Institute for Safe Medication Practices
A Nonprofit Organization Educating the Healthcare Community and Consumers About Safe Medication Practices
A federally certified Patient Safety Organization

QuarterWatch

Monitoring FDA MedWatch Reports

Why Reports of Serious Adverse Drug Events Continue to Grow

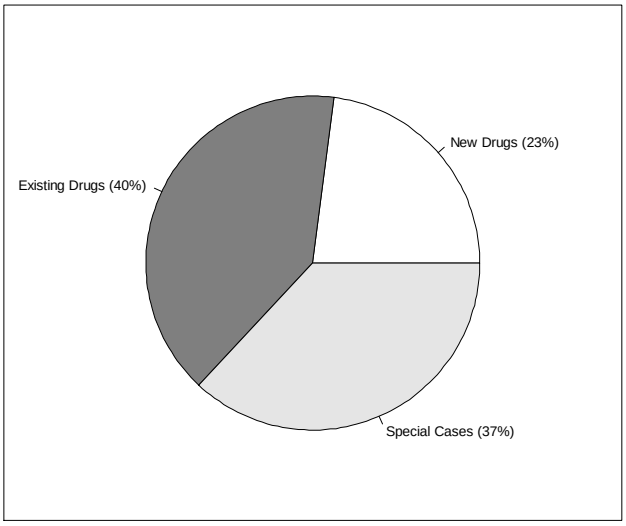
October 3, 2012

Data from 2012 Quarter 1

Executive Summary

The last four years have seen a 90% increase in the number of serious adverse drug event reports received by the Food and Drug Administration (FDA). This sustained and substantial growth in domestic case reports was unabated in the first quarter of 2012, with the FDA receiving 57,393 reports meeting our criteria, an increase of 23.8% from the previous quarter and 30.1% from the same quarter in the previous year. In the past four years, the 90% increase amounted to an additional 27,290 cases per quarter. Investigating the reasons for the four-year trend, we concluded that they could be divided into three groups. Reports for new drugs not widely used in 2008 accounted for 23% of the growth; increasing reports for drugs seen in all four years accounted for 40%. The substantial remainder (37%) was due to special circumstances involving a few suspect drugs that resulted in greatly increased numbers of reports. All the increase was attributable to reports from drug manufacturers rather than cases submitted directly to the FDA. We examine the reasons for the increase in detail in the full report.

Figure 1. Why injury reports increased 90% from 2008-12



In this report we also analyze signals for duloxetine (CYMBALTA) and serious withdrawal symptoms; pioglitazone (ACTOS) and reported bladder cancer; aliskiren (TEKTURNA) and angioedema, and rivaroxaban (XARELTO) and thromboembolic events.

QuarterWatch™ is an independent publication of the Institute for Safe Medication Practices (ISMP) that monitors all domestic, serious adverse drug events reported to the FDA. We analyze computer excerpts from the FDA Adverse Event Reporting System (FAERS).*

* On September 10, 2012, the FDA changed the name of its system from AERS to FAERS.

These voluntary reports (best known as MedWatch reports) are a cornerstone of the nation's system for monitoring the safety of prescription drugs after FDA marketing approval.

Findings for Specific Drugs

Withdrawal Symptoms and Duloxetine (CYMBALTA)

We investigated a signal for duloxetine (CYMBALTA) and serious withdrawal symptoms. In the first quarter of 2012, 48 case reports of withdrawal described an array of problems that included neurological effects such as paresthesia and dizziness, psychiatric problems such as crying, suicidal ideation, and anger, and other symptoms including effects on appetite and weight gain. Early clinical studies of abrupt discontinuation showed that withdrawal effects occurred in 40 to 50% of patients, that 10% of those were severe, and that approximately half had not resolved when side effects monitoring ended after one or two weeks. Serious withdrawal symptoms are not unique to duloxetine, and occur with several other antidepressants, benzodiazepines, amphetamines, and opioids. However, in the full report we study a single drug, duloxetine, in depth and find major shortcomings in the official information for both patients and health care professionals.

Pioglitazone (ACTOS) and Bladder Cancer

The cancer risks associated with prescription drugs rank among the most elusive of adverse effects to establish. The carcinogenic potential of scores of approved drugs was first demonstrated in pre-approval studies in rats and mice fed high doses for their two-year lifetimes. But seldom is human risk either confirmed or ruled out with clarity. The Type 2 diabetes drug pioglitazone (ACTOS) has proved to be the exception. A signal was seen in earlier adverse event reports; an interim report of a 10-year epidemiological study showed an increased risk after two or more years of exposure. Now more than 1,000 cases of bladder cancer have been reported to the FDA since January 2011. The manufacturer, Takeda Pharmaceuticals, acknowledged that some evidence of increased risk has emerged from the interim analysis, but it also said no final conclusions should be drawn until the completion of two 10-year studies.

Aliskiren (TEKTURNA) and Angioedema

Approved in 2007, aliskiren (TEKTURNA) is a newer entrant into the group of more than 70 high blood pressure drugs and drug combinations. It exerts its effect by inhibiting the kidney enzyme renin, which plays a key role in the regulation of blood pressure through the renin-angiotensin system. We observed a signal for a serious hypersensitivity reaction called angioedema, a sudden swelling that can involve the tongue, face, lips, or throat. It can occur at any time during treatment and may be life threatening if the airway is obstructed. Separately, a combination product of aliskiren and valsartan, an angiotensin receptor blocker, was quietly

withdrawn after a clinical trial showed that treating patients with two drugs active in the renin-angiotensin pathway might be harmful in at least some patient groups. The manufacturer, Novartis Pharmaceuticals, told us it was actively investigating the angioedema issue to better understand its causes and incidence.

Rivaroxaban (XARELTO) Safety Profile

We examined the growing number of serious adverse event reports for the newest oral anticoagulant, rivaroxaban (XARELTO), and found a quite different profile from the other new agent, dabigatran (PRADAXA). While dabigatran cases predominantly involved reported hemorrhages in older patients with atrial fibrillation (median age 80), the largest group of rivaroxaban cases described the development of severe blood clots in younger patients (median age 66) taking the anticoagulant drug after hip or knee replacement surgery. Following a successful product launch, rivaroxaban is rapidly replacing generic warfarin (COUMADIN) and enoxaparin (LOVENOX) to reduce post-operative risk of pulmonary and venous thromboembolism. However, pulmonary, venous, and other forms of thromboembolism were the predominant serious adverse events reported, accounting for 158 cases in the first quarter of 2012. The manufacturer, Janssen Pharmaceuticals, told us that it believed the number of reports was not more than might be expected from a newly launched drug and a high-risk post-operative patient population.

