Published in final edited form as:

Ther Innov Regul Sci. 2020 January ; 54(1): 151–157. doi:10.1007/s43441-019-00039-9.

Determinants of Generic Drug Substitution in the United States

Jodi B. Segal, MD, MPH^{1,2,3}, Oluwadamilola Onasanya, MD, MPH^{1,3}, Matthew Daubresse, MHS^{2,3}, Chia-Ying Lee, MHS², Mischka Moechtar, MHS², Xia Pu, PhD⁴, Sarah K. Dutcher, PhD⁴, Robert J. Romanelli, PhD, MPH⁵

¹Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, MD, USA

²Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA

³Center for Drug Safety and Effectiveness, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA

⁴Office of Generic Drugs, Center for Drug Evaluation and Research, US Food and Drug Administration, Silver Spring, MD, USA

⁵Palo Alto Medical Foundation Research Institute, Palo Alto, CA, USA

Abstract

Background—Some classes of drugs have lower than optimal uptake of generic products. We aimed to understand the determinants of generic drug substitution across classes.

Methods—We conducted a cross-sectional analysis of data from the 2013 MarketScan Commercial Claims and Encounters Database from Truven Health Analytics. We quantified generic substitution rates (GSR) for 26 drug classes, choosing one representative week in November 2013. We used mixed-effects logistic regression to estimate the independent relationship between the determinants of interest and generic substitution for 8 classes with low generic utilization.

Results—The GSRs for most classes exceeded 90%, although some were much lower including thyroid hormones (64%), androgens (74%), estrogens (71%), and hydantoin-type anticonvulsants (72%). The determinants of generic substitution varied across classes, albeit with important patterns. Patients using a mail order pharmacy had significantly less generic substitution than patients filling at retail pharmacies for 5 of the 8 studied classes; two additional classes showed no relationship between pharmacy type and generic use. Men relative to women and patients taking more medications were more likely to use generics for most classes. State substitution laws and patient consent laws were largely inconsequential regarding generic substitution.

Corresponding Author: Jodi Segal, MD, MPH, Johns Hopkins School of Medicine, 624 N. Broadway Room 644, Baltimore, MD 21205, USA. jsegal@jhmi.edu.

Declaration of Conflicting Interests
No potential conflicts were declared.

Supplemental Material
Supplemental material for this article is available online.

Conclusions—Policies are needed to support the use of safe, effective and often lower cost generic drugs, when available. Mail order pharmacies, as often required by pharmacy benefits managers, lessen generic use for many classes. These pharmacies may require additional regulatory oversight if this adversely impacts patients.

Keywords

generic; drug utilization; pharmacoepidemiology; mail order

Introduction

The Generic Drug User Fee Amendments of 2012 (GDUFA) led to the accelerated approval of generic drugs since its passage.¹ This, along with the patent and exclusivity expiry of many products recently, has led to the increased availability of generic products. In 2016, generic drugs represented 89% of all prescriptions filled in the United States and yet accounted for only 26% of all costs for prescription drugs.² However, despite the widespread availability and generally favorable costs of these products, their uptake by consumers remains incomplete. Some prescribers and patients have persistent concerns about the bioequivalence of generic products.³ Clinicians express concern about drugs with a narrow therapeutic index such that even small differences in absorption or metabolism between brand and generic products may impact outcomes.^{4,5}

Some Americans, including a small number of pharmacists, still perceive generics as being less safe and efficacious and of lower quality than brand-name drugs.^{6,10} Patient surveys have demonstrated that individuals with lower health literacy and those with lower incomes hold negative views about generic drugs.^{7,8} Both African Americans and Hispanics are also more likely than non-Hispanic whites to report believing that generic drugs have more side effects than branded drugs.⁹ Further, older patients are less likely to believe that generic drugs are as safe as branded drugs, and women are more likely than men to believe that generics are a better value.¹⁰ However, some recent surveys suggest growing acceptance of generics.^{11,12}

