Real-World Evidence and Population Health Analytics: Intersection and Application

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ABSTRACT

Regulatory agencies and pharmaceutical companies use real-world evidence (RWE) to generate clinical evidence derived from real-world data (RWD) for routine regulatory drug review and to monitor the usage and potential benefits or risks associated with a medical product in real-world settings. SAS® Real World Evidence is a visual RWE and visual analytics platform that enables quick discovery and creation of patient cohorts for population health analytics. We used SAS Real World Evidence to create index event cohorts to perform unsupervised and supervised signal detection analyses involving stroke events and atypical/typical antipsychotic medications. Use cases that show how SAS Real World Evidence enables intersection and application of RWE with population health analytics are provided. A population-level estimation example that uses SAS® causal estimation and propensity score matching procedures to examine the association between antipsychotic drugs and stroke risk is presented in this paper.

INTRODUCTION

Regulatory agencies and pharmaceutical companies use real-world evidence (RWE) to generate clinical evidence derived from real-world data (RWD) for routine regulatory drug review and to monitor the usage and potential benefits or risks associated with a medical product in real-world settings (Food and Drug Administration, 2018). In the health-care sector, providers and payers use RWD to predict health care utilization and resource consumption profiles of patients as to curtail costs and improve clinical outcomes. RWD provide opportunities to perform prospective and retrospective studies using data derived from variety of sources such as claims and billing data, patient registries, and electronic medical records. Potential uses of RWD include the collection of longitudinal patient information during routine clinical care, which provides clinical evidence data for assessing trial feasibility; recruitment of clinical trial subjects; generation of testable hypotheses for randomized clinical trials; and construction of episode-of-care profiles and treatment pathways for comparative effectiveness research.

Technologies and tools are needed to facilitate the adoption of RWE for clinical and epidemiological research, and to bridge the clinical evidence data gap from multiple RWD sources. SAS recently released a visual real-world evidence and visual analytics platform that enables quick discovery and creation of patient cohorts for population health analytics and epidemiological studies. SAS® Health Analytics Framework contains accelerators and applications, such as SAS Real World Evidence, which provide the ability to consume and enrich data, as well as address many health care or life science use cases.

In this paper, we show how to use SAS Real World Evidence to create study cohorts for exploratory clinical studies and comparative effectiveness research. In one example, we use SAS Real World Evidence to create analytic data sets to perform unsupervised signal detection of stroke events that might be associated with disproportionate reporting of atypical and typical antipsychotic medications. In another example, we conduct an exploratory supervised signal detection analysis that examines the incidence of stroke events and association with antipsychotic medications. Finally, we show how to use SAS
Real World Evidence to create index event cohorts and analytical data sets for exploratory comparative effectiveness research. SAS Real World Evidence provides some example analytical add-in model templates (built using the SAS Real World Evidence Add-in Builder) to enable users to perform different types of analytical and modeling tasks.

We show how the product enables intersection and application of RWE with population health analytics with a population-level estimation example that uses SAS causal estimation and propensity score matching procedures to examine the association between antipsychotic medications and stroke risk. Recent studies (Taylor 2017; Hsieh 2t. al. 2013) have shown that medications used in the treatment of depression have potential stroke and cardiovascular effects. Some antipsychotic drugs such as aripiprazole, olanzapine, and risperidone, to mention a few, have antipsychotics black-box warnings for cerebrovascular adverse events including stroke. Part of the analyses presented in this paper aim to find out whether retrospective analysis of claims-based clinical care data could be used to signal stroke events among patients exposed to certain types of antipsychotic drugs.

This paper is organized as follows: first, we present the materials and methods that focus on the data source used in this paper and a brief overview of SAS Real World Evidence; second, we briefly present the study research design, the supervised and unsupervised statistical signaling methods; and finally, we present the study findings based on the previously mentioned research use cases. In the appendix, we provide additional information about the most commonly used signal detection methods and strategies for preparing the data to make them suitable for signal detection analyses. For drug safety signals evaluation purposes, we note that these statistical tools enable computation of signals for describing risks that might be associated with certain class of drugs, but due to known limitations of observational databases, additional research is required to properly make statistical inferences and clinical judgments in a meaningful manner.