Improving the Adverse Event Reporting System (FAERS)

FDA Waivers Make FAERS Data Irregular

More than a decade ago, each adverse event report had to be manually entered into the FDA computer system, and data storage was far more expensive. As a result, the FDA decided to manage the growing number of adverse event reports by liberally granting waivers to manufacturers from the requirement to submit reports about adverse events that were considered "not serious." Most waivers were granted after the drug was marketed for three years.

The resulting distortions created by this waiver policy were vividly illustrated when we contacted Abbott Laboratories to ask why the company had submitted more than 19,000 non-serious event reports covering the previous four quarters for the anti-TNF blocker adalimumab (HUMIRA). The company said it could have applied for a waiver and submitted zero reports, but it was company policy to provide the complete safety profile data.

The FDA waiver policy has three drawbacks. Granting waivers rather than establishing a uniform standard means comparisons between drugs can be misleading because thousands of non-serious reports might not have been submitted for one drug because of a waiver. Also, many

non-serious events—such as palpitations or nausea—can be harbingers of far more serious ones. Finally, companies differ in how they apply the definition of "not serious."

About QuarterWatch Data

Our findings should be interpreted in light of the known limitations of a voluntary reporting system. The FDA's Adverse Event Reporting System (FAERS) data combine reports originated by drug manufacturers with cases submitted directly by consumers and health professionals through the agency's MedWatch program. The submission of an individual report does not in itself establish that the suspect drug caused the event described—only that an observer suspected a relationship. However, given numerous reports with credible detail, adverse event data may have important scientific weight in a broader assessment of causality. A majority of new warnings, restrictions, or other major actions by the FDA are based on these data. The overall reporting rate for FAERS is unknown, and published estimates for specific adverse events range from around 1% to 15% in most cases, and up to 30% in unusual cases of enhanced reporting. We use the term *signal* to mean evidence that, in our judgment, is substantial enough to warrant publication but requires further investigation to determine frequency of occurrence and to establish a causal relationship to the suspect drug. More complete disclaimers and descriptions of our criteria are included in the methods summary section of this report. A disclosure statement expands our description of this project and its staff.

Conclusions

In the full report we document a serious lapse in the system that ought to be providing complete information and clear warnings for patients and health professionals about the extensive withdrawal effects of the antidepressant duloxetine. The Medication Guide for patients gives no hint that withdrawal symptoms can affect half of those discontinuing duloxetine, and that many cases may be severe, persistent, or both. The prescribing information for physicians and pharmacists does not provide realistic schedules for dose tapering or a clear picture of the likely incidence of these reactions. While we have studied duloxetine withdrawal effects in this report, the types of withdrawal symptoms seen with abrupt cessation of this drug are also seen with several other antidepressants as well as other psychotropic drugs.

For aliskiren, the angioedema signal combined with issues about the safety of the drug when used in combination with other antihypertensives that act on the renin-angiotensin system raises questions about the clinical utility of this drug for an indication with many alternatives.

The reports about rivaroxaban and thromboembolic events further illustrate our concern that oral anticoagulants are among the riskiest of outpatient drug treatments. These reports of thromboembolic events raise the possibility that some patients may be receiving sub-therapeutic

doses of rivaroxaban, or some other unexpected efficacy issue. Conversely, our concern with dabigatran is that the oldest patients may be getting excessively high doses. Both concerns suggest that a single dose for most patients in the absence of therapeutic drug monitoring to determine the degree of anticoagulation (which is possible with warfarin) may be compromising both the safety and efficacy of this treatment. Being easier to use than warfarin or enoxaparin has helped both rivaroxaban and dabigatran rapidly capture market share, but with consequences for patient safety that have not yet been adequately addressed.

Finally, eliminating future waivers for submission of non-serious adverse event reports would result in a significant improvement in the FAERS system. The reports already exist on manufacturers' computer systems, are routinely transmitted electronically, and can be stored at a vanishingly low cost.

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Methods Summary

QuarterWatch seeks to improve patient safety through regular monitoring and analysis of serious adverse drug events reported to the FDA. The agency releases computer excerpts for research use on a quarterly basis, and these case reports are our primary data source. [1]

Our publication examines domestic adverse drug events that are specifically coded as "serious," which means under FDA regulation events that resulted in death, permanent disability, a birth defect, involved hospitalization, were life threatening, required intervention to prevent harm, or had other medically serious consequences. [2] We exclude reports from foreign sources, cases from clinical studies which have different reporting requirements, and events in which the injuries were not coded as serious. We standardize drug names to an ingredient name based on the National Library of Medicine RxNorm project [3] and do not distinguish between different routes of administration or dosage forms.

We focus on case reports received by the FDA for the first time in the calendar quarter under study. The actual events may have occurred earlier. When case reports are revised or updated we use the most recent version while retaining the original report date.

In these data, the adverse events that occur are described by medical terms selected from the Medical Dictionary for Regulatory Affairs (MedDRA), a terminology developed by the pharmaceutical industry to describe adverse events in clinical studies and postmarketing reports.[4] The MedDRA terminology also defines broader categories of adverse events that can include any of a list of more specific and related medical terms. We use these categories, called Standardized MedDRA Queries (SMQs), to identify possible cases of some adverse events.[4] We also group adverse event terms using a MedDRA category called High Level Terms (HLTs) that combine several related but more specific medical terms. The QuarterWatch database was updated in November 2011 to MedDRA version 14.1.

To provide a broader perspective on the adverse events reported, we assess the patient exposure to drugs on the basis of dispensed outpatient prescription data provided by IMS Health Inc. The data we rely on are an estimate of total non-governmental prescriptions dispensed through retail and mail channels. Our agreement with IMS includes the following disclaimer:

> "The statements, findings, conclusions, views, and opinions contained and expressed in QuarterWatch are based in part on data obtained under license from an IMS Health Inc. information service called the National Prescription Audit™ for 2012 (All Rights Reserved). Such statements, findings, conclusions, views, and opinions are not necessarily those of IMS Health Incorporated or any of its affiliated or subsidiary entities."

