Development of a drug safety ePlatform for physicians, pharmacists, and consumers based on post-marketing adverse events

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Abstract

Rigorous clinical trials under the watchful eye of regulators remain the cornerstone of drug safety. However, the emergence of serious and life-threatening Adverse Events (AEs) across best-selling drug classes [sometimes many years after winning Food and Drug Administration (FDA) approval] underscores the limitations of current clinical trial processes and reinforces the need for careful post-approval pharmacovigilance. The FDA's sizeable repository of patient case reports linking AEs to approved drugs is the Adverse Event Reporting System (FAERS). We believe that open and user-friendly access to the millions of case reports in FAERS would help advance the field of post-marketing pharmacovigilance. However, FAERS data are virtually inaccessible to most physicians, pharmacists, and consumers. Accordingly, we have recently launched a big data platform (www.AdverseEvents.com) that, unlike previous efforts, provides on-demand, user-friendly, and high-impact access to FAERS data. Bringing the power of big data to regular users, such as clinicians, pharmacists, and patients, is the logical next step in the transformation of health care to a model of shared decision making between consumers and the system.

Public health impact of adverse events

Rigorous clinical trials and toxicology studies under the watchful eye of regulators remain the cornerstone of drug safety. However, the emergence of serious and life-threatening Adverse Events (AEs) across best-selling drug classes (severe cardiac complications from sibutramine, fatal muscle-wasting syndrome from cerivastatin, increased heart attack and stroke risk from rofecoxib, etc.) many years *after* they won Food and Drug Administration (FDA) approval, and were taken by tens of thousands of consumers underscores the limitations of current clinical trial processes and reinforces the need for careful post-approval pharmacovigilance.[1-4]

In fact, more than 770,000 injuries or deaths occur each year as a result of AEs linked to FDA approved drugs.[5] It has been estimated that approximately 28% of such events could potentially be prevented through computerized monitoring systems.[1] The FDA's repository of drug-related AEs is the Adverse Event Reporting System (FAERS) while their AE database for medical devices is the Manufacturer and User Facility Device Experience (MAUDE).[6,7] We believe that open and user-friendly access to the millions of case reports in FAERS would help advance the field of post-marketing pharmacovigilance. However, FAERS data are virtually inaccessible to most physicians, pharmacists, and consumers. Here we provide details concerning a newly launched big data platform (www.AdverseEvents.com) that, unlike previous efforts, provides physicians, pharmacists, and consumers with on-demand, user-friendly, and high-impact access to FAERS data.

Current state of the FAERS database

Approximately 700,000 AEs are logged into FAERS each year, across multiple therapeutic categories and ~4500 drugs.[5] Despite the limitations of FAERS (*e.g.* variable quality of reports, inability to calculate incidence or prove causality due to the voluntary nature of reporting), regulatory agencies and the pharmaceutical industry routinely look to FAERS data for drug safety signals. Additionally, recent studies have documented the utility of FAERS for generating safety signals found within FAERS,[8-18] while other investigations have compared FAERS data with AEs established through clinical trials and population studies.[2-4] However, proprietary data mining and signaling tools used by regulatory agencies and major pharmaceutical companies are too expensive and complex for most people to use. Additionally, publicly available FAERS information can only be obtained through complicated data downloads by individuals familiar with relational databases. For these reasons the FAERS database has remained virtually inaccessible to most physicians, pharmacists, and consumers.

The RxFilter™ platform

In reaction to such shortcomings, AdverseEvents, Inc. (AEI) has spent the last three years analyzing and categorizing the extensive FAERS database by using a combination of computer algorithms and in-house data analysis. The platform is known as RxFilter™, and it is making FAERS data accessible to broad groups of healthcare providers and consumers.

