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Comparison of Brand versus Generic Antiepileptic Drug Adverse Event Reporting Rates in the U.S. Food and Drug Administration Adverse Event Reporting System (FAERS)

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Abstract

Objective—Despite the cost saving role of generic anti-epileptic drugs (AEDs), debate exists as to whether generic substitution of branded AEDs may lead to therapeutic failure and increased toxicity. This study compared adverse event (AE) reporting rates for brand vs. authorized generic (AG) vs. generic AEDs. Since AGs are pharmaceutically identical to brand but perceived as generics, the generic vs. AG comparison minimized potential bias against generics.

Methods—Events reported to the U.S. Food and Drug Administration Adverse Event Reporting System between January 2004 to March 2015 with lamotrigine, carbamazepine, and oxcarbazepine listed as primary or secondary suspect were classified as brand, generic, or AG based on the manufacturer. Disproportionality analyses using the reporting odds ratio (ROR) assessed the relative rate of reporting of labeled AEs compared to reporting these events with all other drugs. The Breslow-Day statistic compared RORs across brand, AG, and other generics using a Bonferroni-corrected $P < 0.01$.

Results—A total of 27,150 events with lamotrigine, 13,950 events with carbamazepine, and 5,077 events with oxcarbazepine were reported, with generics accounting for 27%, 41%, and 32% of reports, respectively. Although RORs for the majority of known AEs were different between brand and generics for all three drugs of interest (Breslow-Day $P < 0.001$), RORs generally were

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similar for AG and generic comparisons. Generic lamotrigine and carbamazepine were more commonly involved in reports of suicide or suicidal ideation compared with the respective AGs based on a multiple comparison-adjusted $P < 0.01$.

Significance—Similar AED reporting rates were observed for the AG and generic comparisons for most outcomes and drugs, suggesting that brands and generics have similar reporting rates after accounting for generic perception biases. Disproportional suicide reporting was observed for generics compared with AGs and brand, although this finding needs further study.

Keywords

Authorized generic; generic; brand; lamotrigine; carbamazepine; oxcarbazepine

1. Introduction

Currently, 50 million people in the world live with epilepsy, making it the second most common neurological disorder. (Begley et al., 2000; “WHO | Epilepsy. <http://www.who.int/mediacentre/factsheets/fs999/en/>. Accessed March 10, 2017.,”) In the United States (U.S.) alone, nearly 2.9 million adults and children had epilepsy as of 2013. (“CDC | Epilepsy. <http://www.cdc.gov/epilepsy/basics/fast-facts.htm>. Accessed March 10, 2017.,”) The main objective of epilepsy treatment is “no seizures, no side effects.” (Engel, 2004) To date, the mainstay of treating epilepsy involves anticonvulsant therapies often termed as antiepileptic drugs (AED). (Chong & Lerman, 2016) In the U.S., more than twenty anti-seizure medications and two implantable devices are available for the treatment of epilepsy. (Shih et al., 2017) However, the treatment options depend on the types of epilepsy and individual traits. (Chong & Lerman, 2016) This large number of treatment options can introduce decision-making challenges for clinicians. (Shih et al., 2017) Moreover, debate regarding the comparative safety and effectiveness of AEDs in the real world causes additional clinical difficulties. (Wahab, 2010)

The approximate cost associated with the direct and indirect treatment of epilepsy is estimated to be \$15.5 billion per year in the U.S. (“CDC | Epilepsy. <http://www.cdc.gov/epilepsy/basics/fast-facts.htm>. Accessed March 10, 2017.,”) Direct costs associated with AEDs represent \$ 9.6 billion per year. (Yoon et al., 2009) However, the indirect cost, which includes decline of household earning potential of the whole family, as well as reduced quality of life, accounts for the majority of the expenses in the long run. (Begley et al., 2000) Given the large contribution of drug costs to the cost of treating epilepsy, strategies to control drug costs are important to patients and payers. Use of generic medications represents one mechanism to control these drug costs, with generics having 80% to 85% lower cost than brand medications on average. (Hottinger & Liang, 2012) For generic medications in general, 93% of doctors are more likely to prescribe generic over the brand. (Hottinger & Liang, 2012) For AEDs, however, prescribing of generic medications is questioned more often by prescribers, with some believing there is an increased risk of adverse events (AEs) and recurrent seizures. (Heaney & Sander, 2007; Privitera, 2008) Generic AED prescription rates have been reported to vary depending on the age of the patient, insurance plan, gender, and geographic region. (Meyer et al., 2013) In addition, the American Academy of Neurology opposes generic substitution of AEDs at the point of sale

