

Patterns and Predictors of Generic Narrow Therapeutic Index Drug Use Among Older Adults

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OBJECTIVES: To ascertain predictors of initiation of brand-name versus generic narrow therapeutic index (NTI) drugs.

DESIGN: Retrospective cohort study.

SETTING: Data from CVS Caremark were linked to Medicare claims and to U.S. census data.

PARTICIPANTS: Individuals aged 65 and older who initiated an NTI drug in 2006 and 2007 (N = 36,832).

MEASUREMENTS: Demographic, health service utilization, and geographic predictors of whether participants initiated a generic or brand-name version of their NTI drug were identified using logistic regression.

RESULTS: Overall, 30,014 (81.5%) participants started on a generic version of their NTI drug. The most commonly initiated NTI drugs were warfarin (n = 17,790; 48%), levothyroxine (n = 10,779; 29%), and digoxin (n = 6,414; 17%). Older age (odds ratio (OR) = 1.12, 95% confidence interval (CI) = 1.02–1.22 comparing aged ≥85 with 65–74), higher burden of comorbidity (OR = 1.05, 95% CI = 1.04–1.07 for each 1-point increase in comorbidity score), and prior use of any generic drug (OR = 1.55, 95% CI = 1.29–1.87) were positively associated with generic drug initiation. Independent of other predictors, residing in the census block group with the highest generic use was positively associated with greater odds of generic NTI drug initiation (OR = 1.24, 95% CI = 1.14–1.35 compared with the lowest quintile).

CONCLUSION: Demographic, health service utilization, and geographic characteristics are important determinants of whether individuals initiate treatment with a brand-name or generic NTI drug. These factors may contribute to

disparities in care and highlight potential targets for educational campaigns. *J Am Geriatr Soc* 61:1586–1591, 2013.

Key words: health services research; pharmacoepidemiology; utilization; drugs; Medicare

Generic drugs lessen out-of-pocket drug costs,¹ which promotes better medication adherence² and may lead to better clinical outcomes.³ They also reduce overall health system spending.^{4,5} Despite the potential clinical gains and financial savings associated with their use, people do not always use generic drugs when they are available.

Several studies have identified patient and physician characteristics that are related to generic drug use, including patient income and physician specialty,^{6–9} but no study has examined predictors of narrow therapeutic index (NTI) drugs, for which determinants of generic versus brand-name drug use may be different. NTI drugs are products for which small differences in dose or concentration can lead to serious concentration-dependent therapeutic failures or adverse drug events.¹⁰ These drugs (also called critical dose drugs) often require therapeutic drug concentration or pharmacodynamic monitoring and include commonly used drugs such as warfarin, digoxin, levothyroxine, and phenytoin. Although all generic drugs contain the same amounts of the same active ingredients as their brand-name counterparts, and the U.S. Food and Drug Administration (FDA) must certify them as bioequivalent before they can be approved, small allowable differences in bioavailability have led some to question the safety and effectiveness of generic NTI drugs.¹¹

The current study sought to better understand factors related to receiving a generic NTI drug in a cohort of older adults initiating NTI drugs.

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METHODS

The Brigham and Women's Hospital institutional review board approved the study.

Data Source

Prescription drug data from 2005 to 2007 from CVS Caremark, a large national conglomerate with pharmacy benefits management and retail pharmacy operations in the United States, were used. The drug data were linked to diagnostic, healthcare utilization, and demographic data from Medicare Parts A and B and enrollment files and to U.S. Census data at the census block group level. Medicare beneficiaries aged 65 and older who had prescription drug coverage from a retiree drug plan in 2006 and 2007 were identified.

Participants

Because the FDA does not formally designate specific NTI drugs, the study focused on NTI drugs as defined by the North Carolina Board of Pharmacy.¹² Specifically, individuals who initiated an oral solid dosage form of carbamazepine, cyclosporine, digoxin, levothyroxine, lithium, phenytoin, procainamide, or warfarin were identified. Ethosuximide was excluded because only one eligible individual in the database initiated it during the study period. Tacrolimus was also excluded because generic versions were not available in the United States during the study period. Theophylline was excluded because no versions used by participants during the study period were identified as brand-name products.

