Published in final edited form as:

Clin Drug Investig. 2017 December ; 37(12): 1143–1152. doi:10.1007/s40261-017-0574-4.

Methodological considerations for comparison of brand versus generic versus authorized generic adverse event reports in the U.S. Food and Drug Administration Adverse Event Reporting System (FAERS)

Md. Motiur Rahman, MPharm¹, Yasser Alatawi, PharmD¹, Ning Cheng, MS¹, Jingjing Qian, PhD¹, Peggy L. Peissig, PhD, MBA², Richard L. Berg, MS², David C. Page, PhD³, and Richard A. Hansen, PhD¹

¹Auburn University, Harrison School of Pharmacy, Department of Health Outcomes Research and Policy, Auburn, AL

²Marshfield Clinic Research Foundation, Biomedical Informatics Research Center, Marshfield, WI

³University of Wisconsin, School of Medicine and Public Health, Department of Biostatistics and Medical Informatics, and Department of Computer Science, Madison, WI

Abstract

Background—The U.S. Food and Drug Administration Adverse Event Reporting System (FAERS), a post-marketing safety database, can be used to differentiate brand vs. generic safety signals.

Objective—To explore the methods for identifying and analyzing brand vs. generic adverse event (AE) reports.

Methods—Public release FAERS data from January 2004 to March 2015 were analyzed using alendronate and carbamazepine as examples. Reports were classified as brand, generic, and authorized generic (AG). Disproportionality analyses compared reporting odds ratios (RORs) of selected known labeled serious adverse events stratifying by brand, generic, and AG. The homogeneity of these RORs was compared using the Breslow-Day test. The AG vs. generic was the primary focus since the AG is identical to brand but marketed as a generic, therefore minimizing generic perception bias. Sensitivity analyses explored how methodological approach influenced results.

Results—Based on 17,521 U.S. event reports involving alendronate and 3,733 U.S. event reports involving carbamazepine (immediate and extended release), no consistently significant differences were observed across RORs for the AGs vs. generics. Similar results were obtained when

Correspondence: Richard A. Hansen, PhD, Professor and Dean, Auburn University Harrison School of Pharmacy, 2316 Walker Building, Auburn, AL, 36849, Phone: 334-844-8348, Fax: 334-844-8307, rah0019@auburn.edu.

Presentation: Presented as a poster in the 2017 annual conference of the American Pharmacists Association, San Francisco, CA from March 24 - 27, 2017.

Compliance with Ethical Standards: Conflict of Interest: In the past 3 years, Richard Hansen has provided expert testimony for Boehringer Ingelheim and Daiichi Sankyo. No other authors declare a potential conflict of interest.

comparing reporting patterns over all time and just after generic entry. The most restrictive approach for classifying AE reports yielded smaller report counts but similar results.

Conclusion—Differentiation of FAERS reports as brand vs. generic requires careful attention to risk of product misclassification, but the relative stability of findings across varying assumptions supports the utility of these approaches for potential signal detection.

Keywords

Alendronate; authorized generic; carbamazepine; gastritis; generic; osteonecrosis of jaw

1 Introduction

Generic drugs saved the health industry an estimated \$227 billion in 2015 and \$1.5 trillion over the past 10 years,[1] yet questions have been raised regarding interchangeability between generic and branded drugs.[2-8] For example, switching from branded antiepileptic drugs (AEDs) to generics has been suggested to result in increased risk of therapeutic failure and adverse reactions.[2] The U.S. Food and Drug Administration (FDA) approval process confirms pharmaceutical equivalence and bioequivalence of generic drugs with reference-listed products (i.e., brand).[9] Therefore, one theory surrounding reported differences between brands and generic is that patient and provider biases negatively influence perceptions of generic drug efficacy and safety.[10-12] For example, one study among the university students that tested the effectiveness of fast-acting β -blocker medications in reducing pre-examination anxiety, evaluated the effect of bias against generics by giving placebo to all patients but informing some patients they were given a generic and some they were given the brand drug.[10] The patients told they were given a generic had more adverse reactions and less beneficial results than the patients that were told they were given the brand.[10] Similarly, in a 2016 national survey of 1,442 patients, nearly 13 percent of respondents reported thinking that branded drugs are more effective than generics, and 20 percent believed that the safety profile of branded drugs and generics may vary.[11] In a parallel survey of 1,200 physicians about perceptions of generic drugs, 11 percent of respondents believed that generic drugs were less efficacious than branded drugs and nearly 27 percent reported negative perceptions of generic drug safety.[12] All of these factors illustrate differential perceptions and use of generics that are important to consider in post-market evaluation.