without the approval of the physician. (“American academy of neurology. Position statement on the coverage of anticonvulsant drugs for the treatment of epilepsy, November 2006. https://www.aan.com/uploadedFiles/Website_Library_Assets/Documents/6.Public_Policy/1.Stay_Informed/2.Position_Statements/3.PDFs_of_all_Position_Statements/anticonv.pdf. Accessed March 16, 2017.”) Various AEDs such as carbamazepine and phenytoin have been classified as narrow therapeutic index (NTI) drugs by U.S. Food and Drug Administration (FDA). (Ting et al., 2015) The FDA defines NTI drugs as “drugs where small differences in dose or blood concentration may lead to serious therapeutic failures or adverse drug reactions”. (“FDA | NTI definition. <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AdvisoryCommitteeForPharmaceuticalScienceandClinicalPharmacology/UCM263465.pdf>. Accessed March 16, 2017.”) Thus, AEDs require very close monitoring, especially in “generic-sensitive” patients. (Ting et al., 2015) While generic medications have been proven to be bioequivalent to brand-name formulations, AEs have been reported when switching from brand to generic or even from one generic to another generic AED medication. (Shaw & Hartman, 2010) All of these factors contribute to a negative view of generic AEDs and their lower use respective to other generic drug markets.

Overcoming patient and prescriber reluctance towards the use of generic AEDs could be facilitated by better data to support the brand and generic equivalence, as well as data supporting financial incentives and better medication adherence. (Shrank et al., 2011) Regulatory policy of the U.S. FDA requires rigorous pre-approval clinical studies and submission of a New Drug Application (NDA). Generic drugs, however, are approved through an Abbreviated New Drug Application (ANDA) process, which relies on safety and efficacy information from the reference brand product and does not require direct pre-clinical and clinical safety and efficacy data. Instead, generic formulations only need to demonstrate pharmaceutical equivalence (which means the generic is comparable to the brand drug in terms of active ingredient, dosage form, route of administration, and strength) and bioequivalence (i.e., works in the same way as the innovator drug). (“Drugs@FDA Glossary of Terms. <http://www.fda.gov/Drugs/InformationOnDrugs/ucm079436.htm#ANDA>. Accessed March 16, 2017.” ; Hottinger & Liang, 2012) Equivalence is demonstrated if the 90% CI of the ratio of the generic to the reference compound for the area under the plasma concentration time curve (AUC) and the maximum plasma concentration (C_{max}) falls within a range of 80 to 125%. (Berg, 2007) While requiring additional pre-approval testing for generics would compromise potential cost-savings, evidence generated from post-marketing research may help support or refute controversy over generic AED substitution.

To address the need for better evidence regarding substitutability of brand vs. generic AEDs, we evaluated AE reports over an 11-year period (2004 through first quarter 2015) using the U.S. FDA Adverse Event Reporting System (FAERS) data. Because the FAERS data are spontaneously reported, it is possible that there may be a bias in the number and types of events that get reported for brand vs. generic drugs. To overcome this possible bias, our analyses focus on a special kind of generic known as an “authorized generic (AG)”. AGs have the same formulations, manufacturing processes, active ingredients, and inactive ingredients as the branded drugs and are “marketed, sold, or distributed directly or indirectly

to retail classes of trade with either labeling, packaging (other than repackaging as the listed drug in blister packs, unit doses, or similar packaging for use in institutions), product code, labeler code, trade name, or trademark that differs from that of the listed drug”.(“FDA | List of authorized generic drugs. <http://www.fda.gov/drugs/developmentapprovalprocess/howdrugsaredevelopedandapproved/approvalapplications/abbreviatednewdrugapplicationandagenerics/ucm126389.htm>. Accessed March 16, 2017.,”) Theoretically, the safety and efficacy profiles of AGs should be exactly the same as the branded drug since they contain the same active and inactive ingredients, approved under the brand drug's NDA. We believe that AG drugs can be used as “control drugs” in post-marketing research since they are perceived as any other generics by the patients and prescribers. If brand and AGs differ significantly across different outcomes, it would represent a possible bias against generics; however, if generics and AGs differ significantly, this could be a representation of actual difference across these product types. Our analyses capitalized on the existence of certain AED AGs and we compared known AE reporting rates for the brand, AG, and generic AEDs.