There is far less data, however, about the impact of other influences on generic utilization and substitution, such as insurance plan designs, the types of dispensing pharmacies, and state-level generic substitution and patient consent policies. The US healthcare system has mechanisms that promote generic usage; most insurers incentivize patients to use generic drugs by requiring less patient cost-sharing for generic than branded products. In addition, 14 states currently have mandatory generic substitution laws for pharmacists, and the remainder, excluding Oklahoma, have laws permitting substitution by pharmacists.¹³

In this study, we sought to explore the determinants of generic substitution across therapeutic classes. We aimed to learn, for a given therapeutic class and across classes, what factors are independently associated with filling a drug as a generic rather than a branded product. Our goal was to identify potentially actionable determinants that could be addressed through education, regulation, or legislation.

Methods

Data and Cohort

This work was reviewed by the Institutional Review Board of the Johns Hopkins University and the FDA's Research Involving Human Subjects Committee. We used the 2013 MarketScan Commercial Claims and Encounters Database from Truven Health Analytics. These data are claims from individuals in the US with employer-sponsored private health insurance, as well as their spouses and dependents. These data include complete medical claims that are linked to outpatient prescription drug claims and person-level enrollment information. We used a systematic strategy to select therapeutic classes of high priority for examination (Supplemental Material). Beneficiaries were included in this cross-sectional study if they filled a prescription in our study window (1 week in November 2013), were under age 65 years, and had continuous enrollment in their health plan (or evidence of utilization of healthcare claims) for at least 9 months preceding the study window.

Measuring Generic Substitution

To characterize generic drug usage during this period, we quantified generic substitution rates (GSRs) for the selected therapeutic classes (Supplemental Appendix 1). The GSR represents generic drug use as a fraction of all drug use among the set of drugs for which there are generics available.¹⁴ We calculated the GSR *for each drug* within the classes of interest. We tabulated the number of days within a representative one-week window in November 2013 for which the patient had a generic drug available, following a dispensing of the product, or had the branded product available for the identical active ingredient and route. We calculated an aggregate GSR for each therapeutic class by weighting each drug's GSR by the relative proportion of use of the drug within that class, and calculated a 95% confidence interval assuming a binomial distribution. We selected a class for modeling determinants if it met the following criteria: not exceptionally high GSR (not exceeding 95%), includes prevalently used products, and the products within the class have similar indications for their use.

Covariates

The covariates tested as determinants of generic substitution can be categorized as patient characteristics, prescription characteristics, and state laws. *Patient characteristics* included age in years as a continuous variable, sex, comorbid illnesses as quantified with the Charlson Comorbidity Index¹⁵ and then categorized as 0, 1, or 2 or more comorbid conditions. We also included prescription drug burden as a patient characteristic, defined as the number of prescriptions "on hand" during the study window of interest. The patient's insurance plan type was categorized as a fee-for-service plan, a Health Maintenance Organization (HMO)-like plan, Preferred Provider Organization (PPO)-like plan, or a high-deductible plan. These categories came from assigning the 8 plan types described in the MarketScan data to these descriptive categories. The *prescription characteristics* considered for inclusion in the models were the day-supply dispensed for that fill, the patient copay for the fill, and whether the prescription was filled by a mail order or a retail pharmacy. The *state laws* included as potential determinants were the pharmacist generic substitution laws (mandatory versus permissive) and whether or not patient consent was required for substitution, as according to

the National Association of Boards of Pharmacy's Survey of State Pharmacy Laws.¹³ We used the State Pharmacy Laws in 2010 (Supplemental Appendix 2).

Statistical Analyses

We used mixed-effects logistic regression to estimate the independent relationship between the determinants of interest and generic substitution. Only drugs within a therapeutic class that were available generically in November 2013 were included in these analyses, consistent with modeling the GSR as the outcome of interest. The outcome is "1" if the patient received the generic product and "0" if the patient received the brand product. We separately modeled the determinants of generic substitution for each therapeutic class, using the same set of determinants to facilitate comparisons across classes. We included random effects for region, using the Metropolitan Statistical Areas as delineated by the US Office of Management and Budget. We included fixed effects for the determinants of interest. We used the glimmix command in SAS version 9.4 (SAS Institute, Cary, NC). Ultimately, the dispensed day-supply of a medication, the co-pay for the medication, and the site of fill (mail order or retail) were found to be highly collinear; thus, only the site of fill was included in the models.