The QuarterWatch totals for the quarter include a category of drugs with special reporting requirements, restricted distribution, or active surveillance programs that either result in a much higher reporting rate or capture adverse events in which drug involvement is not necessarily suspected. These special category drugs are included in the total number of reports but are otherwise excluded from comparisons and rankings. In this report the term "regularly monitored drugs" means those remaining after the special reporting drugs have been excluded.

Reported totals for any calendar quarter, specific drug, or adverse event may change over time because thousands of reports are revised, are entered into the FDA system late, or are subject to changes in the QuarterWatch or FDA coding or report criteria. To compensate, all historical comparisons and trends over time are recalculated every quarter and may differ from previously reported totals. The term *signal* as used in QuarterWatch means evidence of sufficient weight to justify an alert to the public and scientific community, and to warrant further investigation.

The QuarterWatch master database of all adverse event reports submitted to the FDA is maintained on a MySQL open source database (http://www.mysql.com/) and analyzed with the R Package for Statistical Computing (http://www.r-project.org/). A full technical description of our methodology can be found on the QuarterWatch web pages (http://www.ismp.org/quarterwatch/detailedmethods.aspx). In this report we made no changes in our methodology.

Results

In the first quarter of 2012, the FDA received 57,393 new reports of serious, disabling, or fatal injury associated with drug therapy in the United States. This was an increase of 11,036 cases (23.8%) from the previous quarter, and 13,273 (30.1%) from the first quarter of 2011. The long-term trend since 2008 has been an increase averaging 18% compared to the same quarter one year earlier. The 2012 increase of 30.1% fell in the upper range of quarterly increases, although it was exceeded three times in the period. (The largest one-quarter increase was a 44% increase in the third quarter of 2010.) As in previous quarters, the short-term and long-term increase is accounted for entirely by reports prepared by drug manufacturers rather than cases reported directly to the FDA by consumers and health professionals. (The number of direct reports to the FDA fluctuates, but is largely unchanged since 2008.)

Probing the Increase

Seeking to understand the reasons for the near doubling of domestic reports since the first quarter of 2008, we divided the increase into three categories: (1) Reports from new drugs appearing in the rankings for the first time after March 2008; (2) increased (and decreased) reports for drugs appearing in both periods; and (3) special reporting for drugs with unusual features.

The first category was newer drugs that accounted for reports in the first quarter of 2012 but not in the same quarter of 2008. We identified 266 drugs and 6,398 case reports that appeared in 2012 but not 2008, accounting for 23% of the increase. These were mostly (but not entirely) newly approved drugs. The largest number of newer drug reports was for the anticoagulant dabigatran (PRADAXA), with 927 reports in the first quarter; second was fingolimod (GILENYA), a new drug for multiple sclerosis, with 509 reports. QuarterWatch has previously examined signals for both drugs. [5] [6] With approximately 20-30 new drugs approved annually, each year more drugs are available with risks to which patients are exposed.

A second category was continuously available drugs—increases attributable to drugs generating reports of serious injury in both 2008 and 2012. We identified 1,064 such drugs that together accounted for an additional 10,785 reports, or 40% of the increase. Examining this group, however, is similar to reporting on trends in stock market averages. An increase in the Dow Jones average combines stocks that increase in price (the majority) with those that decline. The three drugs that increased the most were the anti-Tumor Necrosis Factor drug adalimumab (HUMIRA), with 1,801 cases reported in 2012, compared to 326 four years earlier, and two drugs for cancer, erlotinib (TARCEVA) and imatinib (GLEEVEC).

Where Reports Declined

While the overall trend was sharply upward, the number of reports for some drugs decreased. The biggest decreases were seen for unfractionated heparin, a generic drug to prevent blood clots; varenicline (CHANTIX), an aid to smoking cessation, and the antidepressant paroxetine (PAXIL). In these three examples can be seen three major factors that cause declining reports—a drug safety problem resolved, reduced patient exposure, and reduced reporting because of generic drug status. The case of heparin was an example of a drug safety crisis resolved. In early 2008 many severe and more than 80 fatal anaphylactic reactions were reported for a particular form of this drug used primarily in hospitals.[7] The problem was tracked to contamination of the product introduced by raw materials suppliers in China, the source of 80% of the world's supply of crude heparin. The issue was resolved and the number of serious adverse events plunged from 1,036 in 2008 to 43 cases of all types in the first quarter of 2010. A second factor explains the large drop in reports for the smoking cessation drug varenicline, which decreased 41.4% from 1,305 cases in 2008 to 765 in 2012. In this instance safety concerns about psychiatric side effects, accident risk, and severe allergic reactions led to a major reduction in patient exposure. Dispensed outpatient prescriptions for varenicline declined by 66% from 1.9 million in the first quarter of 2008 to 645,000 in the comparable quarter of 2012, according to data from IMS Health. However, since the volume of reports per 1,000 prescriptions remains high, the decline in the numbers of reports reflects fewer people being exposed rather than safer use of the drug. In the third example, paroxetine reports declined from 1,358 in 2008 Q1 to 148 in 2012. This drug, like varenicline, also saw a decline in total prescription numbers, from 4.2 million prescriptions in the first quarter of 2008 to 3.5 million in the same quarter of 2012. At the same time, several generic equivalents were approved and gained market share, and generic drugs tend to be associated with lower reporting rates than brand name drugs.

Safety Withdrawals

Drugs withdrawn for safety reasons also have the potential to reduce total reports of serious injury in subsequent quarters. In this four-year period, however, few such cases could be identified. In only 96 cases reported in the 2008 quarter was the suspect drug later withdrawn. The largest total was 38 cases for drugs containing the painkiller ingredient propoxyphene, followed by 31 cases for efalizumab (RAPTIVA), an immunosuppressant drug for psoriasis withdrawn because of an association with progressive multifocal encephalopathy (PML), a fatal brain infection. An additional 426 cases involving 144 drugs seen in 2008 generated no reports in 2012. The modest number of reports for some drugs later deemed unsafe and withdrawn is good news in drug safety terms, but in some cases withdrawal occurs only after very large numbers of reports. Some drug withdrawals—notably rofecoxib (VIOXX) in 2004 and the fenfluramine diet drugs in 1998—affected millions of people and generated thousands of adverse event reports.

