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Mixed approach retrospective analyses of suicide and suicidal ideation for brand compared with generic central nervous system drugs

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Abstract

Introduction—Several different types of drugs acting on the central nervous system (CNS) have previously been associated with an increased risk of suicide and suicidal ideation (broadly referred to as suicide). However, a differential association between brand vs. generic CNS drugs and suicide has not been reported.

Objectives—This study compares suicide adverse event rates for brand vs. generic CNS drugs using multiple sources of data.

Methods—Selected examples of CNS drugs (sertraline, gabapentin, zolpidem, and methylphenidate) were evaluated via the FDA Adverse Event Reporting System (FAERS) for a hypothesis generating study, and then via administrative claims and electronic health record (EHR) data for a more rigorous retrospective cohort study. Disproportionality analyses with reporting odds ratios (ROR) and 95% confidence intervals (CIs) were used in the FAERS analyses to

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COMPLIANCE WITH ETHICAL STANDARDS

Conflict of interest: In the past 3 years, Richard Hansen has provided expert testimony for Daiichi Sankyo. Ning Cheng, Md. Motiur Rahman, Yasser Alatawi, Jingjing Qian, Peggy L. Peissig, Richard L. Berg, and David Page have no conflicts of interest that are directly relevant to the content of this study.

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quantify the association between each drug and reported suicide. For the cohort studies, Cox proportional hazards models were used, controlling for demographic and clinical characteristics as well as the background risk of suicide in the insured population.

Results—The FAERS analyses found significantly lower suicide reporting rates for brands compared with generics for all four studied products (Breslow-Day $P < 0.05$). In the claims- and EHR-based cohort study, the adjusted hazard ratio (HR) was statistically significant only for sertraline (HR=0.58; 95% CI=0.38–0.88).

Conclusion—Suicide reporting rates were disproportionately larger for generic compared with brand CNS drugs in FAERS and adjusted retrospective cohort analyses remained significant only for sertraline. But, even for sertraline, temporal confounding related to the close proximity of black boxed warnings and generic availability is possible. Additional analyses in larger data sources with additional drugs are needed.

Keywords

suicide and suicidal ideation; generic drugs; central nervous system drugs; therapeutic equivalence

1 INTRODUCTION

Central nervous system (CNS) drugs are widely used in treating psychiatric and neurological disorders. Twenty percent of the U.S. population used at least one type of CNS drug in 2011. [1] Estimated CNS drug sales in the U.S. were \$80.2 billion in 2015,[2] representing heavy economic burden on the health care system. Generic medicines can significantly reduce health care costs.[3, 4] For antidepressants, 72% of prescriptions were filled with generic drugs, but generic antidepressants made up only 33.4% of costs in 2016.[5] Likely due to their economic benefits, patients have been shown to be more adherent to generic drugs compared to brand drugs.[6, 7] However, some concerns have been raised regarding the therapeutic equivalence of generic drugs with brand name CNS drugs.[8–11]

Brand and generic drugs are approved by the U.S. Food and Drug Administration (FDA) through different processes. While brand drugs must demonstrate clinical efficacy and safety via clinical trials required for approval of a New Drug Application (NDA), the Hatch-Waxman amendments outlined the process by which generic drugs are approved via an Abbreviated New Drug Application (ANDA).[12, 13] The ANDA requires demonstration of pharmaceutical equivalence and bioequivalence between the generic and reference-listed brand drug but does not require demonstration of equivalence via controlled clinical trials. Previous research has questioned whether bioequivalence testing for brand and generic drugs is adequate, particularly for CNS drugs such as antiepileptics, antidepressants, and other CNS-stimulating drugs.[10, 14–18]

One indicator for therapeutic equivalence of medications is the relative occurrence of adverse drug events (ADEs). Suicide and suicidal ideation (broadly referred to as suicide) is considered a severe ADE that can be related to use of CNS drugs, and this needs to be monitored closely to maintain public health safety. Several previous studies suggested strong connections between suicide and CNS drug utilization.[19–24] The FDA labeling on a

number of CNS drugs indicates a potential for suicide risk, including antidepressants, antiepileptics, and other CNS drugs.[25] Previous case reports found occurrences of suicide after switching from brand CNS drugs to generics.[26–29] These observations could lead to the conclusion that the causation of suicide is related to the difference in therapeutic effect between brands and generics.[11, 18] Additional research can help to further explore the potential link between generic CNS drugs and suicide.