Results

Population

More than 5.5 million unique medications of interest, within 26 therapeutic classes (representing 219 unique drugs), had been prescribed to this cohort of 4.2 million patients for use during the 7-day window of interest. (Table 1) The proportion of women filling these prescriptions greatly exceeded the proportion of men (63% vs. 37%). Seventy-five percent of the patients were insured by a plan comparable to a preferred provider organization. Very few patients had fee-for-service type insurance, that is, without incentives to use specific providers. More than three-quarters of the prescriptions were filled at retail pharmacies and less than one-quarter were filled via mail order. Fifty-eight percent of prescriptions were filled as a one-month supply or less rather than as a longer fill.

Therapeutic Classes of Interest

The GSRs during the study window ranged from 64% (thyroid hormones) to 100% in several classes, with 18 of the 26 classes having GSRs above 90% (Table 2). Eight classes met our criteria for examination of the determinants of generic drug use.

Day Supply and Retail or Mail Order Fills

As expected, there was a strong correlation between the day- supply dispensed and whether the prescription was a retail or mail order fill, with the mail order fills more likely than the retail fills to be for more than 30 days of drug. The mean day supply for the mail order fills was 88 days (SD 9.6) with a median of 90 days and the mean day supply for the retail fills was 45 days (SD 27 days) with a median of 30 days. Of the mail order prescriptions, only 1.8 percent were 30 days or less; for the retail fills, 72 percent were 30 days or less.

Determinants of Generic Substitution

The determinants of generic substitution varied markedly across the therapeutic classes, both in bivariate [not shown] and multivariate analyses (Table 3). Younger age was a predictor of generic utilization for five of the eight tested therapeutic classes. However, in three classes, the older individuals were more likely than the younger to use generics (immunosuppressants, stimulants, thyroid hormones). Men and women differed in their likelihood of filling prescriptions, with men more likely to fill with generics than women in six of the seven tested classes. Women were more likely than men to fill immunosuppressants with a generic product. The presence of comorbid illnesses, as classified by the Charlson Comorbidity Index, did not systematically predict use of generic products, that is, the influence of comorbid illness on generic substitution varied across classes. Patients with a higher medication burden were more likely to fill the index prescription with a generic product for six of the eight studied classes.

The impact of insurance type on generic substitution was also variable. Patients with any insurance product *other* than fee-for-service (ie, comparable to a health maintenance organization, a preferred provider organization, or a high-deductible plan) were markedly less likely to use generic ophthalmic drugs than fee-for-service beneficiaries. Yet, beneficiaries in high-deductible health plans were more likely than the fee-for-service beneficiaries to use generics in three classes: anticoagulants, stimulants, and thyroid hormones.

In five of the eight classes, the use of a mail order pharmacy rather than a retail pharmacy was associated with less generic substitution. This was most extreme for stimulant and thyroid hormone drugs (odds ratios of 0.36 and 0.16, respectively), but also so for anticoagulants, ophthalmic drugs, and estrogens.

The state laws had markedly inconsistent effects across the drug classes. In five of the eight classes, filling in a state that requires patient consent for substitution *raised* the likelihood of generic substitution, which would not be expected. The laws about mandatory or permissive substitution of generics by pharmacists had very little impact on the generic substitution rates, although not requiring substitution mandatorily reduced the use of generic ophthalmic drugs and thyroid hormones.

Explained and Unexplained Regional Variation

In the multivariate models, across the therapeutic classes, the intraclass correlations (ICC) for the MSAs were low, ranging from 2.9% to 12.5% suggesting there are only small differences in generic substitution across regions. Further, these ICCs were minimally different than the ICCs for the intercept-only models, suggesting that the included covariates explain little of the differences in use of generics between regions.