The final category, accounting for 37% of the increase, is the miscellaneous cases QuarterWatch labels as "special reporting" drugs. These involved documented cases with unusual influences on the reporting of serious adverse events. One example is Dianeal, a special solution used for kidney dialysis at home. Large and increasing numbers of reports were submitted because the manufacturer, Baxter Healthcare, directly delivers the product to users and trained its drivers to report serious adverse events. Another special reporting drug is the diabetes drug rosiglitazone (AVANDIA), which is restricted in the United States but has been withdrawn in Europe. As the restrictions and safety concerns were widely publicized, use of the drug declined rapidly, but the number of reports increased as people became aware of the safety risks. A third group of drugs involve classification and nomenclature issues. For example, because of poor product identification we group together a large number of estrogen products. The factors involved in special reporting drugs tend to be very varied and require case-by-case investigation.

Findings for Specific Drugs

Duloxetine (CYMBALTA) and Serious Withdrawal Symptoms

We observed a signal for serious drug withdrawal symptoms associated with duloxetine (CYMBALTA), a widely used antidepressant that is also approved to treat arthritis and back pain, anxiety, and fibromyalgia. In the first quarter of 2012 the FDA received 48 case reports of drug withdrawal identifying duloxetine as the suspect drug. They described a wide spectrum of withdrawal effects that began when the patients stopped the drug, including blackouts, suicidal thoughts, tremor, and nausea. Several cases involved hospitalization. Probing deeper into the scientific record for duloxetine we found that withdrawal symptoms were reported in 44-50% of patients abruptly discontinuing duloxetine at the end of clinical studies for depression, and more than half of this total did not resolve within a week or two. In addition, we identified a serious breakdown at both the FDA and the manufacturer, Eli Lilly and Company, in providing adequate warnings and instructions about how to manage this common adverse effect.

Known Before Approval

Duloxetine, approved in 2004, was a relative latecomer to the antidepressant drug class, which includes citalopram (CELEXA), sertraline (ZOLOFT), venlafaxine (EFFEXOR), and fluoxetine (PROZAC). Antidepressants drugs are so widely used that the National Center for Health Statistics estimated that by 2008 11% of the adult population over age 12 was taking one, with 60% taking them for two years or more. [8] Highest use was in women age 40-59, where 23% were taking an antidepressant. Publication of studies showing that in mild and major depression the benefits of these drugs are difficult to distinguish from placebo [9] has not apparently impeded their popularity and use in a growing number of other disorders.

Since at least 2001 it has been recognized that antidepressants are associated with withdrawal syndromes, which were thought to be indirectly proportional in frequency to the half-lives of the individual drugs in the body. [10] Short-acting antidepressants such as venlafaxine and paroxetine appeared to cause more problems than longer lived drugs such as fluoxetine, which provide a kind of automatic built-in taper as it is slowly cleared from the body. [11] While many early reviews noted lack of adequate study, they also tended to be dismissive: "SSRI discontinuation syndromes, although uncomfortable, are self-limited and generally resolve within 1-2 weeks." [12] The FDA safety review of duloxetine showed a similar lack of concern: "It appears that symptoms are relatively mild and reliably predictable for a significant minority of patients. Tapering duloxetine at discontinuation appears to be advisable for optimal patient comfort, but not tapering does not appear to pose any serious risk." [13] A single study of duloxetine in generalized anxiety disorder did not report a statistically significant difference in number withdrawal effects between patients randomized a two-week taper and abrupt discontinuation. [14] However, one would reasonably expect such a short taper to have limited effects.

44% Experience Withdrawal

Eli Lilly and Company, the manufacturer of duloxetine, studied withdrawal effects in nine early clinical trials for depression, with a protocol it called a placebo lead-out phase. [15] As the trials reached the end of the treatment at eight or nine weeks, the patients were abruptly switched to an inactive placebo and then monitored for an additional one or two weeks. Patients who volunteered new symptoms or more severe symptoms were counted as experiencing withdrawal effects. Lilly reported symptoms in 44% of patients discontinuing after nine weeks or less, and 50% in longer-term trials. About 10% of withdrawal events in short-term trials were rated as "severe" and 53.7% had not yet resolved after the one or two weeks of observation.* What happened to these patients after two weeks is unknown. The outcomes of severe and persistent cases remain poorly studied.

Inadequate Warning and Instructions

Good patient information is essential because abrupt withdrawal effects are likely to affect about 50% of duloxetine patients; they will be severe in at least 10% of that total, and persistent in half. Instead of clear warnings and useful instructions, the duloxetine patient Medication Guide says only: [16]

* Lilly also reported a relatively high rate of withdrawal symptoms in the placebo group (22%) but lack of detail about what symptoms occurred (other than that they were different) makes this result difficult to interpret. The most common duloxetine symptoms seldom were reported in the placebo patients.

"**Never stop an antidepressant medicine without first talking to a healthcare provider**. Stopping an antidepressant medicine suddenly can cause other symptoms."

This FDA-approved patient guide is materially deficient. It gives no hint of the persistence or severity of the symptoms known to occur. It does not address basic questions: What kinds of symptoms are most common? Should patients taper off the dose, and if so, how slowly? What should a patient do if depression or other symptoms recur? Is there a way to tell whether these are withdrawal symptoms or the previous illness returning?

We could not identify any FDA-approved or company information for patients about how to discontinue duloxetine. We specifically asked Lilly how the company responded if a patient asked for assistance in stopping duloxetine. "If a consumer requests additional information we inform them to consult their physician because they know the patient's complete medical history," the company said. Consumers could also obtain the prescribing information intended for physicians.

Information for Physicians

Urging patients to consult their doctor before stopping duloxetine raises the question of the quality and quantity of company information provided to doctors to manage discontinuation. Some information is provided in the prescribing information for doctors and pharmacists. [16] The 11 most common discontinuation symptoms are identified. They include dizziness, nausea, headache, and paresthesia. A single sentence describes a tapering regimen: "A gradual dose reduction rather than abrupt discontinuation is recommended whenever possible."

The duloxetine prescribing information also lists 12 topics for physicians to discuss with patients before starting treatment with duloxetine. Withdrawal problems are not on the list.

Drug companies also maintain large libraries of more detailed scientific summaries to respond to specific queries from physicians. At our request, Lilly provided two summaries, one focused on what was known about discontinuation risks, the second on tapering the dose. [17] [18]

The summary of what the company knew about withdrawal symptoms was four pages long, cited two published studies, and excerpted pertinent detail. While half of the report recapitulated the limited information in the prescribing information, the other half of the report summarized the company's studies. It reported the 44% incidence of symptoms in the depression trials and the results of other studies. The company made it easy to obtain the key underlying studies.

