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Post-marketing Drug Safety Evaluation using Data Mining Based on FAERS

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Abstract

Healthcare is going through a big data revolution. The amount of data generated by healthcare is expected to increase significantly in the coming years. Therefore, efficient and effective data processing methods are required to transform data into information. In addition, applying statistical analysis can transform the information into useful knowledge. We developed a data mining method that can uncover new knowledge in this enormous field for clinical decision making while generating scientific methods and hypotheses. The proposed pipeline can be generally applied to a variety of data mining tasks in medical informatics. For this study, we applied the proposed pipeline for post-marketing surveillance on drug safety using FAERS, the data warehouse created by FDA. We used 14 kinds of neurology drugs to illustrate our methods. Our result indicated that this approach can successfully reveal insight for further drug safety evaluation.

Keywords

Data mining; Post-marketing surveillance; Zero-truncated negative binomial regression model

1 Introduction

Healthcare is going through a big data revolution [1]: healthcare data can now be collected in scenarios far beyond traditional clinical trials. For example, the US Food and Drug Administration (FDA) has initiated a drug safety surveillance system, known as FDA Adverse Event Reporting System (FAERS), where health providers and patients can report adverse events (AEs) and medication errors post marketing. The FAERS database contains 6,156,081 reports from the past 13 years and offers a great opportunity to conduct research on post-marketing surveillance of drug safety at the population level. However, with opportunities come challenges. For example, the safety data could be gathered from different resources, such as clinical trials or spontaneous reporting systems; processed under different data standards; contained in different formats including free text or images; and reported by people with different levels of domain knowledge including physicians, caregivers, and patients. With different levels of granularities, standards, and even formats of the data, it is

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important to develop methods to normalize and clean the data for further analyses. It is critical to advance our knowledge on the benefits and risks of healthcare interventions by processing and mining drug safety information using large healthcare data (e.g., FAERS) accurately and efficiently for proper statistical analysis [2]. In this paper, we present a data mining and statistical analysis pipeline to study the drug safety using FAERS data. We devised data mining techniques and statistical models to account for the features of FAERS, and provided visualization tools to present the safety results in an intuitive and comparative fashion so that results can be useful in the medical decision-making process. We use 14 first-line drugs for treating acute mania as a use case to demonstrate our pipeline.

FAERS documented the voluntary inputs on adverse events post drug administration. The term AE refers to uncomfortable, or dangerous effects a drug may have [3]. The reports submitted to FAERS are evaluated by the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER) to monitor the safety of FDA-approved drugs. FDA uses FAERS to construct post-marketing surveillance programs. If a safety concern is identified in FAERS, further action will be taken.

The growing number of treatment options has generated an increasing need for scientifically rigorous comparisons of multiple treatments to inform healthcare decision-making. In a systematic review for efficacy and safety of antimanic drugs in adults, Cipriani et al. reviewed 67 randomized controlled trials (16,073 participants) published from 1980 to 2010. This study compared the 14 first-line pharmacological drugs at therapeutic doses [4]. Through a network meta-analysis, they quantified the relative effectiveness (measured as the mean change on mania rating scales) of these 14 drugs. In addition, they also compared the safety of these drugs by ranking dropout rates within 3 weeks after initiating treatment. From a pharmaco-epidemiological perspective, the dropout rates within 3 weeks can be an inadequate surrogate for drug safety for the following reasons: first, 3 weeks may be not long enough for the long-term AEs to appear; second and perhaps more importantly, many of the AEs are rare and have different degrees of severity (e.g., suicide due to depression) [5]. This information is difficult to uncover using clinical trials with limited sample sizes.

In this paper, we explore the feasibility and usefulness of the post-marketing safety surveillance database by mining and analyzing the FAERS data. We find that our results on the relative safety of these 14 antimanic drugs based on FAERS data are qualitatively in agreement with previously reported results based on systematic review of randomized controlled trials. However, the analysis based on the FAERS data provides considerably more insights on different types of adverse effects with respect to different system organ classes, death, as well as total number of AEs each patient experienced. These findings can contribute important evidence on relative safety, and can be potentially combined with the pre-marketing findings to better aid medical decision-making.

