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Commentary

Pharmacovigilance: An Active Surveillance System to Proactively Identify Risks for Adverse Events

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Postmarketing drug safety surveillance is a challenging and vital component of contemporary medical practice. Obtaining new information about the benefits and risks of a medication should not stop after market authorization, and it has become increasingly clear that the risk profile cannot be fully elucidated via the current approval process. Highly publicized postmarketing crises, including the increased cardiovascular risk with COX-2 inhibitors,[1] heart failure with rosiglitazone,[2] increased risk of suicide in children and adolescents taking selective serotonin reuptake inhibitors (SSRIs),[3] and most recently, increased cardiovascular death with azithromycin,[4] have raised awareness of the shortcomings of the the Food and Drug Administration's (FDA's) Adverse Event Reporting System (AERS), a database for storing and analyzing safety reports.[5,6] Mining clinical databases for health outcomes provides an effective tool for mitigating these various risks, for discovering patient subpopulations that experience increased efficacy or unanticipated delayed adverse effects, and for uncovering drug interactions that typically are not examined in traditional randomized controlled trials. In this commentary, we highlight the challenges of identifying risk in the current approval process and offer steps the FDA can take to realize continuous learning and improvement as described in the Institute of Medicine's recent report on achieving best care at lower cost.[7] We believe the FDA can foster new cross-disciplinary partnerships that leverage the growing amount of electronic clinical data to design an early-warning system that targets risks associated with the areas generating the most costs. A new active surveillance system can be used not simply to identify contraindications but to educate the medical community on real risks and to target subpopulations of patients for whom certain drugs are more beneficial or more harmful.

Examination of a drug's postapproval risk profile began in 1952 when the FDA instituted voluntary reporting of adverse events pursuant to bone marrow suppression seen with chloramphenicol. Little changed with the process until 1993, when the FDA instituted MedWatch, a program for both health care professionals and the public to report adverse effects of drugs and medical devices. AERS, a database used to compile and analyze adverse events and medication error reports, was introduced in 1998. To this point, many of the methods to evaluate postapproval drug safety surveillance were dependent on the voluntary reporting of adverse events by health care practitioners, patients, and companies. This changed in September 2007 with the Food and Drug Administration Amendments Act, which gave the FDA the authority to compel manufacturers to conduct postapproval safety studies, and formalized the Risk Evaluation and Mitigation Strategies program. The most recent initiative undertaken by the FDA, Sentinel, seeks to identify safety concerns more proactively through the use of administrative claims and pharmacy dispensing data, expanding in the future to include inpatient electronic health records and registries.

A medication that is studied in 5–10 thousand patients in a controlled environment may not identify rare adverse reactions, and is likely to underrepresent the myriad variables (age, comorbidities, other medications, clinical context) that the larger population who may be exposed to the drug will have, potentially interacting with the drug and with each other. Many times, these unaccounted variables play a considerable role in the side effect profile of a given medication, and thus may alter the risk-benefit of a given pharmaceutical. Additionally, it is increasingly difficult to determine causality in patients who have multiple chronic disease states, as clinicians may ascribe the adverse drug reaction to the patient's other conditions when that is not necessarily the case. Lastly, the risk rate of adverse drug reactions often changes with increased exposure. An adverse reaction that is seen rarely during a 6-month clinical trial may, in fact, be drastically increased when patients are exposed for a more extended period of time. All of these examples represent areas in which a more informed and systematic approach to postapproval drug evaluation may yield earlier identification of medication risk and subsequent intervention to ensure the balance of risks and benefits to using the medication is maintained.

In the Sentinel initiative, the FDA is making strides in achieving a nationwide rapid-response electronic surveillance system. The FDA announced in June 2012 that the Mini-Sentinel pilot program had exceeded expectations by providing secure access to data of approximately 126 million patients across 17 data partners. Signals detected through AERS prompt the FDA to formulate safety questions for investigation by the data partners. The resulting data

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complements reports from AERS and existing surveillance tools to inform the FDA's final course of action.