Discussion

Among these commercially insured adults across the United States in 2013, generic drug use was high among most of the selected therapeutic classes of interest. GSRs exceeded 90% for

many of these drug classes. However, classes remain where generic usage is less than might be optimal for high-value health care delivery.

In this study, we were most interested in understanding whether there are common determinants of generic drug use across classes, particularly if some might be amenable to interventions. Therefore, we found it informative to look across drug classes to identify patterns. We found differences across drug classes in the determinants of generic drug use, although there were patterns of interest.

The state-based laws regarding the required or not-required consent of the patient for generic substitution did not have consistent impact across classes, although the impact was strong for several classes. A study of Medicaid beneficiaries in 2006 and 2007 found that patient consent requirements for substitution were strongly negatively associated with generic substitution of simvastatin,¹⁶ while in our study, prescription fills in states that require patient consent for substitution increased the likelihood of generic substitution in five of the eight classes. However, the different patient populations, drugs of interest, and study years could explain the discrepant results. We wonder too if required consent may sometimes stimulate favorable discussions about generics. In that study described above,¹⁶ consistent with our findings, mandatory generic substitution laws had no statistically significant effect on the use of generic simvastatin.

A generic use pattern that was mostly consistent across therapeutic classes was the negative impact of mail order pharmacies on generic drug fills. An analysis of Medicare Part D data from 2010 reported that GSRs were slightly lower when drugs were filled by mail order pharmacies than in retail pharmacies (88.8% vs 91.4%) for the 300 most widely used products that were evaluated.¹⁷ In that study, retail pharmacies were more likely to have lower costs for products that included generic alternatives, while mail order pharmacies were more likely to have lower costs for drugs that were available only as brand drugs. This higher usage of brand products with use of mail order pharmacies was also seen in a study of two publicly funded prescription plans in Texas in 2004.¹⁸ In another study, older people initiating drugs with narrow therapeutic indices were more likely to fill generically at retail pharmacies than through mail order pharmacies.¹⁹ We hypothesize that lower costs for brand products at mail order pharmacies may encourage clinicians to choose brand name products or even to do *therapeutic* substitutions of brand drugs from within the same drug class although this was not studied in this present project.

The differences that we saw between mail order and retail pharmacy dispensing of generics suggest that there are competing interests at play. To receive favorable prices on brand products, pharmacies work with pharmacy benefit managers (PBMs) that negotiate prices with the drug manufacturers. Manufacturers of single-source drugs, many of which are brand drugs, charge different prices to different purchasers based on the volume purchased and the purchaser's ability to choose from among therapeutically similar drugs. PBMs can often negotiate lower prices on *brand* products for the large mail order pharmacies (eg, CVS Caremark) and the very large retail chains (eg, Walgreens) because they are such large purchasers. The same negotiations for *generic* products are often done by the pharmacies, rather than the PBM, since there are often, although certainly not always, multiple sources of

product and the pharmacies can choose between manufacturers.²⁰ Mail order pharmacies (and probably the very large retail pharmacies) also receive rebates from manufacturers on the basis of their ability to affect a drug's market share for a large number of consumers. These savings may be passed along to the consumer in the form of lower cost-sharing. Additionally, a mail order pharmacy is sometimes the "preferred pharmacy" for a prescription drug plan and is able to dispense branded drugs more cheaply because of the negotiation of the PBM on behalf of the drug plan. These may be explanations for why the mail order pharmacies can offer lower brand drug prices than retail pharmacies, which would support our observation of less generic substitution with mail order fills in five of the eight classes. The individuals in our cohort are all commercially insured by large employers and most have some sort of managed care plan for their insurance coverage; we expect that these plans most likely employ PBMs for negotiation of drug prices preferentially with mail order pharmacies.

