Use of Regulatory Science Research to Support Post-marketing Surveillance of Generic Drug Products

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Why Generic Drug Surveillance?

New Drug Surveillance	Generic Drug Surveillance
Unknown safety risks in real-world patient population	Unexpected safety outcomes due to allowed differences
Surveillance of the active ingredient	Surveillance of the generic product
Patient and physician unfamiliarity	Perceptions about product quality inferiority
Focus: safety	Focus: substitutability

Postmarketing Surveillance in OGD

- Support OGD Clinical Safety and Surveillance Staff
- Follow up on reports and findings from published literature
- Respond to letters and public comments submitted to FDA

Today's Objective

- Describe the current extramural research activities sponsored by OGD to evaluate post-marketing generic drug substitutability

Methods development for generic drug surveillance

Substitution studies in:
- Patients
- Healthy subjects

Perception and education about generic drugs

Investigation of in-equivalence issues

Secondary Data Sources Used for Generic Drug Surveillance

- FDA adverse event reporting system (FAERS)
- Administrative claims data
  - Collected by health insurers for billing purposes
  - Includes information on health care visits, diagnoses, medical procedures, medications dispensed, costs
- Electronic health records
  - Maintained by health care organizations and institutions
  - Includes information on medical history, clinical diagnoses, laboratory and test results, medication orders
- Registries
  - Disease and drug registries

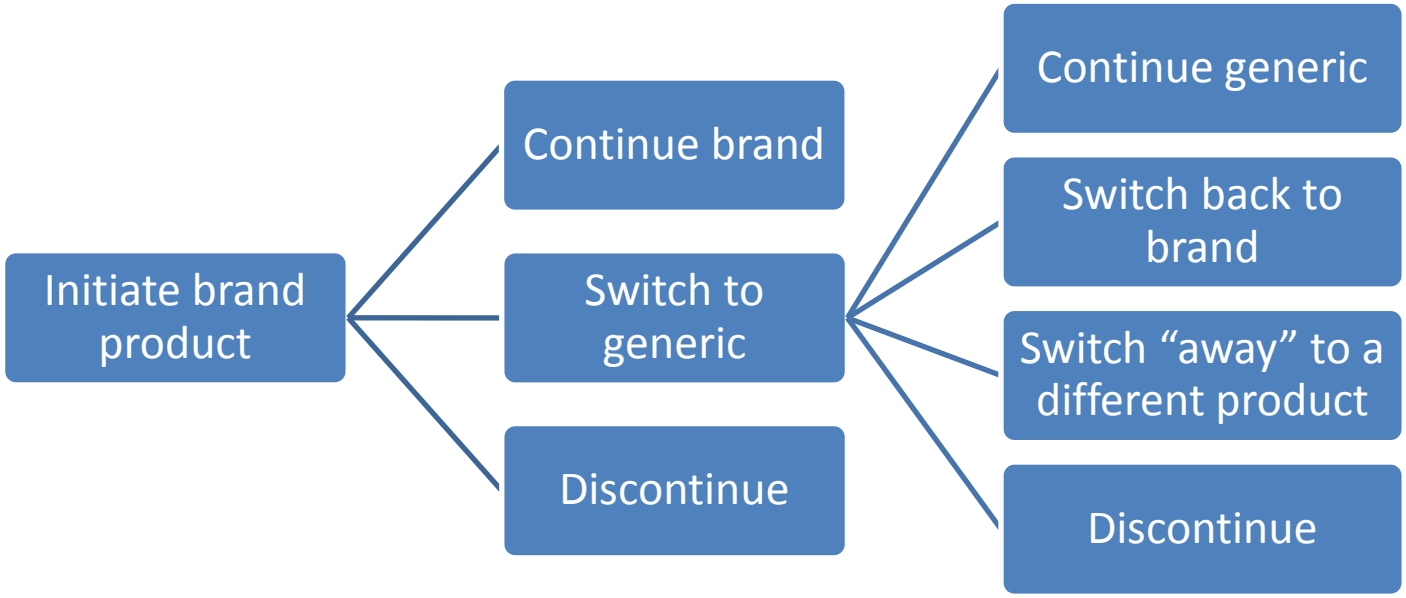
Methods Development Areas

1. Utilization and switching patterns
2. Equivalence in safety and effectiveness
3. Reduction of bias and error
4. Role of authorized generics
5. Analysis of FAERS data
6. Therapeutic class substitution