2 METHODS

To help focus the question of whether suicide risk is different between brand and generic CNS drugs, a two-pronged approach was used. First, we conducted analyses of the FDA Adverse Event Reporting System (FAERS) data for four CNS drugs (sertraline, gabapentin, zolpidem, and methylphenidate). Our FAERS analyses found statistically significantly different risk of suicide between all selected brand and generic drugs, which suggested a potential connection between suicide and generic CNS drugs. Then, stemming from hypotheses generated in these analyses, we studied the same drugs using a more rigorous retrospective cohort design with a repository of administrative claims data from a regional insurance provider (Security Health Plan (SHP)) combined with electronic health record (EHR) data from the Marshfield Clinic.

2.1 Data Source and Selection

FDA Adverse Event Reporting System (FAERS)—The FAERS database is generated from the FDA’s post-marketing safety surveillance program, which is a spontaneous reporting system for ADEs and medication errors.[30] These reports can be directly submitted to the FDA by healthcare professionals, consumers, or others who are aware of patients’ ADEs.[30] Alternatively, these reports can be submitted by healthcare professionals or consumers to manufacturers and then manufacturers are required to forward the reports to the FDA.[30] The ADEs in FAERS are coded using the Medical Dictionary for Regulatory Activities (MedDRA®).[30] FAERS data files are published quarterly and publicly accessible on the FDA web page. The FAERS data files contain case-related medication, reaction, outcome, source of report, and the patient’s demographic information. For this study, we used the publicly available FAERS data and combined data files from January 2004 to December 2015. Duplicated cases were identified and eliminated from the data by adopting the most recent case number according to the FDA’s recommendation.[31]. Records with primary or secondary suspected drugs were included by setting the role code to “Primary Suspect” or “Secondary Suspect”.

Administrative Claims and EHR Data from SHP and Marshfield Clinic—

Administrative claims and EHR data were obtained from SHP and the clinical data warehouse of the Marshfield Clinic. The Marshfield Clinic is an integrated regional health care system located in Marshfield Wisconsin. This clinic includes over 50 centers in northern, central, and western Wisconsin and provides the majority of healthcare services to 1.5 million patients.[32] The SHP, which is owned by Marshfield Clinic, provides health insurance coverages to patients of the clinic.[32] Approximately 68% of SHP beneficiaries have full year coverage of healthcare services including inpatient, outpatient, and pharmacy.

[32] Thus, the majority of claims data users have the same coverage. The data contained a retrospective cohort of 79,102 first time users of the four selected CNS drugs with outpatient and inpatient visits in the Marshfield Clinic system from 1999 to 2014. The first observed use of the selected drugs (sertraline, gabapentin, zolpidem, and methylphenidate) was defined as the index date.[33] Individuals had to have no claims for the selected drugs within 6 months prior to the index date to be considered a new user. The medical records contained International Classification of Diseases Version 9 codes (ICD-9), which were used to identify the ADEs in this study. Drug use was coded using the SHP pharmacy claims.

2.2 Brand and Generic Classification

We included four CNS drugs: one antidepressant (sertraline; brand name Zoloft®; brand manufacturer Pfizer), one antiepileptic (gabapentin; brand name Neurontin®; brand manufacturers Pfizer and Parke Davis), and two other CNS drugs (zolpidem; brand names Ambien™/Edluar®/Zolpimist™; brand manufacturer Sanofi; and methylphenidate; brand names Ritalin®, Concerta®, Aptensio XR®, Daytrana®, Metadate CD®, Methylin®, QuilliChew ER™, Quillivant XR®; brand manufacturers Novartis, Janssen, Rhodes, Noven, UCB, Mallinckrodt, Pfizer, Nextwave). The generic approval dates for the selected CNS drugs were as follows: August 14, 2006 (sertraline); January 28, 2011 (gabapentin); April 23, 2007 (zolpidem); and October 20, 1999 (methylphenidate). These CNS drugs serve as good examples for studying the difference of suicide risks between brand and generic CNS drugs as their generic drug entered the market during our study period (1999 to 2014) with multiple years of available data before and after generic entry.