It is widely accepted that AERS is efficient at detecting rare dangerous adverse events, but more common risks (eg, cardiovascular events) linked to long-term therapy are difficult to detect. AERS should be complemented, if not fully modernized, if it is to remain the first opportunity to detect adverse events. It is our opinion that the FDA should move beyond passive signal discovery to systematic, active database interrogation for safety and efficacy signals. Furthermore, class effects remain difficult to study because registries are hard to launch and maintain for entire drug classes. In addition, claims data are inherently limited by the lack of longitudinal data for many patients, insufficient coding for many confounders (eg, smoking status, body mass index, history of alcohol abuse), and difficulty connecting Medicare patients' medical data (Parts A and B) to prescription drug data with the creation of the Medicare Part D benefit in 2006 (related to the Medicare Modernization Act of 2003). To overcome these limitations, clinical databases will play an increasingly important role in active monitoring and surveillance.

To design such a system, we draw inspiration from the Institute of Medicine report, which defines 3 key questions in designing timely, targeted clinical research. First, what does the system need to know? To identify risk proactively, the application we envision will continuously run a program using a list of the most damaging or expensive adverse events (eg, death, bleeding, cardiovascular event, acute kidney injury, liver failure) as outcomes, with the following as exposures of interest: individual drugs, drug combinations, and drug–clinical context (including patient demographic, comorbidity, and clinical presentation). Confounders can be determined by applying automated feature selection algorithms using clinical databases. Second, how will the information be captured and used? We envision the FDA actively monitoring any growing safety signals until the projected risk rate surpasses a threshold that triggers a more comprehensive investigation and intervention using the Sentinel system. This approach necessitates modeling future benefit and risk profiles, given available evidence. Third, how will the resulting knowledge be organized and shared? The data must be widely available, timely, and presented in a way that provokes clinicians to change their prescribing behavior. Initiatives to disseminate and present this new process must be aligned with the priorities of health care organizations, but remain patient-centered. The FDA has the opportunity to minimize the time historically required in the science-evidence-care learning loop to disseminate new information that indicates changes in a drug's risk profile.

The greatest advantage of such an approach over passive pharmacovigilance systems, such as AERS, is that signals will be easier to pick up against background noise. Adverse events, especially those that result from drug–drug or drug–clinical context interactions, presumably are more likely to occur among the sicker and more complex patient population, making them harder to discover. To illustrate, the occurrence of an increased number of heart attacks from Vioxx was difficult to detect because Vioxx was prescribed more frequently for older patients suffering from degenerative joint disease.[8] But this cohort is also at higher risk of heart disease; when patients on Vioxx had heart attacks, providers did not necessarily link the 2 "events" because they are not uncommon in this patient cohort.

An example of active surveillance as described includes ongoing research using the multiparameter intelligent monitoring of intensive care (MIMIC-II) database, which archives data on patients admitted to one of the Beth Israel Deaconess Medical Center intensive care units (ICUs) since August 2001.[9] MIMIC-II is a free, open access ICU data set ensconced within a model for collaborative data-fueled learning.[10] There are ongoing analyses being undertaken by our group to examine the effect of long-term use of SSRIs and proton pump inhibitors on outcomes of critical illness.

Systematic clinical data mining can accelerate the speed at which adverse event "signals" can be detected. Such an active national surveillance system would allow drugs to be monitored longitudinally over their entire life cycle, providing the FDA with timely access to new information with which to evaluate a drug's risk profile. We have reached a critical junction in drug discovery and safety monitoring. Technology and methods now exist to vastly improve our ability to better elucidate the risk-benefit of pharmaceuticals, and thus better inform both clinicians and patients in treatment decisions. Now is the time to implement these processes to avoid future instances in which large numbers of patients suffer needlessly from previously undetected safety signals.

Author Disclosure Statement

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