Two of the significant limitations that were encountered while building the RxFilter™ platform included: i) over 200,000 separate identifiers exist for the approximately 4500 FDA approved medications listed in FAERS, and ii) reports submitted to the FDA contain spelling errors, misclassifications, various data points either missing or inadequately reported, and are themselves frequently duplicated. RxFilter™ has addressed these and other issues, by employing multiple processing steps, safeguards, and manual oversight. To import data from FAERS, RxFilter uses a

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framework of open source technologies such as Oracle MySQL, Python and PHP. Filtering processes include: i) a system for automated name matching which corrects for drug name misspellings and incorrect data within major fields (*i.e.*, the inclusion of dosages or routes of administration as part of the drug name field); ii) aggregation of generic and non-U.S. brand name drugs under a single brand name; iii) separation of *primary suspect* and *all suspect* designations, iv) removal of duplicate case reports; and v) identification of common adverse event and condition types.

Automated data pre-processing and scrubbing workflow provides for an initial assignment of a *raw* FDA FAERS drug name for approximately 95% of inputted data (within 6 hours of our receipt of those data). Computationally, this automated matching process is accomplished by string searching and phonetic matching algorithms.[19,20] Part of the human analysis side of RxFilter includes recovery and assignment of remaining data, and reassignment of automated matches when needed (which are then corrected for future quarterly uploads). It is this combination of automated and human steps that generates *matched pairs* of raw FDA FAERS drug names with accepted trade or generic names. This process is applied to all FAERS data as they are uploaded to our site quarterly. The differences between what an end user sees when they download FAERS data from FDA *versus* how our RxFilter platform is presented can be seen in Figure 1 which displays FAERS and RxFilter outputs.

The RxFilter™ platform is, to our knowledge, the most thoroughly optimized, user-friendly, and fully searchable drug safety database designed for use by consumers, pharmacists, and clinicians. Our quality checks indicate that the platform accurately standardizes and normalizes all reported side effects (from 1997 on) linked to over 4500 FDA approved medications. Efforts are underway to refine our platform based upon consumer and clinician feedback with features such as personalized reports and e-newsletters with the latest events in drug safety. Additionally, we plan to actively conduct quality comparison checks against other drug safety databases and academic publications.

Who has access to the RxFilter™ platform, and how do they utilize it?

AEI offers primarily a subscription model that provides limited free, and unlimited paid, access to the RxFilter™ platform. By using the site, physicians can have rapid access to FAERS information in order to supplement their sources of data to help form clinical decisions at the point of care. On the consumer side, the platform will empower users with information on adverse events that may have occurred after the launch of the drug (which even their doctors may not be aware of).

For example, a clinician, in response to a recent FDA label change, wishes to look up information on top AEs associated with Lipitor (atorvastatin). The AdverseEvents.com home page interface (Figure 2) consists of a simple search box.

Subscribers who type in the word *Lipitor* in the search box will get a screen (Figure 3) listing the total number of AEs where atorvastatin is designated as the *primary suspect* drug (arrow A), links to recent pertinent news (*e.g. February 29, 2012 FDA announces label changes for Statin drugs*), an expandable list of names (arrow B), and a table of common conditions and comparison buttons (arrow C).

Below those sections is another table (Figure 4) listing the top AEs (arrow A) and both the Proportional Reporting Ratio (PRR) and the Reporting Odds Ratio (ROR) (commonly used by drug safety professionals to look for abnormally high reporting rate of certain adverse event types) (arrows B and C).

Both PRR and ROR calculations are derived by standard formulas and specific drugs are excluded from proportionality analysis if they have less than 25 primary case reports filed over the time period studied.[21] Figure 5 is a screen shot showing the customized searching feature that allows paid users to query any combination of: drugs, adverse events, conditions, indications, and manufacturers.

Arrow A of Figure 5 indicates the drop down menu options from *low-level* Medical Dictionary for Regulatory Activities (MedDRA)® AE terms all the way to *system organ class*, while arrow B indicates a possible collection of low-level AE terms. Figure 6 represents the case report output from the example

Figure 1. FAERS (A) and RxFilter (B) outputs.