As stated, the absence of information about formularies and the copays of the different tiers of drugs limits our ability to know for certain how costs influenced patients' choices about generic and brand usage. We excluded copays from our models as the copays are likely to be determined by the type of fill (generic or brand); we cannot know if the patient was aware of the copay prior to filling and whether this motivated the choice of brand or generic. Indeed, the use of data from November, after deductibles have been met, may have resulted in lower GSRs than would have been seen earlier in the calendar year. Patients taking more medications were more likely to use generics in six of the eight studied classes suggesting that patients or their physicians may be attending to the economic burden posed by multiple medications.

We recognize, too, that we had no information on individual formularies. Although most formularies allow unrestricted access to generics, this is not uniformly so. Also, many plans have generics in more than one tier of copayments, which may affect utilization. We could not know the tier structure from these data. We also did not have information on patient's socioeconomic status or race for inclusion in our models, nor could we account for patients who filled prescriptions without using their insurance. The complicated interplay between copay, site of fill, and the quantity of the fill may best be disentangled with panel data.

Where else might there be opportunities to intervene to increase generic substitution? There remains reluctance among prescribers to use generics although much of the literature about generic prescribing barriers is from the UK and other European countries. In one highly relevant US study, from 2002, the investigators used a database of 6380 prescription orders to look at the association of prescriber, pharmacist, insurance, patient, and drug variables with the prescribing of generic drugs.²¹ Among other findings, they reported that unobserved prescriber characteristics accounted for 23 percent (95% CI, 14%–34%) of the variance in the opportunity for generic drug use. A recent survey of physicians found a shift in the perceptions of board-certified internal medicine physicians and certain specialists toward their having greater confidence in generic drugs' quality and safety.¹¹ Our regional variation in generic usage was fairly low; this provides support for similar generic prescribing patterns by physicians nationwide. Accountable care organizations are

implementing established and novel interventions to optimize medication use including expanded use of generic products.²²

Conclusions

The determinants of generic drug use varied across drug classes albeit with some important patterns emerging. Ultimately, stakeholders committed to getting affordable medications to patients and impacting the healthcare system may need to focus specifically on classes with substantially low GSRs, and on classes where there is a high volume of drug use or expensive brand drugs; and design targeted interventions according to the observed determinants. Additionally, further investigation of the impact of mail order pharmacies, or PBMs, may be indicated if the goal is increased generic usage nationwide for the affected therapeutic classes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Funding

This work was funded by a grant (U010005267) from the Food and Drug Administration. As this was a cooperative agreement, the funders participated in the design of the study and interpretation of study results, but had no role in the decision to publish the results. 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.

References

1. US Department of Health & Human Services, Office of the Assistant Secretary for Planning and Evaluation. ASPE Issue Brief. Expanding the Use of Generic Drugs. <https://aspe.hhs.gov/basic-report/expanding-use-generic-drugs> Published December 1, 2010.
2. Quintiles IMS. Medicines use and spending in the US. http://www.imshealth.com/en_US/thought-leadership/quintilesims-institute/reports/medicines-use-and-spending-in-the-us-review-of-2016-outlook-to-2021#form.
3. Keenum AJ, Chisolm DJ, Wallace LS. Generic medications for you, but brand-name medications for me. *Res Social Adm Pharm*. 2012;8(6):574–578. [PubMed: 22357268]
4. Dunne SS, Shannon B, Cullen W, Dunne CP. Perceptions and attitudes of community pharmacists towards generic medicines. *JManag Care Spec Pharm*. 2014;20(11):1138–1146. [PubMed: 25351975]
5. Nielsen KA, Dahl M, Tommerup E, Hansen B, Erdal J, Wolf P. Diurnal lamotrigine plasma level fluctuations: clinical significance and indication of shorter half-life with chronic administration. *Epilepsy Behav*. 2008;13(3):470–473. [PubMed: 18611447]
6. Halkin H, Shapiro J, Kurnik D, Loebstein R, Shalev V, Kokia E. Increased warfarin doses and decreased international normalized ratio response after nationwide generic switching. *Clin Pharmacol Ther*. 2003;74(3):215–221. [PubMed: 12966365]
7. Piette JD, Heisler M, Harand A, Juip M. Beliefs about prescription medications among patients with diabetes: variation across racial groups and influences on cost-related medication underuse. *J Health Care Poor Underserved*. 2010;21(1):349–361. [PubMed: 20173274]
8. Sewell K, Andreae S, Luke E, Safford MM. Perceptions of and barriers to use of generic medications in a rural African American population, Alabama, 2011. *Prev Chronic Dis*. 2012;9:E142. [PubMed: 22935144]