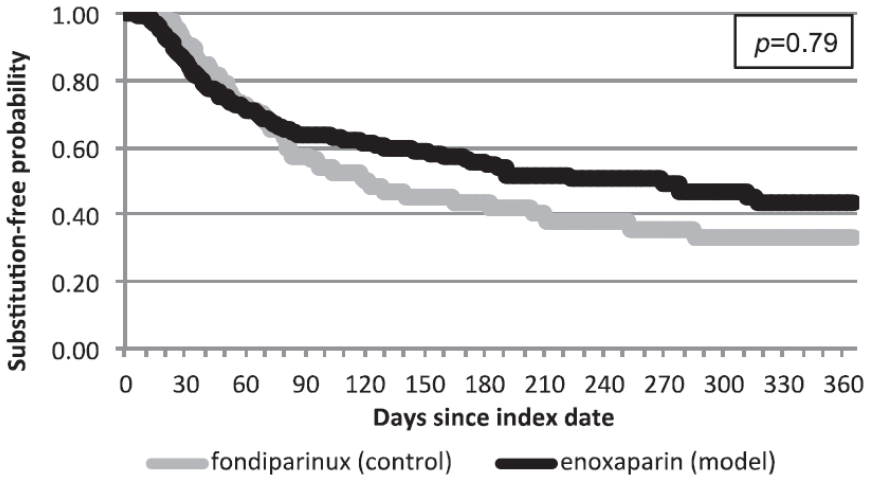
1. Utilization and Switching Patterns

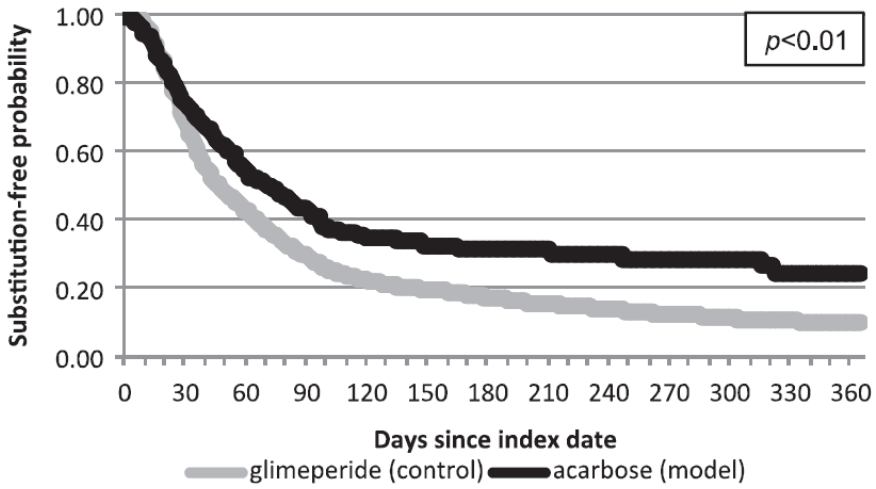
What evidence can utilization and switching patterns provide on generic substitution in the real-world?

- Can these patterns help identify substitutability issues?
- Do these patterns vary across populations?