**MATERIALS AND METHODS**

The study cohort design employed to guide the drug safety analytics process flow and signals detection analysis presented in this paper is displayed in Figure 1. The process flow and analytical tasks are presented as follows: (a) the real-world data domain source and the cohort definition setup that use SAS Real World Evidence to identify and create the index event drug cohorts, the index antipsychotic drug profiles, the index stroke outcome event, and the data sets for signal detection analyses; (b) the data exploration step presents the demographic characteristics of the study cohort, as well as the frequency distribution of the study drug and outcome event profiles; (c) the analysis and results step present the unsupervised and supervised signal detection findings and the causal estimation and propensity score matching results for the example use cases (that is, association of stroke event and selected antipsychotic drugs); and (d) the interpretation of the RWE-based signal detection results in relation to population health analytics.
DATA SOURCES

Data used for this study come from the publicly available Centers for Medicare and Medicaid Services (CMS) Data Entrepreneurs’ Synthetic Public Use Files (DE-SynPUF) for Medicare recipients. As stated on the CMS website, DE-SynPUF was created with the goal of providing a realistic set of claims data in the public domain while providing the highest degree of protection to the Medicare beneficiaries’ protected health information. We use the entire 2.3 million-member population data for our study. The database provides de-identified patient information that included patient demographics, dates of service, diagnoses, procedures, and limited years of medications.

We use SAS Real World Evidence to identify and build cohort of patients with at least one record of drug prescription in either the typical or atypical antipsychotic drug class (list of drugs considered for analysis is provided in the appendix and in Display 1) regardless of service setting. The study setup follows a retrospective cohort study design and consists of patients aged 18 years and older. The first identified prescription fill date in the database for each antipsychotic medication is tagged as the index event date and used to create the drug exposure profile for each drug. NDC codes are used to identify records of prescription and standardized to a common generic drug name, because a drug might be classified under one or multiple NDC codes. The final cohort sample consists of 234,352 patients. User-defined analysis variables capturing the outcomes, demographics, comorbidity risk factors, and other analysis variables are created and added to the final data set used for analysis.

DRUG EXPOSURE PROFILES AND OUTCOME EVENTS

The methodology governing the framework for signal detection analyses is a set of composite events \((T_i, X_i, E_i)\) representing the time period-exposure drug-outcome event profile constructed for each patient that met the study eligibility criteria. The \(T_i\) events represent contiguous time periods used to divide the study window, the \(X_i\) events capture the drug exposure profile information by time period, and the \(E_i\) events capture the stroke event observed during each drug exposure period.

For signal detection analysis purposes, each drug exposure profile (defined by the index prescription fill date and subject to the occurrence of first stroke event, or death, or the study end date) is binned into one or more model periods. The model period is the time window used to accumulate and assign incurred prescription claims and refills to the associated window. The model period assignment logic breaks the exposure period into 90-day contiguous periods that are set between the drug exposure start and end dates, starting with the most recent 90 days from the index fill date. For example, for a given index drug, if the index fill date and last fill date were to match the study period start and end dates, then the possible maximum number of 90-day increment periods is 16. For the study drugs
analyzed in this paper, the minimum, median, and maximum number of contiguous model periods are 1, 1, and 5, respectively. Model periods are evaluated and constructed independently for each selected antipsychotic medication listed in the Appendix. Binning the study period into contiguous model periods ensures that the study drugs are examined over a consistent time interval. This also allows for temporal analysis of antipsychotic drugs – stroke event pairs over time. For cumulative trend analysis, all available data from the first to last model periods are analyzed, and prior model period data are iteratively added to subsequent model periods for each drug.

For each patient, the presence or absence of the health outcome of interest (in this case, stroke event) was checked for during each model period that spans the drug exposure window. The study endpoint for each evaluative patient for the stroke event (identified by ICD-9 codes listed in the appendix) is the date associated with the first occurrence of stroke event detected during the associated model period for the drug, death (from any cause), the last known prescription claim interval, or the end of the study in 2011.

**SAS REAL WORLD EVIDENCE**

SAS Real World Evidence is a visual real-world evidence and analytics platform that enables quick discovery and creation of patient cohorts for epidemiological studies and population health analytics. The platform workflows simplify the process of defining and building a cohort, which is a set of patients that meet some specific inclusion and exclusion eligibility criteria.