FAERS data—Target drugs were identified by searching reported drug names with text strings containing brand names, generic names, abbreviations, and possible misspellings. For example, sertraline records were selected by searching for the generic name “SERTRALINE”, the brand name “ZOLOFT”, and the abbreviations “SERTR” and “ZOLO”. Selected CNS drugs were classified into “brand” and “generic” based on the drug manufacturer receiving the report. For example, sertraline reported from “PFIZER” was considered as a brand drug, and from all other manufacturers was considered as a generic drug. When the same manufacturer produced both brand and generic drugs, drugs were classified into “brand” and “generic” based on their reported names. For example, methylphenidate reported from “MALLINCKRODT” with reported name “METHYLIN” was considered a brand drug, and all other reported names from the same manufacturer were considered generics. Reports directly submitted to the FDA were excluded from the analysis since our methods focused on using manufacturers’ information to distinguish brand and generic drugs.

Administrative Claims and EHR Data from SHP and Marshfield Clinic—Brand and generic sertraline, gabapentin, zolpidem, and methylphenidate were identified by National Drug Code (NDC) numbers in the SHP pharmacy claims. The NDC codes representing the brand manufacturers were marked as brand drugs, and the NDCs for all other manufacturers were marked as generic drugs.

2.3 Suicide and Suicidal Ideation Identification

FAERS data—We focused on outcomes associated with suicide, which were defined by MedDRA[®] terminology for coding and searching within FAERS data. The Standardized MedDRA[®] Query (SMQ v17.0) for “suicide and suicidal ideation” was used to identify a group of Preferred Terms (PTs) related to this event.[34] The SMQ-based suicide PTs were then used to match with the reported PTs in the FAERS reaction files.[34] For records with PTs other than suicide and suicidal ideation, we identified them as non-suicide.

Administrative Claims and EHR Data from SHP and Marshfield Clinic—The ICD-9 codes of E950-E959 (suicide and self-inflicted injury) and V62.84 (suicidal ideation) measured suicide and suicidal ideation.[20, 35–37] The validity of using these diagnostic codes for identifying suicide and suicidal ideation has been previously studied.[36, 37] The ICD-9 codes E950-E959 stand for “intentional self-injury” and “late effects of self-inflicted injury”, with a Positive Predictive Value (PPV) of 86%.[36] The ICD-9 code V62.84 stand for “suicidal ideation” with a PPV of 86% when combined with other ICD-9 codes.[37] Eligible drug users were followed throughout the study period with the addition of the explicit censoring at one year after the index date and treatment was considered continuous as long as a gap in medication supply did not exceed 90 days. The 90 day period was selected as a maximum period of time to washout drug effects based on previous research on antidepressant and epilepsy drugs.[32, 38–40] Observation was censored if a patient switched between brand and generic or a patient switched from one drug to a different drug within the same therapeutic class. The evaluation time was from the index date until first suicide event. When absent of a suicide event, the evaluation time of patients started from the index date until first switching of drug or the end of the SHP enrollment with the addition of the explicit censoring at one year after the index date.

To ensure that the claims and EHR definition was consistent with the SMQ-based definition, we had two clinicians independently review the coding and select a subgroup of MedDRA[®] PTs that best matched the ICD-9 codes for suicide and suicidal ideation found in the claims and EHR data. Because this approach only included a subset of PTs in the SMQ-based definition, we considered this a sensitivity analysis of the FAERS data.

2.4 Covariates

FAERS data—Patients were divided into five age groups (<18, 18–44, 45–64, 65 years, and age missing) to show the reporting distribution by age. Three gender groups (female, male, and gender missing) were coded across identified reports. Report source was classified by six categories: physician, pharmacist, other health professional, consumer, lawyer, and report source missing. Report country indicated the geographic location of the reported event, which was categorized into US and non-US. These covariates were used for descriptive purposes only.

Administrative Claims and EHR Data from SHP and Marshfield Clinic—The covariates were defined based on patients’ medication records within 6 months before their index date. In the claims data, the patient’s age was recorded in years, and the patient’s gender was recorded as female or male. The patient’s histories of diabetes status and

smoking status were obtained from the EHR. The Charlson Comorbidity Index (CCI) was calculated according to each individual's chronic conditions, which were obtained from both the claims and EHR.[41] These covariates were used for descriptive purposes and for confounding adjustment in multivariable models. A covariate for background risk of suicide and suicidal ideation was created by calculating the rate of these events in the SHP population not using the drug of interest. This variable was measured at quarterly intervals and treated as a time-dependent confounder.