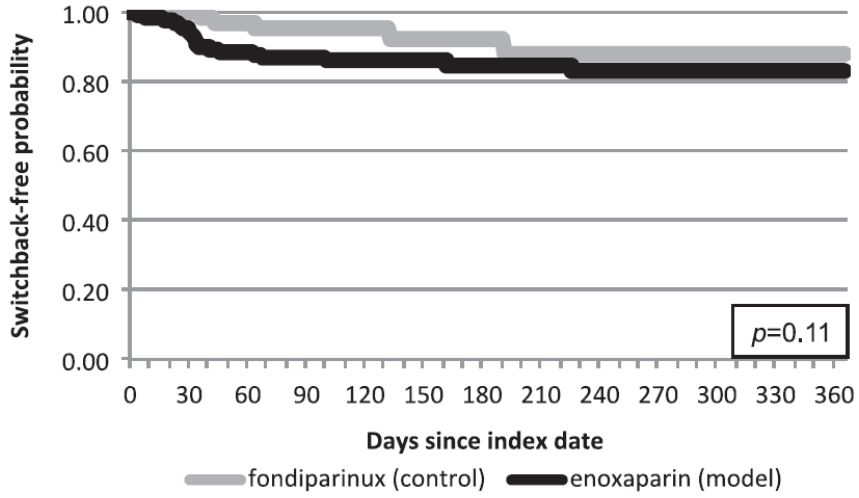


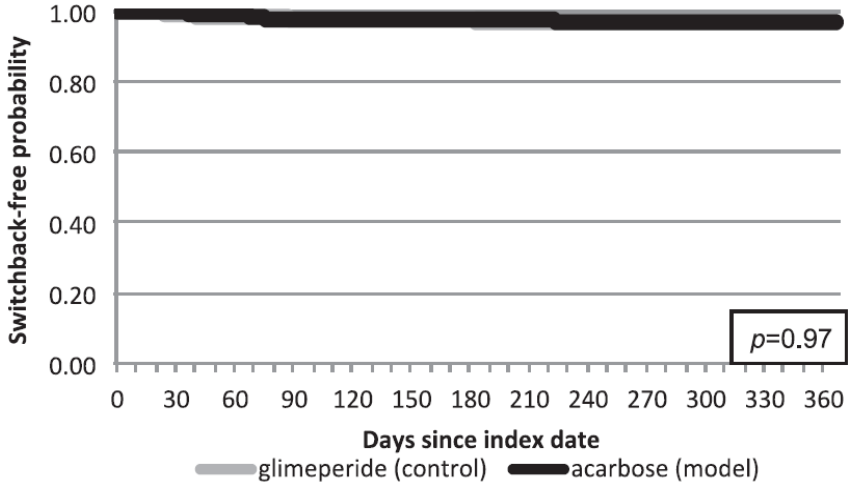
Brand-to-Generic Switch





Generic-to-Brand Switchback



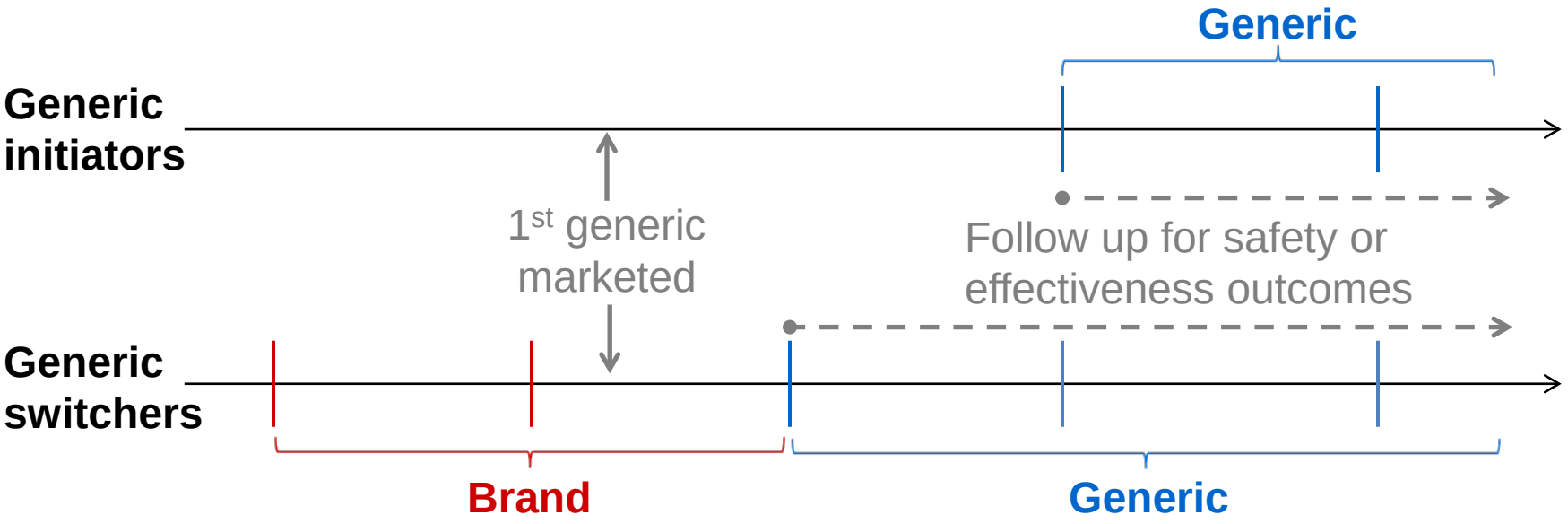


Gagne JJ et al. Switch-backs associated with generic drugs approved using product-specific determinations of therapeutic equivalence. Pharmacoepidemiol Drug Saf. 2016 Aug;25(8):944-52.

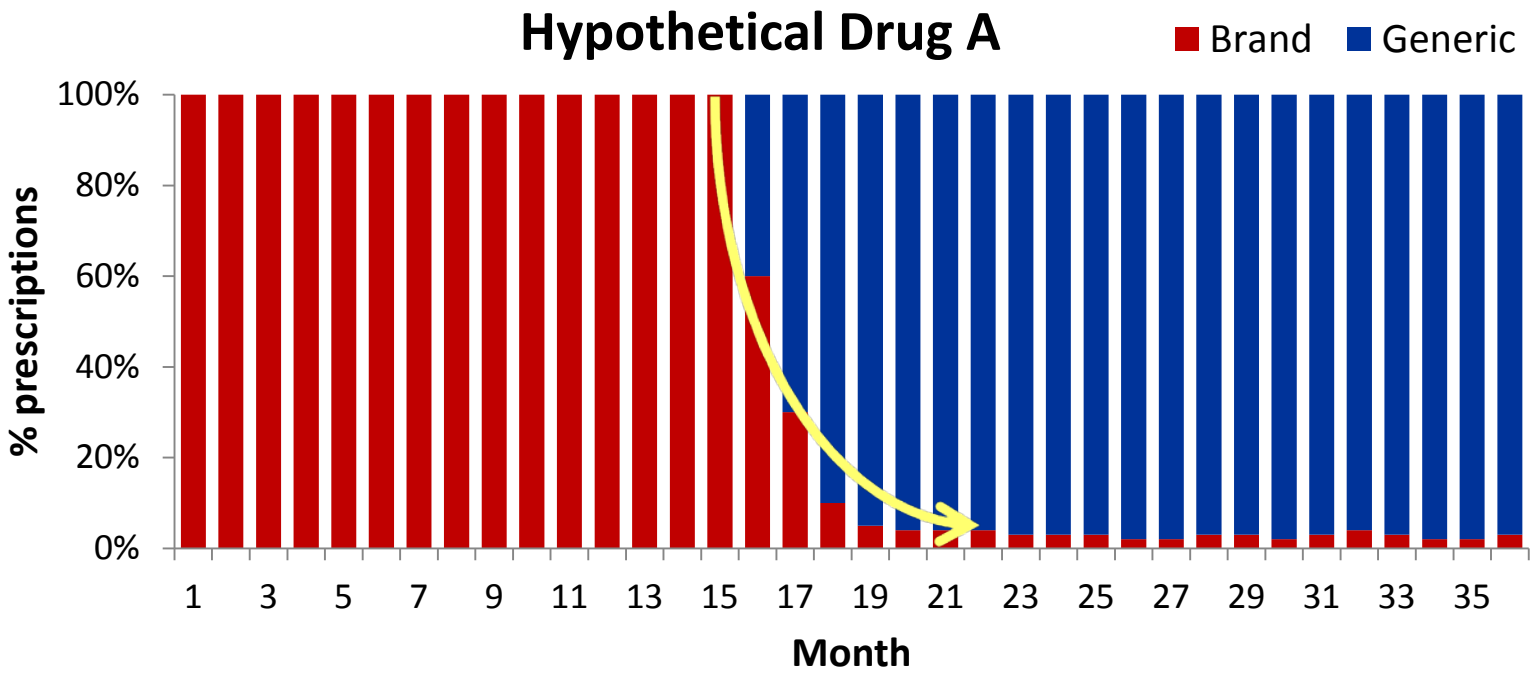
2. Equivalence in Safety and Effectiveness

