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Improving Drug Safety: The Importance of Postmarketing Drug Surveillance

Introduction

Postmarketing drug surveillance refers to the monitoring of drugs once they reach the market after clinical trials. It is a critical part of the effort to ensure that drugs are safe and effective. Clinical trials, which are used to test the safety and efficacy of new drugs, are, by their very nature, limited. They generally involve evaluating drugs on a small number of people over a limited time frame under controlled conditions. Postmarketing drug surveillance evaluates drugs taken by a wide variety of people under a wide range of circumstances over an extended period of time. Such surveillance, given its more expansive evaluation, is much more likely to detect any undiscovered effects, positive and negative, that may be associated with a drug.

The Food and Drug Administration (FDA), the primary entity responsible for monitoring postmarketing drug surveillance, relies mainly on reports generated by pharmaceutical companies, physicians, and ongoing studies of drugs once they reach the marketplace. This approach has been helpful in detecting both adverse drug events as well as unintended benefits; however, a more systematic one may be more effective. For example, better surveillance may have discovered the problems with the statin Baycol earlier and reduced the number of people who developed severe and deadly side effects. Conversely, postmarketing studies have also recently provided some indications that statins may have a beneficial effect on a variety of conditions, including cancer and Alzheimer's disease.

Nevertheless, the current system is fragmented and relies to a large extent on voluntary reporting. Given the ever increasing use of prescription drugs, coupled with an aging population, a streamlined and integrated postmarketing drug surveillance system would better detect any unintended effects. This issue brief discusses the importance of postmarketing drug surveillance and suggests one way that the current system can be revamped to benefit the federal government, pharmaceutical companies, and, most importantly, the patients who depend on drugs to be safe and effective.

Improving Drug Safety: The Importance of Postmarketing Drug Surveillance

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Postmarketing drug surveillance monitors the safety of medicines being used by patients upon prescription by a medical provider. It is the phase four of a clinical trial and takes place after the FDA has approved a drug for marketing. A drug is approved after it has passed through three phases of clinical trials, which are designed to test safety and efficacy. These first three phases usually total about 3,000 patients and are generally conducted under strictly defined conditions in a limited time frame. The limited number of people used in clinical trials is due to time and cost constraints of developing a drug. The Tufts Center for the Study of Drug Development estimates that the average cost of bringing one new medicine to market is \$802 million¹ and that it takes an average of 12 to 15 years to discover and develop a new medicine.² Other studies estimate the costs to be even higher.

Phase four of a clinical trial is key to evaluating the safety and efficacy of a drug in real-world conditions over an extended period of time. The FDA is primarily responsible for postmarketing surveillance of drugs in the United States through its MedWatch program. This entails gathering information from the pharmaceutical industry, medical providers, and patients. Pharmaceutical companies operate systems to monitor their drugs for adverse reactions and provide periodic postmarket reports to the FDA. They also report whenever a serious adverse drug reaction is detected. The medical community also plays a voluntary role in reporting adverse drug reactions. In addition, the federal government, pharmaceutical companies, or universities often conduct ongoing studies after marketing to gather

additional information or to explore further any negative drug reactions. However, although much has been done to enhance postmarketing surveillance, the current system remains fragmented and limited. Given the growing importance of prescription drugs, a comprehensive, systematic reporting and monitoring program would greatly enhance our nation's capacity to increase drug safety.

The Importance of Postmarketing Drug Surveillance

The use of prescription drugs is increasing every year. In 2000 in the United States, more than 170 million people filled 2.2 billion prescriptions, accounting for over \$100 billion in expenditures.³ Given the scope of use, postmarketing surveillance is critical in tracking the real-world effects of prescription drugs. As noted earlier, clinical trials are limited by time and cost constraints and therefore may fail to detect adverse or beneficial reactions among users. Even the largest and most well-designed clinical trials cannot uncover every problem that may be revealed once a product is widely used. For example, to detect the possibility of a severe drug-induced liver injury, which is the most frequent reason a drug is removed from the market after approval, a trial would require upwards of 30,000 people. Postmarketing drug surveillance is therefore critical to ensuring that a medication is safe for use by a wide variety of people (i.e., varying ages, genders, races, lifestyles, etc.) under a wide range of circumstances (i.e., people with comorbidities or on multiple drugs, with varying nutritional status, taking over-the-counter supplements, etc.). Adverse drug reac-

tions are a major reason for the importance of post-marketing drug surveillance, and although the current system is focused on detecting adverse drug reactions, it is not comprehensive. Most people consider adverse drug reactions to be underreported.

