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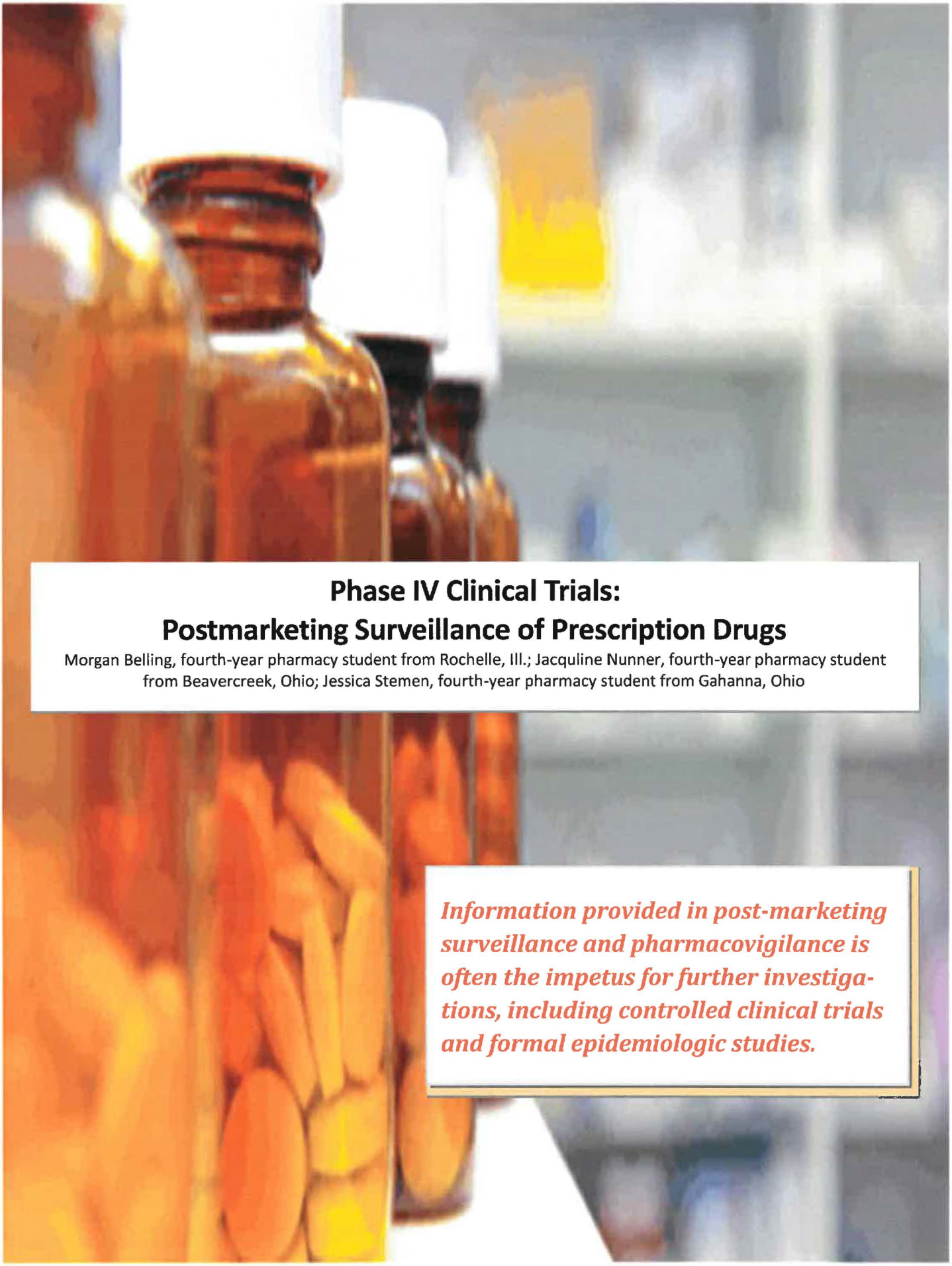

Phase IV Clinical Trials: Postmarketing Surveillance of Prescription Drugs

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Introduction

When a newly developed drug is approved by a regulatory body for initial licensure, researchers have already conducted extensive testing and evaluation of adverse events and risks associated with the medication. However, due to constraints involving the patient population of the testing group, it is possible that additional or rare side effects have yet to be seen. For this reason, drugs are subject to phase IV trials after approval for patient use. Phase IV clinical trials, which include postmarketing surveillance, are observational studies performed on U.S. Food and Drug Administration (FDA)-approved drugs primarily to identify adverse reactions not manifested during phases I, II, and III of the drug development process. Also assessed is drug effectiveness in real world therapeutic use, which may be markedly dissimilar to restricted clinical trials.[1] Because clinical trials may not have the statistical power to reveal these rare occurrences nor the temporal scope to detect long-latent events, it is imperative that drug manufacturers, health care professionals, and consumers themselves submit reports of adverse events. Adverse drug reaction (ADR) reports may be submitted via the FDA's MedWatch program, designed for spontaneous and voluntary reporting of serious adverse drug reactions (Table 1).