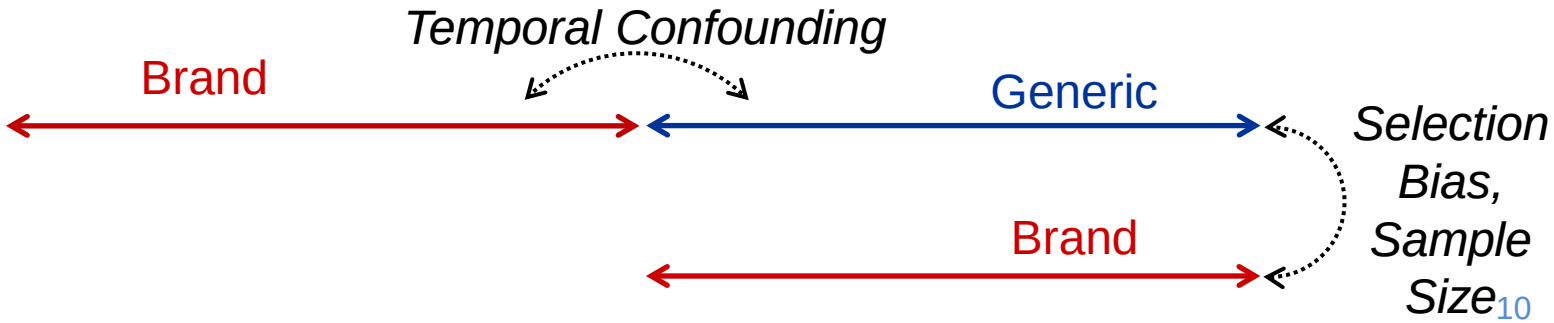
How can secondary data be used to assess safety and effectiveness of generic vs. brand name drugs?

- Clinical outcomes
- Health services outcomes
- Medication outcomes



3. Reduction of Bias and Error





3. Reduction of Bias and Error

Can we develop and apply methods to reduce bias and error in observational studies using secondary data?

- Confounding control
  - Cohort sample selection
  - Covariate control
- Analytical approaches
  - Summary score matching techniques (e.g., PS matching)
  - Difference-in-difference analysis
  - Regression discontinuity analysis
  - Machine learning
- Multiple linked data sources
  - Linked at patient-level or region-level

4. Role of Authorized Generics

Can authorized generics act as a "control" group to reduce bias in observational studies evaluating generic vs. brand name drugs?

Authorized generic: a listed drug that has been approved under subsection 505(c) of the act and is marketed, sold, or distributed directly or indirectly to retail class of trade with either labeling, packaging, product code, labeler code, trade name, or trade mark that differs from that of the listed drug

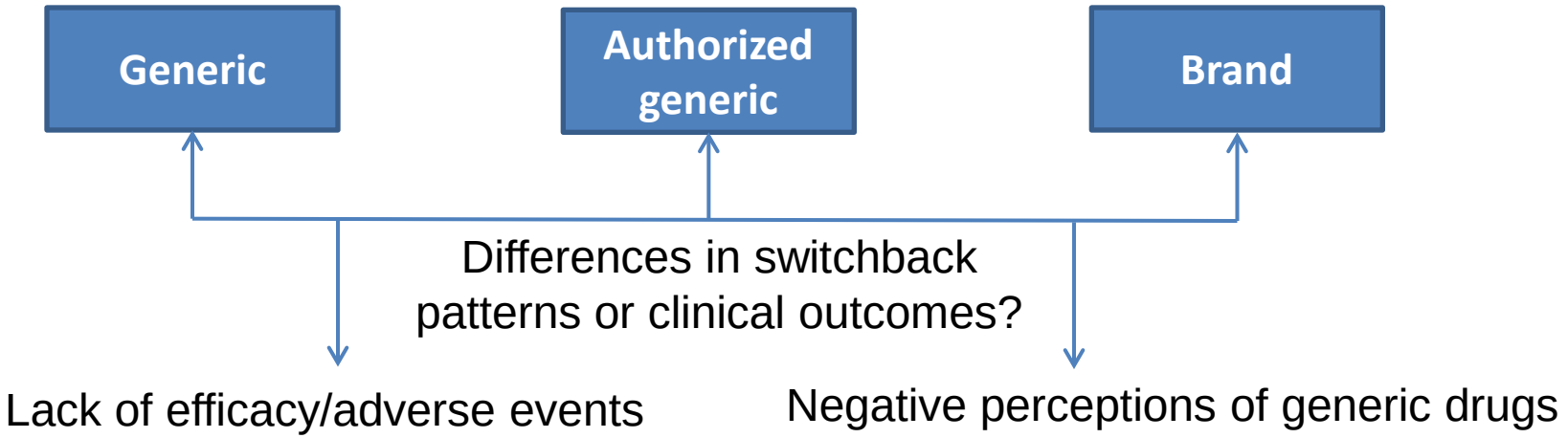
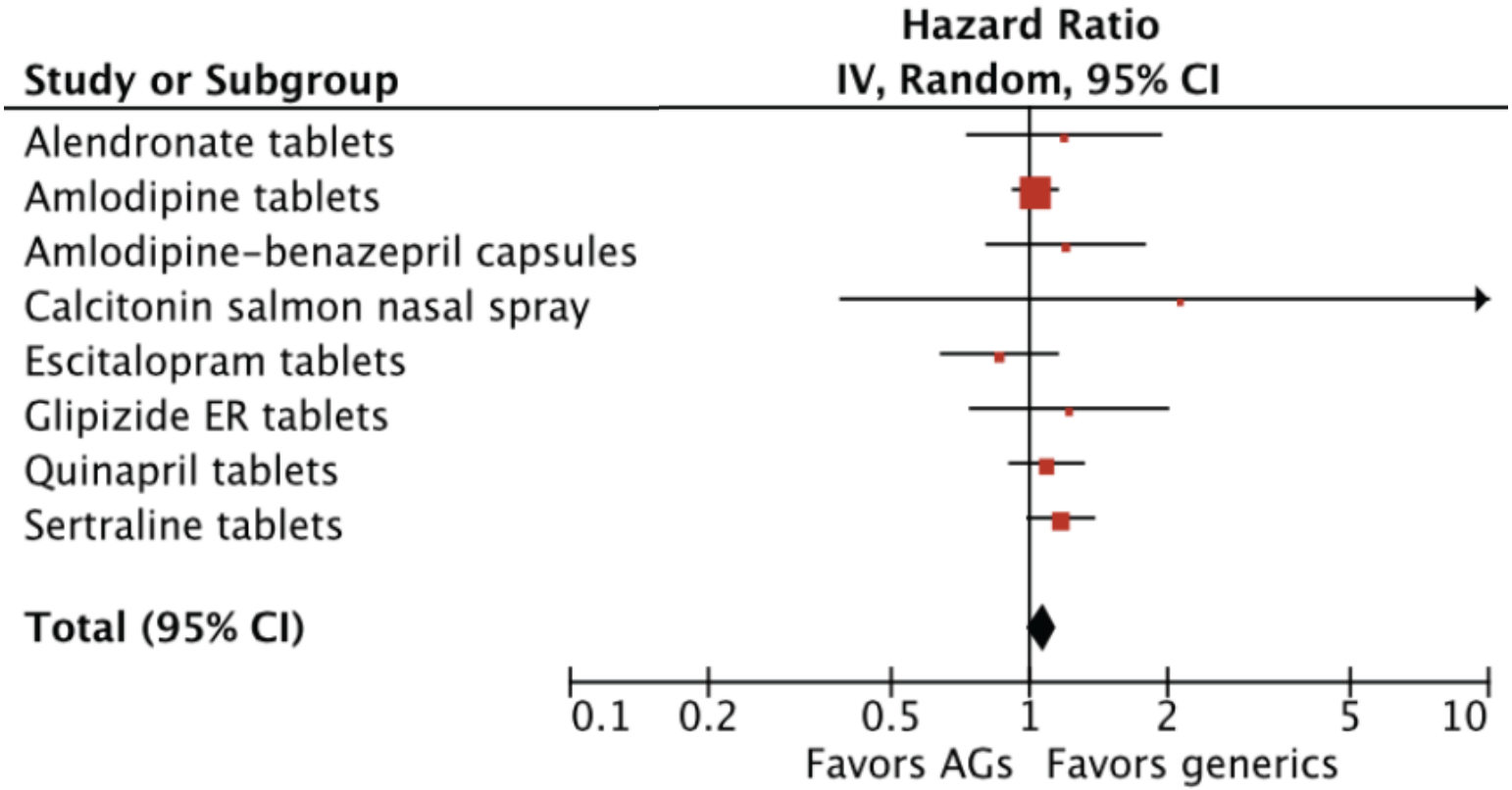