Participants' index dates were defined as the dispensation date of their first prescription dispensation for a study drug during 2006 or 2007 after a minimum 365-day period with no use of that drug. Participants were required to have a minimum of 365 days of continuous enrollment in Caremark and Medicare leading up to the index date to ensure new user status and sufficient opportunity to capture predictors of interest. If a participant initiated more than one NTI drug, only the first occurrence was included.

Outcomes

The main outcome of interest was whether a participant's index prescription was for a generic or brand-name version. Generic versions were distinguished from brand-name versions using the FDA's Approved Drug Products with Therapeutic Equivalence Evaluations (the Orange Book), which lists all FDA-approved drug products and therapeutic equivalence evaluations.¹³ Reference listed drugs are products with which generic versions are compared in bioequivalence studies required for market authorization.

Predictors

Participant demographic, comorbidity, and health service utilization variables during the 365 days preceding each participant's index prescription date were measured. Demographic variables included age, sex, and race. To ascertain participant comorbidity, a measure that combines

conditions from the Charlson Index and the Elixhauser system into a single numeric index was used.¹⁴ Whether participants received their index prescription through a retail or mail order pharmacy was also determined, and other health service utilization variables, including number of physician visits in the prior year; number of unique drugs, dosage forms, and strengths used (as defined by the Generic Product Identifier (GPI)); whether participants had any nursing home stay, emergency department visit, or hospitalization during the prior year; and whether participants had used one or more other generic drugs in the prior year, were measured.

Participants' street addresses were geocoded and linked to U.S. Census 2000 data at the block group level, which is the smallest level for which census data are made publicly available. The median age, median unemployment rate, median household income, and median home value in each participant's census block group were identified. For each census block group containing at least one analysis-eligible participant, total prescriptions filled for all drugs (NTI and non-NTI) by all participants in the database (those who initiated NTI drugs and those who did not) who resided in the block group were enumerated over a 1-year period. The proportion of prescriptions filled as generics in each block group was then calculated. Census-level variables were discretized into quintiles for analysis.

Statistical Analysis

Descriptive statistics of NTI drug initiators were tabulated, and univariate odds ratios (ORs) and 95% confidence intervals (CIs) were estimated to describe the associations between each covariate described above and initiation of a generic versus brand-name NTI drug. A multivariable logistic regression model that included all covariates as independent variables was then constructed.

RESULTS

Description of Cohort

A cohort of 36,832 participants who initiated an NTI drug of interest in the study time period was identified. The mean age of the cohort was 76.6 ± 7.2 , 54% were female, and 94% were white (Table 1). Sixty percent of participants ($n = 22,012$) had used more than 10 different GPI combinations in the year leading up to the index date, and 98% had received one or more generic drugs in the prior year ($n = 35,910$). The most commonly initiated NTI drugs were warfarin ($n = 17,790$, 48%), levothyroxine ($n = 10,779$, 29%), and digoxin ($n = 6,414$, 17%). Overall, 30,014 (81.5%) participants started on a generic version of their NTI drugs.

Predictors of Generic NTI Initiation

In univariate and multivariable analyses, older age was associated with greater likelihood of initiating a generic drug (odds ratio (OR) = 1.15, 95% confidence interval (CI) = 1.08–1.22 aged 75–84 vs 65–74; OR = 1.12, 95% CI = 1.02–1.22 aged ≥ 85 vs 65–74; Table 2). Degree of comorbidity (OR = 1.05, 95% CI = 1.04–1.07 for each

Table 1. Characteristics of Participants Initiating Narrow Therapeutic Index Drugs