The proposed analytical pipeline is generally applicable to large healthcare data, although we describe the methods using antimanic drugs in FAERS data for concreteness. More precisely, we describe a methodological framework to extract safety data, pre-process them, and conduct statistical analysis on comparative effectiveness. We hypothesize that the proposed procedure can effectively produce useful insights from large-scale datasets. The

proposed pipeline is ready to implement, and results are easy to interpret. It can be used to select drugs that are important for future investigation, and is also applicable to other types of data warehouses.

2 Methodology

2.1 Data extraction method

To make the data clean and standardized for further analysis, we followed Banda's work [6] to normalize FAERS data by removing duplicate records and mapping the drug name to RxNorm [7]. For this study, we focused on the FAERS reports from 01/01/2004 to 12/31/2015. There are 6,156,081 unique records in total. Even though we have matched the drug names to the same standard, there is still a mixture of brand names and generic names for the drug name list in FAERS data. We further linked the brand names to the corresponding generic names based on the [Drugs.com](https://www.drugs.com) database [8]. For example, the generic name Lithium has Eskalith, Lithobid, Lithonate, Lithotabs, and Eskalith-CR as its brand names. After data extraction and normalization, the details of the records for the 14 antimanic drugs are as follows:

2.2 Data-processing methods

Since we wanted to use adverse reaction as a variable for analysis, we selected "drug name list" and "reaction-PT list" from the FAERS database. "PT" refers to "preferred term in Medical Dictionary for Regulatory Activities (MedDRA), which serves as a medical terminology used during the pharmaceutical regulatory process [9]. MedDRA also provides a hierarchical structure of the terms where PT is the second lowest level descriptor for AEs. In addition, we included "age" and "sex" information for future analysis. Since there are too many terms on the PT level, we further linked the PT terms to the System Organ Class (SOC) level, which is the highest level of descriptors in MedDRA. There are 26 SOC's in total. These SOC's (details are in Table 2) describe medical symptoms on the organ system level, which gives an overview of how these drugs targeting mental illness can influence physical health [10]. In the final step, we labeled different levels of severities to each report. The levels of severities include death, life-threatening, hospitalization, disability, congenital anomaly, required intervention to prevent permanent impairment/damage, and other serious medical event. After this data processing, we created 14 matrixes for the 14 drugs containing AEs, age, sex, and severity level for each report.

2.3 Statistical method

We proposed a statistical analysis pipeline for comparative effectiveness research that accounts for the unique features of the AE outcomes obtained from the FAERS database. More precisely, the dimension of FAERS datasets was large in terms of both number of AE reports and types of AEs. Specifically, the number of columns (corresponding to the types of AEs) varied from 1,176 to 8,246 for each antimanic drug. The number of patients reported AEs for each drug varied from 5,872 to 77,682. Another feature of the FAERS data was that the data matrices were very sparse since each patient generally only had several AEs reported. We included both exploratory analyses and confirmatory data analyses. The exploratory data analyses included direct comparisons of proportions of classes of AEs

among 14 drugs using grouped bar plots, and evaluation of model assumptions such as over-dispersion. The confirmatory data analysis included fitting a modified generalized linear regression model on the total number of AEs reported by each patient.

Exploratory Data Analysis—To account for the high dimensionality of types of AEs reported for each drug, we collapsed them into 26 categories based on system organ classification [10]. The definitions of the 26 system organ classes were listed in Table 2. The proportion of patients who had at least one report within each system organ class is calculated. These proportions were compared across drugs for each system organ classes. Figure 1 presented grouped bar plots to visualize the differences among drugs. In addition to different types of system organ classes, we also compared the all-cause death proportion for each drug using bar plots, and it was calculated by the number of patients who died dividing the total number of the people who have reported at least one AE. This all-cause death proportion might not be a direct reflection of the drug safety, but it might provide complementary information that is of interest.