However, when it came to managing discontinuation or recommending how slowly to taper the dose, or discussing severe or persistent cases, the company information could not help physicians. Its one-page summary of "Discontinuation Taper Schedules" merely reports that in only a few trials were the doses tapered, and then only over two weeks. Lilly's response may well be limited because neither the company nor the government has adequately studied how to discontinue patients comfortably and safely, or how to manage those patients in which withdrawal symptoms are severe or persistent.

Withdrawal Time Underestimated

We identified three useful publications that deal directly with the problem of discontinuing antidepressant drugs: a review article in the *American Family Physician* medical journal and two books. [19] [20] [11] The journal article emphasizes the importance of forewarning patients about side effects and recommends taking at least six to eight weeks to taper the drug. *Your Drug May Be Your Proble*m, a book by psychiatrist Peter Breggin and social work professor David Cohen, suggests a starting point of about a 10% dose reduction per week for most psychiatric drugs. Psychiatrist Joseph Glenmullen provides a step-by-step guide in his book *The Antidepressant Solution*. His tapering regimen is tailored to the drug dose and the severity and persistence of the side effects. For duloxetine, tapering would typically last 8 to 30 weeks, but could last even longer in severe cases.

These withdrawal protocols may involve dose reductions so small that pills have to be cut or, in the case of duloxetine, the capsules broken open and the tiny granules divided. These three practical guides also suggest that one to two weeks is a substantial underestimate of the withdrawal problem faced by many duloxetine patients. In addition, Glenmullen's book provides a useful suggestion for distinguishing withdrawal effects from a recurrence of the underlying illness. A withdrawal symptom normally resolves quickly when the drug is restarted, or the dose increased to the previous level.

Adverse Event Report Results

Duloxetine was notable in the first quarter of 2012 because reports of serious drug withdrawal effects (n = 48) outnumbered all other regularly monitored drugs, including an opioid treatment for narcotics addiction, buprenorphine-naloxone (SUBOXONE) (n = 43) and the potent synthetic opioid fentanyl (DURAGESIC) (n = 34). Such comparisons, especially for one quarter, are approximate, but signaled that duloxetine had a withdrawal issue warranting further investigation. The specific symptoms spanned a wide range of disorders. They included physical and neurological symptoms such as dizziness, paresthesia, and abnormal sweating. But psychiatric symptoms were also reported such as crying, anger, suicidal ideation, hallucinations, and personality change. Effects on weight and appetite (side effects also reported during

treatment) were also reported on discontinuation. While all the duloxetine cases were coded as serious, more detailed information about the severity and persistence could not be determined from these computer excerpts. However, case reports from clinicians and patient reports at web sites illustrate how severe and disabling even the milder-sounding symptoms can be. For example, "dizziness" can describe vertigo so severe that patients cannot get out of bed. While "paresthesia" usually means a tingling or pins-and-needles sensation, duloxetine patients also describe a painful electric shock or "zapping" sensation.

Conclusions

A major lapse has occurred in the FDA-approved information for patients about the risks of stopping duloxetine. The information for prescribing physicians is somewhat better, but still inadequate about counseling patients; instructions for an adequate taper regime are omitted entirely. Furthermore, a major gap exists in our scientific understanding of the incidence and management of withdrawal syndrome cases that are severe and persistent.

Excessive and unnecessary long-term use is another likely consequence of serious withdrawal effects without adequate warnings. Patients try to discontinue, encounter severe symptoms, and discover that these problems disappear quickly if they resume the drug. While antidepressants are not classified as drugs of abuse, they share the risk of withdrawal symptoms with the opioids and benzodiazepines. Given that antidepressant drugs were tested primarily in short-term trials of six to nine weeks, the fact that that 60% of the large population taking antidepressants had done so for two years or more moves this issue onto the short list of major drug safety issues. While this report is limited to studying a single drug in depth, it is clear that discontinuation issues involve some other antidepressants, benzodiazepines, and other psychoactive drugs.

Pioglitazone (ACTOS) and Reports of Bladder Cancer

Since the beginning of 2011, the FDA's adverse event system has received 1,025 reports of bladder cancer in which pioglitazone (ACTOS) was the primary suspect drug. This included 235 new cases in the first quarter of 2012 alone. Of this total, 71% came from consumers and 29% from health professionals. These data illustrate larger lessons about two different issues: first, they provide an example of the extremely slow and uncertain process through which the cancer risks of prescription drugs are identified and their significance assessed. Also, it shows that both the fairly small numbers of bladder cases reported to the FDA in previous years and the current surge of reports can provide useful but different kinds of information.

First Signal Was 13 Years Earlier

A signal of bladder cancer risk was already present when the FDA was first considering pioglitazone for use in Type 2 diabetes in 1999.[21] The cancer risk of most new drugs is assessed in lifetime (typically about two years) studies of rats and mice fed the highest dose of the target drug that the animals can tolerate. Depending on the drug and the animal, the doses can be less than, similar to, or substantially higher than in humans. The rats fed pioglitazone did not do well. FDA reviewers noted "multiple toxicities" occurring in vital organs, and a "low margin of safety" based on dose comparisons between animals and expected human exposure. (The rats could tolerate only about 7 times the human dose.) In particular the rats had enlarged and distended hearts, and calcium nodules had formed in the adipose tissue and urinary bladder. And notably, the rats had an increased incidence of bladder cancer, possibly a result of the calcium nodules. The significance of this was debated by Takeda Pharmaceuticals, the Japanese manufacturer, and the FDA. The effects were worse in the male rats than the females. Bladder cancer was not seen in the mice, although these animals had adverse effects on their hearts, livers, bone marrow, and adipose tissue. The question of whether the cancer might also be manifest in humans could not be answered. But the FDA required that it be disclosed in the prescribing information, which said "Drug induced tumors were not observed in any organ except for the urinary bladder." [22]

A Study Begins

Nevertheless, by 2003 the FDA, the European Medicines Agency, and Takeda had agreed that the bladder cancer risk warranted further study. The company commissioned a 10-year epidemiological study with a drug safety research center at the University of Pennsylvania and the Kaiser Permanente health plan. By 2010 pioglitazone became the most frequently prescribed brand name drug for Type 2 diabetes, with 11.1 million prescriptions.[23] Then came the bad news. The 5-year interim results showed an increased risk of bladder cancer in those who had taken pioglitazone for 24 months or more, but not among those with shorter exposure.[24] France, citing confirmatory evidence from its own pharmacovigilance data, suspended the sale of pioglitazone. [25] Germany recommended that physicians not prescribe the drug for new patients. [26] Regulators at the European Medicines Agency and the FDA allowed the drug to remain on the market, but required new warnings of increased bladder cancer risk. [27] [28] In the year following this announcement, dispensed outpatient prescriptions for pioglitazone declined 38% in the United States, from 3 million in the first quarter of 2011 to 1.8 million in the first quarter of 2012, according to data from IMS Health.