Figure adapted from Brigham & Women's Hospital meeting presentation

4. Role of Authorized Generics

Risk of adverse clinical outcomes was not statistically different between AGs and generic switchers

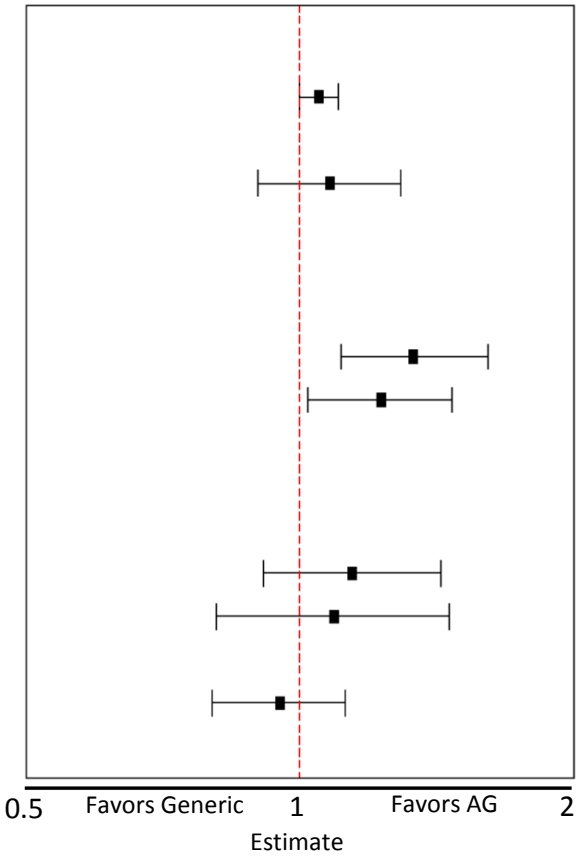


Desai RJ et al. Comparative effectiveness of generic, authorized generic, and brand-name medications. Manuscript in preparation.

4. Role of Authorized Generics

Generic switchers did not have worse outcomes than AG switchers

Outcome	Estimate	P-Value
Number of all-cause outpatient visits per year	1.05	0.071
Number of all-cause urgent care visits per year	1.08	0.395
All-cause emergency department visits		
Any visit	1.33	0.003
Number per year	1.23	0.026
All-cause hospitalizations		
Any visit	1.14	0.257
Number per year	1.09	0.582
Medication discontinuation	0.95	0.508



Hansen RA et al. Comparison of outcomes following a switch from a brand to an authorized vs. independent generic drug. Clin Pharmacol Ther. 2016 [epub].