2.5 Statistical Analysis

FAERS—Descriptive analyses were done to show the distributions of age, gender, reporting source, and reporting country with sertraline, gabapentin, methylphenidate, and zolpidem. The dynamic changes of yearly suicide events for each selected drug were plotted. Disproportionality analyses were used to identify whether reporting rates of suicide with each drug were similar to reporting rates of suicide with all other drugs.[42] The Breslow-Day statistic was used to identify the homogeneity of the brand and generic drugs' RORs for suicide. The study period included in disproportionality analyses focused on post-generic marketing time. Sensitivity analyses were done using the secondary PT selection that better matched the codes in the EHR data. The RORs and 95% CI were calculated for each selected drug (brand, generic, and total) within this PT subgroup. While the focus of these analyses was not hypothesis testing, we considered multiple comparison-adjusted p-values of <0.0125 to be potentially significant (i.e., $0.05 \div 4$ comparisons).

Administrative Claims and EHR Data from SHP and Marshfield Clinic—Means and standard deviations (SD) of patient age and the CCI at first prescription for each brand and generic drug were calculated. Numbers and percentages of female patients, patients with diabetes, and patients who smoke were counted and calculated. Cox proportional hazards models were used to compare the suicide hazard rates for each brand and generic drug, controlling for demographic and clinical characteristics as well as the background risk of suicide in the insured population over time.[43, 44] The hazard ratio measures the risk of suicide within brand drug users divided by the risk of suicide within generic drug users. The positive signal of the risk of suicide should be indicated by a hazard ratio >1 with the lower limit of the 95% confidence interval also >1 . [43]

3 RESULTS

3.1 Characteristics of adverse event reports

For all included drugs, a total of 24,277 suicide events were reported to the FDA from 2004 to 2015. There were 3,508 brand and 4,033 generic sertraline reports, 6,693 brand and 2,909 generic gabapentin reports, 2,783 brand and 1,362 generic methylphenidate reports, and 584 brand and 2,405 generic zolpidem reports (Table 1). Reports directly submitted to the FDA were excluded from the analysis (14.85% of sertraline, 6.52% of gabapentin, 15.16% of zolpidem, and 10.27% of methylphenidate). Tables 1 and 2 summarize the characteristics of adverse event reports for the four drugs studied. Looking across brands and generics there were interesting but inconsistent patterns. For example, both females and males had higher brand reporting rates for gabapentin and methylphenidate, and a higher generic reporting

rate for zolpidem (Table 1). Pharmacists and other health care providers had higher reporting rates for generic rather than brand drugs for most studied CNS drugs, while consumers and lawyers had higher reporting rates for all brand rather than generic drugs (Table 2).

3.2 Suicide and Suicidal Ideation Reporting Change Over Time for FAERS

Figure 1 illustrates the dynamic changes of brand and generic drug suicide reports over time for sertraline (Panel A), gabapentin (Panel B), methylphenidate (Panel C), and zolpidem (Panel D), using total suicide reports for all drugs (including these) as a background comparison (i.e., solid line in Figure 1). The total number of suicide reports for all drugs increased slowly from 2004 to 2009 (average 11.45% per year) and then rapidly from 2009 to 2015 (average 35.60% per year). Comparing the total reporting patterns for each drug (i.e., stacked bar of brand and generic in Figure 1) with the total reports of suicide and suicidal ideation across all drugs in the FAERS database, the CNS drugs we studied appear to mostly follow trends of suicide reporting in the database as a whole (shown by the line representing total reports).

3.3 Reporting Odd Ratios and Forest Plots for FAERS

The RORs and forest plots for suicide and suicidal ideation are shown in Figure 2. For the SMQ-based definition of suicide and suicidal ideation events (Panel A), all studied CNS drugs (except for brand zolpidem) had elevated suicide reporting compared to all other drugs in the FAERS database ($ROR > 1$). All analyzed generic drugs had significantly higher suicide reporting rates than their brand competitors ($p < 0.001$). This is illustrated in that the generic ROR was statistically significantly higher than brand for all drugs ($P < 0.001$).

