Evaluation of Switching Patterns in FDA’s Sentinel System – A New Tool to Assess the Substitutability of Generic Drugs

Sarah K. Dutcher,1 Jennifer R. Popovic2,3 Michael Nguyen,1 Sukhminder K. Sandhu,1 Patty Greene,1 Rima Izem,1 Wenlei Jiang,1 Zhong Wang,1 Yueqin Zhao,1 Andrew B. Petrone,2 Anita K. Wagner,2 Joshua J. Gagne4

1. Center for Drug Evaluation and Research, US Food and Drug Administration, Silver Spring, MD
2. Department of Population Medicine, Harvard Medical School and Harvard Pilgrim Health Care Institute, Boston, MA
3. RTI International, Waltham, MA
4. Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Brigham and Women’s Hospital and Harvard Medical School, Boston, MA
Disclosures

• Joshua Gagne has received salary support from grants from Novartis Pharmaceuticals Corporation and Eli Lilly and Company to Brigham and Women’s Hospital and is a consultant to Aetion, Inc. and to Optum, Inc., all for unrelated work

• All other coauthors have no conflicts of interest

• The Sentinel program is funded by the U.S. Food and Drug Administration (FDA) through the Department of Health and Human Services contract number HHSF223201400030I

• The views expressed in this presentation are those of the authors and are not intended to convey official U.S. FDA policy or guidance
Generic Drugs

• Most drugs dispensed in the U.S. (90%) are generic products\(^1\)

• FDA’s Office of Generic Drugs (OGD) approved 1,027 generic drugs in 2017\(^2\)
Generic Drug Substitutability

• Over the past decade, several observational studies have been published that question the bioequivalence of generic drugs\textsuperscript{3-6}

• From 2011-2016, OGD took regulatory action on three products related to issues of therapeutic inequivalence\textsuperscript{7-9}

• In 2017, OGD received \textasciitilde 640 individual spontaneous case reports related to the quality of generic drugs each month
  – 55% described issues related to switching between brand and generic
Generic Drug Substitutability

Why switch?
• Insurance formulary
• Lower patient costs (e.g., copays)
• State generic substitution laws (permissive or mandatory)
• Drug availability

Why switchback?
• Patient experiences effectiveness or safety issue
• Patient preference
• Physician preference (“Dispense as written”)
Objective

• Existing Sentinel tools were limited in their ability to study brand and generic switching patterns

• To develop and implement a modular, reusable tool for describing manufacturer-level drug utilization and switching patterns in the US FDA’s Sentinel System
Data Source: Sentinel

• FDA’s active surveillance system for medical products
• Uses electronic healthcare data from a distributed data network of 18 Data Partners formatted into a common data model
• For tool testing, data from the 4 largest Data Partners in Sentinel were used
  – National health insurers
  – Comprise 88% of total patient data

https://www.sentinelinitiative.org/
Tool Development: Groups

- Captures utilization and switching patterns for user-specified groups
- Unit of analysis: user-specified groups
  - Defined by product national drug codes (NDCs) or procedure codes
  - Used to create treatment episodes, identify switching patterns, report utilization metrics
- For this analysis, groups were defined by manufacturer
Tool Development: Switching

Switch pattern evaluation start

First evaluation
- Start first product
- Switch to second product
- Censored: no switch

Second evaluation
- Switch to different product
- Switch back to first product
- Censored: no 2nd switch
Tool Development: Metrics

- Utilization metrics
  - Utilization over time
  - Summary statistics: product uptake, episode duration
- Switching metrics
  - Summary statistics
    - Time to 1\textsuperscript{st} switch and 2\textsuperscript{nd} switch
    - Switch pattern episode duration
  - Frequency distributions
    - People who switch, by months to 1\textsuperscript{st} switch and to 2\textsuperscript{nd} switch
    - Kaplan-Meier curves
      - Time to 1\textsuperscript{st} switch and 2\textsuperscript{nd} switch
Use Cases

1. Metoprolol extended release (ER)
   • Beta blocker indicated for the treatment of hypertension, angina pectoris, and heart failure
   • First generic was approved July 31, 2006
   • From 2008-2014, several manufacturers recalled some generic products due to failures meeting quality standards\textsuperscript{10-13}

2. Lamotrigine ER
   • Anticonvulsant agent indicated for treatment of certain types of seizures in patients aged 13 years and older
   • First generic was approved December 26, 2012
   • Equivalence of generic antiepileptic drugs is an area of debate among healthcare providers\textsuperscript{14,15}
Results: Metoprolol ER

Monthly Number of New Users, Metoprolol ER

- All Metoprolol ER
- Par (AG)
- Actavis
- Dr Reddys
- Mylan
- Nesher
- Sandoz
- Sandoz
- Wockhardt
- Toprol XL (Brand)
Results: Metoprolol ER

Monthly Number of New Users, Metoprolol ER

Sep 2008
Sandoz recall & discontinuation

Jan 2009
Nesher shipment suspension & discontinuation

Nov 2013
Wockhardt exports banned from two Indian manufacturing facilities; subsequent recalls
Results: Metoprolol ER

Time to Switch from Generic to Any Other Generic, Metoprolol ER

Proportion of users remaining on initial generic product

Time to switch to any other generic (months)

- Dr Reddys
- Actavis
- Par
- Mylan
- Nesher
- Sandoz
- Wockhardt
Results: Lamotrigine ER

Monthly Numbers of New Users, Lamotrigine ER

- All lamotrigine ER
- Lamictal XR (brand)
- Actavis
- Dr Reddys
- Par
- Wilshire
- Wockhardt
Results: Lamotrigine ER

Time to Switchback to Brand, Lamotrigine ER

Range of switchbacks at 12 months: 9% to 17%

- Wilshire
- Par
- Wockhardt
- Dr Reddys

Proportion of users remaining on respective generic product

Time to switchback to brand (months)
Use Cases: Summary

• Metoprolol ER
  – Substantial changes in utilization following several manufacturer-specific production and availability issues
  – High rates of switching from generic products that were recalled and later discontinued

• Lamotrigine ER
  – Overall increase in use upon generic introduction
  – High rates of switchback from generic to brand: 9%-17% at 12 months
    • Consistent with previous studies, which found switchback rates of 13% – 28% for lamotrigine IR vs. 2% – 9% for antihyperlipidemics and antidepressants\textsuperscript{5,6}
Conclusions

• Successfully developed a reusable, parameterized, descriptive analysis tool to characterize manufacturer-level drug utilization and switching patterns within FDA’s Sentinel System

• Tool confirmed expected utilization and switching patterns in 2 case studies

• Characterizing and evaluating switching or switchback patterns is potentially important in exploratory analyses of generic drugs and biosimilars in the postmarket setting

• Potential future enhancements:
  – Link this tool to existing tools for descriptive baseline cohort information
  – Evaluation of clinical outcomes associated with use of, or switching among, products from different manufacturers
Many thanks are due to Data Partners who provided data used in the analysis.


References