Characteristic	Total, n = 36,832	Generic Initiators, n = 30,014	Brand-Name Initiators, n = 6,818
Female	19,960 (54.2)	15,959 (53.2)	4,001 (58.7)
Age, n (%)			
65–74	15,560 (42.3)	12,379 (41.2)	3,181 (46.7)
75–84	15,640 (42.5)	12,928 (43.1)	2,712 (39.8)
≥85	5,632 (15.3)	4,707 (15.7)	925 (13.6)
Race and ethnicity, n (%)			
White	34,669 (94.0)	28,237 (94.1)	6,432 (94.3)
Black	1,606 (4.4)	1,347 (4.5)	259 (3.8)
Hispanic	193 (0.5)	160 (0.5)	33 (0.5)
Asian	82 (0.2)	62 (0.2)	20 (0.3)
Native American	66 (0.2)	40 (0.1)	26 (0.4)
Other or unknown	216 (0.6)	168 (0.6)	48 (0.7)
Mail order prescription, n (%)	2,639 (7.2)	1,766 (5.9)	873 (12.8)
Comorbidity score, mean ± standard deviation	2.8 (3.1)	2.9 (3.1)	2.0 (2.8)
Index drug, n (%)			
Carbamazepine	648 (1.8)	477 (1.6)	171 (2.5)
Cyclosporine	123 (0.3)	57 (0.2)	66 (1.0)
Digoxin	6,414 (17.4)	5,899 (19.7)	515 (7.6)
Levothyroxine	10,779 (29.3)	7,043 (23.5)	3,736 (54.8)
Lithium	45 (0.1)	36 (0.1)	9 (0.1)
Phenytoin	1,017 (2.8)	851 (2.8)	166 (2.4)
Procainamide	16 (0.0)	10 (0.0)	6 (0.1)
Warfarin	17,790 (48.3)	15,641 (52.1)	2,149 (31.5)
Number of physician visits in prior year, median (interquartile range)	9 (4, 14)	9 (4, 14)	9 (5, 14)
Number of unique drugs, dosage forms, and strengths used in prior year, n (%)			
0–5	6,779 (18.4)	5,008 (16.7)	1,771 (26.0)
6–10	8,041 (21.8)	6,527 (21.8)	1,514 (22.2)
11–20	14,313 (38.9)	12,035 (40.1)	2,278 (33.4)
>20	7,699 (20.9)	6,444 (21.5)	1,255 (18.4)
Nursing home stay in prior year, n (%)	4,938 (13.4)	4,470 (14.5)	468 (6.9)
Emergency department visit in prior year, n (%)	16,489 (44.8)	14,065 (46.9)	2,424 (35.6)
Hospitalization in prior year, n (%)	21,158 (57.4)	18,489 (61.6)	2,669 (39.2)
Prior use of generic drug, n (%)	35,910 (97.5)	29,426 (98.0)	6,484 (95.1)

1-point increase in combined comorbidity score¹⁴), use of more GPI combinations (OR = 1.24, 95% CI = 1.13–1.37 comparing >20 with 0–5 drugs), and other health service use markers (nursing home stay, OR = 1.69, 95% CI = 1.51–1.89; hospitalization, OR = 1.43, 95% CI = 0.96–1.09) were all positively associated with generic drug initiation. Generic drug initiation was positively associated with prior use of any generic drug (OR = 1.55, 95% CI = 1.29–1.87).

Participants residing in census block groups in the highest quintile of median household income were less likely to initiate a generic NTI drug (OR = 0.85, 95% CI = 0.75–0.96 vs lowest quintile), whereas participants living in block groups with higher generic utilization were more likely to initiate a generic NTI drug (OR = 1.24, 95% CI = 1.14–1.35 vs lowest quintile).

DISCUSSION

Although previous research has identified various factors related to whether people use generic drugs, this study is the first to specifically assess determinants of generic NTI drug use. It was found that some predictors of whether individuals initiated generic NTI drugs differ from what

other research has found are predictors of whether individuals initiate other generic drugs.^{7–9} For example, previous studies have found that older age is not associated^{7,8} or inversely associated⁹ with the initiation of generic versus brand-name drugs. Older adults were more likely to initiate generic NTI drugs. Similarly, for Medicare beneficiaries, poorer health status has been previously associated with a lower likelihood of initiating generic cardiovascular medications.^{7,8} An inverse relation was also found between mail order use and generic NTI initiation, whereas other studies on general generic drug initiation have not. Finally, individuals living in census block groups with higher median household incomes were less likely to initiate generic NTI drugs, which is consistent with the association found in some but not all studies between income and generic drug initiation.

