.67 (1.60, 1.75)	81.0	<0.001
Level-2 Provider Covariates				
Levodopa prescriptions per week				
<2 (reference)	1.00	1.00	80.0	—
2 To 4	1.23 (1.07, 1.42)	0.98 (0.85, 1.12)	79.6	0.733
>4 To 6	1.26 (1.05, 1.51)	0.94 (0.79, 1.12)	79.0	0.490
6 Or more	0.83 (0.68, 1.03)	0.82 (0.65, 1.02)	76.6	0.072
Total patient volume per week				
<40 (reference)	1.00	1.00	76.1	—
40 To 60	1.07 (0.93, 1.24)	1.01 (0.88, 1.17)	76.3	0.856

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>60 To 75	1.44 (1.31, 1.85)	1.41 (1.19, 1.67)	81.8	<0.001
>75	1.49 (1.22, 1.82)	1.30 (1.06, 1.60)	80.6	0.010
Provider type				
Primary care (reference)	1.00	1.00	80.6	—
Endocrinologist	0.32 (0.26, 0.40)	0.43 (0.33, 0.55)	63.9	<0.001

^aMultivariable models included all covariates shown as well as those covariates in Table 4. Predicted probability was derived from post hoc estimation of adjusted means, holding all other variables constant.