Postmarketing adverse drug reactions

A duty to report?

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Summary

Physicians play an important role in recognizing and reporting suspected adverse drug reactions (ADRs) to the Food and Drug Administration (FDA). Physicians can report suspected ADRs directly to the FDA via its MedWatch program, by contacting the manufacturer of the drug, and by publishing case reports. While this takes time, physicians have an ethical obligation to participate in recognizing and reporting ADR.

The Food and Drug Administration (FDA) approved fingolimod, a sphingosine-1-phosphate receptor modulator that inhibits lymphocyte migration from lymph nodes, for the treatment of relapsing multiple sclerosis (MS) in September 2012. Clinical trials established that transient bradycardia could occur in patients treated with fingolimod, with maximal onset 6 hours after the first dose. Serious bradycardia and delayed heart effects were not known to occur. As a result, the FDA initially only mandated medical supervision during the initial 6 hours after a patient's first treatment with fingolimod but did not recommend cardiac monitoring beyond 6 hours.

Vignette

In January 2011, a 20-year-old man experienced an episode of bradycardia and asystole 21 hours following his first dose of fingolimod while hospitalized for a MS relapse. Inpatient telemetry captured the patient's delayed symptomatic bradycardia and transient (7.5-second) asystole, before spontaneous recovery. The patient was concomitantly taking risperidone, which can cause cardiac conduction abnormalities. The delayed, symptomatic bradycardia and transient asystole prompted the physician caring for the patient to report this adverse

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drug reaction (ADR) to the FDA using the MedWatch system and to notify Novartis, which markets fingolimod. Novartis representatives gathered information and reported the event to the FDA. Finally, the physician and a colleague submitted a manuscript to *Multiple Sclerosis* describing the ADR in March 2011 and the case report was published in November 2011.¹ This case, along with reports of sudden death associated with fingolimod use, led the FDA to require a package insert change in May 2012.² These changes included more intense monitoring of patients taking their first dose and a list of cardiac conditions and medications that are contraindications to using fingolimod.

Adverse drug reactions

Deciding whether or not to prescribe a medication for a patient requires weighing benefits and risks. We base these decisions on our personal experience with the drug but also rely upon what is known about the efficacy of the drug and the ADRs that occurred during the clinical trials that supported FDA approval of the drug. While the benefits of a drug are generally well-defined by the end of clinical trials—trials are designed to determine efficacy—the nature and extent of ADRs are usually not fully apparent until after a drug reaches clinical use, as the late cardiac effects of fingolimod demonstrate. This makes the clinician's assessment of benefits and risks problematic, especially for drugs that the FDA has recently approved.

At the time a new drug is released by the FDA, ADR risks are only partially defined for two reasons. First, randomized controlled trials leading to FDA approval involve a limited number of subjects who are exposed to the drug for a relatively short period of time. Second, subjects included in the trials are a select group, with pediatric or older people, people with significant comorbidities, and those taking medications that might interact with the study drug often being excluded. Once a drug is released, a larger number and more diverse group of people will take the drug, and often for much longer periods of time. As a result, new, rare, but significant ADRs may be detected in the postmarketing period once a larger group of people is exposed to the drug. In addition, the risk of a known ADR may be determined to be higher than previously assumed as the drug is used in a more diverse patient population. Notable recent examples of ADRs that first appeared in the postmarketing period include fenfluramine and pulmonary hypertension, vigabatrin and visual field defects, and tolcapone and liver toxicity.³ A recent example of increased risk of a known ADR determined after drug approval is the occurrence of symptomatic cardiac toxicity in some patients taking fingolimod.¹ A more accurate assessment of the risks of ADRs thus only becomes possible once a drug is used in a larger number of patients. Practicing clinicians, by recognizing and reporting ADRs, play a critical role in defining the full range of risks associated with prescription drugs.

Postmarketing pharmacovigilance

Prescription medications are estimated to cause 46 million adverse reactions annually in the United States, resulting in 2.2 million hospitalizations and 111,000 deaths.⁴ The Institute of Medicine issued a report in 2007, *Preventing Medication Errors*, recommending strategies for reducing ADRs, including better assessment after regulatory approval.⁵ Pharmacovigilance (PV) refers to the science and activities of detection, assessment, understanding, and prevention of ADRs or any other drug-related problem.⁶ Rigorous PV is important throughout the

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life of an FDA-approved drug, from first human exposure in safety studies to postmarketing surveillance during clinical practice. Legal and ethical standards govern PV during preauthorization clinical trials through reporting of adverse events.^{7,8} Adverse events noted during preapproval research on drugs are reported by researchers to various oversight bodies such as institutional review boards, data safety monitoring boards, the FDA, and funding entities. While the FDA has an extensive process in place to analyze reported ADRs before drug approval, typically there is no systematic or mandatory reporting system for gathering information on ADRs once a drug is FDA-approved. There is emerging consensus on the need for ethical standards to govern postauthorization PV.⁹ The FDA Amendments Act of 2007 (FDAAA), which authorized the FDA to monitor and require postauthorization safety trials, is a recognition of the increased attention to postauthorization PV.¹⁰ However, reporting by physicians, pharmacists, and health care agencies remains voluntary.