Lamotrigine (Lamictal), carbamazepine (Tegretol), and oxcarbazepine (Trileptal) were chosen as example drugs as these drugs had generics and AGs entered the market in the past decade. Lamictal was approved by the FDA in 1994 (“Drugs@FDA: FDA Approved Drug Products. <https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=BasicSearch.process>. Accessed May 08, 2017,”) and AG by Teva Pharmaceutical Industries Ltd. came into the market in 2005.(“Teva. Lamotrigine. http://ir.tevapharm.com/phoenix.zhtml?c=73925&p=irol-newsArticle_Print&ID=1557132. Accessed May 8, 2017,”) Tegretol by Novartis was approved by the FDA in 1968 (“Drugs@FDA: FDA Approved Drug Products. <https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=BasicSearch.process>. Accessed May 08, 2017,”) Tegretol-XR by Novartis, Carbatrol by Shire, and Equetro by Validus were approved in 1996, 1997, and 2004, respectively. (“Drugs@FDA: FDA Approved Drug Products. <https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=BasicSearch.process>. Accessed May 08, 2017,”) Equetro doesn't have an AG or other generics in the market. Sandoz and Prasco marketed the AG versions of Tegretol-XR and Carbatrol in 2009 and 2012, respectively and both the AGs are still on the market. Trileptal by Novartis and Oxtellar XR by Supernus Pharmaceutical were approved in 2000 and 2012, respectively.(“Drugs@FDA: FDA Approved Drug Products. <https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=BasicSearch.process>. Accessed May 08, 2017,”) Oxtellar XR does not have an AG in the market. Sandoz marketed the AG of Trileptal in 2011. (“FDA | List of authorized generic drugs. <http://www.fda.gov/drugs/developmentapprovalprocess/howdrugsaredevelopedandapproved/approvalapplications/abbreviatednewdrugapplicationandagenerics/ucm126389.htm>. Accessed March 16, 2017.,”) We believe that these drugs are good candidates for this study as adequate historical data exists to evaluate trends and have hypothesized concerns about the safety and efficacy of their generic version.

2. Materials and Methods

2.1. Study design

Retrospective analyses of known AE reports for lamotrigine, carbamazepine, and oxcarbazepine were conducted to comparatively assess AE reporting rates across brand, generic, and AG products.

2.2. Data sources

This study utilized data from the public release of the FAERS from January 2004 through March 2015. Both U.S. and non-U.S. pharmaceutical companies, healthcare professionals, and consumers can submit reports to FAERS through the FDA MedWatch program. (Ahmad, 2003) More than 90% of reports in the FAERS are submitted by pharmaceutical companies and other reports are submitted directly to the FDA from various sources. ("Reports Received and Reports Entered into FAERS by Year. <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/ucm070434.htm>. Accessed March 16, 2017,") A full description of this database is available online. ("FAERS. <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm>. Accessed March 16, 2017,") Prior to conducting any analyses, we deleted duplicate reports and adopted the most recent CASE number as per FDA's recommendation. (Sakaeda et al., 2013)

2.3. Identification of Drugs

For identifying AE reports with lamotrigine (Lamictal), carbamazepine (Tegretol), and oxcarbazepine (Trileptal), text string searches of brand names, generic names, and abbreviations were employed. To ensure the accuracy of the search method, an iterative process of complete drug name searches versus shorter text string searches was used. Shorter text string searches yielded a messy but all-inclusive list of drug names which was cleaned and recoded by two independent adjudicators to correct misspellings, abbreviations, and remove the reports with non-drugs of interest.

Drugs listed only as primary suspect (PS) or secondary suspect (SS) were classified as brand, generic, or AG based on drug name and manufacturers receiving or submitting the report. Since direct reports to the FDA (i.e., REPT_COD = DIR) could not be differentiated by the manufacturer, we excluded them from the analyses (about 8% of reports for lamotrigine, 4% of reports for carbamazepine, and 10% of reports for oxcarbazepine were excluded). For lamotrigine, brand reports were from GlaxoSmithKline (Lamictal) and AG reports were from Teva Pharmaceutical Industries Ltd.; for carbamazepine, brand reports were from Novartis (Tegretol), Shire (Carbatrol), and Validus (Equetro), and AG reports were from Sandoz and Prasco; for oxcarbazepine, brand reports were from Novartis (Trileptal) and Supernus (Oxtellar), and AG reports were from Sandoz. Equetro does not have an AG or generics in the market. All reports from manufacturers other than the brand or AG companies were considered as reports for generic drugs across each of the three drugs, resulting in the following manufacturers as generics: lamotrigine (Mylan, Dr. Reddy's Laboratories., Watson Laboratories Inc, Roxane, Zydus Pharmaceuticals USA, Cipla Ltd., Hikma Pharmaceuticals, Pharmascience Inc, Sandoz, Taro Pharmaceuticals Ltd., Apotex

