THE ROLE OF EPIDEMIOLOGY IN DRUG SAFETY LITIGATIONS

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Drug safety is perhaps the most pressing public health issue of our time. As a result of continued scientific breakthroughs, tens of millions of Americans now regularly take medications to control chronic health problems such as hypertension, diabetes, arthritis, hyperlipidemia and depression. At the same time, the aging of the U.S. population has caused the medical profiles of patients consuming these drugs to become more complex. Not surprisingly, doctors and patients are now reporting more and more adverse events (AEs) associated with the widespread use of these drugs. As of 2005, the Food and Drug Administration's (FDA's) Adverse Events Reporting System (AERS) contained more than 3 million reports, with nearly 500,000 more being added every year.

However, as both the General Accounting Office (GAO) and the Institute of Medicine (IOM) noted in separate reports last year, few reliable studies address the safety of on-market drugs. This lack of information leaves key questions unanswered. Do many patients who take popular drugs face undue risks? Or does the increased detection of AEs simply reflect a greater awareness of the drug safety problem on the part of doctors, patients, drug companies, and policy makers?

One major obstacle to adequate definitive research is the limited nature of existing databases. FDA's MedWatch database, for example, is "numerator-based," meaning that it includes only those AEs that a physician or a patient has chosen to report. It provides no information on the total number of users of the drug in question and, therefore, no insight into the magnitude of AE "risk." FDA does have cooperative agreements with several health maintenance organizations to access their health insurance claims databases, which are "denominator-based." However, claims databases also have limitations—billing records, for example, often lack a clinical context.

The FDA has often been accused of not serving the public effectively. At times, regulators have exercised excessive caution—a stance that has hampered pharmaceutical companies from bringing new drugs to market and thus denied some patients access to new treatments. But at other times—notably in the case of Vioxx—FDA was criticized for not having acted swiftly enough to prevent harm to patients. At present, about 20 percent of all drugs receive "black-box" safety warnings and about 4 percent are withdrawn for safety reasons. With the recently passed Prescription Drug User Fee Act (PDUFA)—the act under which

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pharmaceutical companies pay user fees to the FDA for reviewing drug applications—Congress has been forced to put drug safety on the front burner. But the new PDUFA would require FDA to devote only $ 29 million, a mere 7 percent of its user-fee revenue, to postmarketing surveillance.

FLAWS IN 3 DRUG SAFETY STUDIES

While researchers typically lack access to good data sources on the safety of marketed drugs, medical journals are nevertheless replete with studies analyzing the adverse events associated with popular drugs. These studies are, in turn, widely disseminated through multiple media outlets. But what remains largely unknown to the public at large is that many of these studies—even those that have become the basis for high-profile lawsuits—are often plagued by methodological flaws. Rather than drawing on new empirical research on patients with AEs, these reports frequently apply various statistical techniques to re-analyze previously collected data (e.g., data generated during clinical trials).

On close examination informed by the science of epidemiology (that is, the study of health and illness in populations rather than individuals), it becomes apparent that in many of these influential journal articles, the alleged causal relationship between use of a given drug and the advent of AEs remains unproven. In the discussion that follows, we use an epidemiologic perspective to assess the methodologies used in three widely publicized recent medical studies. In each case, the research indicating risk suffered from a common bias, yet the author came to a definitive conclusion—one which has ultimately spread a climate of fear around the drug in question

Avandia: The Limits of Meta-analyses

In a study published on the website of *The New England Journal of Medicine* in May 2007, prominent Cleveland Clinic cardiologist Dr. Steven Nissen concluded that Avandia (rosiglitazone), a member of the class of drugs known as thiazolidinediones, which lower blood glucose by increasing insulin sensitivity, increased the risk of heart attacks by 43 percent and the risk of cardiovascular death by 64 percent (when compared to placebo or older antidiabetic regimens). The stature of both the journal and the paper's lead author, combined with the high prevalence of Type II diabetes, ensured the ensuing media attention as well as the scrutiny of regulatory and elected officials. In fact, a month later, FDA requested that a black box warning be placed on the label of on Avandia to alert physicians and patients to potential cardiac risks of the drug.