There remain significant problems of underrepresentation in clinical trials, especially of older people, who tend to use the most drugs and are also more liable to suffer from adverse drug reactions.⁴ Unfortunately, too little is known about the effects of drugs on older people, and it has been estimated that as many as 35 percent of people over 65 experience adverse drug reactions each year.⁵ Postmarketing surveillance is therefore critical to detecting any negative effects in this population and intervening promptly to reduce such situations.

Often little is known about the effects of drugs in younger populations. For example, there has been much concern about the use of some antidepressants in children as young as age 3. A recent study has found that such drugs are barely effective in this population.⁶ Moreover, since individuals of this age are not commonly chosen to participate in clinical trials, very little is known about the effects of such drugs on the developing brain. However, there is strong evidence that they play a role in suicide among adolescents. In fact, British regulators have advised physicians to stop prescribing almost all antidepressants to children under 18.

Another component involves the use of drugs over an extended period of time. Since most clinical trials are for a limited time period, information regarding long-term effects is scarce. Indeed, some physicians are worried about the long-term effects of cholesterol-lowering statins on muscles. Thorough, ongoing surveillance systems are therefore critical in responding to these concerns.

Conversely, it should also be noted that clinical trials may not detect unforeseen benefits of a new drug. Statins are a good example. Developed to lower cholesterol, they may also have beneficial effects, some believe, in forestalling some cancers, Alzheimer's disease, multiple sclerosis, and other conditions. Another factor in the importance of postmarketing

surveillance stems from efforts to expedite the drug approval process. In an effort to bring potentially life-saving drugs to the market sooner while also reducing the costs of drug development, the FDA has been working to expedite drug approvals. Former Commissioner Mark McClellan outlined a series of steps designed to improve the prescription drug approval process, including efforts to reduce the number of new drugs that must be reviewed more than one time; review the costs of agency regulations, conducting an external independent review of the FDA's entire approval process; and other measures. While these efforts are laudable, they simultaneously enhance the importance of postmarketing surveillance. If a drug reaches the market more quickly, again regardless of the soundness of the clinical trials, less may be known about its potential effects. Thus the need for continued review of these drugs is critical. Indeed, McClellan recognized this need and made learning more about benefits and side effects of drugs after approval a priority for the FDA.

Other important reasons for expanding and enhancing postmarketing drug surveillance include:

- **Unapproved or off-label usage:** This routine practice by physicians of prescribing drugs to patients to treat conditions for which the drug was not tested can be very useful, but keeping track of the effects of this practice is critical.
- **Increased use of international clinical trials:** Some pharmaceutical companies have increased the number of clinical trials conducted abroad in order to reduce costs. This has raised concerns about the stringency of trial procedures, appropriate documentation of outcomes, and other matters critical to a well-conducted clinical trial. Although the legitimacy of these claims is not well understood, postmarketing surveillance is critical to compensating for potential flaws in these international clinical trials. Of course, eliminating the practice altogether would be the best alternative.
- **Reduced conflicts of interest in academia:** There has been concern about the relationships between academic researchers, universities, and pharmaceutical companies when the pharmaceuti-

cal industry sponsors studies. One comprehensive study of potential conflicts of interest in the biomedical field found that industry-sponsored research is more likely to have results more favorable to the company that funded the research.⁷ A national postmarketing surveillance system could help eliminate the conflicts of interest that can arise with specific research endeavors.

Recommendations

One way to enhance a postmarketing surveillance system would be to establish regional centers to be responsible for monitoring new drugs that come on the market. The Department of Health and Human Services (DHHS) is currently organized into ten regions in the United States. A system funded by the government and the pharmaceutical industry that selects an academic medical center in each region through a competitive process to be responsible for monitoring prescription drug use would help ensure a more integrated postmarketing surveillance system. The National Institutes of Health (NIH), alone or in collaboration with the FDA, could plan the coordination and carry out the reviewing process. This is not an entirely new concept; indeed Raymond Woosley, a research physician at Georgetown University, proposed years ago that 15 centers of education and research be created to test the safety, efficacy, and cost-effectiveness of prescription drugs.