In a sensitivity analysis where we defined the PTs to more closely match existing ICD-9 codes, we found similar patterns (Panel B). The RORs for generics were statistically significantly greater than with brands for all four drugs ($P < 0.001$).

3.4 Analysis from Administrative Claims and EHR Data from SHP and Marshfield Clinic

We replicated the analyses of FAERS using a stronger retrospective cohort study design and a more complete data source of administrative claims and EHR data. These results are shown in Table 3. A total of 79,102 eligible users were identified from 1999 through 2014, including 26,483 for sertraline, 23,927 for gabapentin, 12,120 for methylphenidate, and 20,893 for zolpidem. The mean ages for generic drug users were higher than the mean ages for brand drug users among all selected drugs. For most selected drugs, brand users had lower CCI, lower diabetes rates, and lower smoking rates than generic users. Gabapentin users had the highest CCI and the highest rates of diabetes and smoking. Methylphenidate users had the lowest CCI and the lowest diabetes and smoking rates.

Among all of the eligible CNS drug users, 621 incident suicide events were identified, including 35 brand and 249 generic sertraline cases, 14 brand and 103 generic gabapentin cases, 39 brand and 123 generic zolpidem cases, and 29 brand and 29 generic methylphenidate cases. The unadjusted data showed higher suicide rates for generic users compared with brand users for sertraline and zolpidem. Generic sertraline users had the highest absolute suicide rate (1.31% vs. 0.47% for brand, $p < 0.001$), and generic zolpidem

users had the lowest absolute suicide rate (0.93% vs. 0.51% for brand, $p<0.001$). However, the adjusted HR for brand compared with generic users only indicated a significantly lower risk for brand compared with generic sertraline (brand vs. generic HR=0.58, with 95% CI 0.38–0.88). After adjustment, the HRs for gabapentin, methylphenidate, and zolpidem users showed no statistically significant difference in the rate of suicide between brand and generic users.

4. DISCUSSION

This study compared suicide ADE reporting rates between four brand and generic CNS drugs. Our FAERS-based hypothesis-generating analyses first explored potential brand versus generic signals, and then we followed this up with a stronger retrospective cohort study using administrative claims data combined with EHR data. From the FAERS data analyses, all selected generic CNS drugs had significantly higher suicide RORs than their brand competitors. In our confirmatory studies using administrative claims data combined with EHR data, all selected generic CNS drug users had a higher percentage of suicide events than brand drug users. However, after adjustment for potential confounders and background suicide rates in the population, only sertraline had a significantly higher suicide risk for generic compared with brand.

Our initial finding of higher suicide rates among generics is consistent with previous studies, although we focused on different CNS drugs. For example, previous studies found generic bupropion, paroxetine, valproic acid, and clozapine had more reports involving suicide compared with brand drugs.[26–29] The literature suggests potential differences in the therapeutic equivalence of generic and brand psychoactive drugs and antiepileptic drugs.[10, 18, 45] The FDA also previously changed equivalence ratings for specific formulations of generic methylphenidate and bupropion.[17]

The potential connection between suicide risk and generic CNS drugs observed in our study should be interpreted cautiously. There are several possible explanations for our observations. One explanation could be the increased public attention toward suicide risk evoked by black box warnings. More specifically, it is possible that the timing of these warnings paralleled the broader availability and use of generic drugs, and therefore our analyses might be subject to temporal confounding. The FDA updated 174 black box warnings to include risk of suicide from 2004 to 2007.[25] The majority of drugs within the warning list were CNS drugs, including all of our study drugs except methylphenidate. With the increasing number of black box warnings, public attention has been drawn to suicide among CNS drugs. The suicide reports from both brand and generic drugs could have been stimulated by the increased public attention. We observed a rapid increase in the total number of suicide reports for all drugs in the FAERS database after 2009, and brand drug utilization declined for all four selected CNS drugs. The generic entry times for sertraline, zolpidem, and gabapentin were all around or after that period. Moreover, at the time of the black box warning update for sertraline in 2007, more than 96% of patients used generic sertraline. Thus, the collinear effect of generic entry and the black box warning may have prevented us from adequately controlling for confounding effects of the black box warning when analyzing the relationship between generic drug use and suicide risk. While we

controlled for background rates of suicide in the population with the claims data analysis, this may still be insufficient to address the collinear relationship.