Inc, Actavis, Lupin Ltd., Torrent Pharmaceuticals, Aurobindo Pharma, Wockhardt, Glenmark Generics, Jubilant Cadista, Taro Pharmaceuticals Ltd., Unichem Laboratories Ltd., Alembic Pharmaceuticals Ltd., Actavis Elizabeth, Alkem Laboratories, Impax Laboratories Inc, Anchen Pharmaceuticals, Par Pharmaceuticals, Handa Pharmaceuticals LLC); carbamazepine (Inwood Labs, USL Pharma, Warner Chilcott, Pliva, Actavis Elizabeth, Jubilant Cadista, Taro Pharmaceuticals Ltd., Torrent Pharmaceuticals, Wockhardt, Apotex Inc, Mylan Ireland Ltd., Teva Pharmaceuticals); oxcarbazepine (Apotex Inc, Sun Pharmaceuticals Ltd., West-Ward Pharmaceuticals, Taro Pharmaceuticals Ltd., Glenmark Generics, ANI Pharmaceuticals, Inc, Breckenridge Pharmaceutical Inc, Jubilant Cadista, Amneal Pharmaceuticals). ("Drugs@FDA: FDA Approved Drug Products. <https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=BasicSearch.process>. Accessed May 08, 2017,")

2.4. Definition of Adverse Events

Package labels of these three drugs and drug reference databases such as Lexi-comp and Micromedex were used to select the specific AEs, which included severe dermatologic events, suicide/suicidal ideation, diplopia/blurred vision, aseptic meningitis, and dementia for lamotrigine; severe dermatologic events, liver injury, suicide/suicidal ideation, and pancreatitis for carbamazepine; and severe dermatologic events, angioedema, suicide/suicidal ideation, and hyponatremia for oxcarbazepine. These AEs were identified using the Medical Dictionary for Regulatory Activities (MedDRA) preferred terms (PTs) from the REAC files. All the information from different datasets were linked through a unique ID (called "PRIMARYID"). We defined cases as the reports of the aforementioned specific AEs per drug according to Standardized MedDRA Queries (SMQs) (version 17.0) which are groupings of PTs.

2.5. Data Analysis

Descriptive statistics were used to illustrate AE reporting rates across different products. Reporting Odds Ratios (RORs) were calculated for disproportionality analyses which assessed the relative rate of reporting of specific AEs compared to reporting these events with all other drugs. For example, the odds of reporting suicide/suicidal ideation in the lamotrigine group was divided by the odds of reporting suicide/suicidal ideation in those who were not exposed to lamotrigine (i.e., all other drugs in the database) to measure RORs. (Almenoff et al., 2005) A potential signal was considered to be detected if the lower bound of the 95% confidence interval (95% CI) exceeded one. (Egberts et al., 2002) The same approach was used to calculate RORs across brand, generics, and AGs for all of the drug-AE pairs. The homogeneity of the RORs across brand, AG, and generics was compared by the Breslow-Day statistic. As three comparisons were conducted across different product types (i.e., brand, generic, and AG), a Bonferroni-corrected P value of $P < 0.01$ (i.e., $P < 0.05/3$) was used to define statistical significance in order to minimize the risk of *Type I* error. Statistical analyses were performed using SAS (version 9.4; SAS Institute, Cary, NC). This study was reviewed and approved by the Auburn University Institutional Review Board for research involving human subjects (protocol 14-465 EP1410).

3. Results

A total of 27,150 AE reports for lamotrigine, 13,950 AE reports for carbamazepine, and 5,077 AE reports for oxcarbazepine as PS or SS drugs were found worldwide from January 2004 through March 2015. For lamotrigine, brand, generics, and AG accounted for 19,363 (71.32%), 7,343 (27.04%), and 444 (1.64%) reports, respectively. For carbamazepine, these numbers were 7,953 (57.01%), 5,694 (40.82%), and 303 (2.17%) for brand, generics, and AG, respectively. For oxcarbazepine, the number of reports were 3,369 (66.36%), 1,648 (32.46%), and 60 (1.18%) for brand, generics, and AG, respectively. A summary of drug marketing information and reporting is shown in Table 1.