There is an effort under way that is a step in this direction. The Agency for Healthcare Research and Quality (AHRQ) operates the Centers for Education and Research on Therapeutics (CERTs) demonstration program, which is intended to conduct research and provide education to advance the optimal use of therapeutics such as prescription drugs. In existence since 1999, its three goals are to increase awareness of both the uses and risks of new drugs; to provide clinical information to patients, health care providers, and other components of the health care system; and to improve quality while reducing the cost of care. CERTs consists of seven research centers and a coordinating center, as well as partnerships with various public and private organizations. This program is still very small, however, receiving less than \$10 million per year. Nevertheless, it serves as a

model for how an effective postmarketing drug surveillance system can be established.

Another pioneering effort is the Boston Collaborative Drug Surveillance Program (BCDSP) at Boston University, under the leadership of Hershel Jick, M.D. In operation since 1967, BCDSP conducts epidemiological research to quantify the potential adverse effects of prescription drugs using large automated patient databases. Recently, it has been using medical record data from the United Kingdom for research purposes as the National Health Service has been using electronic medical records for years. The BCDSP exemplifies the effective role that academic health centers can play in postmarketing drug surveillance.

There are promising indications that postmarketing surveillance is becoming a higher priority. The Prescription Drug User Fee Act, which is intended to speed up the drug review and approval process by providing for user fees paid by the pharmaceutical industry to support such activities, recently was renewed with a provision that a larger portion of such fees be used for postmarketing activities. Moreover, through its recent Roadmap initiative, the NIH has indicated an interest in developing a national network for clinical trials that uses standard data protocols. This will help save resources in designing trials and facilitate the comparison of data across trials. Such an effort would presumably benefit phase four trials. In addition, a key aspect of any postmarketing drug surveillance involves the use of electronic medical records. Given the growing use of such records in the United States, coupled with the Bush administration's recent call for the creation of a nationwide electronic medical records system in the next ten years, the idea of a comprehensive, integrated postmarketing surveillance is more feasible.

Conclusion

All parties involved in postmarketing surveillance would benefit from an expanded, systematic postmarketing system. The federal government would be establishing a streamlined and integrated system to detect drug reactions and better ensure the safety of drugs. The pharmaceutical industry, which already

supports numerous studies to evaluate the safety of drugs, would benefit from the potential cost savings of a common, standardized system⁸ as well as being less susceptible to liability claims. Physicians, hospitals, and other health care providers would benefit from the additional information about drug safety and efficacy that such a system would entail. Lastly, and most importantly, patients would benefit from the improved quality of care that would result from more comprehensive information about drug safety and efficacy.

Afterword

By Michael K. Gusmano, Ph.D.

Prescription drugs are a powerful tool for combating disease and preserving health, but there are risks associated with pharmaceuticals that cannot be ignored. A 1998 report in the *Journal of the American Medical Association*, for example, estimated that 106,000 fatal drug reactions occur each year. The expanding use of these drugs demands a comprehensive system to track adverse side effects, investigate the consequences of long-term use, and compare the relative efficacy of alternative drugs. As explained in this issue brief, such a system does not exist. At a time when Congress should be expanding the capacity of the Food and Drug Administration to engage in post-marketing surveillance of drugs, it has instead reduced the agency's budget and undermined its ability to track drugs after they are approved for marketing. As a result, the United States continues to rely on a disjointed, and largely voluntary, reporting system. Recently reported health problems associated with popular Cox-2 inhibitors suggest that this approach is not serving us well.

Our failure to develop an effective national system of postmarketing surveillance, combined with efforts to speed up the initial drug approval process and the exclusion of children and older adults from clinical trials, creates a risky situation for the public, the government, health care providers and the pharmaceutical industry.

Former Representative Billy Tauzin, now president of the Pharmaceutical Research and Manufacturers

of America, stated that "it [the pharmaceutical industry] has to earn the trust and confidence of consumers again." Working with the president and Congress to establish a credible and effective system of postmarketing surveillance would be a good step in that direction.

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The organization is part of a multinational research and education consortium, which includes centers in the United States, Japan, Great Britain, France, and the Dominican Republic. These centers work both autonomously and collaboratively to study how greater life expectancy and increased proportions of older people impact nations around the world.

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