Taking into consideration the possible perception bias against generics, post-marketing surveillance of the effectiveness and safety of generic drugs proves to be difficult. Over the past two decades, however, brand companies have sometimes marketed a special kind of generic, known as an “authorized generic” (referred to as AG from here forward). AGs are drugs that have the same formulations, manufacturing processes, and are pharmaceutically identical to the branded product but that are marketed, sold, or distributed as a generic.[13] Since AGs contain the same active and inactive ingredients as the branded drug, and are in fact marketed under the brand drug's approval, the safety and efficacy profiles should be identical. But, given that patient and prescriber perception is that AGs are the same as any other generic, AG drugs can be used as “control drugs” in post-market research. In other words, AGs can serve as a brand proxy to minimize generic perception bias. Any significant

differences across brands and AGs would be interpreted as possible bias towards generics whereas, significant differences across generics and AGs would correspond to an actual difference across these product types.

This study depicts different ways of identifying brand, AG, and generic drugs from the FAERS database and explores whether the odds of AE reports are similar between brand and generic drugs, using AG drugs as a control for possible generic drug biases. Alendronate (Fosamax, Binosto) was chosen as an example drug since this drug had a generic and an AG introduced during the past decade. Carbamazepine (Tegretol) was chosen as an example as it has an extended release (ER) form, i.e., carbamazepine ER (Tegretol-XR, Carbatrol, Equetro), available in the market which allowed us to study the reporting patterns of the regular and modified release dosage forms of the same drug.

2 Methods

2.1 Study Design

We conducted retrospective analyses of AE reports from the FAERS database for alendronate and carbamazepine, comparing reporting rates and trends for events associated with brand, generic, and AG products.

2.2 Data Sources

Public release data from FAERS were obtained from January, 2004 through March, 2015. The FAERS is a post-marketing safety database composed of AEs spontaneously reported from both U.S. and non-U.S. sources. Pharmaceutical companies are required to submit reports to FAERS, and healthcare providers and consumers also can directly submit reports to FAERS through the MedWatch program.[14, 15] Duplicate reports were deleted prior to analysis using the FDA's recommendation for adopting the most recent case number.[16]

2.3 Drug Identification

Reports involving alendronate (Fosamax, Binosto), carbamazepine (Tegretol), and carbamazepine ER (Tegretol-XR, Carbatrol, Equetro) as primary suspect (PS) or secondary suspect (SS) drugs were identified using text string searches by generic names, brand names, and abbreviations. A similar approach was taken for their respective combination products except for carbamazepine/ carbamazepine ER as no such products existed in the market. An iterative process was used to examine the accuracy of complete name searches as opposed to shorter character string searches. The shortest character string search yielding mostly reports for alendronate/ carbamazepine/ carbamazepine ER (as opposed to other drugs or gross misspellings) was used to identify a subset of reports, and these reports were then recoded by two independent adjudicators to eliminate reports that were not for these drugs and correct for misspellings and abbreviations. The two adjudicators agreed upon 100% of the cases.

Reports were classified as brand, generic, or AG based on the manufacturer receiving or making the report. We excluded direct reports made to the FDA that did not report the manufacturers' name (about 3% of reports for alendronate, 4% for carbamazepine, and 5%

for carbamazepine ER were excluded) since these reports could not be differentiated by manufacturer. For alendronate, brand reports were from Merck and Mission Pharma, AG reports were from Watson labs, and generic reports were from all other manufacturers. For carbamazepine/ carbamazepine ER, brand reports were from Novartis, Shire, and Validus, whereas AG reports were from Sandoz and Prasco. All other reports were classified as generics. Full drug marketing information is noted in the supplemental data.