Another strategy to account for the high dimensionality of types of AEs was to simply calculate the total number of AEs per subject. We can compare the pattern of the total number of AEs per subject across different drugs. To explore the distribution of the total number of AEs per subject, we calculated the empirical variance and compared it with sample mean for each drug. Such exploration can be used to investigate the distribution assumption of the Poisson model based on the fact that Poisson model assumes the mean and variance of the observed data to be equivalent.

Confirmatory data analysis—For each patient, we summarized the total number of AEs reported. Since a patient needed to have at least one report to be included in the dataset, the total number of AE for each patient was a positive integer. When comparing the empirical mean and variance of the total number of AE, the variance was substantially larger than the mean. This indicates the over-dispersion of the data, which is likely due to co-occurrences of AEs. To model the total number of AEs, we used a zero truncated negative binomial regression to account for the facts that the data are positive and over-dispersed [12, 13]. The model assumes the total number of AEs for every patient follows a zero-truncated-binomial distribution which has the probability mass function:

$$\Pr(Y_i = k) = \frac{f(k; \mu_i, \alpha_i)}{1 - f(0; \mu_i, \alpha_i)} \quad (1)$$

where Y_i denotes the total number of AEs for the i -th patient and $f(y; \mu_i, \alpha_i)$ is the probability mass function of the negative binomial distribution with mean μ_i and over-dispersion parameter α_i .

To quantify the rate ratio of AE per subject across different drug user groups, we proposed to use the following generalized linear regression model:

$$\log(\mu_i) = \beta_0 + \beta_1 x_{1,i} + \beta_2 x_{2,i} + \dots + \beta_{13} x_{13,i} \quad (2)$$

where placebo is used as the reference group and $x_{1,i}, x_{2,i}, \dots, x_{13,i}$ are the dummy variables created for the other 13 antipsychotic drugs. The variable $x_{j,i}$ takes value 1 if the i -th patient takes the drug j . The coefficient β_j is the log rate ratio of AE comparing drug j to the placebo. The Wald test can be used to test each $\beta_j = 0$, which is to test whether the AE rate of drug j is the same as the placebo. To test any of the two drugs having the same AE rate, the likelihood ratio test can be constructed while the parameters under the null are estimated with the constrain $\beta_j = \beta_{j'}$. The test statistic follows a chi-square distribution with one degree of freedom when the null hypothesis is true. The global likelihood ratio test in this case is to test all the drugs having the same AE rate, which follows a chi-square distribution with 13 degrees of freedom. This regression was fitted using R package “VGAM” and the log rate ratios were estimated with 95% confidence intervals. The drugs were then ranked based on the rate ratios.

3 Results

The analytic results suggested that the post-marketing results of AEs have some agreements with the pre-marketing results of drug acceptability, while also showing differences in some aspects. The premarketing acceptability is measured by the dropout rate in clinical trials, and the causes for dropout may include multiple factors. Therefore, the dropout rate is related to drug safety but not a direct measure of drug safety. Figure 1 displayed the proportions of patients who had at least one report of AE in this class for each of the 14 drugs for each one of the system organ classes. It showed that for most of these antipsychotic drugs, the most frequent AEs are related to psychiatric disorders (SOC 7) and nervous system disorders (SOC 8), which is consistent with previous findings [14]. Also, Haloperidol, which was showed to be the drug with highest efficacy with middle-ranked acceptability (7th of the 14 drugs) based on the pre-marketing clinical results [4]. Based on the post-marketing data (i.e., FAERS data) and our analysis, the relative rank of the AEs rate for Haloperidol was also lying in the middle of the 14 drugs. More precisely, for all the SOC classes, the relative rank varied from the 3rd in SOC 18 and SOC 23 to the 11th for SOC 25, among 14 drugs. We also found sizable differences between the results from FAERS and the findings from clinical studies. For instance, relative rankings in safety from pre-marketing clinical trials showed that Gabapentin had the highest dropout rate; in our analysis, Gabapentin had relatively low AE rates for SOC 7 and SOC 8 among all the 14 drugs. In addition, Olanzapine was reported as the drug with lowest dropout rate based on premarketing clinical trials, but it was found to have the highest AE rate in SOC 5, 6, and 23 among all drugs.