Figure 2. The AdverseEvents.com home page interface.

search terms linking amnesia-related AEs to atorvastatin. If a user wishes to search for a specific AE (*e.g.* amnesia), subscribers can type this term into the search bar and the system will help them find the accurate AE term and list the top drugs linked to this AE. As can be seen from the Figure 7, atorvastatin is one of the top 2 agents linked to amnesia (with 823 primary suspect reports), consistent with a recent FDA warning.[22]

Less commonly used drugs

The data handling for all drugs is the same. Figure 8 is a screenshot showing data for everolimus, which we selected as an example of a less commonly used drug. Everolimus is a cell growth inhibitor first approved by the FDA in 2009 that is used to treat advanced kidney and breast cancers as well as giant cell astrocytoma and pancreatic neuroendocrine tumor. As shown below, pyrexia, dysnea, diarrhea, anemia and cough are among the top AEs reported. This platform might be particularly useful for less commonly used drugs where rare AE signals that were not apparent in clinical trials might become apparent in post-marketing data after larger numbers of patients are exposed to them.

Quarterly summary updates of newest FAERS cases

Finally, Figure 9 is page one (of seven) from our quarterly newsletter that details RxFilter analysis of the newest FAERS case reports released by FDA.

Highlighted topics include: drugs with the most adverse events reported in the given quarter, drugs linked to serious outcomes, first AE reports on newly introduced drugs, and new AE trends associated with specific drugs.

Paid access programs provide: i) deeper levels of data analysis, ii) custom reports, iii) disproportionality analysis, iv) statistical tools, as well as access to v) individual case reports, vi) prescription volumes, and vi) full MedDRA hierarchy integration. These paid access platforms are designed to support competitive intelligence, drug development, and business strategies for pharmaceutical companies, healthcare organizations and insurers. More information can be found at: http://www.adverseevents.com/signup.php.

Manufacturer and user facility device experience

Manufacturer and user facility device experience (MAUDE) captures voluntary, clinical hospital, distributor, and manufacturer reports regarding medical device and information technology related AEs.[7] Like our platform, MAUDE allows

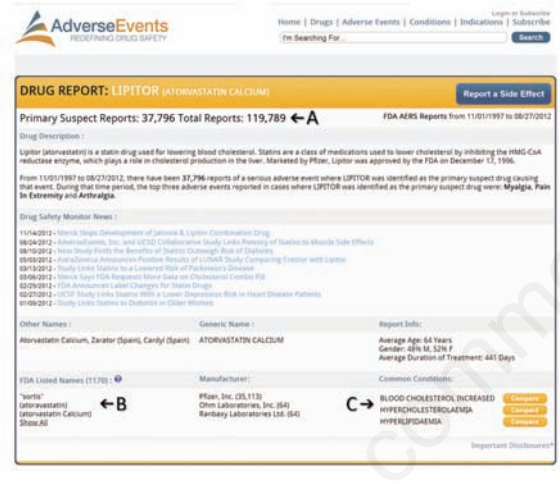

Figure 3. Screen shot: search box.

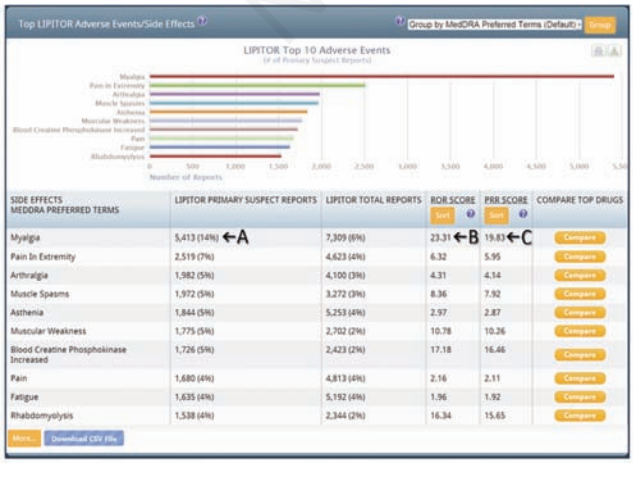

Figure 4. Screen shot listing the top AEs and both the Proportional Reporting Ratio and the Reporting Odds Ratio.