Dr. Nissen's study was based on a meta-analysis, which involves pulling together the results from multiple studies that may have conflicting results and attempting to aggregate the findings to arrive at a summary conclusion. Epidemiologists tend to regard meta-analysis with skepticism for several reasons. First, the overall quality of a meta-analysis ultimately depends on the soundness of the underlying studies; if even just a couple of these prior studies have serious flaws—a fact which often is not known—the results of the meta-analysis may not be valid. Second, the decision regarding which studies to include or exclude often reflects bias. For example, meta-analyses that predominantly include published studies may suffer from publication bias, as published studies are more likely to show "positive" associations (i.e., increased risks). Third, meta-analyses may also mask important differences across individual studies, and the large number of subjects may lead to results that appear more conclusive than they really are.

In his meta-analysis, Dr. Nissen used summary data from 42 separate trials comparing Avandia with either a placebo or active comparators. These studies all focused on the overall efficacy and safety of Avandia rather than on its particular cardiovascular side effects. Though Dr. Nissen attempted to include both published and unpublished studies, he ended up excluding 74 of the 116 studies originally screened. Most of the excluded studies failed to meet pre-defined exclusion criteria, though six were excluded because they did not report any myocardial infarctions. By excluding these trials with zero myocardial infarction events, Dr. Nissen may well have introduced a selection bias and skewed the association between Avandia and cardiovascular adverse events.

In addition to publication bias, Dr. Nissen's meta-analysis also suffers from other methodological flaws. The clinical trials included in Dr. Nissen's analysis are heterogeneous, including diverse comparators and disease indications, which make the inferences from the meta-analysis difficult to interpret (i.e., the results may vary based on different sub-populations). Another limitation, and one that has been noted by the authors, is that they did not have access to the original source data from the individual studies, thus precluding them from using patient-level (rather than study-level) time-to-event analysis. This kind of analysis, which considers not only the number of patients in a study, but also the length of time they are observed, allows research-

ers to discern whether a higher number of adverse events is due to greater risk, or simply to the fact that patients receiving the drug were observed for longer periods of time.

Despite the biases associated with meta-analyses in general, and Dr. Nissen's meta-analysis in particular, this study has already had a major impact. The black-box warning has generated confusion and fear in the medical community and dissuaded patients from joining or continuing participation in clinical trials of Avandia geared specifically at evaluating the cardiovascular effects of the drug, such as the ongoing RECORD trial. Application of FDA's toughest safety warning to Avandia is affecting manufacturer GlaxoSmithKline as well, with new prescriptions for the drug falling by about 40 percent since May 2007.

Zelnorm: Problems with Pooled Analysis

In March 2007, Novartis Pharmaceuticals complied with an FDA request to voluntarily cease U.S. marketing of Zelnorm (tegaserod), a drug used to treat constipation related to irritable bowel syndrome. The controversy stemmed from the findings of a pooled analysis of 29 clinical trials performed by Novartis after a routine request from a Swiss regulatory agency. The pooled analysis found that 13 out of 11,614 patients treated with Zelnorm experienced cardiovascular events such as heart attack, stroke or angina (0.11 percent), while one out of 7,031 placebo-treated patients experienced such an event (0.01 percent). Though the absolute risks of these cardiovascular events are undeniably small, the divergence in the observed risk between Zelnorm- and placebo-treated patients was enough to persuade regulators to call for pulling the product from the U.S. market.

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However, Novartis reported that all of the patients in the pooled analysis who experienced a cardiovascular event had pre-existing cardiovascular disease and/or risk factors. Thus, it is difficult to determine whether the higher risk cardiovascular events observed in the Zelnorm group are due to the product or to a confounding variable—in this case, the fact that those patients had a greater predisposition to these types of events in the first place.

Individual clinical trials typically are randomized to avoid confounding. If assignment to the treatment or placebo arm of a study is truly random, one would expect that, on average, the two groups of patients would look similar with respect to various baseline characteristics, including predisposition to cardiovascular events. Thus, randomization allows investigators to say with greater confidence that any observed differences between the two groups are attributable to the drug itself rather than other factors.

However, in a pooled analysis of multiple clinical trials, such as that performed by Novartis, true randomization no longer exists. While patients were randomly assigned *within* individual studies, they were not randomly assigned *across* studies; i.e., a patient may have been randomly assigned to receive Zelnorm in Study X, however he or she was not randomly assigned to participate in Study X as opposed to Study Y. In the absence of randomization, researchers must be careful to adjust for potential confounding factors before drawing firm conclusions about drug efficacy or safety. To the extent that this was not properly done in this pooled analysis of these clinical trials, both Novartis and the patients who depend on Zelnorm for symptom relief for irritable bowel syndrome may have been unnecessarily harmed.