Specific known AEs for lamotrigine were analyzed and the RORs across different product types were compared (Fig. 1). While comparing brand vs. generics, significant differences across RORs for all the known AEs with lamotrigine were observed except for aseptic meningitis. RORs for brand lamotrigine were higher in cases of severe dermatologic events and diplopia or blurred vision compared with AGs and generics; whereas RORs for generic drugs were higher for suicide/ suicidal ideation and dementia compared with their brand and AG counterparts. RORs for brand and AG differed significantly only for severe dermatologic events. However, RORs for suicide/suicidal ideation only differed significantly ($P<0.001$) for the comparison of AG vs. generics, which we considered to be the most reliable since it is less likely subject to public perception bias towards generics. This could be an indication of a possible signal that should be studied more rigorously. Although not statistically significant considering our Bonferroni-corrected $P<0.01$, the ROR for generic lamotrigine was higher than its AG counterpart in the case of dementia ($P=0.01$).

Similar analyses were performed for carbamazepine (Fig. 2). RORs for generic drugs were significantly higher than the branded ones in the cases of liver injury and suicide/suicidal ideation; however, only suicide/suicidal ideation showed statistically significant differences ($P<0.001$) while focusing on the AG vs. generic comparison. This illustrates a potential signal that needs further study. RORs for generic carbamazepine tended to be higher than that of the AGs for liver injury and pancreatitis ($P=0.01$), but they were not statistically significant according to our Bonferroni-adjusted critical $P<0.01$.

RORs for severe dermatologic events, suicide/suicidal ideation, and hyponatremia with generic oxcarbazepine were significantly higher than the brand counterpart. RORs for brand and AG differed significantly only for suicide/suicidal ideation. However, no significant differences between AG and generic were observed for any of the AEs studied (Fig. 3).

To test the possible misattribution of AE reports for AG to brands or generics, sensitivity analyses were conducted by assigning AE reports for AGs to brand and then similarly assigning AE reports for AGs to generics. RORs for all the specific known events with lamotrigine were calculated and compared for this purpose. Very similar results were observed across all of the event types and product categories (Fig. 4).

4. Discussion

Generic substitution is highly recommended as a means of lowering healthcare expenditures. To gain approval, generic drug products have to undergo pharmaceutical equivalence and bioequivalence studies. According to the FDA, “there is no more than a 5% chance that a generic product that is not truly equivalent to the reference will be approved.” (“Approved drug products with therapeutic equivalence evaluations (Orange Book), 33rd ed. 2013. <https://books.google.com/books?id=5uSMDAAQBAJ&pg=PR10&lpg=PR10&dq=there+is+no+more+than+a+5%25+chance+that+a+generic+product+that+is+not+truly+equivalent+to+the+reference+will+be+approved&source=bl&ots=5W68qzSFqV&sig=KEUyQJ5eWbrqCh1xNZJCN18FsNY&hl=en&sa=X&ved=0ahUKEwjaro3zt4rQAhXCYSYKHej9DHsQ6AEIIDAB#v=onepage&g=there%20is%20no%20more%20than%20a%205%25%20chance%20that%20a%20generic%20product%20that%20is%20not%20truly%20equivalent%20to%20the%20reference%20will%20be%20approved&f=false>. Accessed March 16, 2017.,” ; Berg, 2007; Ng, 2009) FDA is confident in their position that bioequivalent products are anticipated to have the same risk-benefit profiles as that of the reference standards. (Berg, 2007) However, the American Academy of Neurology (AAN) has an opposing position regarding the generic substitution of AEDs, which states that the variations in generic and brand products allowed by the FDA may result in increased seizures in patients. (“American academy of neurology. Position statement on the coverage of anticonvulsant drugs for the treatment of epilepsy, November 2006. https://www.aan.com/uploadedFiles/Website_Library_Assets/Documents/6.Public_Policy/1.Stay_Informed/2.Position_Statements/3.PDFs_of_all_Position_Statements/anticonv.pdf. Accessed March 16, 2017.” ; Berg, 2007; Liow et al., 2007) Nevertheless, the American Epilepsy Society (AES) has recently changed its position on generic AEDs. It supports the notion that the generic substitution of AEDs will produce the same efficacy with lower drug costs. (Vossler et al., 2016) A recent study that confirmed the bioequivalence of generic vs. brand lamotrigine found that more seizures were observed with the generic products despite similar pharmacokinetic profiles with the brand. (Ting et al., 2015) Previous studies also found that the current bioequivalent standard may not be easily assignable to the generic AEDs. (Berg et al., 2008a, 2008b; Sirven et al., 2012) On the contrary, a recent randomized controlled trial that studied generic to generic switches in people with epilepsy found no significant differences across AE profiles with drug switches. (Privitera et al., 2016) These contradictory findings illustrate the need for more population-based studies in these regards.