Another possible explanation could be preconceived beliefs or concerns regarding therapeutic equivalence between brand and generic CNS drugs.[8–11] Desmarais found generic CNS drugs often had higher ADE rates and this might cause lower adherence than with brand drugs.[11] Shrank reported that 37.6% of patients would prefer to take generic drugs, 30% of patients believed that brand drugs were more effective than generic drugs,[8] 50% of physicians were concerned about generic drug quality, and 23% of physicians had negative perceptions about generic drug efficacy.[46] Such concerns might generate bias toward generic drugs when reporting suicide or even when seeking health care and discussing suicidal ideation.

The third explanation for the potential association between suicide and generic CNS drugs could be the different therapeutic effects of generic drugs. Previous research found that generic CNS drugs are introduced more commonly in higher dosage.[11, 45] For example, Andermann reported that generic had a 6.2% higher dose compared with brand drug.[45] Miller described a case report involving ADEs with higher doses of generic sertraline.[47] Thus, the same scenario could help to explain our observations. Our adjusted retrospective cohort analyses found that generic sertraline had a significantly higher suicide reporting rate. While we do not have a biological basis to suspect higher suicide rates with generic sertraline, one hypothesis may be related to use of generics at higher doses than brands.[47, 48] It may be possible that the higher dose is related to symptoms such as akathisia and this in turn might be related to suicide. Further study is needed to explore such ideas.

Our study has several limitations. First, for the FAERS data, causality between suicide and the primary or secondary suspected drugs is not proven. The reported suicide might also be caused by drug-drug interactions, food-drug interactions, or other unreported reasons. Second, the spontaneous reporting system for the FAERS data is known to have substantial under-reporting, duplicated reports, and large amounts of missing data. In order to reduce the bias from duplication and missing data, we cleaned the duplicated cases and labeled the missing data in our analyses. Third, the FAERS data contain imprecise drug information including the misspelling of drug names and lack of dose information. To improve data quality, we recoded drug names manually in our analyses. However, our recoding could introduce error even though we used two independent adjudicators. Fourth, the FAERS data do not link to medical records, which prevented us from evaluating alternative explanations. Thus, we were not able to track individuals' medication history and comorbid disease. Fifth, the publicly available FAERS data does not have adequate information for us to reliably identify brand and generic products. Previous studies found that even through careful review of case narratives, several FAERS reports still could not be identified as brand and generic drugs reliably.[49, 50] Sixth, using manufacturer names to classify brand and generic drugs could present its own limitations. This strategy might cause misattribution of generic ADEs to brand manufacturers, since patients and physicians could be more likely to submit their reports under brand name.[49, 50] While potentially problematic, we have attempted to follow best practices. For example, Iyer's study found that the method of using manufacturer names is as reliable as the method of using NDA or ANDA numbers when identifying brand

and generic drugs.[50] Thus, we believe that using manufacturer names to classify brand and generic drugs in FAERS data analysis is reasonable for signal detection but results should be interpreted cautiously.

Compared with FAERS, our retrospective cohort study is a stronger design and our administrative claims data combined with EHR data is a stronger data source. These secondary analyses complement the hypothesis generating FAERS analysis and address some of the limitations in FAERS data. For example, with the combination of claims and EHR data, we could measure the adjusted hazard ratio of suicide with confounding factors (CII, diabetes, and smoking). However, the demographic differences between the two databases might lead to variances in results, since our claims data covered a regional population whereas the FAERS data covered a worldwide population. Another limitation in our EHR data analyses is the challenge of capturing suicide and suicidal ideation, especially the latter. Our algorithms of capturing suicide and suicidal ideation is screening for ICD-9 codes E950-E959 and V62.84 in patients' EHR data and insurance claims. However, both E950-E959 and V62.84 were not proven to be sensitive enough to detect suicide by previous studies.[36, 37] In addition, we did not have sufficient information to ascertain suicide, especially suicidal ideation in our EHR data. Nevertheless, the FAERS analyses in our mixed methods used SMQ to capture suicide, which was created through a thorough process. The third limitation in our EHR data analyses is related to health insurance coverage. Although the majority of patients at Marshfield Clinic have the same full year coverage from SHP, insurance coverage related factors such as geographic location, social economic status, and insurance copayment could still influence the patient's chance of getting a brand or generic drug. However, based on our previous research, controlling insurance copayment did not significantly influence the choice of brand and generic.[32] Fourth, other uncontrolled confounders could bias our analyses. Although there are limitations in claims and EHR data analyses, it is noteworthy that our mixed methods approach using two databases and multiple analyses found potential connections between generic CNS drugs and suicide.