Postmarketing continuation studies, observational surveillance of patients prescribed medications, and data mining of large health center databases and patient registries represent ways that ADRs can be captured following FDA approval of a drug.¹¹ However, physicians have a special role to play in capturing ADRs. When a patient experiences an ADR, the physician prescribing the drug usually is involved in treating the ADR. The physician has the clinical expertise and knowledge of the case to estimate the probability that a drug has caused an adverse event in the patient. Unfortunately, physicians infrequently report suspected ADRs and it is commonly estimated that only 1% to 10% of significant ADRs are reported by physicians.¹² Thus, the most detailed and accurate information about ADRs too often is not shared with the FDA and the broader community of physicians. This represents a lost opportunity to improve the care of patients.

How to report an ADR

When ADRs happen, what is the physician to do? The clinician must first identify that an adverse event has occurred. An adverse event is any undesirable experience associated with the use of a medical product in a patient.¹³ ADRs are broadly grouped into serious or nonserious events. Criteria for a serious ADR include causing death, a life-threatening state, hospitalization (or prolonged hospitalization), disability or permanent damage, a congenital anomaly or birth defect, or the need for intervention to prevent permanent impairment of bodily function or damage to body structure. While serious adverse events are of particular interest to the FDA, many nonserious adverse events are significant and warrant reporting. The FDA is interested in receiving reports about previously unrecognized and serious ADRs but also in learning more about significant ADRs once drugs become widely used in clinical practice.

Once recognizing an ADR has occurred, the neurologist participates in postauthorization PV by reporting the suspected ADR. Reporting can take different forms (table). First, a physician can directly report an adverse event to the FDA through the Medwatch program. Second, a physician who suspects a causal relationship between a drug and an adverse event can report this directly to the pharmaceutical company that markets the drug. The pharmaceutical company is required to gather additional information and provide this to the FDA. Third, a report can be made through institutional channels (e.g., a hospital's pharmacy

Table Reporting suspected adverse reactions^a

Reporting to FDA	Reporting to pharmaceutical company	Reporting to local ADR monitoring body	Publication in peer-reviewed journal
Phone call: 1-800-FDA-1088	Use 1-800 provided in product label to contact company to report suspected ADR	Contact your institutional committee responsible for monitoring ADRs	Publication of single case report or case series
Report ADR online (Online Resources at www.fda.gov/safety/MedWatch) or	Notify pharmaceutical representative and he or she is required to relay your report to the company; company will contact you for more information		
Download Form 3500 and complete; fax to 1-800-FDA-0178 or mail using postage-paid addressed form			
^a You can use all 4 methods. If you are planning to submit a manuscript describing the suspect adverse drug reactions (ADRs), we recommend that you proceed with reporting directly to the Food and Drug Administration (FDA) or the pharmaceutical company to ensure timely notification of the FDA.			

department or patient safety committee), which in turn passes this information to regulatory bodies. Finally, a physician can submit a case report for publication in a medical journal. Publication serves to “report” the ADR to the medical community by making relevant information about the event available through a widely distributed peer-reviewed medical journal. Importantly, a physician can report the suspected ADR through more than one of these methods and it is often advisable to do so.

While clinicians can report adverse drug effects directly to the FDA, they often fail to do so. In *Preventing Medication Errors*, the Institute of Medicine suggests that “time pressures, fear of liability, and lack of perceived benefits” are in part responsible for “significant underreporting of adverse outcomes and thus the inability to calculate true rates of such events.”⁵ The FDA Medwatch system is an effort to make clinician reporting of ADRs easier. Medwatch allows physicians to report adverse events by submitting an online form through the FDA Web site (<http://www.fda.gov/Safety/MedWatch>) or by answering a series of questions by telephone (1-800-FDA-1088). This system is easy to use and does not take an excessive amount of time. Importantly, it ensures that the report goes directly to the FDA in a timely manner, as it did in the case of fingolimod described in the vignette.