In some cases, there may be market complexity that creates challenges for classifying the AG (e.g., manufacturer mergers, multiple AG distributors, legal challenges impacting AG or generic marketing). To illustrate these instances, a sensitivity analysis was performed where reports were classified as brand, generics, and AG based on both manufacturers' name and the verbatim drug name reported. For example, if the drug name was reported as Fosamax or Binosto and the reporting manufacturers were Merck or Mission Pharma, then it was classified as brand. On the other hand, if the drug name was reported as alendronate and the reporting manufacturers were Merck or Mission Pharma, then it was classified as AG. All other reports were classified as generics.

2.4 Measures

We quantified the total number of AE reports as well as the number of serious AE reports, defined as death, disability (i.e., disability or congenital anomaly), and other serious outcomes (i.e., life-threatening, hospitalization, required intervention to prevent harm, and other outcomes). Specific pre-defined AEs were prioritized based on the package label and from proprietary drug reference databases (e.g., Lexi-Comp and Micromedex). These events included hypophosphatemia, gastritis, hypocalcemia, and osteonecrosis of jaw for alendronate, and severe dermatologic events and liver injury for carbamazepine/ carbamazepine ER. These events were identified from the REAC files using the Medical Dictionary for Regulatory Activities (MedDRA) preferred terms (PTs) noted in the supplemental data. When AEs corresponded with a Structured MedDRA Query (SMQ) (version 17.0), we grouped all PTs included in the SMQ to define the events of interest.[17] When SMQs were too broad to capture the specific event of interest, we used a hierarchical search process whereby we first examined High Level Group Terms (HLGTs), then High Level Terms (HLTs), and lastly individual PTs.[18] The broadest of these definitions that appropriately captured the event of interest was selected for use in the study.

2.5 Data Analysis

Descriptive analyses were used to summarize characteristics of AE reports. Reporting rates were qualitatively compared with estimated prescribing rates by quarter using Medicaid estimates (see supplemental data). To show the differences in odds of reporting across brand vs. AG vs. other generics across different years, both cumulative and annual reporting odds ratio (ROR) trends for each specific AE (e.g., gastritis) were calculated.

Sensitivity analyses were performed to explore the potential implications of anticipated misclassification bias. For this purpose, we examined PS reports only, U.S. reports only, U.S. PS reports only, and U.S. valid serious PS reports along with the total reports for a specific AE (e.g., gastritis). Valid reports (VAL_VBM= 1) are the reports associated with

validated trade names and thus are less prone to misclassification biases. Serious reports are believed to be less biased and have more complete information capture as they are more likely to get reported in FAERS because the manufacturers must submit any serious AE reports to FDA within 15 calendar days of the initial receipt of the information,[19] whereas manufacturers can request a waiver for submission of non-serious reports.[20]

Disproportionality analyses with RORs were used to evaluate the likelihood of specific known events to be reported with a specific type of product as opposed to all other drugs. The ROR estimates the odds of the event of interest in those exposed to each target drug of interest divided by the odds of the event of interest in those not exposed to the drug of interest (all other drugs in the database).[21] A significant disproportionality, or in other words a possible signal, was defined as the lower bound of the 95% confidence interval (95% CI) exceeding 1.[22] This algorithm was performed for each drug-AE pair and product type (i.e., brand, generic, AG).

Because of anticipated measurement error with our approach to classifying brand vs. generic vs. AG reports was believed to be non-constant over time, we stratified disproportionality analyses by time periods representing before and after the introduction of the generic. Because we made three comparisons across product types, to control the risk of *Type I* error we used a Bonferroni correction to adjust our critical P value to be $P < 0.01$ (i.e., $P < 0.05/3$). [23] All statistical analyses were conducted using SAS (version 9.4; SAS Institute, Cary, NC). The study was determined to be exempt human subjects research by the Auburn University Institutional Review Board.

3 Results

Worldwide, a total of 25,576 AE reports for alendronate, 13,950 AE reports for carbamazepine, and 668 AE reports for carbamazepine ER as primary or secondary suspect drugs were found between January 2004 and March 2015. Of these, 17,521 for alendronate, 3,733 for carbamazepine, and 220 for carbamazepine ER were U.S. reports. Of the U.S. reports, 14,025 (80.1%), 232 (1.3%), and 3,264 (18.6%) were reports for brand, AG, and generic alendronate, respectively; 1,810 (48.5%), 49 (1.3%), and 1,874 (50.2%) were reports for brand, AG, and generic carbamazepine, respectively; and 163 (74.1%), 2 (0.9%), and 55 (25.0%) were reports for brand, AG, and generic carbamazepine ER, respectively.