Safety and efficacy of new drugs are established through extensive clinical trials prior to their approval in the market; however, the generalizability of these trials are an issue due to the small number of study participants, homogenous characteristics of study participants, and short study durations. Once the product is in the market, we have to rely on post-marketing safety surveillance to ensure the product safety throughout its entire lifespan. This safety surveillance is even more crucial for generic drugs as they do not go through the same clinical trials prior to their approval. The FAERS database provides us with such an opportunity to explore brand vs. generic safety signals in the post-marketing period. This paper illustrates an application of the FAERS database to study brand vs. generic AED

safety signals, employing AGs as a control for possible generic drug perception bias. We found that although RORs for the majority of known AEs were different between brand and generics for all three drugs of interest, RORs were only different for suicide or suicidal ideation when we compared generics vs. AGs (except for oxcarbazepine). Similar AE reporting rates for AGs and generics for most outcomes and drugs suggest that brands and generics generally have similar reporting rates after accounting for generic perception biases.

Brand and AGs differed significantly for severe dermatologic events with lamotrigine and suicide/suicidal ideation with oxcarbazepine. Although the safety and efficacy of brands and AGs should be the same, the differences in RORs illustrates possible perception bias and supports our assumption that AGs are also considered as generics by the consumers. Although brands and generics differed significantly in both the cases mentioned above, RORs across AGs and generics did not reach statistical significance in either of the cases which also is likely a manifestation of public perception bias towards generic drugs.

When considering the total reports worldwide, we found that the brand reporting rates were higher than generics for all of the three drugs. This was also true across the total U.S. reports except for carbamazepine. Total U.S. reports for generic carbamazepine were slightly higher compared to the brand and AG. One reason for this high brand reporting could be the misattribution of AE reports to the branded drugs as they are more familiar to patients and providers. In most of the cases, the RORs for generics were higher than the branded drugs; however, the AG vs. generic comparison reached Bonferroni-corrected statistical significance only in the case of suicide/suicidal ideation with lamotrigine and carbamazepine. The small AE reports for AG with oxcarbazepine might be a reason for this non-significance. The number of reports for brand, and generic oxcarbazepine also were low compared to the other two drugs. This could be a function of lower utilization of oxcarbazepine compared with the other two AEDs. Moreover, oxcarbazepine generics were approved later, so there was a shorter period of time for them to be reported to FAERS. Although RORs between generics and AG for dementia with lamotrigine and liver injury with carbamazepine were marginally non-significant ($P=0.01$) considering our multiple comparison-adjusted $P<0.01$, they can be scrutinized further for potential signals. In the rest of the cases, the AG vs. generic comparison did not reach statistical significance which is suggestive of public perception bias towards generic drugs.

The association between AED use and suicidality, defined as complete suicide, suicide attempt, and/or suicidal ideation has been reasonably well studied. (Schuerch et al., 2016) In 2008, based on a meta-analysis of 199 randomized control trials, FDA issued a safety warning regarding the association between suicidality and AED use. ("FDA Requires Warnings about Risk of Suicidal Thoughts and Behavior for Antiepileptic Medications. <https://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm100197.htm>. Accessed May 09, 2017," ; Grimaldi-Bensouda et al., 2017; "Statistical Review and Evaluation: Antiepileptic Drugs and Suicidality. <https://www.fda.gov/ohrms/dockets/ac/08/briefing/2008-4372b1-01-FDA.pdf>. Accessed May 09, 2017,") However, some later studies did conclude that the suicidality with AEDs may depend on the underlying psychiatric or

neurological conditions of the patients as well as the clinical indications in which they are prescribed. (Arana et al., 2010; Grimaldi-Bensouda et al., 2017) Still, no study evaluated the risk of suicidality across brand vs. generic AEDs. In our study, RORs for suicide/suicidal ideation with generic lamotrigine and carbamazepine were significantly higher than their brand counterparts after accounting for the generic perception biases. These consistent results might be indicative of a potential signal that calls for further scrutiny.