Table 1. Reporting an adverse event to the FDA[9]

- Online reporting form
  - MedWatch: the FDA Safety Information and Adverse Event Reporting System
    - Go to www.fda.gov/Safety/MedWatch/default.htm
    - Under the "Resources for You" side menu, select "Report a Serious Medical Product Problem Online"
    - Proceed to fill out the MedWatch Online Voluntary Submission Form 3500, including as much pertinent information as possible
- Download a copy of the paper form and either fax it to 1-800-FDA-0178 or mail it using the postage-paid addressed form. (Send only one page plus any continuation pages-do not send instruction pages.)
- Call FDA at 1-800-FDA-1088 to report by telephone

"Pharmacovigilance," or the process of broadening known information about a drug by way of detection, analysis, and prevention of these events, is an evolving science with novel techniques in development.[2,3] Information provided in postmarketing surveillance and pharmacovigilance is often the impetus for further investigations, including controlled clinical trials and formal epidemiologic studies.[4]

Therapeutic Modifications: What Role does Postmarketing Surveillance Play?

The majority of postmarketing requirements mandated by the FDA are categorized into one of four areas: general reporting requirements, current good manufacturing practices, phase IV clinical study commitments, and adverse drug event (AE) reporting requirements. In regard to the latter, New Drug Application (NDA) holders and "nonapplicants" (any manufacturer, packer, or distributor included on the pharmaceutical product's label) have ADR reporting responsibilities. [4]As per the FDA's Code of Federal Regulations, NDA holders must "promptly review all adverse drug experience information obtained or otherwise received by the applicant from any source, foreign or domestic, including information derived from commercial marketing experience, postmarketing clinical investigations, postmarketing epidemiological/surveillance studies, reports in the scientific literature, and unpublished scientific papers."[5]

Uncovering Simvastatin-associated Myopathy

As a direct result of these obligations, postmarketing surveillance has been an integral tool in the discovery of dangerous interactions between various drugs. For example, a significant interaction between Zocor® (simvastatin) and Lopid® (gemfibrozil) was uncovered during a 2010 double-blind, randomized crossover study that was conducted as a result of several case reports detailing myopathy in patients concurrently using simvastatin and gemfibrozil.[6] This study showed that plasma concentrations of active simvastatin were increased by concomitant gemfibrozil treatment. Prior to this study, no information was available regarding if or how gemfibrozil affected the pharmacokinetics of simvastatin. The area under the curve (AUC) of simvastatin acid was 185 percent larger with the co-administration of gemfibrozil than with placebo (P<0.001). Researchers concluded that because gemfibrozil significantly increased the concentration of simvastatin acid, the pharmacokinetics of the drugs impact the increased risk of myopathy.

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On June 8, 2011, the FDA advised that simvastatin 80 mg should not be used as a starting dose of the medication.[7] This decision was based on a review of the seven-year Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH) trial. The results of SEARCH augmented the researchers' decision that simvastatin 80 mg was more likely to induce myopathy than simvastatin 20 mg. Additionally, FDA officials assessed postmarketing surveillance information contained in the agency's Adverse Event Reporting System (AERS) database which supported the conclusions of the SEARCH trial.

As evidenced by this example of postmarketing surveillance, the process for identifying serious drug interactions, as well as altering dosage recommendations, may demand copious amounts of time and additional studies. Case reports and subsequent trials which indicated that simvastatin bore an increased risk of myopathy when used in combination with certain drugs were published in the late 1990s into 2000. More than a decade later, in 2011, the FDA made a recommendation to limit the use of simvastatin 80 mg due to the significant risk of myopathy. The appropriate utilization of postmarketing surveillance has allowed health care professionals and patients to be cognizant of potentially detrimental interactions and side effects of simvastatin and many other medications when taken under specific therapeutic conditions.

Pharmacists' Unique Experience and Perspective

To gain insight into further practical application of ADR monitoring and assessment, we interviewed two pharmacists working in the postmarketing surveillance sector. The interviews were conducted independently of one another and later intercalated in the format below. For over 12 years, Kathleen Rand, PharmD, has worked in pharmacovigilance and safety surveillance and is currently product manager and senior scientist of global safety surveillance and analysis at Procter and Gamble. Christina Cognata Smith, PharmD, MBA, has held medical leadership positions at Johnson and Johnson and Bristol-Myers Squibb; she is currently executive director of medical affairs at Medicis Pharmaceutical Corporation.

Q: By whom are the majority of ADRs reported? After received, how is the supplied information processed?

KR: ADRs may be reported by anyone—health care professionals, physicians, nurses, the person who experienced the event, or his or her family or friend. Because the reporter may not necessarily have a medical background, it can be very challenging to obtain a medically meaningful report. To obtain additional information, a medical release may be requested to obtain medical records if necessary. The report is entered into our safety database after an initial screening. Depending on the seriousness of the report, it may be expedited to the FDA.