We first examined a subset of specific known AEs for alendronate (Fig. 1a) and found multiple significant differences across RORs when comparing brand vs. AG and brand vs. generic. But, when we focused on the AG vs. generic comparison, only osteonecrosis of the jaw was indicative of a possible difference between the brand proxy (AG) and the generic. However, in this case, the AG ROR was significantly higher than the brand which is indicative of possible bias against generics. The high ROR value and wide 95% CI for AG could be a function of small sample size. A sensitivity analysis based on our second approach of defining brand, AG, and generics yielded similar results (Fig. 1b).

To illustrate how RORs are influenced by temporal variation as opposed to cumulative pooling of AE reporting over time, we plotted the RORs over time for gastritis under two

scenarios (Fig.2). The trends in RORs across generics and branded drugs in both the cumulative (Fig. 2a) and annual (Fig. 2b) plots were similar. This illustrates a minimal influence of temporal variation on the reporting trends. When calculating annual RORs for the AG, we observed inconsistency over the years which could be a function of small reporting numbers in some periods.

We considered our initial inclusion of all worldwide PS and SS reports to be most error prone to misclassification of brand vs. AG vs. generic. Using a hierarchy of decreasing likelihood of misclassification bias, we illustrated how event sample size and RORs changed as the inferred specificity of our classification approach improved. In this manner, we sequentially restricted to PS reports, U.S. reports, U.S. PS reports, and U.S. valid serious PS reports for gastritis with alendronate. This sensitivity analysis illustrates how conclusions change across methodological approaches to defining cohorts of AE reports (Fig. 3). RORs for gastritis were significantly greater than one for brand and generics across all the drug categories except for U.S. PS reports; however, none of the differences proved to be statistically significant.

Prior to generic entry, any adverse events with the brand should have been reported to the brand company or directly to the FDA. This results in an accumulation of reports over the longer initial marketing period for brands and could introduce a bias when considering generics. Likewise, post-generic entry utilization and safety reporting tends to shift more towards the generic, and this could result in a similar bias in the interpretation of reporting patterns. To evaluate this, we explored differences in reporting patterns over all times and just after generic entry. In these analyses, we illustrated results for gastritis and hypocalcemia with alendronate (Fig. 4). RORs for both of these AEs were consistent across all of the reporting patterns and examined time periods.

To assess the differences in reporting patterns between the immediate and modified release dosage forms of the same drug, a sensitivity analysis was performed for severe dermatologic events and liver injury with all formulations of carbamazepine vs. carbamazepine ER (Fig. 5). No AG reports were found for these two events with carbamazepine ER. RORs for generics were significantly higher than brand for liver injury with both the formulations of carbamazepine; however, generics did not differ significantly from the AG in any of the cases which is suggestive of possible bias towards generic drugs.

4 Discussion

AGs are drugs usually sold by a subsidiary of the brand company or licensed to another company and sold under the same NDA as the branded product.[24] While the use of AGs as control groups seems promising, small numbers of FAERS reports associated with AGs may be a limiting factor for broadly using this approach. For example, the number of reports for gastritis was 32 for the alendronate AG, whereas for brand and generics it was 1844 and 500, respectively. Medicaid expenditure reports also suggest that prescribing rates of alendronate and carbamazepine AGs were very low compared to the brand and generics which could be a reason for their lower reporting rates (see supplemental data).

To minimize the chance of misclassification bias (i.e., the possibility of attributing reports of one drug type to another), we sequentially restricted the analyses to PS reports, U.S. reports, U.S. PS reports, and U.S. valid serious PS reports. The number of AE reports lowered dramatically as we restricted from total reports to U.S. valid serious PS reports (from 1,844 to 1,342 for brand, 32 to 1 for AG, and 500 to 26 for generics in case of gastritis with alendronate) which we consider to be the most restrictive approach. As the number of reports gets smaller, the confidence intervals get wider and therefore the signal threshold may need to be more tolerant (i.e., larger).[25] Even considering this, the relative ROR estimates for brand vs. generic comparisons were consistent across different report types which could suggest that tolerating some report misclassification may be acceptable as a hypothesis generating tool for signal detection.