![Display 1: SAS Real World Evidence: index event definition](image)

The platform supports:
- a common data submission model for managing real-world data from multiple disparate data sources
- creation and management of ontology code-based index event definitions (Display 1)
- creation and processing of cohorts of patients based on simple and complex query logic and rules that are customized to address different clinical scenarios and temporal relationships across different event codes: diagnoses, procedures, prescriptions, vitals, and laboratory tests (see Display 2)
- easy-to-navigate point-and-click interface to assist users with exploring and querying large data sources
• loading of predefined analysis variables and creation of user-defined analysis variables (see Display 2)
• add-in models and report templates that run against cohort outputs and leverage the power of SAS advanced analytics and machine learning algorithms for real-world data insights (see Display 3)
• add-in builder that enables users to develop and execute customized or user-written SAS programs and open-source code against cohort outputs

Display 2: SAS Real World Evidence: cohort discovery and processing workflow

Display 3: SAS Real World Evidence: add-in model job workflow
STATISTICAL ANALYSIS

The exploratory signal detection analysis presented is based on statistical methodology generally used to detect signals in a safety database such as the United States Food and Drug Administration Adverse Event Reporting System (FAERS). For statistical algorithm differentiation purposes, we use the term ‘unsupervised signal detection’ analysis to refer to this type of disproportionality analysis and compute signal scores that detect ‘more-than-expected frequency count’ of drug-event associations derived from RWD. The methods are used to discover and signal frequency count anomalies or association patterns in a large database containing records of exposure to different drugs and reported adverse drug reactions. For supervised signal detection analysis, we assume there is a functional underlying distribution to model association between an outcome variable of interest (say, stroke event) and selected medications of interest (for example, atypical antipsychotic (AAP) or typical antipsychotic (TAP) drugs). For both types of analysis, we use the ‘distinct’ patient count method to obtain the frequency counts of patients exposed to each AAP or TAP drug, those reporting stroke event, and those with both AAP or TAP encounters and stroke events.

For each patient included in the study, the first recorded AAP or TAP drug triggered in the data is assigned as the index drug for the patient. As illustrated in the frequency table displayed in Figure 2, $n_\cdot \cdot$ equals the total number of patients in the database, $n_{11}$ is the number of patients with exposure to the study drug during the model period and reporting stroke events, $n_{10}$ is the number of patients that have used the study drug but did not experience stroke event during any of the model periods associated with the drug, $n_{01}$ is the number of patients that did not use the study drug but experienced stroke event, and $n_{00}$ is the number of patients that were not exposed to the study drug and did not report stroke condition. Crude reporting rates for the AAP/TAP drug-stroke event pairs are computed for unsupervised signal detection analysis and crude rate ratios and average treatment effect (ATE) estimates are obtained using the supervised analysis method. For the latter method, we compute both the unadjusted and adjusted potential ATE estimates as signal measures to represent and characterize the antipsychotic medication-stroke event pairs. For each index study drug, the comparator drugs are the ‘other’ index AAP/TAP medications mentioned earlier.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Event</th>
<th>No Event</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exposed</td>
<td>$n_{11}$</td>
<td>$n_{10}$</td>
<td>$n_{1}$</td>
</tr>
<tr>
<td>Not exposed</td>
<td>$n_{01}$</td>
<td>$n_{00}$</td>
<td>$n_{0}$</td>
</tr>
<tr>
<td>Total</td>
<td>$n_{\cdot1}$</td>
<td>$n_{\cdot0}$</td>
<td>$n_{\cdot\cdot}$</td>
</tr>
</tbody>
</table>

Method Score Metric = $O/E = \frac{\text{Observed frequency}}{\text{Expected frequency}}$

Figure 2 – The 2x2 drug-event association tabular representation for signal detection analysis

For unsupervised signal detection analysis, we use the standard disproportionality methods that include the Bayesian Confidence Propagation Neural Network (BCPNN) Information Component (IC), the Relative Odds Ratio (ROR), and the Proportional Reporting Ratio (PRR). A risk ratio or score for each signaling method is represented by the lower bound of the 95% CI > 1.0 for ROR and PRR, or 95% CI > 0 for BCPNN/IC. The score is computed as the ratio of the observed count of stroke to the expected count of stroke.
event, and if it exceeds the pre-specified method threshold, is considered as significant and flagged as a signal. Additional information about the analysis methods is provided in the appendix of this paper.