These findings are important because they may reflect differences in the use of generic NTI drugs and other generic drugs or changing attitudes and perceptions toward generics. Understanding factors related to generic NTI use can identify targets for improving prescribing patterns for these clinically important drugs. Reducing out-of-pocket spending on essential medications can enhance clinical

Table 2. Predictors of Whether Participants Starting on Narrow Therapeutic Index Drug Initiated a Generic Versus a Brand-Name Version

Characteristic	Odds Ratio (95% Confidence Interval)	
	Univariate	Multivariate
Female	0.81 (0.77–0.86)	0.83 (0.78–0.87)
Age (reference 65–74)		
75–84	1.22 (1.15–1.29)	1.15 (1.08–1.22)
≥85	1.31 (1.21–1.42)	1.12 (1.02–1.22)
White (vs all other races)	0.93 (0.83–1.05)	1.01 (0.89–1.14)
Mail order prescription (vs retail pharmacy)	0.42 (0.38–0.46)	0.57 (0.52–0.62)
Comorbidity score (per point increase)	1.11 (1.10–1.12)	1.05 (1.04–1.07)
Number of physician visits in prior year	0.99 (0.99–1.00)	0.98 (0.98–0.99)
Number of unique drugs, dosage forms, and strengths used in prior year (reference 0–5)		
6–10	1.47 (1.36–1.59)	1.21 (1.11–1.32)
11–20	1.80 (1.68–1.94)	1.34 (1.24–1.46)
>20	1.75 (1.61–1.91)	1.24 (1.13–1.37)
Nursing home stay in prior year	2.37 (2.14–2.62)	1.69 (1.51–1.89)
Emergency department visit in prior year	1.57 (1.49–1.66)	1.02 (0.96–1.09)
Hospitalization in prior year	2.46 (2.33–2.60)	1.43 (1.32–1.55)
Quintile of median age in census block group (reference 1)		
2	0.98 (0.90–1.07)	0.97 (0.88–1.06)
3	1.00 (0.91–1.09)	1.01 (0.92–1.10)
4	0.97 (0.89–1.06)	0.96 (0.87–1.05)
5	0.88 (0.81–0.95)	0.90 (0.82–0.98)
Quintile of median unemployment rate in census block group (reference 1)		
2	0.94 (0.86–1.02)	0.92 (0.85–1.01)
3	0.98 (0.90–1.07)	0.96 (0.88–1.05)
4	0.96 (0.88–1.04)	0.94 (0.86–1.03)
5	1.01 (0.93–1.10)	0.94 (0.86–1.03)
Quintile of median household income in census block group (reference 1)		
2	0.84 (0.77–0.91)	0.99 (0.90–1.09)
3	0.84 (0.77–0.92)	1.03 (0.93–1.14)
4	0.68 (0.63–0.74)	0.87 (0.78–0.97)
5	0.61 (0.56–0.66)	0.85 (0.75–0.96)
Quintile of median home value in census block group (reference 1)		
2	0.96 (0.88–1.04)	1.04 (0.94–1.14)
3	1.00 (0.92–1.09)	1.09 (0.99–1.21)
4	0.86 (0.79–0.94)	1.19 (1.07–1.33)
5	0.79 (0.73–0.86)	0.99 (0.88–1.12)
Prior use of generic drug	2.63 (2.22–3.13)	1.55 (1.29–1.87)
Quintile of proportion of drugs filled as generic in census block group (reference 1)		
2	1.16 (1.07–1.26)	1.03 (0.95–1.12)
3	1.29 (1.19–1.41)	1.14 (1.04–1.24)
4	1.39 (1.28–1.52)	1.20 (1.10–1.31)
5	1.32 (1.21–1.43)	1.24 (1.14–1.35)

outcomes,³ and use of generic drugs can reduce out-of-pocket spending while also reducing total health spending at a time of increasing concern over rising drug costs.¹⁵