Prior to generic entry, any AE for a particular drug should have been attributed to the brand product. However, we observed some generic reports for alendronate even before the generic entry into the market (Fig. 4). However, the number of generic reports prior to the generic entry was very small which we believe will have little effect on the analyses. Moreover, similar RORs across all reports and post-generic only reports illustrate minimal influence of misclassification bias.

Although analyses of carbamazepine and carbamazepine ER yielded similar results, the small sample size with the modified release products in the FAERS database could be an indicator of challenges with formulation-specific dosage forms when making brand vs. generic comparisons. It is possible that reporters may attribute the AE associated with the extended release formulation to the immediate release formulations by writing “Tegretol” or “carbamazepine” rather than “Tegretol XR” or “carbamazepine ER” in the FAERS report. This further limits sample size and likely introduces misclassification bias.

Our methodological approach is subject to misclassification of brand, AG, and generic products. For example, generic alendronate obtained the majority of the alendronate market share by the end of our observation period. However, reporting rates for brands were higher than both the generics and AG. This could be a function of misattribution of generic drug AE reports to branded drugs. Patients may be on generics but the AE was still reported to the brand manufacturer since patients and providers may be more familiar with the brand name. This potential misclassification could hamper FDA's ability to conduct accurate pharmacovigilance of generic products. However, in a recent analysis of FAERS data, a relatively similar generic drug attribution approach that required reports to specify the NDA or ANDA number was compared to an assumed reference standard that included full text abstraction from the full reports. The authors found that the use of manufacturer's name to identify generic drugs in FAERS was as reliable as using NDA or ANDA numbers with high concordance and positive predictive value.[26] Moreover, the use of NDA number to differentiate generics from brand may not be applicable to identify AG as it is marketed under the same NDA number as the brand.

4.1 Limitations

This study has several limitations. In general, spontaneous reports are prone to some known biases such as over/underreporting and reporting biases. The same event may be reported

multiple times by different stakeholders such as patients, physicians, and/or manufacturers, and even after correcting for duplicates this may result in an overestimation of the reporting rates. Moreover, we have classified brands, generics, and AGs based on the manufacturers' name. It is possible that the brand manufacturers receive reports about the generics as well. So, there may be some degree of misclassification of brand vs. generic in our analyses. Finally, there is no actual denominator in the FAERS database and information is incomplete regarding patients' co-morbid conditions, concomitant medications, dosage, family history, or other risk factors. Thus, this database is not meant for establishing causal relationships or testing of hypotheses, but rather for generating hypotheses.

Some limitations are specific to the brand/generic vs. AG comparison. For instance, identification of the AG in FAERS may be very challenging for several reasons including the following: the AG marketing period or marketer cannot be precisely identified using historical data, the AG may be dosage form specific, or the same manufacturer may have both an AG and generic in the market. For example, lamotrigine (Lamictal by GLAXOSMITHKLINE) has four dosage forms in the market: tablet, chewable tablet, orally disintegrating tablet, and extended release tablet. [27] Only the chewable tablet form had an AG marketed by Teva Pharmaceutical Industries Ltd. However, Teva later marketed an ANDA-approved generic. Similarly, Watson Labs distributed an AG for Fosamax for 6-months and then an ANDA-approved generic afterwards. Thus, there may be some misclassification in the results. This could limit the use of AGs as control drugs in brand vs. generic comparison studies. Moreover, different dosage forms have generic availabilities at different times and identifying dosage forms in the FAERS database is challenging. This could complicate the time trend analyses using this database.

5 Conclusion

In conclusion, this study demonstrates an approach to signal detection for comparing brand vs. generic drugs in the FAERS data. We demonstrate use of the AG as a brand proxy that is believed to minimize generic drug perception bias. Future work in this area should explore validity of generated signals using stronger epidemiological designs and data sources.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The authors thank Wenlei Jiang, PhD (Food and Drug Administration) and Saranrat Wittayanukorn, PhD (Food and Drug Administration) for their thoughtful contributions to study design and data analysis.

Funding for this work was made possible by the Food and Drug Administration through grant 1U01FD005272. Views expressed 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.

Funding: This study was funded by the Food and Drug Administration through grant 1U01FD005272.