5 CONCLUSIONS

We observed a potential association between suicide and generic sertraline across two analyses using different databases and methodologies. In the hypothesis generating analysis with the FAERS data, we found disproportionally higher suicide reporting rates for all four generic CNS drugs studied. In the stronger retrospective cohort studies, the multivariable adjusted models showed statistical significance only for sertraline. This association may still be confounded by the temporal association of generic sertraline entry and the addition of a black boxed warning to the product labeling. For future work, extensions of our study in larger data sources with additional drugs will be needed to further explore the association between generic CNS drugs and suicide.

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Key Points

- The suicide risk comparison between brand and generic CNS drugs is important because CNS drugs have previously been associated with an increased risk of suicide.
- We found disproportionately larger suicide reporting rates for generic compared with brand CNS drugs in FAERS data analyses and a significantly higher risk of suicide for generic compared with brand sertraline in adjusted retrospective cohort analyses.
- Due to the temporal association of black box warnings and generic entry, confounding is possible and additional analyses in larger data sources with additional drugs are needed.

Panel A: sertraline

*Generic entry date for sertraline is August 14, 2006

Panel B: gabapentin

*Generic entry date for gabapentin is January 28, 2011

Panel C: methylphenidate

*Generic entry date for methylphenidate is October 20, 1999

Panel D: zolpidem

*Generic entry date for zolpidem is April 23, 2007

Figure 1.
Suicide and suicidal ideation reporting change over time for brands vs. generics (2004–2015)

Panel A: Suicide/suicidal ideation events defined by Standardized MedDRA Query

Panel B: Suicide/suicidal ideation events defined by matching Preferred Terms with ICD-9 codes

Figure 2.

Forest plot of reporting odds ratio (ROR) for suicide and suicidal ideation for brand and generic drugs

Table 1

Demographic information for FAERS reports of suicide and suicidal ideation

AGE	sertraline		gabapentin		methylphenidate		zolpidem		All Other Drugs	Total
	Brand	Generic	Brand	Generic	Brand	Generic	Brand	Generic		
<18	302	242	88	69	971	506	20	26	37817	40041
	55.51%	44.49%	56.05%	43.95%	65.74%	34.26%	43.48%	56.52%		
18–44	990	1640	1498	973	540	275	167	854	251534	258471
	37.64%	62.36%	60.62%	39.38%	66.26%	33.74%	16.36%	83.64%		
45–64	800	1114	1814	1059	114	160	164	1000	232864	239089
	41.80%	58.20%	63.14%	36.86%	41.61%	58.39%	14.09%	85.91%		
>=65	319	289	602	337	28	41	54	300	82468	84438
	52.47%	47.53%	64.11%	35.89%	40.58%	59.42%	15.25%	84.75%		
Age Missing	1097	748	2691	471	1130	380	179	225	211721	218642
	59.46%	40.54%	85.10%	14.90%	74.83%	25.17%	44.31%	55.69%		
Gender										
Female	2179	2156	3732	1775	881	510	260	1425	466345	479263
	50.27%	49.73%	67.77%	32.23%	63.34%	36.66%	15.43%	84.57%		
Male	1099	1455	2564	930	1651	756	244	847	302176	311722
	43.03%	56.97%	73.38%	26.62%	68.59%	31.41%	22.36%	77.64%		
Gender Missing	230	422	397	204	251	96	80	133	47883	49696
	35.28%	64.72%	66.06%	33.94%	72.33%	27.67%	37.56%	62.44%		
Total	3508	4033	6693	2909	2783	1362	584	2405	816404	840681
	46.52%	53.48%	69.70%	30.30%	67.14%	32.86%	19.54%	80.46%		