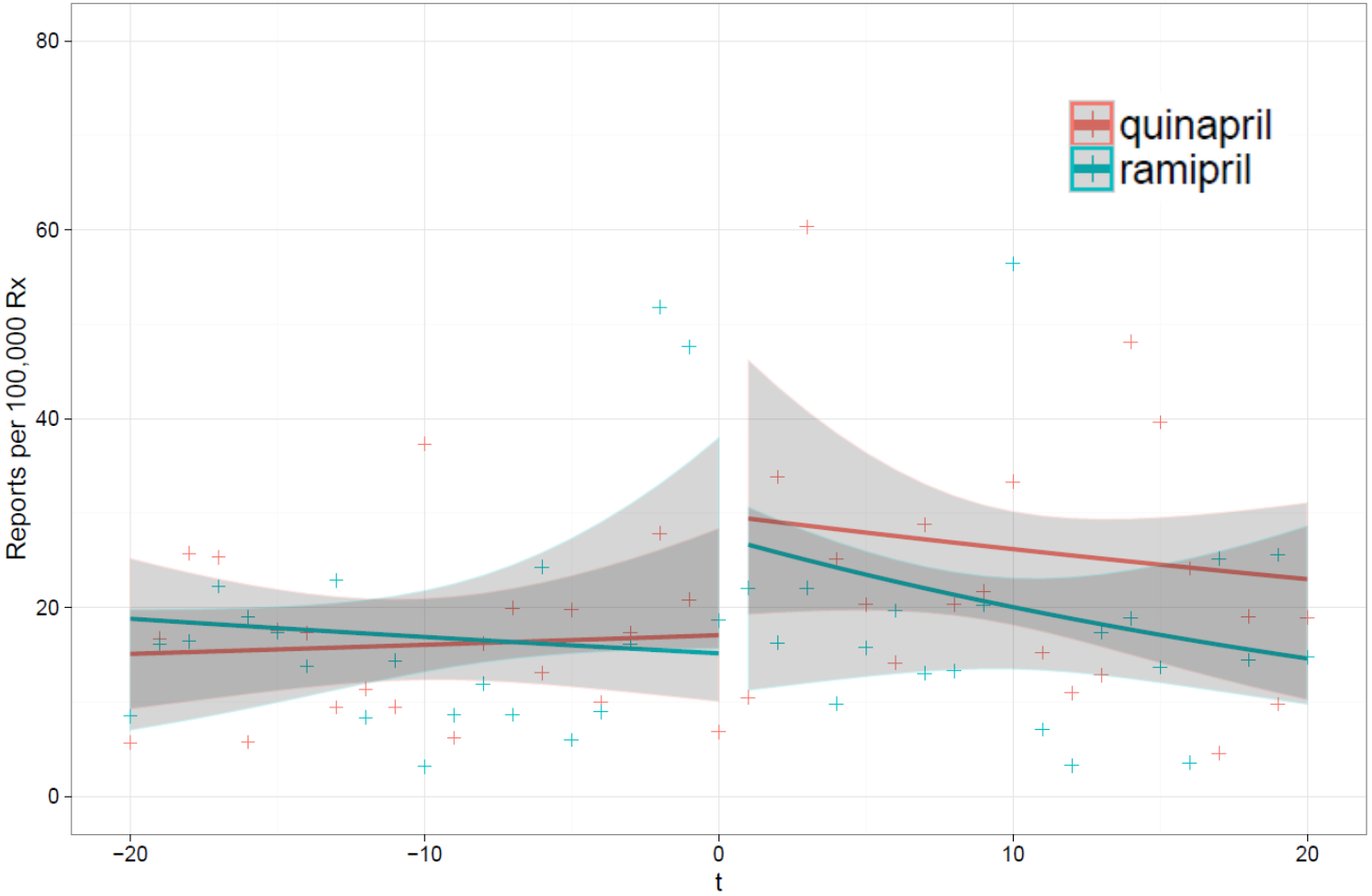
5. Analysis of FAERS Data

How can we use FAERS data to identify potential signals of generic drug inequivalence?

- Disproportionality analysis
- Development of algorithms to identify generic drug reports
- Interrupted time series analysis

5. Analysis of FAERS Data

Interrupted time series analysis



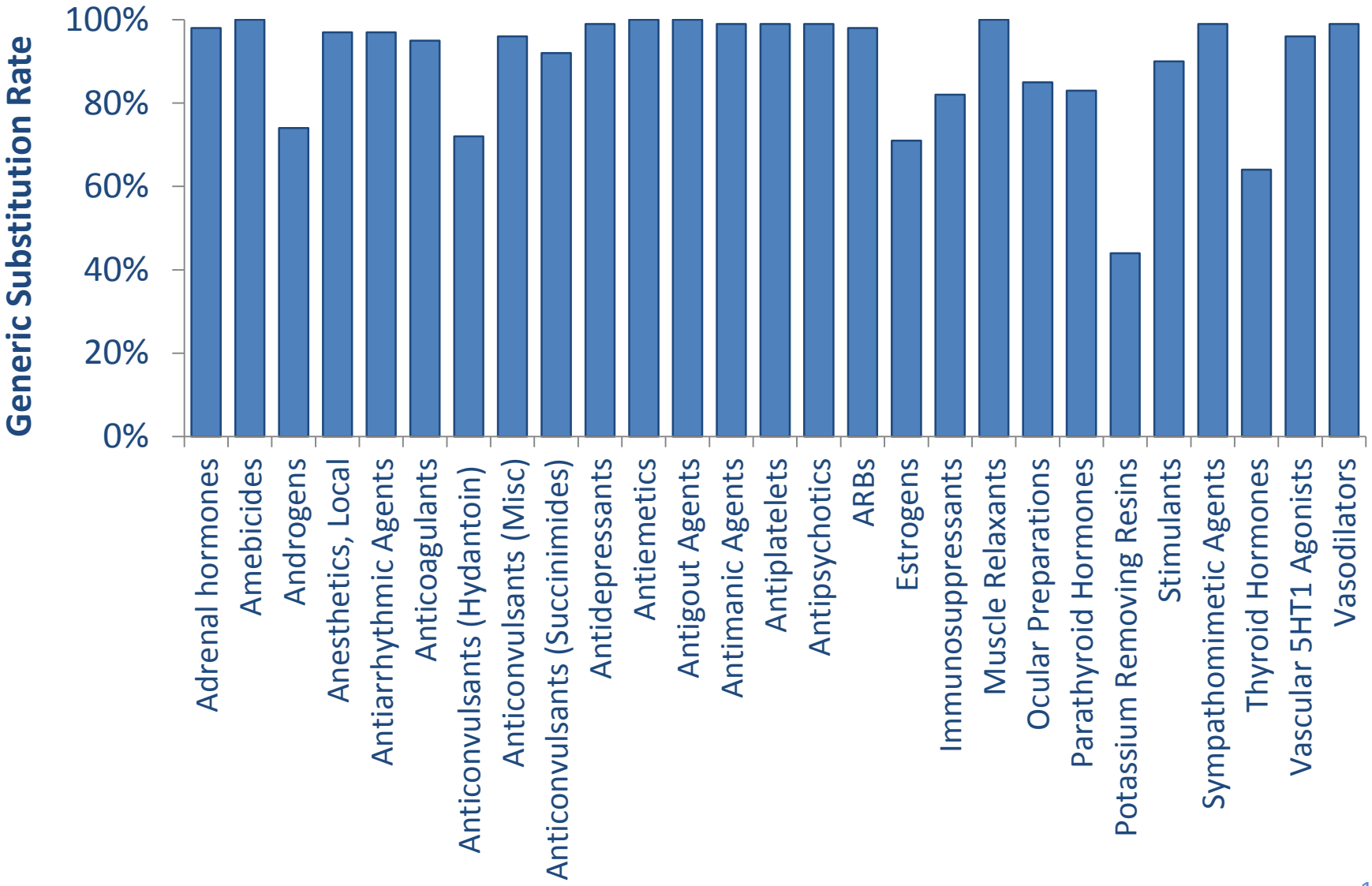
Sarpatwari A et al. Differences in adverse event reporting following the loss of market exclusivity among drugs with and without authorized generics. Manuscript in preparation.