The sponsor of this study (FDA) has provided suggestions for study design, interpretation of the results and development of the manuscripts. However, the ultimate decisions came from all the authors. Views expressed 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. [Accessed November 28, 2016] Generic Pharmaceutical Association (GPhA) 2016 Generic Drug Savings & Access in the United States Report. <http://www.gphaonline.org/media/generic-drug-savings-2016/index.html>
2. Crawford P, et al. Are there potential problems with generic substitution of antiepileptic drugs? A review of issues. *Seizure*. 2006; 15(3):165–76. [PubMed: 16504545]
3. Del Tacca M, et al. Lack of pharmacokinetic bioequivalence between generic and branded amoxicillin formulations. A post-marketing clinical study on healthy volunteers. *Br J Clin Pharmacol*. 2009; 68(1):34–42. [PubMed: 19660001]
4. Colombo GL, et al. Off-patent generic medicines vs. off-patent brand medicines for six reference drugs: a retrospective claims data study from five local healthcare units in the Lombardy Region of Italy. *PLoS One*. 2013; 8(12):e82990. [PubMed: 24367576]
5. Erickson SC, et al. Clinical and pharmacy utilization outcomes with brand to generic antiepileptic switches in patients with epilepsy. *Epilepsia*. 2011; 52(7):1365–71. [PubMed: 21692778]
6. Kim SH, et al. Efficacy and tolerability of a generic and a branded formulation of atorvastatin 20 mg/d in hypercholesterolemic Korean adults at high risk for cardiovascular disease: a multicenter, prospective, randomized, double-blind, double-dummy clinical trial. *Clin Ther*. 2010; 32(11):1896–905. [PubMed: 21095484]
7. Tsadok MA, et al. Amiodarone-induced thyroid dysfunction: brand-name versus generic formulations. *CMAJ*. 2011; 183(12):E817–23. [PubMed: 21746822]
8. Borgheini G. The bioequivalence and therapeutic efficacy of generic versus brand-name psychoactive drugs. *Clinical Therapeutics*. 2003; 25(6):1578–1592. [PubMed: 12860486]
9. [Accessed November 28, 2016] Drugs@FDA Glossary of Terms. <http://www.fda.gov/Drugs/InformationOnDrugs/ucm079436.htm#ANDA>
10. Kate Faasse TC, Greg Gamble, Petrie Keith J. The Effect of an Apparent Change to a Branded or Generic Medication on Drug Effectiveness and Side Effects. *Psychosomatic Medicine*. 2013; 75:90–96. [PubMed: 23115341]
11. Kesselheim AS, et al. Variations in Patients' Perceptions and Use of Generic Drugs: Results of a National Survey. *J Gen Intern Med*. 2016; 31(6):609–14. [PubMed: 26883524]
12. Kesselheim AS, et al. Prevalence and Predictors of Generic Drug Skepticism Among Physicians: Results of a National Survey. *JAMA Intern Med*. 2016; 176(6):845–7. [PubMed: 27158897]
13. U.S. Food and Drug Administration. List of authorized generic drugs. 2014 May 22. 2014]; Available from: <http://www.fda.gov/drugs/developmentapprovalprocess/howdrugsaredevelopedandapproved/approvalapplications/abbreviatednewdrugapplicationandgenerics/ucm126389.htm>
14. Ahmad SR. Adverse drug event monitoring at the Food and Drug Administration. *J Gen Intern Med*. 2003; 18(1):57–60. [PubMed: 12534765]
15. [Accessed April 24, 2017] FDA Adverse Event Reporting System (FAERS). <https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm>
16. Sakaeda T, et al. Data mining of the public version of the FDA Adverse Event Reporting System. *Int J Med Sci*. 2013; 10(7):796–803. [PubMed: 23794943]
17. [cited 2015 January 3] Medical Dictionary for Regulatory Activities. Standardised MedDRA Queries. 2015. Available from: <http://www.meddra.org/standardised-meddra-queries>
18. [cited 2015 January 3] Medical Dictionary for Regulatory Activities. MedDRA Hierarchy. 2015. Available from: <http://www.meddra.org/how-to-use/basics/hierarchy>
19. [Accessed September 22, 2016] Postmarketing reporting of adverse drug experiences. <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=314.80>
20. [Accessed September 22, 2016] Request for waiver to postmarketing safety reporting requirements. <http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Vaccines/>