Evidence Late and Limited

While the evidence was sufficient to convince global regulators that pioglitazone increased bladder cancer risk, each of the three major data sources also had significant limitations. Lifetime animal carcinogenicity studies frequently disclose a cancer risk; whether this is relevant to humans is debated in each case. One 1994 study showed that among 242 newer drugs, 42% had caused cancer in one or more animal species. However, it is rare that human studies of sufficient size and treatment duration are conducted to determine one way or another whether cancer risks were present in humans. (The increased breast cancer risks of hormone replacement therapy took decades to establish). Furthermore, the five-year University of Pennsylvania and Kaiser Permanente interim results were based on 90 cases of bladder cancer among 30,173 pioglitazone patients; elevated risk was confirmed only in those taking the drug two or more years. However, the Kaiser results were confirmed in other database studies in France and the United Kingdom, and in a clinical trial. [29] [30]

Takeda Pharmaceuticals told us that the company believed that the jury was still out on the issue of cancer risk. While the company said it included warnings based on the animal and Kaiser study results, it noted that the Kaiser study is scheduled to last 10 years, and that these were only interim results. "No final conclusions should be made until the study is completed," the company said. Another eight-year European study, the company noted, did not detect increased bladder cancer risk.

Adverse Event Data

A possible risk of bladder cancer could be identified both in early adverse drug event reports, and in the most recent surge of more than 1,000 reports noted above. But the two signals differed. A study published in 2011 surveyed all the bladder cancer reports from 2005 to 2009 for the major oral therapy drugs for Type 2 diabetes. [31] The study reported a four-fold risk of increased reporting of bladder cancer for pioglitazone. However, the study was based on only 138 case reports overall, including 31 for pioglitazone. But in four calendar quarters following the published studies, a total of 1,025 possible bladder cancer case reports were received in the United States alone. The cases were identified using the MedDRA High Level Term (HLT) "Bladder neoplasms malignant." Sometimes both pharmaceutical companies and regulators discount these reports as "stimulated reporting." Indeed, report totals can increase as the result of a feedback loop that we call enhanced awareness. A small number of credible reports or a new epidemiological study triggers public awareness and concern. Regulators issue alerts. Warning letters are sent to prescribing physicians. Law firms may set up web sites to collect possible cases for litigation. This process can produce a spike in reported cases, such as we identified for pioglitazone. But we believe such cases should not be discounted and likely contain valuable data about the association. The more people learn about a possible connection, the more likely

they are to identify a case and report it. Any risk of bladder cancer is likely to have been present over the 13-year history of pioglitazone; it is simply the enhanced awareness of the risk that is new. We have previously noted that from less than 1% to 15% of serious adverse events associated with drug therapy are reported, with wide variation over time, for event and drug. The enhanced awareness process exposes a larger part of the iceberg, and these spikes are an identifiable form of signal.

Conclusions

Marked signals have now been seen in animal data, clinical trials, epidemiological studies, and reported adverse drug events. However, some ambiguity in the data remains. It is not so much that the evidence is weak, but rather that cancer risks from prescription drugs are likely to develop over many years and are notably hard to document. On the other hand, significant cancer risks of other drugs may have been overlooked. A new bladder cancer study [32] also implicates the chemically-similar diabetes drug rosiglitazone (AVANDIA), which has now been withdrawn in Europe and restricted in the United States because of increased cardiovascular risks.

Aliskiren (TEKTURNA) Safety Issues

In the first quarter of 2012 we observed a signal for an often-severe hypersensitivity reaction called angioedema associated with aliskiren (TEKTURNA), a newer antihypertensive drug. In the first quarter we identified 100 reports of angioedema using the broad-scope SMQ of that name, more than for any other blood pressure drug. Also, in one of the lowest-key safety withdrawals we have seen, the combination product of aliskiren and valsartan (VALTURNA) was withdrawn following a clinical trial that had to be stopped for safety and lack of efficacy. These two developments raise questions about the clinical future of this hypertension drug and its role in combination therapy.

A Different Mechanism of Action

Aliskiren (TEKTURNA) is a newer member of the family of blood pressure lowering agents that now numbers more than 70 drugs and combinations, with six or more different mechanisms of action. At least 13 drugs target the renin-angiotensin system, a central mechanism through which the body regulates fluid balance and blood pressure. The kidneys secrete an enzyme called renin, which is converted in a series of steps to angiotensin I and subsequently to angiotensin II, a powerful systemic vasoconstrictor that maintains or increases blood pressure. A family of drugs called ACE Inhibitors prevents the conversion of angiotensin I to angiotensin II. An example is lisinopril (PRINIVIL, ZESTRIL), the fourth most widely dispensed outpatient drug, with more than 20 million prescriptions in the first quarter of 2012,

according to IMS Heath. A second family of blood pressure drugs are commonly called ARBs (Angiotensin Receptor Blockers), thus named because rather than inhibiting the conversion of angiotensin I to angiotensin II, they block the cellular receptors that are activated by angiotensin II. An example of an ARB is valsartan (DIOVAN).

Approved in 2007, aliskiren was a latecomer to the treatment of hypertension—a condition for which various drugs have been available for decades. Aliskiren works by directly inhibiting the kidneys' secretion of renin, the enzyme at the top of the chemical cascade affected by all the drugs active in the renin-angiotensin system. At the time it was approved, it had shown similar efficacy to several other antihypertensives, but it had not been evaluated in trials of sufficient duration to assess its hoped-for clinical benefits of antihypertensive treatment—reducing the risk of heart attack, stroke, and end-organ failure.