CCS: ADRs are reported by non-health care professionals and health care professionals. As an employee within the industry, when I become aware of an ADR for one of my company's drug products, I am required to gather the appropriate information and report the event to the Pharmacovigilance Department immediately. The case is reviewed by drug safety experts in the Pharmacovigilance Department and additional information is gathered, as necessary, for case and trend analysis. In my company, the Pharmacovigilance Department oversees all drug safety reports and is responsible for ensuring that the company reports adverse events to the FDA as required by federal regulations.

Q: How has postmarketing surveillance developed throughout your career?

KR: Postmarketing surveillance has evolved over the past 12 years with increasing use of technology in the reporting process; it is certainly more "real time." Additionally, surveillance is more rigorous and is focused on detecting and preventing safety issues. The postmarketing surveillance team is comprised of members with varied backgrounds: physicians, pharmacists, nurses, epidemiologists, statisticians, and data entry personnel.

CCS: The FDA is evolving how postmarketing surveillance reports are collected and used in an effort to better inform patients and health care providers about the safe and appropriate use of medicines. Because many spontaneous ADR reports do not result in a definitive conclusion about a drug's safety, postmarketing surveillance frequently serves as a foundation for further investigation via epidemiologic or clinical research to determine a drug's relationship to an ADR. Advances in information technology, such as the electronic medical record, are providing additional information and resources to support postmarketing surveillance programs and facilitating a shift to include more active surveillance methodologies.

Q: In what ways can a pharmacist practicing clinically contribute to accurate postmarketing data?

KR: The FDA's MedWatch reports are an important tool. A pharmacist can also call the manufacturer and provide as much information about the event as possible. Despite the time constraints, a pharmacist can provide high quality data.

CCS: Pharmacists are an important part of the postmarketing surveillance process due to their expertise in pharmacology and patient care role. Pharmacists in all health care settings not only play a key role in collecting and reporting complete and accurate information when presented with an ADR, but can also play a key role in patient counseling as it relates to the ADR.

Possibilities for Future Advancement: the Sentinel Initiative

With spontaneous and voluntary reporting as the current basis for documenting ADRs, under-reporting and a dearth of complete information denote challenges in developing an accurate assessment of such occurrences. To transition to the implementation of a signal-based active surveillance program, the purpose of which is to "ascertain completely the number of adverse events" associated with a medical product, the FDA has created the Sentinel Initiative.[8] Launched in 2008, the Sentinel Initiative is a system designed to build and implement a national electronic system for monitoring the safety of FDA-approved drugs and other medical products. In this system, electronic data regarding drug safety is collected from a number of participating data partners. These health information sources consist of academic medical centers, health care practices, health insurance companies, and regulatory industry, including Weill Cornell Medical College, Cincinnati Children's Hospital Medical Center, Humana, and Kaiser Permanente Center for Effectiveness and Safety Research. The collaboration features a distributed system in which data are not consolidated, but rather remain in their secure local environments. This system seeks to enhance the passive collection of voluntarily reported information by monitoring these databases in order to proactively discover potential adverse events.

...the Sentinel Initiative provides a representative picture of the range of patients using a drug, biologic, vaccine, or medical product while still allowing clinicians to focus on a particular data set of interest.

Through the Mini Sentinel pilot program, a systematic format is being tested for large-scale applications. The process starts with the FDA submitting a safety inquiry based on its analysis of the database to a Coordinating Center. The Coordinating Center will send the question to data partners, who will assess the safety signal in their own databases. Following this evaluation, the data partners' responses will consist of only summaries of results in an effort to protect patient privacy. The Coordinating Center then aggregates the submitted results and relays the information to the FDA, which then disseminates the findings to the health care community. In this way, the Sentinel Initiative provides a representative picture of the range of patients using a drug, biologic, vaccine, or medical product while still allowing clinicians to focus on a particular data set of interest. Since the data is collected directly, it can be evaluated as being as credible as possible in the practical setting. In an August 2011 report to Congress, the Department of Health and Human Services and the FDA announced that safety data from 25 million patients had been conglomerated, with that number expected to increase to 100 million by July 2012. Although encouraging progress has been achieved, technological, financial and security challenges, especially in regard to protection of patient privacy, mandate extensive collaboration and further study to determine the most effective and accurate novel postmarketing surveillance methodology. Following total implementation of the Sentinel Initiative, the field of pharmacovigilance will continue to enhance drug development and the methods by which adverse drug events are reported and evaluated.

Conclusion

Postmarketing surveillance plays an integral role in the evidence-based approach to drug development and therapy. With technological advancements that allow for greater facility of reporting, as well as analysis-driven databases, postmarketing surveillance is an important tool for meeting the ever increasing standards for optimal patient care. Pharmacists, as medication experts, will continue to foster innovative approaches to the challenges presented by pharmacovigilance.

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