ucm074850.htm#REQUESTSFORWAIVERSTOPOSTMARKETINGSAFETYREPORTINGREQUIREMENTS

21. Almenoff J, et al. Perspectives on the use of data mining in pharmaco-vigilance. *Drug Saf.* 2005; 28(11):981–1007. [PubMed: 16231953]
22. Egberts AC, Meyboom RH, van Puijenbroek EP. Use of measures of disproportionality in pharmacovigilance: three Dutch examples. *Drug Saf.* 2002; 25(6):453–8. [PubMed: 12071783]
23. Rahman MM, et al. Comparison of brand versus generic antiepileptic drug adverse event reporting rates in the U.S. Food and Drug Administration Adverse Event Reporting System (FAERS). *Epilepsy Res.* 2017; 135:71–78. [PubMed: 28641219]
24. [Accessed September 19, 2016] Authorized Generics. <http://www.authorizedgenerics.com/default.asp?contentID=29>
25. [Accessed April 24, 2017] Guidance for Industry. E2E Pharmacovigilance Planning. <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073107.pdf>
26. Iyer G, et al. An Algorithm to Identify Generic Drugs in the FDA Adverse Event Reporting System. *Drug Saf.* 2017
27. [Accessed December 01, 2016] Drugs@FDA Lamotrigine. <http://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=BasicSearch.process>

Key points

- The FDA Adverse Event Reporting System (FAERS) may be useful for comparative safety surveillance of brand vs. generic drugs.
- Brand reporting rates were higher than for generic drugs which could be a function of more familiarity of the branded drugs to consumers and providers.
- Small sample size could limit the analyses of modified release products in the FAERS database. It is possible that reporters may attribute the adverse event associated with the extended release formulation to the immediate release formulations.
- We proposed a method in which authorized generic (AG) drugs were used as a control group in brand vs. generic comparisons, but given we only illustrated specific drugs and specific events, more work is needed to determine if AGs could be a suitable control or not.

Fig. 1. Comparison of known labeled events across two different methods of defining brand, AG, and generic alendronate

ROR- Reporting Odds Ratio

NA- Not applicable

AG- Authorized Generic

a Defined brand, AG, and generics based on the manufacturers name only

For alendronate, brand reports were from Merck and Mission Pharma, AG reports were from Watson labs, and generic reports were from all other manufacturers. Although brand vs. generic comparison generated multiple significant RORs, generic vs. AG comparison was significant only for osteonecrosis of the jaw.

b Defined brand, AG, and generics based on the manufacturers name and whether reported by brand or generic name

A sensitivity analysis was performed where reports were classified as brand, generics, and AG based on both manufacturers' name and the verbatim drug name reported. For example, if the drug name was reported as Fosamax or Binosto and the reporting manufacturers were Merck or Mission Pharma, then it was classified as brand. Similar results were obtained as before.

Fig. 2. ROR trend for gastritis with alendronate

ROR- Reporting Odds Ratio

AG- Authorized Generic

a Cumulative ROR trend, b Annual ROR trend

▲ = The actual value was censored to a value of 13.5 for illustration purpose

* = actual ROR, 22.69

Both the cumulative (a) and annual (b) ROR trends were similar which explains minimal influence of temporal variation on reporting trends.

Fig. 3. Sensitivity analysis of report type for gastritis with alendronate

ROR- Reporting Odds Ratio

AG- Authorized Generic

Although brand vs. generic comparison reached statistical significance for all the cases except for US primary suspect reports, none of the generic vs. AG comparison showed statistical significance. The confidence interval gets wider as the number of reports get smaller.

Fig. 4. Sensitivity analysis comparing reporting patterns for alendronate over all time vs. just after generic entry

ROR- Reporting Odds Ratio

AG- Authorized Generic

None of the generic vs. AG comparison yielded statistically significant result. Consistent reporting patterns were observed across over all times and just after generic entry.

Fig. 5. Sensitivity analysis comparing reporting patterns for extended release vs. all formulations for carbamazepine

ROR- Reporting Odds Ratio

NA- Not applicable

AG- Authorized Generic

ER- Extended Release

No AG report was found for carbamazepine ER. RORs for generics were higher than brand for both the formulations of carbamazepine in case of liver injury; however, none of the generic vs. AG comparison reached statistical significance.