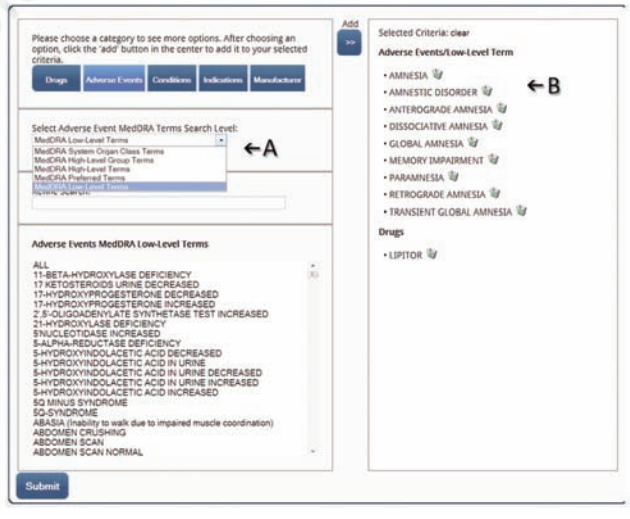

Figure 5. Screen shot showing the customized searching feature that allows paid users to query any combination of drugs, adverse events, conditions, indications, and manufacturers.

Figure 6. Screen shot: case report output from the example search terms linking amnesia-related AEs to atorvastatin.

on-line searching of data. Analyses of MAUDE's device related reports of malfunction, serious AEs, or death has yielded substantial new safety information on devices such as implantable cardioverter-defibrillators, the da Vinci surgical system, spinal cord stimulators, and even health information systems.[7] These data enable the design of safer processes and earlier identification of risks for both consumers and clinicians, and therefore support our creation of a similar platform for drugs and biologics.

Limitations

FAERS and, accordingly, RxFilter, has limitations including: duplicate reporting, masking, amplification, incomplete information, physicians might disproportionately report effects associated with newer drugs, the influence of other drugs or factors cannot be ruled out from a given case report, reporting can be influenced by publicity and marketing, lack of true incidence rates, and accurate usage data, all of which have been described elsewhere more thoroughly.[2,6,8,14,17,18] Despite such limitations, accumulating evidence from several hundred published studies of dozens of drugs confirms the utility of FAERS data mining for yielding new insights about drug safety signals.[2,9-24] Nevertheless, FAERS limitations and other qualifications noted here should always be considered when using the RxFilter. We strongly recommend that patients consult with their prescribing physician before taking any action that relates to information they find in FAERS or our platform.

Future directions

Future work will further integrate post-marketing AE databases with electronic medical records,[23,24] prescription data,[2] drug interaction databases,[23] and emerging biomarker and genomics data.[15] The development of new algorithmsto further improve the accuracy of signal detection,[2,19] and the development of user-friendly visual analytics and display techniques, will further enhance these systems. Combining AE data with chemical structures of drugs is also proving useful for target prediction and to engineer the development of novel therapies with better safety profiles. The impact of AE monitoring systems on patient outcomes, clinician treatment choices, and regulatory decision making will also be important to study further. Such studies will likely contribute to reducing the growing morbidity associated with serious drug safety events.

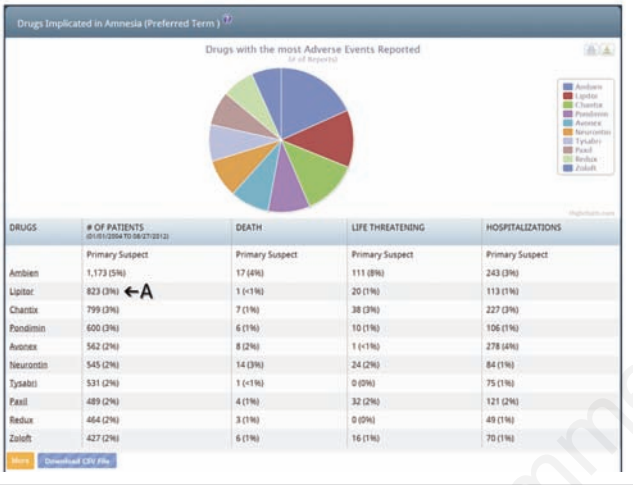

Figure 7. Screen shot. Example: atorvastatin is one of the top 2 agents linked to amnesia with 823 primary suspect reports.