Trials to Document Heart Benefits Fail

Scientists for Novartis Pharmaceuticals, the manufacturer, believed there could be additional benefits in combining two drugs that blocked the renin-angiotensin system at different points. To that end, the company won FDA approval for a pill combining aliskiren with an ARB, valsartan. In addition, to demonstrate that dual blockade produced measurable health benefits, the company launched a clinical trial named ALTITUDE, with more than 8,000 patients with diabetes and renal impairment, hoping to demonstrate that the treatment would show reductions in cardiovascular events and slow the decline in renal function. In December 2011, Novartis announced it had terminated the trial, having detected no advantage in efficacy and a higher incidence of adverse events, including non-fatal stroke, kidney complications, and hypotension. [33] Dual blockade in patients with impaired renal function looked possibly harmful rather than beneficial.

Aliskiren also failed in another clinical trial intended to demonstrate tangible clinical benefits. In a group of patients who had recently experienced a heart attack, Novartis investigators hoped to limit further deterioration of cardiac function using aliskiren combined with either an ACE Inhibitor or an ARB. [34] This trial also showed no benefit and more adverse effects.

A Warning and Quiet Safety Withdrawal

Within a few months, regulators in Europe and the United States had acted on the most obvious implication of the ALTITUDE trial: the specific patient population in the trial—those with diabetes or impaired kidney function—should not take aliskiren in combination with another drug active in the renin-angiotensin system.

But should this evidence be interpreted as showing that combining aliskiren with an ACE Inhibitor or ARB ought to be avoided entirely? Novartis had an FDA-approved combination product using the ARB valsartan. In both Europe and the United States, the combination product was withdrawn, effective July 2012.

Safety withdrawals are rare, typically trigger national publicity, and may spur some searching questions about whether people were exposed to unsafe drugs and why. This withdrawal went virtually unnoticed. The FDA's mention of the Valturna safety withdrawal consisted of nine words in the 15th paragraph of a 1,300 word Drug Safety Communication about the new restrictions. [35] The European Medicines Agency press release on this topic did not mention the withdrawal. [36] A Novartis press statement, on the other hand, mentioned the withdrawal in a headline. [37] Physicians, however, frequently combine blood pressure drugs using prescriptions for each medication rather than combination pills. Was it safe to combine aliskiren with an ACE Inhibitor or ARB for other patients than those in the failed ALTITUDE trial? Oddly, there are two different answers to this significant safety question.

The EMA concluded in the negative. "The combination of aliskiren with ACE inhibitor or ARB is not recommended."

The FDA, on the other hand, has made no public comment about the broader implications except to say it was studying the matter and "will communicate any new information when it becomes available." [35]

Angioedema, an Additional Risk

Meanwhile, new information was emerging about an additional risk of aliskiren, a form of hypersensitivity called angioedema, a rapid swelling of the face, lips, tongue, or throat that can become a life-threatening emergency if the airway becomes obstructed. This side effect was identified in clinical trials for approval and resulted in a warning in the prescribing information for physicians, recommended patient counseling, and patient Medication Guide.

In the aliskiren adverse event reports for the first quarter of 2011, various forms of angioedema were predominant serious adverse events reported for the drug and its remaining combination product, aliskiren and hydrochlorothiazide (TEKTURNA HCT). The drug accounted for 237 reports overall, more than any other blood pressure drug but fewer than 43 other regularly monitored drugs. Using a broad definition of angioedema, we identified 100 possible cases of angioedema in the Standardized MedDRA Query of that name, all classified separately as serious. The cases included 1 patient death, 2 classified as life threatening, and 15 requiring hospitalization. Death cases in particular and other severe cases as well may involve many factors, including those unrelated to the drug or angioedema.

Novartis told us that the company is aware of the angioedema signal and is actively investigating it. The company said it has consulted with experts, reviewed preclinical and clinical data, and analyzed adverse event reports from its global safety program. In addition, it said the event was rare, but that it was planning to undertake an epidemiological study to estimate the incidence of angioedema.

Conclusions

While the current angioedema warnings for both physicians and patients are explicit and clear, we are concerned about the severity and uncertain incidence of angioedema—as well as the fact that it can occur at any time during treatment, as opposed to following the first or second dose. With two negative clinical trials, we agree with the EMA that combination therapy with either ACE Inhibitors or ARBs should not be recommended. But with the FDA's handling of the safety withdrawal and its silence on the combination therapy question, we think the agency has not kept doctors and patients well informed about the risks and safe use of aliskiren.

Rivaroxaban (XARELTO) Safety Profile

Rivaroxaban (XARELTO) is the second recently-approved oral anticoagulant drug, joining dabigatran (PRADAXA) as a replacement for the five-decades-old mainstay, warfarin (COUMADIN). Like dabigatran, it requires no dose individualization or regular blood testing, and it has also begun to account for large numbers of serious adverse event reports. But otherwise, rivaroxaban's safety profile differs. The primary use thus far for rivaroxaban has been for post-operative prevention of thromboembolic events following knee or hip replacement surgery. The primary complaint seen has been lack of efficacy—reports of the very venous and pulmonary thromboembolisms and other serious blood-clot-related events that the drug is intended to prevent. For the other anticoagulants, the leading issue has been excessive anticoagulation leading to hemorrhages.

The Race to Replace Warfarin

Both dabigatran and rivaroxaban were contenders in the race to replace warfarin, the widely prescribed anticoagulant approved in 1956. It is perceived as difficult to use because of numerous interactions with other drugs and the need to monitor anticoagulation with frequent blood tests. Both contenders had new mechanisms of action and featured no recommended lab tests, and only a single primary dose for each indication. Also, the new agents would cost about 15 times more than the generic warfarin.[38]

Dabigatran was the first to win approval, in November 2010, but in the United States was approved for only one of the two major anticoagulant patient populations—long-term use for

stroke prevention in patients with atrial fibrillation. It did not get FDA approval for short-term use to prevent blood clots after knee or hip replacement surgery, although the European Medicines Agency did approve this use. Dabigatran moved rapidly into the medical market, and by the fourth quarter of 2011 had captured approximately 28% of the atrial fibrillation market, as measured by the share of office visits where an anticoagulant was prescribed. [38]

Because the new agents were substantially more costly, spending for anticoagulants had doubled by the end of 2011. But the rapid uptake of dabigatran also triggered a large increase in serious adverse event reports, primarily of hemorrhages in older patients. In two previous reports, QuarterWatch has called for an examination of whether older patients with declining kidney function were receiving excessive doses. [5] [39]