6. Therapeutic Class Substitution

Does generic uptake vary across drug classes?

- What factors are associated with generic drug substitution?
- Do these factors vary across therapeutic classes or across different populations?

6. Therapeutic Class Substitution

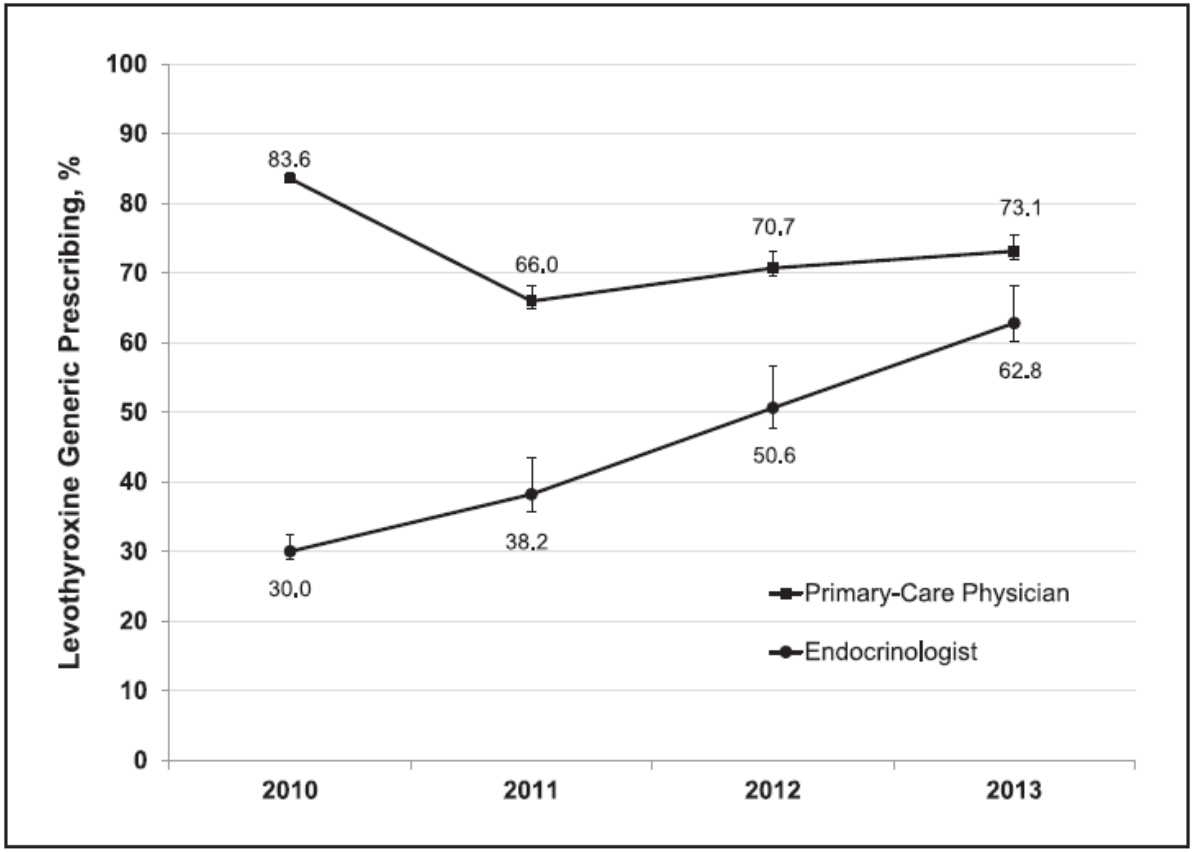


Segal J et al. Determinants of generic drug substitution in the United States. Manuscript in preparation.

6. Therapeutic Class Substitution

Factors associated with lower generic levothyroxine prescribing:

- Younger age
- Fewer co-medications
- Higher income
- Severe disease status
- Initial prescription
- In-person visit
- Prescribed by endocrinologist



Romanelli RJ et al. Provider and patient determinants of generic levothyroxine prescribing: an electronic health records-based study. Ann Pharmacother. 2017 Aug;51(8):640-648.