The patients having mental disorders are subject to certain risk of suicide related death [15]. On the contrary, some severe adverse events of the drugs might also cause death. The proportion of all-cause death calculated from the FAERS dataset for each drug can be a useful measure for drug safety, and is presented in Figure 2. More precisely, the proportion of all-cause death for each drug was calculated by the number of patients who died divided by the total number of the people who have reported at least one AE. It was showed in

Figure 2 that Haloperidol had the highest death rate (17.26%) while Asenapine had the lowest death rate (4.81%). Under the assumption of no ascertainment bias, which means that the populations under different drug treatments have similar characteristics, the death rate can be considered as a combination of both drug safety and efficacy. However, if the drugs were assigned to the patients selectively based on their conditions (e.g., the patients with relatively severe disorder were more likely to be assigned to Haloperidol), this death rate comparison may not directly reflect drug efficacy or safety.

The results for the zero-truncated negative binomial regression model were shown in Figure 3. Each black dot in the plot was the estimated ratio of number of AEs per patient for each of the 13 drugs compared to Placebo, which served as the control group. The corresponding line segments showed the 95% confidence intervals of the rate ratio estimates. The p-value for the global test was less than 0.001, suggesting significant difference for at least two of the drugs.

Among all the 13 drugs, only Asenapine had a ratio smaller than 1, which suggested that Asenapine has smaller expected number of AEs compared to the Placebo. However, since the p-value for testing the difference was 0.152, we cannot claim that Asenapine is significantly better than the Placebo in terms of number of AEs. The rest of the drugs all had rate ratios significantly greater than 1, meaning that these drugs on average would cause more AEs per person compared to Placebo.

In Figure 3, we also ranked the 14 drugs based on the point estimates of the rate ratio (Placebo has a ratio equals to 1), and the rank was listed on the vertical axes of Figure 3 from the top to the bottom. Our result indicated that Asenapine was the drug associate with smallest number of AEs per patient, placebo was in the second place, and Gabapentin was the drug associated with the largest number of AEs per person. The pre-marketing results also supported that Gabapentin had the highest dropout rate in clinical trials, and it was possible that too many AEs might be a reason for the high dropout rate [4].

4 Discussion and Conclusion

While the revolution of healthcare data greatly increases the amount of available information, extracting the data and conducting proper analysis become new challenges. With many events reported after the administration of FDA-approved drugs to the FAERS database, the safety of drugs can be evaluated using post-marketing information. In this study, we extracted data from the FAERS database to investigate post-marketing drug safety of 14 antimanic drugs. We prepared datasets according to information needed for further analysis by cleaning and normalizing the original database. To account for the unique features of the FAERS data, we proposed a statistical analysis pipeline for drug safety comparison. To explore the major types of AEs of each drug, we classified the reported events according to the system organ classification. The proportion of patients reporting at least one event for each drug and each SOC class was calculated. These proportions help us better understand the possible AEs of a certain drug, and also allow comparison across all drugs.

A truncated negative binomial regression was fitted to the total number of AEs, and the ratios of the expected event counts compared to the placebo were reported with 95% confidence interval. The 14 drugs were then ranked based on the estimated ratios and compared to the results from pre-marketing clinical trials.

Our study showed that for most of these antimanic drugs, the most frequent AEs are related to psychiatric disorders (SOC 7) and nervous system disorders (SOC 8). The drug that has the highest or lowest proportion for a certain SOC class varies. Olanzapine, which is reported to have the highest acceptability based on pre-marketing clinical trials, is found to have the highest proportion of AEs in SOC 5, 6 and 23. Haloperidol, which is reported to have the highest efficacy, ranks in the middle of the 14 drugs. The model fitting results show that Asenapine is the drug associated with the least number of AEs per person and Gabapentin associated with the most number of AEs per person. The pre-marketing clinical trials usually report the dropout rate as an indicator for the acceptability of the drugs. Sometimes people tend to evaluate drug safety based on the acceptability. However, because the reasons for dropouts are not clearly specified, dropout rates do not completely correlate to drug safety. The findings in our study therefore provide complementary information for drug safety evaluation by analyzing the post-marketing AE data. The important contribution of our study is that we create a data-mining and statistical analysis pipeline to compare multiple drugs in terms of their reported AEs through the FAERS database. Similar works for comparing multiple drugs are based solely on the counts of events for each drug or only one specific AE such as bleeding, while our work is designed for all the AEs combined and specifically for the FAERS data. [16,17]