For supervised signal detection analysis, we use the causal estimation procedure (PROC CAUSALTRT) to compute both the unadjusted and adjusted effect of each AAP/TAP medication on the target variable (stroke event), and the STDRATE procedure to obtain the unadjusted rate ratio estimates. The CAUSALTRT procedure uses various estimation methods to adjust for the effects of confounding variables by fitting models for the treatment assignment T (in this case, each AAP/TAP drug versus ‘other’ antipsychotic drugs) or the outcome Y (in this case, stroke event), or both. We lump together other non-target AAP or TAP drugs into the ‘other’ antipsychotic medications category to allow for comparing the unsupervised signal detection results with the supervised analysis. Ideally, the comparator drug is limited to one drug type for causal estimation analysis. Because we consider the analysis presented here still exploratory, we are interested in examining how the results compare based on choice of analysis method. For the analysis presented in this paper, we use the augmented inverse probability weights (AIPW) estimation method to jointly fit both the treatment assignment and outcome event models, and to compute the average treatment effect (ATE) for each target antipsychotic medication relative to other medications in the same class. The AIPW estimation method fits the propensity score model for treatment assignment and incorporates a model for the outcome variable into the estimation of the potential outcome means and ATE. The AIPW estimation method is doubly robust and provides unbiased estimates for the ATE even if one of the outcome or treatment models is mis-specified. For more detailed information about this procedure, see SAS/STAT® 14.3 User’s Guide: The CAUSALTRT Procedure.

The supervised unadjusted model is an ATE model with the effects of covariates and other confounding variables unaccounted for. To obtain the adjusted ATE for each AAP/TAP drug-stroke event pair, we include and adjust for demographic factors, number of concomitant medications (excluding the study drugs or medications in their drug class), and comorbidity risk factors in the outcome event multivariate model. Elixhauser comorbidity diagnosis codes are used to capture the patient’s comorbidity status prior to the start of the index medication event and transformed into binary variables, coded as a 1 or 0 flag, based on information known prior to the index event date (Elixhauser et. al. 1998). For the supervised adjusted and unadjusted models that are estimated using the CAUSALTRT procedure, the lower bound of the 95% CI for estimated ATE > 0 is flagged as a safety signal. For unadjusted rate ratio that is derived using the STDRATE procedure, the lower bound of the 95% CI for rate ratio > 1 is flagged as a safety signal.

For the exploratory population-level estimation analysis, we look at whether (a) users of typical APs (target group) have a higher risk of stroke compared to users of atypical APs (comparator group) and (b) whether users of aripiprazole drug (target group) have a higher risk of stroke compared to users of risperidone drug (comparator group). Analysis in (a) is completed at the drug class level while analysis in (b) is completed at the drug level. The SAS causal estimation procedure is used for the analysis. All analyses are performed using SAS statistical software and SAS Real World Evidence 4.4.

STUDY POPULATION

The index cohort population consists of 234,352 patients that meet the inclusion and exclusion criteria and are treated with at least one prescription fill for antipsychotic drug (16 different drugs in all). The respective number of patients for each medication and associated
stroke events are reported in Table 1. Cohort patient demographic characteristics are presented in Display 4. There are approximately 180,039 atypical AP users versus 54,313 typical AP users. Frequency distributions by gender and race look similar across both groups, while there is a higher prevalence of comorbidity risk factors in the typical AP group relative to the atypical AP group.