When informed of a suspected ADR to one of their FDA-approved drugs, pharmaceutical companies are obligated to gather information on the event and report it to the FDA. Physicians can notify a pharmaceutical company of a suspected ADR by calling the 800 number provided in the package insert for the drug or by telling a local representative of the company that a suspected ADR has occurred. Either will lead to the pharmaceutical company collecting, analyzing, and reporting this information to regulatory bodies. The physician’s reporting of a delayed cardiac conduction abnormality to Novartis marshaled company resources in just this way. Relying solely on industry as an intermediary, however, can complicate the reporting of an ADR, adding opportunity for information to get lost, delayed, or misinterpreted.

Clinicians associated with hospitals or health systems may also report ADRs through institution-specific reporting mechanisms. Hospital pharmacies, for instance, may have committees tasked with collecting reports of ADRs and forwarding these reports to the FDA. Similarly, patient safety or quality improvement departments often collect adverse drug or device reports as part of efforts to improve care. This is less direct than physicians reporting to the FDA through the Medwatch program as it depends on personnel or committees to process the information and then report it to the FDA.

Publication of case reports is an additional avenue for reporting ADRs. Published case reports disseminate new information about a drug to the medical community. However, relying exclusively on publishing a case report is not optimal. As illustrated by the vignette, it can take months before the case is actually published, whereas direct notification to the FDA or the pharmaceutical company can be done shortly after recognition of the ADR. In addition, reliance on case reports as a form of PV has come under criticism.¹⁴ What information about ADRs is reported, when ADRs are reported, and who reports them vary widely. In one study, a review of 1,520 case reports of serious adverse events over a 20-year period was conducted, and more than 75% were found not to include analysis of key variables, such as sex, comorbidities, liver and renal function, and drug abuse history.¹⁵ Lack of standards in publishing case reports undermines their usefulness as a leg of PV.

It is important to note that clinicians are legally permitted to disclose health information when reporting ADRs. The Health Insurance Portability and Accountability Act (HIPAA) allows for clinician disclosure of limited patient health information to the FDA. The protection is confined to the minimum personal health information necessary for understanding a new adverse event. For instance, the FDA reporting form asks for sex, weight, diagnosis, and relevant laboratory data but does not ask for patient name, date of birth, or city of residence.¹³

Legal and ethical reporting responsibilities

Outside the context of clinical research, is a busy physician who suspects an ADR obligated to take the time and effort to report? There is no legal obligation to do this, but we would argue that there is an ethical obligation to do so. Physicians are bound by ethical and professional obligations to their patients and the wider public. The extent and context of these obligations vary. The Hippocratic tradition binds physicians to advocate for the best interest of their patients. Clinicians also have responsibilities to the community, for example, by reporting potentially contagious infections or physical dangers posed by their patients. The American Medical Association's Council on Ethical and Judicial Affairs has long contended that "[a] physician who suspects the occurrence of an adverse reaction to a drug or medical device has an obligation to communicate that information to the broader community, including, in the case of a serious adverse event, the Food and Drug Administration (FDA)."¹⁶

The ethical obligations of physicians to report ADRs derive from several sources. The physician has obligations to a patient who experiences an adverse reaction. The clinician's reporting of an event may lead to a better understanding of the medication or medication class and ultimately improve future decision-making for that affected patient. This falls well within the obligations of the Hippocratic tradition. Additionally, patients may want "something good" to come of the adverse event, such as advancing knowledge of the drug so that future patients with their condition avoid a similar experience; the clinician should help facilitate this. The individual clinician also has obligations to other patients who are prescribed or may one day be prescribed the medication. The more complete knowledge is about a given medication, the better informed patients and clinicians can be in contemplating their therapeutic options. There also are professional obligations to colleagues who care for patients and could benefit from knowing more about the medications they prescribe.

Finally, the physician has an obligation to the public to advance what is known about diseases and medications used in treatment. There was once a considerable burden to physicians who wanted to report adverse events, and the usefulness of doing so appeared questionable. Now, in an era of expanding data collection and dissemination, the burden on individual clinicians has been reduced significantly. The FDA's Medwatch Web site and form is easy to access and simple to use (as is the telephone alternative). Most reports can be completed in 5 minutes. In addition, just as the burden is coming down, the likelihood of benefit is greater. Information from an individual report can be collected in a timely manner, analyzed along with other reports, and form the basis of new regulatory or practice recommendations that can be rapidly communicated to practitioners.

We all should contribute to what one author has called “eternal pharmacovigilance.”¹⁷ As illustrated by the vignette, it is only by diligent recognition and reporting that we will have more accurate assessments of the risks of the drugs we prescribe and only with this knowledge can we make better informed decisions about benefits and risks of these treatments.

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