The inactive ingredients (referred to as excipients) of the generic drugs differ from that of the brands. Although the excipients are supposed to be inert, it is possible that differences in excipients could be related to differences in AEs in some patients. (Crawford et al., 2006) Previous studies also suggested that excipients in the generic drugs can cause anaphylaxis and skin rashes in some patients. (Calogiuri et al., 2016; De Vuono et al., 2014; Duenas-Laita et al., 2009) Bioequivalence, thus, may not necessarily translate into therapeutic equivalence and the AE profile of the generic drugs may not be the same as of their brand counterparts. (Besag, 2000; Guberman & Corman, 2000) Achieving therapeutic equivalence can be more challenging for the generic AEDs due to the complexity of disease etiology and management regimen. (Crawford et al., 2006)

In some clinical trials placebos were found to reduce seizures in patients with epilepsy which could be attributed to the natural course of the disease itself. (Goldenholz et al., 2015) Moreover, patient and provider biases may exist regarding the generic drug safety and efficacy. To assess such biases, one study provided placebo to all patients but informed some were given generics and some were given the branded drugs. (Kate Faasse TC, 2013) The patients who thought were given generics had more adverse reactions and less beneficial effects than the patients who were told they were given the brand. (Kate Faasse TC, 2013) Our findings support the notion that the problem of generic efficacy and tolerability could be partially psychological.

4.1 Limitations

The FAERS database is subject to some inherent limitations. As AEs are reported to FAERS spontaneously, reporting rates may be influenced by some external factors such as mass media advertisements, labeling changes, or other unmeasurable factors. Moreover, overestimation of reporting rates due to duplicate reports for the same event is possible. As per the FDA's recommendation, we deleted duplicate reports and kept the most recent CASE number to deal with this problem; however, duplicate reports may still exist.

Additionally, defining AG by manufacturers' name may be very challenging for some drugs. For example, there are four dosage forms available in the market for lamotrigine (Lamictal by GLAXOSMITHKLINE): tablet, chewable tablet, orally disintegrating tablet, and extended release tablet. ("Drugs@FDA: FDA Approved Drug Products. <https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=BasicSearch.process>. Accessed May 08, 2017,") Only the chewable tablet form has an AG in the market manufactured by Teva Pharmaceutical Industries Ltd.; however, a regular generic lamotrigine also was marketed by Teva once they stopped marketing the AG. Methodologically in our study, this could result in an overestimation of AG and possibly bias the analyses. To test this possible bias, we performed a sensitivity analyses by assigning AE reports for AG to brand and then

similarly assigning AG reports to generics and calculated RORs for all the known AEs with lamotrigine. Nearly identical results were observed throughout the analyses. For example, RORs for brand vs. generic for severe dermatologic events was 6.48 vs. 3.27, $P < 0.001$ when the AG was assigned to brand; RORs for brand vs. generic was 6.58 vs. 3.26, $P < 0.001$ when the AG was assigned to generic. Similar results were obtained across all the AEs studied. This consistent result demonstrates minimal or no effect of misclassification bias on the analyses.

Further, there is no utilization denominator in the FAERS database so comparison across drugs cannot be standardized to reflect the reporting rate in context of the population at risk. Moreover, many epileptic patients may be on multiple drug therapies which could contribute to the AEs studied. We did not have comprehensive patient-level information regarding their comorbid conditions, indications for which these medications were prescribed, the dose and duration of the medications used, and drug-drug interactions, which could potentially limit the scope of this analysis. Thus, this database is not intended to establish causality. The FAERS data is more appropriate for exploratory analyses.

We used the reported manufacturer's name to define brands, generics, and AGs. It is possible that we misattributed AE reports to the branded drugs since they are more familiar to providers and patients. One recent study with the FAERS database used both manufacture's name and NDA number to distinguish brand and generics and found similar reliability with both of the approaches. (Geetha Iyer et al., 2016) Since AGs and brand have the same NDA number we cannot use this approach to identify the AG, and therefore our approach is most practical to identify these sort of drugs. However, this approach may still be limited by misclassification and the small number of reports for AGs may limit its widespread use as a control group in future studies. In addition, our study did not focus on manufacturer specific brand vs. generic or generic vs. generic analyses. It is possible that the variations in AE profile may be related to the differences in excipients and pharmacokinetic profiles of each drug (Crawford et al., 2006) which calls for further study.