Surprisingly, if the pooled methodology used in the Zelnorm analysis were applied to Dr. Nissen's Avandia study, his meta-analysis would have shown that Avandia actually protects patients from cardiovascular events. Using this technique, Avandia would have been associated with a reduced myocardial infarction risk with an odds ratio of 0.94, rather than the reported 1.43. These diametrically contrasting conclusions about the same drug highlight the importance of employing appropriate epidemiological and statistical analysis when handling vast amounts of data from diverse sources.

Prempro: Ecologic Studies Cannot Prove Causality

In 2002, the Women's Health Initiative (WHI), a randomized trial investigating the effects of commonly

used hormone replacement therapy (HRT), was halted early after investigators found an increased incidence of breast cancer that was not offset by the anticipated chronic disease benefits in the population that was studied. The preliminary finding for breast cancer was that women receiving combined estrogen and progestin therapy were 1.26 times more likely to be diagnosed with breast cancer than women receiving placebo after an average follow-up of 5.2 years. Prescriptions for Prempro, a fixed dose combination of estrogen and progestin, marketed by Wyeth Pharmaceuticals, plummeted following the publicity generated by the announcement of the preliminary study results. Data regarding the potential connection between HRT and breast cancer became news again last fall when researchers from the MD Anderson Cancer Center in Houston, Texas (Ravdin et al), presented data showing a large decline in reported breast cancer incidence between 2002 and 2003, (after millions of women discontinued HRT following publication of the WHI findings). The study, later published in *The New England Journal of Medicine,* garnered much media attention and led to claims that the product caused breast cancer.

The study by Ravdin and his colleagues that reinvigorated the debate over the association between hormone replacement therapy and breast cancer is known in epidemiology as an "ecologic" study. In this type of study, the units of observation are groups of people rather than individuals. An ecologic study evaluates the temporal incidence trends of two factors, for example A versus B, and makes a correlational assessment between them. If both factors A and B correlate in their trends, an association between the two might exist. However, ecologic studies are best used as a way to generate hypotheses since they cannot prove a *causal* relationship between the two factors. In fact, this study design is typically considered one of the least reliable of all non-experimental observational study designs; in1981, renowned epidemiologists Sir Richard Doll and Richard Peto published an influential paper that banished ecologic studies from serious consideration as epidemiologic evidence.

In the study by Ravdin and colleagues, *overall* breast cancer incidence declined soon after *overall* HRT use declined. The study did not investigate HRT exposure and breast cancer outcomes for individual women. In fact, it could be the case that breast cancer rates stayed the same among women who stopped taking HRT, but fell dramatically for other women, or that other confounding factors are at work. Without patient-level analysis there is no definitive way of knowing. This tendency to ascribe group-level associations to individuals is known as the ecologic fallacy. In fact, a closer look at the data reveals that breast cancer incidence declined even among specific age groups of women unlikely to be receiving HRT for menopausal symptoms (e.g., those aged 45 to 49, and those aged 70 and older), suggesting that something other than HRT was playing a significant role in the observed trends. Though the researchers acknowledge the limitations of their analysis, the casual reader is left with the strong impression of causality.

Adding to the complexity, large government-sponsored randomized clinical trials and large observational studies have at times generated contradictory findings. For example, in July 2002, the WHI reported preliminary data suggesting that Prempro was associated with a small increase in heart attack risk. This appeared to be completely at odds with the findings of the Nurses' Health Study, a large observational epidemiology effort headed by researchers at Harvard Medical School and Harvard School of Public Health. Other examples of conflicting epidemiological results are not difficult to find. And since drug side effects are experienced by a minority of patients, compared to the therapeutic efficacy experienced by a majority, they are often idiosyncratic, confounded and idiopathic (unknown etiology) in nature. The observed risk of a patient suffering from a drug side effect such as cardiotoxicity, for example, could well be comparable to the baseline cardiovascular risk for that patient.

Conclusion

In the coming years, as the Baby Boom generation ages, the number of AEs related to prescription drug use will continue to increase, with a similar upswing in mass tort litigation likely to follow. And stakeholders—from patients and their families to regulators, manufacturers and attorneys representing both sides—may continue to encounter safety studies that must, at the very least, be interpreted with caution. But ideally, in the not-too-distant future, researchers will be able to examine individual patient medical records to determine whether the AE may have been due to the drug or to an underlying medical condition or other cause, such as the individual's genetic make-up. Further exploration is clearly required, on a scale that will ensure reliable investigations of drug safety issues in the future.