Display 4: Cohort patient characteristics

Unsupervised signal detection analysis

Table 1 shows the results of the unsupervised signal detection analysis for the three disproportionality analysis methods. Of the nineteen antipsychotic medications analyzed, the expected count of stroke events, based on PRR disproportionality signaling method, range from 1844 stroke events for risperidone therapy, about 356 stroke events for haloperidol, about 314 stroke events for quetiapine fumarate, to 31 stroke events for iloperidone drug. The associated PRR values are 0.94, 1.18, 0.97 and 0.97, respectively. Based on the PRR threshold [(PRR – 1.96SE)>1] for signaling disproportionate reporting of stroke condition, only haloperidol (95% CI 1.066-1.30), perphenazine (95% CI 1.15-1.47), and thioridazine therapy (95% CI 1.02-1.52) show evidence of elevated risk of stroke relative to all other AP medications. The stroke signal results for these medications are consistent with those obtained for the unsupervised ROR and BCPNN/IC methods. Unadjusted signal results based on these three methods also show decreased stroke risk for certain antipsychotic medications such as clozapine therapy relative to other AP drugs in the database.
Table 1: Unsupervised signal detection results for selected antipsychotic drugs and stroke

**Unsupervised signal detection trend analysis**

For each study drug, the cumulative trend analysis plot shown in Figure 3 is used to examine which of the model periods is likely to contain the signaled stroke event. Consistent with what was reported in the unadjusted analysis, only haloperidol shows an elevated risk of stroke event and the risk remains consistent until the end of the cumulative therapy window. Based on the pre-specified signal threshold, some AP medications show evidence of elevated risk of stroke that will require additional follow-up investigation. We further examine the significance of signaled stroke event associations with supervised signal detection analyses.

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**Unsupervised disproportionality signaling method**

<table>
<thead>
<tr>
<th>Generic Drug Name</th>
<th>No. of Patients</th>
<th>Observed Events</th>
<th>Expected Events</th>
<th>PRR</th>
<th>95% CI</th>
<th>Expected Events</th>
<th>ROR</th>
<th>95% CI</th>
<th>Expected Events</th>
<th>IC</th>
<th>IC-2SD</th>
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<tbody>
<tr>
<td>Arripiprazole</td>
<td>8038</td>
<td>132</td>
<td>137.43</td>
<td>0.961</td>
<td>0.806, 1.144</td>
<td>137.51</td>
<td>0.969</td>
<td>0.806, 1.144</td>
<td>137.23</td>
<td>-0.056</td>
<td>-0.312</td>
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<td>-0.312</td>
</tr>
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**Figure 3:** Trend analysis plot of unsupervised signal detection scores for selected antipsychotic drugs and stroke
**Supervised signal detection analysis**

We report the unadjusted rate ratio and adjusted ATE estimates for the AP medications based on the supervised signal detection methods in Table 2. In comparison with the unsupervised disproportionality analysis findings, the supervised signal detection results for stroke event are somewhat similar with relatively few changes. Haloperidol, perphenazine, and thioridazine AP drugs all demonstrate unadjusted and adjusted elevated risk of stroke. For haloperidol drug, the unadjusted rate ratio is 1.27 (95% CI 1.15-1.41) and ATE of 0.0028 (95% CI 0.001-0.005). When we adjust for the effects of covariates in the multivariable causal model, the risk increases with ATE of 0.0046 (95% CI 0.003-0.007). Similar results are found for perphenazine and thioridazine drugs.