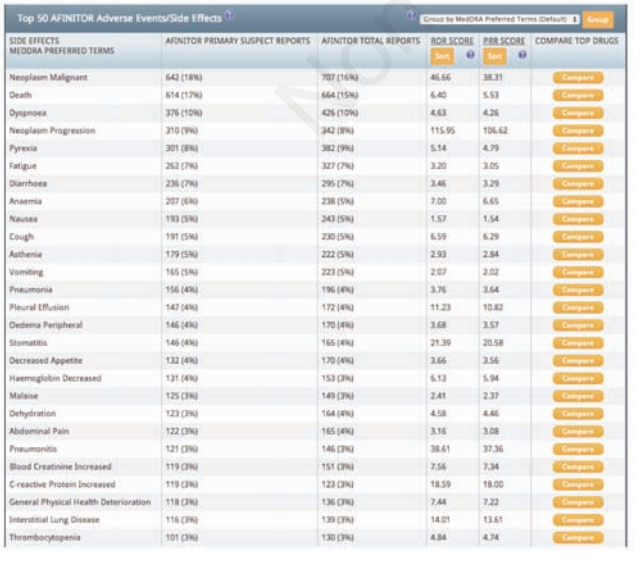

Figure 8. Screen shot showing data for everolimus, which was selected as an example of a less commonly used drug.

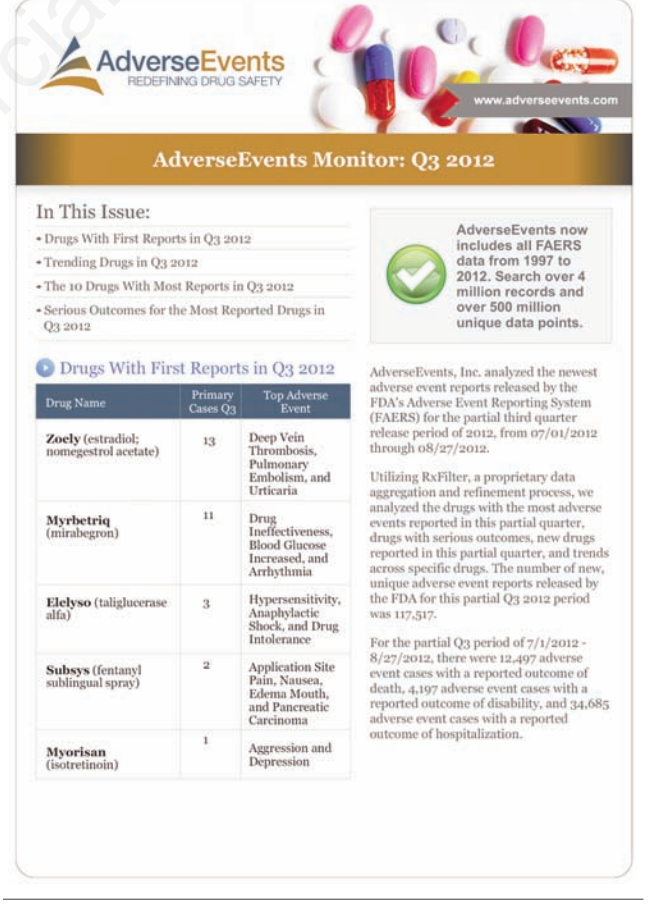

Figure 9. Page one (of seven) from the quarterly newsletter that details RxFilter analysis of the newest FAERS case reports released by FDA.

Conclusions

A central tenet of the Hippocratic oath, *primum non nocere* (first, do no harm), has remained the cornerstone of medical practice for centuries. Bringing the power of big data to regular users, such as clinicians and patients, is the logical next step in the transformation of health care to a model of shared decision making between doctors, consumers, and the system.

Note

MedDRA®, the Medical Dictionary for Regulatory Activities terminology is the international medical terminology developed under the auspices of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). The MedDRA® trademark is owned by IFPMA on behalf of ICH.

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