Table 2

Suicide and suicidal ideation FAERS report source

	sertraline		gabapentin		methylphenidate		zolpidem		All Other Drugs	Total
	BRAND	GENERIC	BRAND	GENERIC	BRAND	GENERIC	BRAND	GENERIC		
REPORT SOURCE										
Physician	831	723	1190	506	472	429	125	743	146402	151421
	53.47%	46.53%	70.17%	29.83%	52.39%	47.61%	14.40%	85.60%		
Pharmacist	178	264	190	197	91	46	52	213	38162	39393
	40.27%	59.73%	49.10%	50.90%	66.42%	33.58%	19.62%	80.38%		
Other health professional	409	967	593	599	318	230	76	553	111957	115702
	29.72%	70.28%	49.75%	50.25%	58.03%	41.97%	12.08%	87.92%		
Consumer	1118	665	1306	425	1111	361	137	104	206772	211999
	62.70%	37.30%	75.45%	24.55%	75.48%	24.52%	56.85%	43.15%		
Lawyer	58	9	1207	3	3	3	46	7	36046	37382
	86.57%	13.43%	99.75%	0.25%	50.00%	50.00%	86.79%	13.21%		
Report Source Missing	914	1405	2207	1179	788	293	148	785	277065	284784
	39.41%	60.59%	65.18%	34.82%	72.90%	27.10%	15.86%	84.14%		
REPORT COUNTRY										
Non-US	1035	2228	1003	1101	1636	527	114	601	222512	230757
	31.72%	68.28%	47.67%	52.33%	75.64%	24.36%	15.94%	84.06%		
US	2473	1805	5690	1808	1147	835	470	1804	593892	609924
	57.81%	42.19%	75.89%	24.11%	57.87%	42.13%	20.67%	79.33%		
TOTAL										
	3508	4033	6693	2909	2783	1362	584	2405	816404	840681
	46.52%	53.48%	69.70%	30.30%	67.14%	32.86%	19.54%	80.46%		

Table 3
Cohort characteristics and suicide/suicidal ideation events in the Marshfield Clinic and Security Health Plan cohorts

	sertraline		gabapentin		methylphenidate		zolpidem	
	BRAND	GENERIC	BRAND	GENERIC	BRAND	GENERIC	BRAND	GENERIC
SAMPLE SIZE	7468	19015	3330	20597	7388	4732	7678	13215
COVARIATES								
Age (mean, SD)	40.30	41.30	50.60	55.00	17.00	21.30	47.10	49.60
	19.30	20.50	18.90	18.10	13.90	17.60	17.80	17.70
Female (n, %)	5539	13707	2093	12624	2687	1892	5254	8473
	74.20%	72.10%	62.90%	61.30%	36.40%	40.00%	68.40%	64.10%
Charlson Index (mean, SD)	0.40	0.40	0.70	0.80	0.20	0.30	0.50	0.60
	0.90	1.00	1.20	1.40	0.70	0.90	1.00	1.20
Diabetes (n, %)	502	1404	526	3365	152	159	650	1309
	6.70%	7.40%	15.80%	16.30%	2.10%	3.40%	8.50%	9.90%
Smoking (n, %)	3193	8626	1564	11217	2485	1542	3390	6640
	42.80%	45.40%	47.00%	54.50%	33.60%	32.60%	44.20%	50.20%
MESA * residence (n, %)	1490	2960	774	3830	1520	853	1312	1965
	20.00%	15.60%	23.20%	18.60%	20.60%	18.00%	17.10%	14.90%
SUICIDE/SUICIDAL IDEATION								
Event count (n, %)	35	249	14	103	29	29	39	123
	0.47%	1.31%	0.42%	0.50%	0.39%	0.61%	0.51%	0.93%
Unadjusted p-value	<.0001	Ref	0.6873	Ref	0.1048	Ref	0.0007	Ref
Adjusted Hazard Ratio (95% CI)	0.58	Ref	1.36	Ref	1.32	Ref	1.29	Ref
	0.38– 0.88		0.66– 2.84		0.53– 3.27		0.77– 2.15	

* MESA stand for Marshfield Epidemiologic Study Area.

SD stand for Standard Deviation

CI stand for Confidence Interval