Due to nature of the self-reported FAERS data, the statistical analysis in our study may have limitations. Unlike data from clinical trials, the FAERS data are reported when patients have AEs after the treatment. Therefore, the causal relationship between the drugs and the reported events is not certain. In addition, the population of patients taking each drug might be different. For example, based on the pre-marketing results, doctors might prescribe the drug according to the health conditions of patients, which may cause ascertainment bias in our results. Also, there is no certainty linking between one AE and one product. For drugs that treat serious mental disorder, death cannot be simply considered as an extreme severe AE since patients are under certain risk of suicide related death. Further, whether an event will be reported or not depends on many factors, making it more difficult to evaluate the drug safety.

In the future, through the methods of data mining and statistical analysis, the FAERS data can be used to gain more insight into drug safety and AEs. For example, if the time interval between taking the drug and each report can be extracted, we may use the patterns of AEs to predict the risk of having certain extremely severe AEs such as death or hospitalization, which will help make decision in clinical practice and monitor severe events. Furthermore, our workflow can be applied to a variety of data mining tasks in medical informatics.

In conclusion, the results of analyzing the post-marketing AEs for the 14 antimanic drugs are largely consistent with the pre-marketing conclusions and can help further understand the pre-marketing results. More importantly, analyzing post-marketing data provides a more

comprehensive evaluation of drug safety. Rigorous frameworks that can effectively combine the pre-marketing data (e.g., clinical trials data) with the post-marketing data (e.g., FAERS data) can potentially generate new research hypotheses, help better understanding of the association of drug use and AEs, and provide better evidence in aiding medical decision-making.

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Fig. 1. Proportions of patients having at least one AE in each SOC class for 14 antiepileptic drugs.

Fig. 2.
All-cause death proportions for the 14 antimanic drugs.

Fig. 3.
Estimated rate ratios with 95% confidence intervals for the 13 antimanic drugs compared to placebo.

Table 1

The number of records extracted from FAERS for 14 antimanic drugs.

Drug Name	Number of Records
Aripiprazole(ari)	43,126
Asenapine(ase)	5,872
Carbamazepine(cbz)	30,557
Gabapentin(gbt)	102,774
Haloperidol(hal)	18,182
Lamotrigine(lam)	53,957
Lithium(lit)	19,638
Olanzapine(olz)	43033
Quetiapine(qtp)	77,682
Risperidone(ris)	52,758
Topiramate(top)	32,623
Valproate(val)	18,679
Ziprasidone(zip)	13,757
Placebo(pbo)	8,869

Table 2

Definitions of system organ classes on internationally agreed order [11]

System Organ Class	Order
Infections and infestations	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2
Blood and lymphatic system disorders	3
Immune system disorders	4
Endocrine disorders	5
Metabolism and nutrition disorders	6
Psychiatric disorders	7
Nervous system disorders	8
Eye disorders	9
Ear and labyrinth disorders	10
Cardiac disorders	11
Vascular disorders	12
Respiratory, thoracic and mediastinal disorders	13
Gastrointestinal disorders	14
Hepatobiliary disorders	15
Skin and subcutaneous tissue disorders	16
Musculoskeletal and connective tissue disorders	17
Renal and urinary disorders	18
Pregnancy, puerperium and perinatal conditions	19
Reproductive system and breast disorders	20
Congenital, familial and genetic disorders	21
General disorders and administration site conditions	22
Investigations	23
Injury, poisoning and procedural complications	24
Surgical and medical procedures	25
Social circumstances	26