Comparison of clinical outcomes following a switch from a brand to an authorized vs. independent generic drug

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Background

- Generic drugs save healthcare dollars, but public perception about the potential for inferior efficacy and safety compared to the brand products sometimes limits adoption.
- Generic drugs can enter the U.S. market via two mechanisms:
  1. Generic drugs may be approved by the U.S. Food and Drug Administration (FDA) via an Abbreviated New Drug Application (ANDA) which requires demonstration of bioequivalence;
  2. Authorized generics (AGs) can enter the market under the reference products New Drug Application (NDA), and are pharmaceutically and therapeutically identical to the brand product.
- Comparison of clinical outcomes for patients switching from brand →AG vs. brand →ANDA-approved generic is a proxy evaluation of generic drug efficacy and safety, minimizing generic perception bias.

Objectives

- To compare brand-to-generic switching patterns among products with both an AG and one or more ANDA-approved generic drugs ("generics") competing in the market
- To broadly compare clinical outcomes following a switch from brand →AG vs. brand →generic

Methods

- A series of retrospective cohort studies were conducted among patients receiving select branded drugs prior to generic drug entry.
- Drugs were selected based on evidence that both an AG and generic were marketed at an overlapping point between the years 1999 and 2014.
- Health services use (i.e., outpatient, emergency department (ED), and hospitalization) and medication discontinuation were measured for up to 12 months following the brand →AG switch, brand →generic switch, or a randomly selected counterfactual switch date (for non-switchers).
- Multivariable Cox proportional hazards models were used to evaluate factors associated with the time to generic switch, reporting the median estimated hazard ratio (HR) and 95% confidence interval (CI) across 1000 bootstrapped samples.
- For binary outcome variables (hospitalization, ED events, and medication discontinuation), generalized logistic regression was used to fit a cumulative logit model reporting the median odds ratio (OR) and 95% CI across 20 bootstrapped samples.
- Negative binomial regression was used to model count variables (number of outpatient or urgent care visits), reporting the median rate ratio (RR) and 95% CI across 20 bootstrapped samples.

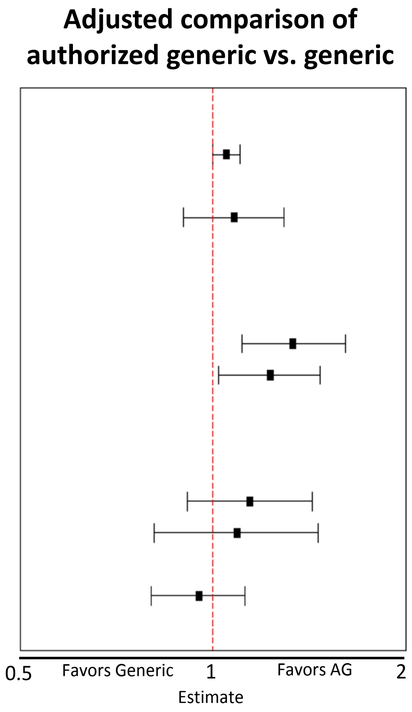
Results

Predictors of time to generic switch (N=5234)*	Hazard Ratio	95% Confidence Interval		P-value
		Lower Limit	Upper Limit	
Age (in years)	1.00	1.00	1.00	0.9313
Male	0.97	0.91	1.03	0.3593
Proportion of pre-index brand use; %	0.91	0.81	1.04	0.158
Pre-index defined daily dose	1.09	1.05	1.13	<0.0001
Charlson comorbidity index	0.98	0.95	1.01	0.1833
Pre-index hospitalization	1.15	1.02	1.29	0.0195
Pre-index ED visit	0.96	0.87	1.05	0.367
Pre-index outpatient visit count	1.00	1.00	1.00	0.8124
Alendronate**	1.25	1.15	1.36	<0.0001
Amlodipine	1.43	1.33	1.53	<0.0001
Citalopram	0.78	0.72	0.84	<0.0001
Gabapentin	0.67	0.58	0.77	<0.0001
Paroxetine	0.91	0.83	0.99	0.031
Sertraline	1.17	1.07	1.27	0.0006
Simvastatin	0.71	0.64	0.78	<0.0001

* Analyses include 5234 unique patients; for those (among the 5544) exposed to more than one of the seven drugs, the drug of first exposure is the drug analyzed.
** In the absence of a specific comparison (control) drug, we present results for each drug contrasted with the combined cohort for the other six drugs. Results for each drug come from separate models, each using a unique indicator (e.g., Alendronate=1, all other drugs=0).