Moving Forward

- Proactively monitor drug use, effectiveness, and safety in the real-world
  - Internal: Sentinel Initiative, FAERS
  - External: Grants and contracts
- Assess clinical or regulatory issues that arise
- Develop and refine methodological approaches to evaluate generic drug substitutability
- Continue to provide additional evidence for the interchangeability of brand-name and generic drugs

U.S. FOOD & DRUG ADMINISTRATION

www.fda.gov/GDUFARegScience

Backup Slides

Methods Development for Generic Drug Surveillance

Project Title	Site Name	Grant/ Contract	Year Funded
Utilization, Switching, and Switchback Safety and Effectiveness Outcomes in Secondary Data			
Assessing clinical equivalence for generic drugs approved by innovative methods	Brigham & Women's Hospital	Grant	2013
Postmarketing surveillance of generic drug usage and substitution patterns	University of Maryland Baltimore	Grant	2013
Transplant outcomes using generic and brand name immunosuppressants: studying medications used by people who have received kidney and liver transplants	Arbor Research Collaborative for Health	Grant	2014
Generic Drug Substitution in Special Populations	Auburn University	Grant	2016

Methods Development for Generic Drug Surveillance

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Authorized Generics			
Assessing the post-marketing safety of authorized generic drug products	Brigham & Women's Hospital	Grant	2014
Post-market authorized generic evaluation (PAGE)	Auburn University	Grant	2014
Generic drug substitution across therapeutic classes			
Effect of therapeutic class on generic drug substitution	Johns Hopkins University	Grant	2014

Methods Development for Generic Drug Surveillance

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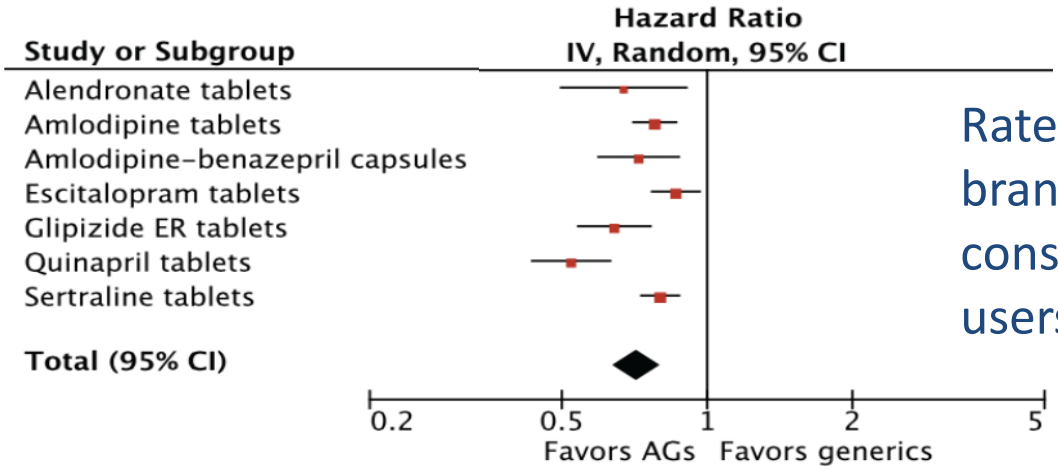
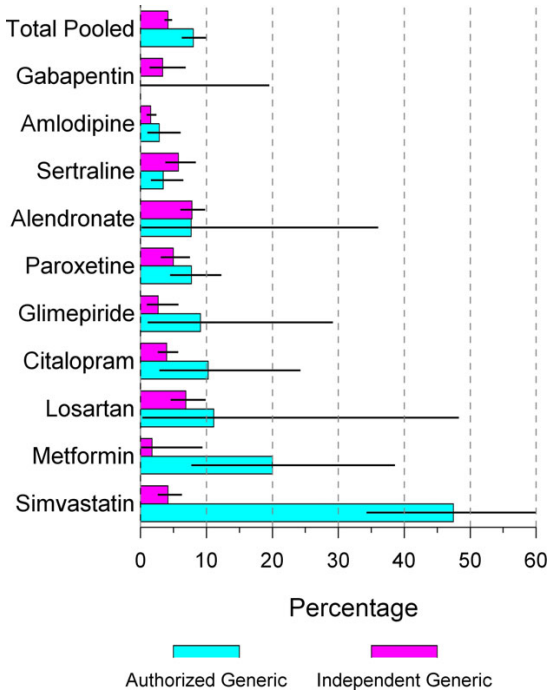
Statistical Methods for Observational Studies			
Novel approaches for confounding control in observational studies of generic drugs	Brigham & Women's Hospital	Grant	2015
Structural nested models for assessing the safety and effectiveness of generic drugs	Johns Hopkins University	Grant	2015
Comparative surveillance of generic drugs by machine learning	Marshfield Clinic Research Foundation	Contract	2015
Use of Pharmacometric Modeling in Surveillance			
Pharmacometric modeling and simulation for a generic drug substitutability evaluation and post marketing risk assessment (U01FD005192)	University of Maryland Baltimore	Grant	2014
A model- and systems-based approach to efficacy and safety questions related to generic substitution (U01FD005210)	University of Florida	Grant	2014

Authorized Generics



Rates of switchback to the brand-name product were consistently lower among AG users compared to generic users

- No significant difference in brand switchback rates for generic vs. AG for 9 of 10 study drugs
- Trend toward higher AG switchback rates for 7 drugs



Hansen RA et al. Pharmacotherapy. 2017 Apr;37(4):429-437.

Desai RJ et al. Manuscript in preparation.