9. Omojasola A, Hernandez M, Sansgiry S, Jones L. Perception of generic prescription drugs and utilization of generic drug discount programs. *Ethn Dis* 2012;22(4):479–485. [PubMed: 23140080]
10. Shrank WH, Cox ER, Fischer MA, Mehta J, Choudhry NK. Patients' perceptions of generic medications. *Health Aff (Millwood)*. 2009;28(2):546–556. [PubMed: 19276015]
11. Kesselheim AS, Gagne JJ, Eddings W, et al. Prevalence and predictors of generic drug skepticism among physicians: results of a national survey. *JAMA Intern Med*. 2016;176(6):845–710. [PubMed: 27158897]
12. Kesselheim AS, Gagne JJ, Franklin JM, et al. Variations in patient's perception and use of generic drugs: results of a national survey. *J Gen Intern Med*. 2016;31(6):609–614. [PubMed: 26883524]
13. Survey of Pharmacy Law—2015. Mount Prospect, IL: National Association of Boards of Pharmacy, 2016.
14. Levinson DR. Generic drug utilization in state Medicaid programs, 2006 Department of Health and Human Services, Office of Inspector General. Published November 2007. Report no. OEI- 05–07-00130.
15. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis*. 1987;40(5):373–383. [PubMed: 3558716]
16. Shrank WH, Choudhry NK, Agnew-Blais J, et al. State generic substitution laws can lower drug outlays under Medicaid. *Health Aff (Millwood)*. 2010;29(7):1383–1390. [PubMed: 20606192]
17. Carroll NV. A comparison of costs of Medicare Part D prescriptions dispensed at retail and mail order pharmacies. *J Manag Care Spec Pharm*. 2014;20(9):959–967. [PubMed: 25166295]
18. Johnsrud M, Lawson KA, Shepherd MD. Comparison of mailorder with community pharmacy in plan sponsor cost and member cost in two large pharmacy benefit plans. *J Manag Care Pharm*. 2007;13(2):122–134. [PubMed: 17330973]
19. Gagne JJ, Polinski JM, Kesselhiem AS, et al. Patterns and predictors of Generic Narrow Therapeutic Index drug use among older adults. *J Am Geriatr Soc*. 2013;61:1586–1591. [PubMed: 24001285]
20. The Congress of the United States. Congressional Budget Office. Prescription Drug Pricing in the Private Sector. Pub. No. 2703. 1 2007.
21. Mott DA, Cline RR. Exploring generic drug use behavior: the role of prescribers and pharmacists in the opportunity for generic drug use and generic substitution. *Med Care*. 2002;40(8):662–674. [PubMed: 12187180]
22. Wilks C, Krisle E, Westrich K, Lunner K, Muhlestein D, Dubois R. Optimization of medication use at accountable care organizations. *J Manag Care Spec Pharm*. 2017;23(10):1054–1064. [PubMed: 28944730]

Table 1.

Characteristics of Patients and Prescriptions Dispensed for Drugs Where a Generic Drug Option Was Available in 1 Week in November 2013 Among 26 Therapeutic Classes of Interest.