Experience with one or more prior generic drugs was highly predictive of whether participants initiated generic or brand-name NTI drugs. To the knowledge of the authors, this is the first study to make this observation. Participants who used more drugs overall were also more likely to initiate generic NTI drugs. Participant and provider experiences may have contributed to these findings. Prior satisfaction with generic drugs may increase people's acceptance of generic versions of subsequent drugs, including NTI drugs. Conversely, some people may always opt for brand-name versions owing to fixed negative perceptions of generic drugs. Despite potential clinical gains and financial savings associated with generic drug use, negative perceptions of generic drugs remain prevalent. In a survey

of perceptions of generic drugs, nearly one-quarter of responding physicians expressed concerns about the efficacy of generic drugs, and almost half indicated concerns about the quality of generic drugs,¹⁶ but contrary to these negative perceptions, accumulating empirical evidence suggests that brand-name and generic drugs, including brand-name and generic NTI drugs, are equally safe and effective.^{17–21} Dispelling unwarranted negative perceptions of generic drugs, of providers and patients, may enhance the appropriate use of these medications.²² Increasing an individual's generic drug use may promote medication adherence,² which may improve clinical outcomes.³

Several census block group variables were associated with generic initiation. Participants living in areas where other people more commonly used generic drugs were themselves more likely to initiate a generic drug, independent of their age, comorbidity status, health service

utilization, and prior generic drug use. These findings may reflect differences in prescription drug benefit design and availability,²³ differences in geographic distributions of community pharmacy generic drug discount programs,²⁴ differential generic substitution laws,¹⁵ varying beliefs about the safety and effectiveness of generic drugs,¹⁶ and regional variation in the use of “dispense as written” designations by patients and prescribers requesting brand-name products where pharmacists would otherwise dispense generic versions.²⁵

The finding that greater degree of comorbidity was positively associated with initiation of a generic NTI drug may reflect that individuals with higher comorbidity burdens incur higher healthcare costs²⁶ and therefore may use generic drugs in an attempt to minimize costs. Additionally, whereas previous studies have reported mixed findings regarding the association between income and generic drug initiation, participants living in census blocks with higher median household incomes were less likely to initiate generic NTI drugs. This finding underscores the extent of diffusion of negative perceptions of generic NTI drugs. Individuals living in areas with higher household incomes tend to have higher health literacy,²⁷ but even specialists who prescribe NTI drugs report negative perceptions of generic versions of these drugs.²⁸

This study has a few notable limitations. Although it involved a large population of older adults receiving prescription drug coverage from retiree drug plans, predictors of generic NTI drugs might differ in other populations, such as younger populations and those receiving pharmacy benefits through Medicare’s prescription drug program. In particular, the study cohort was predominantly white, which may limit the generalizability of the findings. This study was the first to examine geographic variation in generic drug initiation, but the focus on the controversial subset of NTI drugs may limit generalizability to all generic drugs. In addition, the data source used does not contain prescriber information, so prescriber-level variables could not be evaluated as predictors of generic initiation. Finally, the fact that other studies have focused on different populations in addition to different types of drugs complicates the comparison between this study and prior studies that have examined predictors of generic drug use in general (e.g., cardiovascular vs NTI drugs).

Despite these limitations, prior experience with generic drug use increases people’s subsequent use of generic NTI drugs, and predictors of generic NTI drug initiation may differ from predictors of generic drug use overall. Where individuals live appears to be an important determinant of whether they begin therapy with a generic version of a NTI drug. In particular, individuals who live in areas where people commonly use generic drugs are much more likely to initiate generic NTI drugs, as are individuals who have previous experience with a generic drug, independent of where they live. Education and outreach programs and other interventions aimed at improving prescription benefit design and substitution laws should target communities with the lowest overall generic utilization. Future studies should also examine whether geography is also an important determinant of generic drug initiation in other drug groups and should focus on better understanding the underlying causes of geographic variation in generic drug use.

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