<table>
<thead>
<tr>
<th>Generic Drugname</th>
<th>N(Patients)</th>
<th>Rate Ratio</th>
<th>Z Score</th>
<th>95% CI</th>
<th>ATE</th>
<th>Z Score</th>
<th>95% CI</th>
<th>Adjusted Rate Ratio</th>
<th>Z Score</th>
<th>95% CI</th>
</tr>
</thead>
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<td>0.36672</td>
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<td>-0.46975</td>
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<td>1.29292</td>
<td>-0.001, 0.005</td>
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<td>3293</td>
<td>0.7884</td>
<td>2.3807</td>
<td>0.526, 0.981</td>
<td>-0.0038</td>
<td>1.78969</td>
<td>-0.008, 0.000</td>
<td>0.0018</td>
<td>-1.0046</td>
<td>0.005, 0.002</td>
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<td>CLOZAPINE</td>
<td>10895</td>
<td>0.8416</td>
<td>2.6259</td>
<td>0.712, 0.995</td>
<td>0.0027</td>
<td>2.30929</td>
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<td>(0.003, 0.002)</td>
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<td>22761</td>
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<td>4.26777</td>
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<td>2.59261</td>
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<td>ILOPERIDONE</td>
<td>1955</td>
<td>0.8952</td>
<td>0.57931</td>
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<td>-0.0005</td>
<td>-0.19542</td>
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<td>12943</td>
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<td>3.70119</td>
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<td>QUETIAPINE PUMARATE</td>
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<td>1.0405</td>
<td>0.66277</td>
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<td>4.20973</td>
<td>0.797, 0.990</td>
<td>-0.0039</td>
<td>1.01696</td>
<td>0.002, 0.000</td>
<td>-0.0004</td>
<td>-0.82324</td>
<td>0.005, 0.005</td>
</tr>
<tr>
<td>THIOLOXETINE HYDROCHLORIDE</td>
<td>4892</td>
<td>1.3451</td>
<td>2.85955</td>
<td>1.102, 1.552</td>
<td>0.0038</td>
<td>1.99849</td>
<td>0.006, 0.000</td>
<td>0.0009</td>
<td>4.30841</td>
<td>0.006, 0.013</td>
</tr>
<tr>
<td>THIOLOXETINE</td>
<td>4947</td>
<td>1.1296</td>
<td>1.16300</td>
<td>0.914, 1.420</td>
<td>0.0008</td>
<td>0.43510</td>
<td>0.004, 0.001</td>
<td>0.0004</td>
<td>2.10508</td>
<td>0.001, 0.008</td>
</tr>
<tr>
<td>TRIPLOPERAZINE</td>
<td>6321</td>
<td>0.9606</td>
<td>0.64322</td>
<td>0.724, 1.119</td>
<td>-0.0028</td>
<td>-1.54545</td>
<td>0.006, 0.000</td>
<td>0.0009</td>
<td>0.53924</td>
<td>0.002, 0.004</td>
</tr>
<tr>
<td>ZIPRASIDONE</td>
<td>7193</td>
<td>1.1233</td>
<td>1.24300</td>
<td>0.935, 1.349</td>
<td>0.0005</td>
<td>0.35170</td>
<td>-0.002, 0.004</td>
<td>0.0006</td>
<td>2.14737</td>
<td>0.000, 0.007</td>
</tr>
</tbody>
</table>

Table 2: Supervised signal detection analysis results for selected antipsychotic drugs and stroke

**Population-level estimation analysis**

The population-level estimation results that test for higher risk of stroke event for typical AP versus atypical AP medications are shown in Display 5 and Display 6. The AIPW estimation method that we use combines the modeling of the treatment assignment with the modeling of the outcome variable to estimate the potential outcome means and the ATE for typical/atypical AP drugs association with stroke event. Both the robust and bootstrap-based estimation of the standard error and confidence limits are provided for the ATE estimates and confidence intervals. The positive value of AIPW estimate of 0.0186 indicates that typical AP drugs exhibit higher than average risk of stroke event compared to atypical AP drugs. The ATE is significantly different from 0 at the 0.05 alpha level as shown by both the standard and bootstrapped Wald 95% confidence interval (bootstrap: 0.0154, 0.0218). Notice that both the standard and bootstrap-based confidence intervals are very close.

We conduct similar analyses for the association between aripiprazole AP versus risperidone AP drugs and stroke event (results not displayed) and find a higher than average risk of stroke event for aripiprazole AP drugs. The AIPW ATE estimate and bootstrap-based confidence intervals are 0.00239 (95% CI: 0.0165 – 0.0312).
Display 5: AIPW potential outcome means and ATE estimates for typical and atypical AP drugs comparative analysis

Causal Effects Estimation Analysis Using Augmented Inverse Probability Weights (Method=AIPW)

Display 6: Histograms of bootstrap ATE estimates for typical and atypical AP drugs comparative analysis
CONCLUSION

Given the known limitations of spontaneous adverse drug event data often used to generate and monitor safety signals, especially for newly marketed drugs, RWD provide additional and complementary clinical evidence-based information that can be used to further investigate the validity and reliability of such signals. RWD capture utilization of health care services collected at points of care and contribute to our understanding of treatment effectiveness and safety, treatment patterns, and patient interactions with the health care system. These factors enable the study of patient behaviors, disease diagnoses, proactive surveillance of medications, and adverse health outcomes. It is noteworthy that real-world data has its own limitations and potential sources of biases that must be considered when conducting studies of this nature.