Characteristics of recipient (N = 4,676,167 people)	
Age, y, mean (SD)	45.4 (15)
Gender, %	
Females	63.1
Males	36.8
Charlson Comorbidity Index, %	
None	88.0
1	7.5
2 or more	4.6
Insurance type, %	
Basic/major medical/comprehensive	2.9
PPO-like	75.3
HMO-like	15.5
HDHP	4.8
Unspecified	1.5
Medication burden, mean count of products (SD)	3.6 (3.0)
Characteristics of the prescription (N = 5,710,549 prescriptions)	
Copayments, %	
\$0	27.7
\$1–\$10	37.2
\$11–\$25	19.0
>\$25	14.9
Unspecified	1.3
Medication day supply, %	
30-d supply or less	58.7
31–90-d supply	41.3
Pharmacy type, %	
Retail	77.1
Mail order	20.8
Unspecified	2.0
State generic substitution laws, %	
Mandatory	13.6
Permissive	82.5
None (Oklahoma)	0.7
Unspecified ^a	3.17
Prescription patient consent requirement, %	
Not required for generic substitution	36.0

Required for generic substitution	60.9
Unspecified ^a	3.1

^aDue to missing patient geographic information.

Abbreviations: HDHP, insurance is similar to a high deductible health plan; HMO, insurance is similar to a health maintenance organization plan; PPO, insurance is similar to a preferred provider organization plan; SD, standard deviation.

Table 2.
Generic Substitutions Rates for 1 Week in November 2013, Ordered by Generic Substitution Rate.

Therapeutic Class	Generic Substitution Rate % (95% CI)	Therapeutic Class	Generic Substitution Rate % (95% CI)
Thyroid hormones	64 (64 to 64)	Cardiac, antiarrhythmic agents ^a	97 (97 to 97)
Estrogens and combinations	71 (71 to 72)	ARBs/ combinations ^a	98 (98 to 98)
Anticonvulsants, hydantoin	72 (71 to 72)	Adrenal hormones and combinations ^a	98 (98 to 98)
Androgens and combinations	74 (74 to 75)	Antipsychotics ^a	99 (98 to 99)
Immunosuppressants	82 (82 to 82)	Antidepressants ^a	99 (98 to 99)
Parathyroid hormones (calcitonin, spray) ^a	83 (82 to 84)	Antiplatelet Agents ^a	99 (99 to 99)
Ocular preparations for pressure lowering	85 (84 to 85)	Vasodilating Agents ^a	99 (99 to 99)
Stimulant, amphetamine type	90 (90 to 90)	Antimanic agents ^a (lithium)	99 (99 to 99)
Anticonvulsants, succinimides ^a	92 (92 to 93)	Sympathomimetic agents ^a	99 (99 to 99)
Anticoagulants (warfarin)	95 (95 to 96)	Bladder muscle relaxants ^a	100 (99 to 100)
Anticonvulsants, miscellaneous ^a	96 (96 to 96)	Antiemetics ^a	100 (99 to 100)
Vascular 5HT1 AGONIST ^a	96 (96 to 97)	Amebicides ^a (puromycin)	100 (99 to 100)
Anesthetics, local (lidocaine) ^a	97 (95 to 98)	Antigout ^a	100 (99 to 100)

Abbreviations: ARBs, angiotensin receptor blocker, 5-hydroxytryptamine; CI confidence interval.

^aSome classes not selected for modeling due to very high GSR (>95%), low total usage, or very mixed product class.

Table 3.

