Visual Analysis of Complex Adverse Drug Reactions in Claims Data

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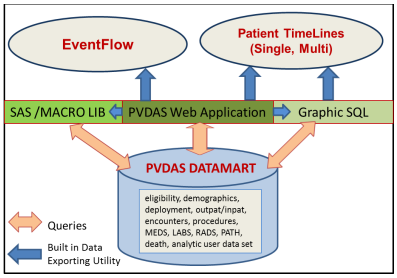
Abstract

The Army Pharmacovigilance Center (PVC) developed the Pharmacovigilance Defense Application System (PVDAS) to perform medication safety surveillance for the Military Health System (MHS). We describe visual analytic capabilities in PVDAS that support pharmacovigilance safety studies, illustrated with the complex ADR example of Drug Reaction Eosinophilia and Systemic Symptom (DRESS) as the use case.

Background

PVDAS is a software suite with an accompanying medical datamart that currently contains data from 2005 to the present for about 16 million patients. PVDAS visualization tools include EventFlow[3] and single and multiple-patient timeline displays, as shown in figure 1.



EventFlow includes a visual query facility allowing the user to subset the timeline displays, and also has an innovative display in which the individual timelines are aggregated to highlight common temporal patterns.

Single-patient timelines display a complete patient history, while the multi-patient timelines focus on providing a visual overview of the temporal distribution of the suspected drug(s)-event(s) relationship.

Figure 1. PVDAS VISUALIZATION TOOL SET

In December 2014, the FDA warned that ziprasidone may be associated with the serious condition DRESS[4]. Symptoms include: rash, fever, lymphadenopathy, eosinophilia, hepatitis, nephritis, pancreatitis, and inflammation of other organs. The current diagnosis standard for DRESS[5] specifies a list of seven criteria, the occurrence of any three of which qualify as a "notification case," with medical review required to confirm the diagnosis. Correctly identifying this syndrome based on claims data is extremely challenging.

[3] www.cs.umd.edu/hcil/eventflow
[4] http://www.fda.gov/Drugs/DrugSafety/ucm426391.htm
[5] http://www.regiscar.org/Diseases_HSS_DRESS.html

Methods

Our approach was to identify the occurrence of a set of "single outcomes" for each of the criteria (fever, blood abnormalities, acute rash, lymph node symptoms or organ inflammation), based on ICD9 codes for each of these outcomes. From these we created a second-level set of "compound outcomes" which represented co-occurrence of three or more of these single outcomes within a specified time window (60 days), or of two or more single outcomes together with hospitalization. We then identified patients having the occurrence of at least one of these compound outcomes within a specified time window of exposure to ziprasidone. For initial review we loaded these cases into EventFlow and used it to identify overall patterns of exposure and condition onset (Figure 2). We then presented the cases for detailed review using the multi-patient timeline and single-patient timeline (Figures 3A, 3B).

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Results

The MHS dataset included 42,000 ziprasidone users, of which approximately 2000 patients had at least one "compound DRESS outcome" within their medical record, and 339 patients qualified as potential notification cases, having at least two or more of the individual DRESS criteria occurring within 60 days after exposure to ziprasidone.

Using the visualization displays shown below, a medical reviewer was able to rapidly eliminate about two-thirds of the potential cases, and then make an initial determination on the remainder in just a few minutes per case. A full chart review will be required for final determination on the set of 30-60 "likely" cases identified through this process.

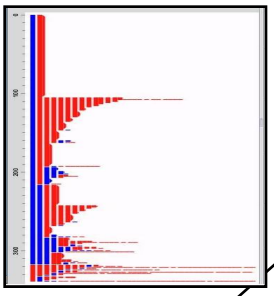
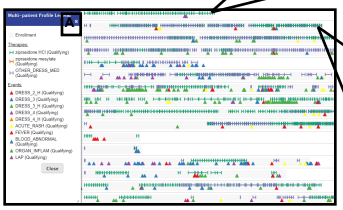


Figure 2. EventFlow aggregate view of 339 suspected cases

Vertical axis represents cases, horizontal axis represents time. Blue bar indicates ziprasidone exposure, red bar indicates "compound" outcome. Cases are aggregated by the temporal pattern of drug exposure and outcome occurrence. Cases that have outcomes prior to the exposure, or have multiple outcomes over a lengthy period of time, or have the outcome but still remain on the drug are quickly identified and eliminated.



B1. Ziprasidone only, shows the AE occurrence after long exposure. Causation ruled-out due to continuation. Patient remained on drug.

B2. Patient exposed to multiple drugs. First AE occurred during exposure to other DRESS medications. Patient remained on ziprasidone, indicating this was not considered an AE.

Figure 3A, 3B. Example multi-patient timeline with drilldown to two single-patient timelines

Conclusions

When dealing with complex outcomes such as DRESS, "blind" algorithmic approaches are not sufficiently precise – medical review is needed on a case-by-case basis for the final classification. For large cohorts of suspect cases, the cost can be prohibitive. By contrast, the approach described above first used a sophisticated algorithmic approach to filter the suspect cohort to a minimum number requiring human review, and then used innovative visual displays to support a rapid and efficient assessment by a medical reviewer.

The visual-analytic review described above could be used to validate query algorithms, or to cross-check certain cases for which the algorithm is unable to make a full determination.

EventFlow can be configured to work with any data sources. The current version of the patient timelines software has been tested with the OMOP CDM subset used by OSIM2. As such, the approach described above will be accessible to the OHDSI community through these PVDAS visualization tools.

Conflict of Interest:

Mr. Gordon is the President of Commonwealth Informatics, which has SBIR Phase II and Phase III funding from DOD to develop the applications described in this presentation. The multiple- and single-patient timelines will be part of a clinical informatics analysis package offered commercially by Commonwealth Informatics.