Outcome	Estimate	Lower CI	Upper CI	P-Value
Number of all-cause outpatient visits per year	1.05	1	1.1	0.071
Number of all-cause urgent care visits per year	1.08	0.9	1.29	0.395
All-cause emergency department visits				
Any visit	1.33	1.11	1.61	0.003
Number per year	1.23	1.02	1.47	0.026
All-cause hospitalizations				
Any visit	1.14	0.91	1.43	0.257
Number per year	1.09	0.81	1.46	0.582
Medication discontinuation	0.95	0.8	1.12	0.508

Estimates greater than 1 suggest that the outcome was more likely to occur in the AG group, while estimates less than 1 suggest that the outcome was more likely to occur in the generic group.



Drug and health services utilization among non-switchers and switchers (by switch type)	Non-Switchers	Switchers by Type		AG vs. Generic P-value
		Brand to AG	Brand to Generic	
Annual number of all-cause outpatient visits (mean, 95% CI)	20.8 (18.4-23.6)	17.5 (16.6-18.5)	17.4 (16.9-17.9)	0.819
Annual number of all-cause urgent care visits (mean, 95% CI)	11.4 (8.2-15.8)	0.6 (0.5-0.7)	0.5 (0.5-0.6)	0.140
Annual all-cause emergency department visits				
Any visit (%, 95% CI)	32.2 (23.8-41.9)	27.6 (24.5-30.8)	22.8 (21.3-24.3)	0.006
Number per year (mean, 95% CI)	0.7 (0.4-1.0)	0.5 (0.4-0.6)	0.4 (0.4-0.5)	0.074
Annual all-cause hospitalizations				
Any visit (%, 95% CI)	26.0 (18.1-35.8)	17.7 (15.1-20.6)	17.7 (16.4-19.1)	0.997
Number per year (mean, 95% CI)	2.5 (1.4-4.6)	1.4 (1.0-1.8)	1.5 (1.3-1.7)	0.641
Medication discontinuation (%, 95% CI)	99.4 (99.2-99.6)	35.2 (32.0-38.5)	34.8 (33.2-36.5)	0.854

The difference in utilization between switchers to AG and switchers to generic was assessed via rate ratios for the negative binomial models and odds ratios for the logistic models, with statistical significance reflected by P<0.05.

- Switching from brand to generic was common (94% overall), with the majority of brand to generic switching (i.e., 80-95%) occurring within 3 months following generic entry.
- The mean observation time was 78 days for non-switchers, 220 days for switchers to AG, and 276 days for switchers to generic.
- Brand-to-generic switching was faster for alendronate, amlodipine, and sertraline, and slower for citalopram, gabapentin, paroxetine and simvastatin
- No statistically significant differences were found between the AG and the generic switch groups in terms of the number of outpatient visits, the number of urgent care visits, the occurrence or number of hospitalizations, or the occurrence of medication discontinuation (P>0.05).
- Emergency department visits were slightly higher for AGs compared with generics (OR = 1.33; 95% CI 1.11-1.61).

Discussion

- We observed a similar likelihood of outpatient visits, urgent care visits, hospitalizations, and medication discontinuation for patients switching from brand →AG vs. brand →generic.
- Higher likelihood of an ED visit among AG users compared with generic users is surprising, but still suggested that generics did not have worse outcomes than AGs (brand proxy).
- The individual drug analyses illustrated that the higher likelihood of an ED visit and the higher number of ED visits for AG vs. generic was driven by alendronate and amlodipine, while simvastatin illustrated an opposite relationship.
- Limitations included pooling of heterogeneous drugs when individual drugs may be different, differences in the timing of generic drug availability, limited sample size for some drugs, and potential confounding by regional differences in distribution of AGs vs. generics.

Conclusions

- This study found similar likelihood of hospitalization and medication discontinuation between AG and generic drugs.
- Results indirectly support similar outcomes for generic compared with brand drugs.
- Further investigation is needed to understand the higher ED visits occurrence among AG users compared to generic users.

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