Odds Ratios for Generic Substitution Relative to Reference Group.^a

	Androgens			Anticoagulants			Anticonvulsants			Ophthalmic Drugs			Estrogens			Immunosuppressants			Stimulants			Thyroid Hormones		
	OR	LL	UL	OR	LL	UL	OR	LL	UL	OR	LL	UL	OR	LL	UL	OR	LL	UL	OR	LL	UL	OR	LL	UL
	(N = 20,924)			(N = 69,512)			(N = 12,187)			(N = 55,066)			(N = 194,982)			(N = 20,459)			(N = 306,746)			(N = 916,831)		
For each 5-year change in age	0.97	0.95	0.98	0.97	0.95	0.99	0.94	0.92	0.96	0.99	0.97	1.00	0.91	0.91	0.92	1.07	1.05	1.08	1.01	1.00	1.01	1.02	1.01	1.02
Men	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Women	0.69	0.59	0.82	0.70	0.65	0.76	0.84	0.77	0.91	0.91	0.87	0.96	NA	NA	NA	1.23	1.14	1.32	0.89	0.87	0.91	0.71	0.70	0.72
For every 1-drug increase	1.01	1.00	1.01	1.02	1.01	1.03	1.08	1.06	1.10	1.00	0.99	1.00	1.04	1.04	1.05	1.00	0.99	1.01	1.06	1.05	1.06	1.05	1.05	1.05
Fee-for-service [ref]	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
HMO type	1.11	0.92	1.34	1.05	0.88	1.26	0.89	0.72	1.09	0.60	0.52	0.69	0.96	0.90	1.02	0.83	0.65	1.06	0.81	0.72	0.91	1.77	1.72	1.82
PPO type	1.08	0.88	1.33	1.48	1.20	1.82	1.21	0.96	1.53	0.78	0.67	0.91	1.35	1.26	1.44	0.89	0.68	1.17	0.42	0.37	0.47	3.41	3.30	3.52
High-deductible plan	0.82	0.66	1.03	1.30	1.01	1.68	0.95	0.72	1.26	0.80	0.67	0.97	1.06	0.98	1.14	0.91	0.67	1.25	1.35	1.19	1.54	1.68	1.63	1.74
Charlson Comorbidity Index of 0 [ref]	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Charlson Comorbidity Index of 1	0.98	0.91	1.05	1.13	1.03	1.24	1.23	1.09	1.38	1.03	0.97	1.10	1.03	1.00	1.06	0.64	0.54	0.76	0.97	0.93	1.00	1.01	1.00	1.03
Charlson Comorbidity Index of 2 or more	1.01	0.93	1.10	1.48	1.34	1.62	1.46	1.28	1.65	1.07	1.00	1.14	0.98	0.94	1.02	0.40	0.35	0.47	0.99	0.92	1.06	0.80	0.79	0.81
No patient consent required [ref]	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Patient consent required	1.19	1.09	1.29	1.25	1.11	1.41	1.09	0.98	1.22	0.93	0.86	1.01	0.92	0.88	0.96	1.41	1.24	1.60	1.39	1.31	1.47	1.04	1.02	1.07
Substitution mandatory [ref]	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00

	Androgens (N = 20,924)			Anticoagulants (N = 69,512)			Anticonvulsants (N = 12,187)			Ophthalmic Drugs (N = 55,066)			Estrogens (N = 194,982)			Immunosuppressants (N = 20,459)			Stimulants (N = 306,746)			Thyroid Hormones (N = 916,831)		
	OR	LL	UL	OR	LL	UL	OR	LL	UL	OR	LL	UL	OR	LL	UL	OR	LL	UL	OR	LL	UL	OR	LL	UL
Substitution permitted, not mandatory	1.32	0.92	1.88	0.94	0.52	1.71	1.46	0.80	2.67	0.58	0.39	0.85	0.85	0.71	1.02	1.27	0.62	2.60	1.26	0.92	1.73	0.61	0.55	0.68
No substitution permitted	1.47	1.30	1.67	0.91	0.77	1.07	1.09	0.93	1.27	1.07	0.96	1.19	1.10	1.03	1.16	1.01	0.85	1.21	0.92	0.84	1.00	0.98	0.95	1.01
Retail fill [ref]	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Mail order fill	0.98	0.89	1.08	0.77	0.70	0.84	1.08	0.98	1.19	0.78	0.74	0.83	0.59	0.58	0.60	1.15	1.05	1.25	0.36	0.35	0.38	0.16	0.16	0.16

Abbreviations: LL, lower limit of 95% confidence interval; OR, odds ratio; UL, upper limit of 95% confidence interval.

^aModels include all covariates shown in table; dark-gray cells are point estimates below 1.0 where 95% confidence interval does not include 1, light-gray cells are point estimates above 1.0 where 95% confidence interval does not include 1.