5. Conclusion

To conclude, our study found similar reporting patterns for brands and generics in most of the cases after accounting for generic perception biases. Disproportional reporting for suicide with generics compared to brands and AGs were observed. Further study with more reliable data sources such as administrative claims databases or electronic health records and stringent epidemiological methods is required to test this generated signal.

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Fig. 1.

Comparison of known labeled events for brand, authorized generic (AG), and generic lamotrigine.

Although reporting odds ratios (RORs) for brand and generics differed significantly for all the adverse event (AE)-drug type pairs except for aseptic meningitis, RORs for suicide/ suicidal ideation only differed significantly across generic vs. AG comparison (ROR 4.6 vs. 1.9, $P < 0.001$) which is suggestive of a potential signal. In the case of dementia, the ROR for generic lamotrigine was higher than its AG counterpart (2.0 vs. 1.5, $P = 0.01$); however, it was not considered statistically significant considering our Bonferroni-corrected $P < 0.01$.

Fig. 2.

Comparison of known labeled events for brand, authorized generic (AG), and generic carbamazepine.

Reporting odds ratios (RORs) for only suicide/suicidal ideation showed statistically significant differences while focusing on the generic vs. AG comparison (2.8 vs. 1.3, $P=0.001$) which illustrates a potential signal that needs further scrutiny. RORs for generic carbamazepine were also higher than that of the AGs for liver injury and pancreatitis ($P=0.01$), but were not statistically significant according to our Bonferroni-adjusted critical $P<0.01$.

Fig. 3.

Comparison of known labeled events for brand, authorized generic (AG), and generic oxcabazepine.

Reporting odds ratios (RORs) for generic oxcabazepine were significantly higher than the brands in cases of suicide/suicidal ideation ($P < 0.001$) and hyponatremia ($P = 0.004$). However, no significant differences between AG and generics were observed for any of the adverse events (AEs) studied. RORs for brand and AG differed significantly only for suicide/suicidal ideation which is suggestive of public perception bias towards generic drugs.

Fig. 4.

Sensitivity analysis by assigning authorized generic (AG) to brand and AG to generics for lamotrigine.

This test was performed to test the possible misattribution bias of adverse event (AE) reports for AG to brands or generics. Reporting odds ratios (RORs) for all the specific known AEs with lamotrigine were calculated and compared. Almost identical results were observed across all AE-drug type pairs. For example, RORs for generic vs. brand for suicide/ suicidal ideation was 4.61 vs. 1.26, $P < 0.001$ when the AG was assigned to brand; RORs for generic vs. brand was 4.47 vs. 1.25, $P < 0.001$ when the AG was assigned to generics. This is suggestive of minimal or no effect of misattribution bias on the analyses.

Table 1

Drug marketing information and reports.

	Lamotrigine	Carbamazepine	Oxcarbazepine
Brand manufacturer	GlaxoSmithKline	Novartis, Shire, Validus	Novartis, Supernus
AG manufacturer	Teva *	Sandoz **, Prasco ***	Sandoz
Adverse events	Severe dermatologic events, suicide/suicidal ideation, aseptic meningitis, diplopia/blurred vision, and dementia	Severe dermatologic events, liver injury, suicide/suicidal ideation, and pancreatitis	Severe dermatologic events, angioedema, suicide/suicidal ideation, and hyponatremia
Total reports	27,150	13,950	5,077
Brand, n (%)	19,363 (71.32%)	7,953 (57.01%)	3,369 (66.36%)
AG, n (%)	444 (1.64%)	303 (2.17%)	60 (1.18%)
Generic, n (%)	7,343 (27.04%)	5,694 (40.82%)	1,648 (32.46%)
Total U.S. reports	18,825	3,733	2,255
Brand, n (%)	1,5347 (81.52%)	1,810 (48.49%)	1,369 (60.71%)
AG, n (%)	163 (0.87%)	49 (1.31%)	16 (0.71%)
Generic, n (%)	3,315 (17.61%)	1,874 (50.20%)	870 (38.58%)

ER- Extended release; AG- Authorized generic;

*

Teva is the AG manufacturer of lamotrigine chewable tablets. It also has a regular generic in the market;

**

Sandoz is the AG manufacturer of Tegretol-XR (Novartis);

Prasco is the AG manufacturer of Carbatrol (Shire)

All other generic manufacturers were classified as “generic”