Key Points

• Observational healthcare databases with longitudinal data on patient medical conditions and treatment information can be used in the surveillance and signal detection of unexpected and serious adverse events.

• Use of multiple signaling algorithms to signal disproportionately reported counts of drug-adverse event pairs might provide more accurate information and minimize the number of false positives for signaling unexpected and serious adverse events than can be predicted using a single signaling method.

• Combining results from supervised and unsupervised prediction models that evaluate treatment effectiveness and adverse drug reactions can provide more information to help make informed judgment on the hypothesized association than those based on one method of analysis.

• Results from the signal detection analysis of AP medications and association with stroke presented in this paper tend to support findings that have already been published in the literature.

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REFERENCES


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APPENDIX

DISPROPORTIONALITY ASSOCIATION SIGNALING METHODS

A brief discussion of some of the common disproportionality association and statistical safety data mining methods is presented in this appendix. A list of some useful articles and textbooks where you can get more information about each method is presented in this appendix.

One way to characterize and summarize an association between a drug and an event (for example, adverse event or health outcome of interest) is to use a 2x2 frequency table as shown in figure A. The table usually displays the counts of the cross-classification of the two variables and uses an association metric or measure such as risk ratio or rate ratio to quantify the relative importance and significance of the association between the two variables. Data used to derive these measures can originate from spontaneous adverse event reports such as those collected by the United States Food and Drug Administration (FDA), or from longitudinal health records or administrative claims databases. Statistical techniques or algorithms used to derive such association metrics (often called disproportionality analysis methods when applied to spontaneous reports data) can be as simple as proportional reporting ratio (PRR), or reporting odds ratio (ROR), and some embedded in Bayesian logic such as the Bayesian Confidence Propagation Neural Network (BCPNN) or the Multi-Gamma Poisson Shrinker. In its simplest form, the analysis metric that connects all the three disproportionality methods is the ratio of the observed count of reports to the expected count of reports for the drug-event pair given the assumption of statistical independence in the reporting of the drug and reporting of the event in question. The score serves as a statistical measure of deviation and the extent that the number of reports associated with a drug-event combination is reported to the SRS database more often than expected relative to the rest of the reports in the database. Each of the three statistical algorithms attempts to quantify the disproportionality between the observed and expected values for the drug-event combination to a chosen threshold. The representation of the association between the drug and event and the definition for each method metric are provided in the following table.

Table A: The 2x2 drug-event association tabular representation for signal detection analysis

<table>
<thead>
<tr>
<th>Measure</th>
<th>Definition/Formula</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug-Event Pair Association</td>
<td>Score = Observed(O)/Expected(E)</td>
</tr>
<tr>
<td>Proportional Reporting Ratio (PRR)</td>
<td>Score metric/threshold = (PRR – 1.96SE) &gt; 1, where PRR = (n_{11}/n_{1.}) / (n_{01} / n_{0.}) SE(ln PRR) = \sqrt{1/n_{11} + 1/n_{1.} + 1/n_{01} + 1/n_{0.}}</td>
</tr>
<tr>
<td>Reporting Odds Ratio (ROR)</td>
<td>Score metric/threshold = (ROR – 1.96SE) &gt; 1, where ROR = (n_{11}*n_{00}) / (n_{10} * n_{01}) SE(ln ROR) = \sqrt{1/n_{11} + 1/n_{10} + 1/n_{01} + 1/n_{00}}</td>
</tr>
</tbody>
</table>
| Bayesian Confidence Propagation Neural Network (BCPNN/IC) | Measures strength of dependency between a product and a specific AE term. Score metric/threshold (IC): E(IC) -2\sqrt{V(IC)} > 0 E(IC_i) = log2 \{ [(c_i + \gamma_i)(C + \alpha_i)(C + \beta_i)] / [(C + \gamma)(C + \alpha)(C + \beta)] \} and V(IC_i) = 1/((log_2)^2 \{ [(C - c_i + y - \gamma_i)/(c_i + \gamma_i + 1+C+y)] +
SUPERVISED SIGNALING METHODS

For the supervised signal detection analysis, the unadjusted method uses the Mantel-Haenszel rate ratio statistic from the STDRATE procedure, and the unadjusted average treatment effect (ATE) estimate from the intercept-only treatment and outcome model using the CAUSALTRT procedure. The latter method is the same as computing the Mantel-Haenszel risk difference statistic for two-sample populations. The supervised adjusted method approach uses the doubly robust estimation method to obtain ATE which in this case measures the estimated potential outcome means difference of the event occurrence between the drug of interest relative to the other drugs in the database. The method fits models for both the outcome event and the treatment drug groups being compared. They combine inverse probability weighting and regression adjustment to estimate the potential outcome means. The methods are said to be doubly robust because they provide unbiased estimates for \( \mu \) even if one of the models is mis-specified (Bang and Robins 2005). The CAUSALTRT procedure implements two doubly robust estimation methods: the augmented inverse probability weighting (AIPW) method described in Lunceford and Davidian (2004) and the inverse probability weighted regression adjustment (IPWREG) method described in Wooldridge (2010). For more detailed information about this procedure, see SAS/STAT® User's Guide: The CAUSALTRT Procedure and The STDRATE Procedure. The code syntax for STDRATE and CAUSALTRT procedure is provided:

**PROC STDRATE:** computes directly standardized rates and risks for study populations.

```sas
PROC STDRATE data=<name of dataset>
   METHOD=mh
   STAT=risk/rate
   EFFECT=diff/ratio
   plots=all;
   POPULATION GROUP=<treatment variable>
   EVENT=<outcome event> TOTAL=<Patients/PYears>;
   STRATA <List of stratification variables> / order=data
   STATS (cl=<options>) EFFECT;
RUN;
```
**PROC CAUSALTRT**: estimates the average causal effect of a binary treatment, $T$, on a continuous or discrete outcome, $Y$. Good for data from nonrandomized trials or observational studies.

```sas
PROC CAUSALTRT data=<input data set> method=AIPW COVDIFFS PPSMODEL
POUTCOMEMOD;
  CLASS <list of class variables>;
  PPSMODEL <treatment variable> = < List of variables for propensity score matching> / plots=(PSDist PSCOVDEN(effects(name of variables)));
  MODEL <outcome variable> = <List of variables for outcome event prediction> / <options>;
  BOOTSTRAP bootci(all) plot=hist seed=1234;
RUN;
```

List of antipsychotic drugs and stroke event diagnosis codes

<table>
<thead>
<tr>
<th>Atypical APs</th>
<th>Typical APs</th>
<th>Stroke ICD-9-CM Dx</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARIPIPRAZOLE</td>
<td>CHLORPROMAZINE HCL</td>
<td>430</td>
</tr>
<tr>
<td>ASENAPINE</td>
<td>FLUPHENAZINE</td>
<td>431</td>
</tr>
<tr>
<td>BREXPIPRAZOLE</td>
<td>HALOPERIDOL</td>
<td>433.01, 433.21, 433.31, 433.81, 433.91, 434.01, 434.11, 434.91</td>
</tr>
<tr>
<td>CARIPRAZINE</td>
<td>LOXAPINE</td>
<td>436</td>
</tr>
<tr>
<td>CLOZAPINE</td>
<td>MOLINDONE</td>
<td></td>
</tr>
<tr>
<td>ILOPERIDONE</td>
<td>PERPHENAZINE</td>
<td></td>
</tr>
<tr>
<td>LURASIDONE</td>
<td>PERPHENAZINE/AMITRIPTYLINE</td>
<td></td>
</tr>
<tr>
<td>OLANZAPINE</td>
<td>THIORIDAZINE</td>
<td></td>
</tr>
<tr>
<td>OLANZEPINE/FLUOXETINE</td>
<td>THIOTHIXENE</td>
<td></td>
</tr>
<tr>
<td>PALIPERIDONE</td>
<td>TRIFLUOPERAZINE</td>
<td></td>
</tr>
<tr>
<td>QUETIAPINE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RISPERIDONE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ZIPRASIDONE</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**RECOMMENDED LIST OF READINGS**


DuMouchel, W., Bayesian Data Mining in Large Frequency Tables, with an Application to the FDA Spontaneous Reporting System. The American Statistician, 1999:177-190.