Enter Rivaroxaban

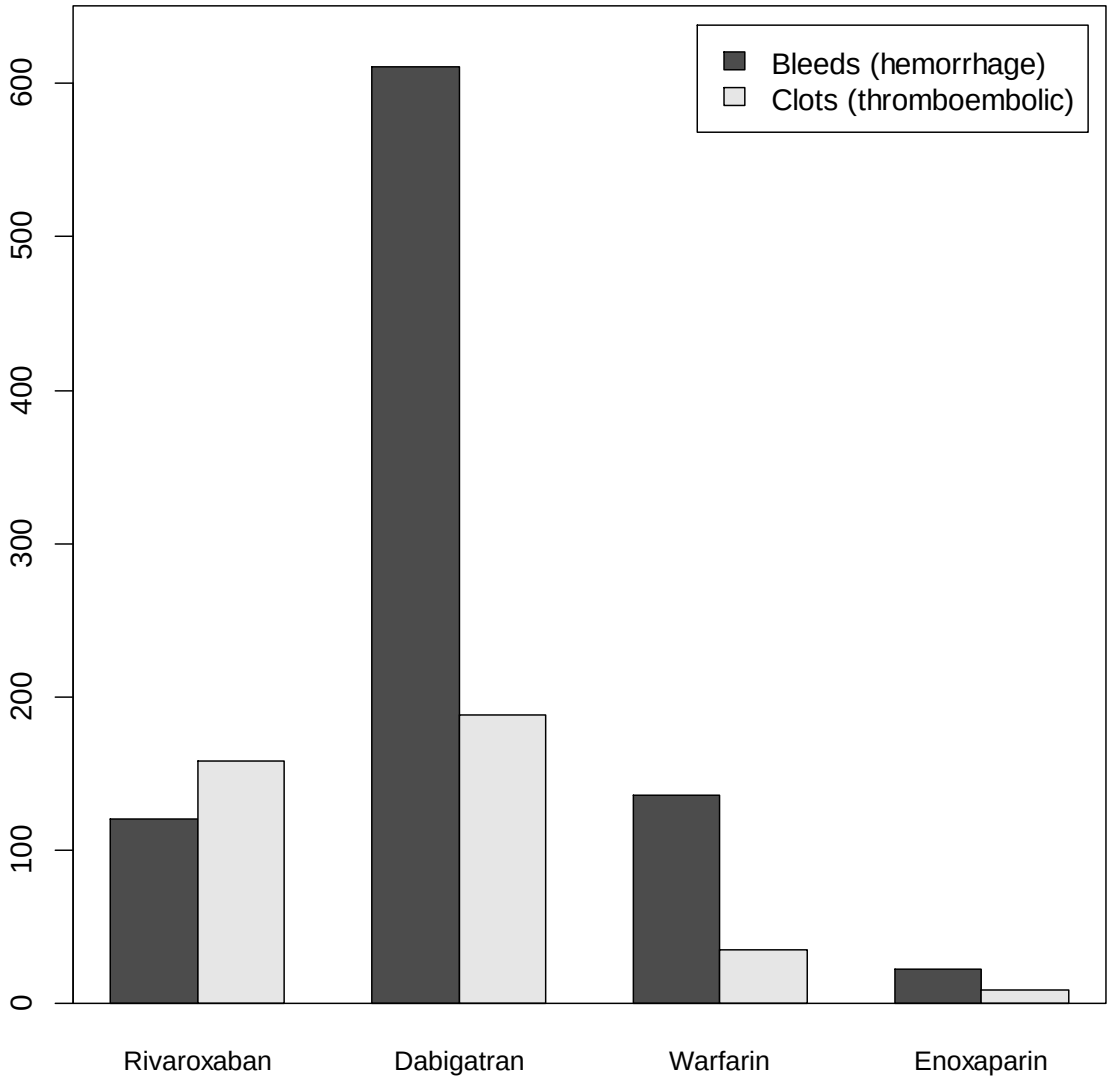
Rivaroxaban succeeded where dabigatran failed. In July 2011 it won FDA approval for short-term use in preventing venous and pulmonary embolism in patients undergoing knee or hip replacement. The drug nearly failed where dabigatran succeeded—the FDA primary review team recommended against approving rivaroxaban for long-term use to prevent strokes in patients with atrial fibrillation. A clinical trial with 14,000 patients had shown that rivaroxaban was no worse than warfarin. [40] But reviewers noted that warfarin had not been optimally used. If rivaroxaban were really inferior to optimally used warfarin—but this was not proven, only suspected—its use could lead to increased death and injury. [41] Reviewers also questioned the convenient once-a-day dosing scheme, saying blood level studies had shown peaks and troughs that could be eliminated by twice-a-day dosing. However, both FDA senior management and an advisory committee disagreed, and rivaroxaban was approved for preventing stroke in non-valvular atrial fibrillation. As with other anticoagulants, the rate of clinically relevant bleeding in clinical studies was high—15% per year of treatment. These high bleeding rates have led QuarterWatch to the conclusion that oral anticoagulant treatment is among the riskiest of all outpatient drug treatments.

Adverse Event Data Results

In the first quarter of 2012 we identified 356 reports of serious, disabling, or fatal injury in which rivaroxaban was the primary suspect drug. The report total more than doubled from the previous quarter total of 128 cases. The unexpected result was that unlike other anticoagulants (warfarin, dabigatran, and enoxaparin) the primary reported event was not the well-understood risk of hemorrhage. Instead, the largest identifiable category was serious blood-clot-related injury—most frequently pulmonary embolism—the very events rivaroxaban is intended to prevent. We identified 158 cases (44%) falling in the embolic-thrombotic SMQ. As might be expected, there were also numerous reports of hemorrhage, 121 cases (34%). While we have

previously reported that dabigatran hemorrhage cases were occurring in the oldest patients (median age 80 years) these thromboembolic events with rivaroxaban occurred in younger patients (median age 66 years). The patient populations were also different. Dabigatran events were occurring primarily in its indicated population of patients with atrial fibrillation. The rivaroxaban events were reported primarily in patients taking the drug short term after surgery or other orthopedic procedures. Figure 2 compares bleeding and clot-related adverse events for the four major anticoagulants. For the other drugs except rivaroxaban, bleeding events greatly

Figure 2. Reported anticoagulant bleeds vs blood clot events in 2012 Q1



outnumber thrombotic or clot-related events. The total number of events for each drug shown is influenced by different levels of patient exposure, brand name or generic status, and other

factors. Overall, rivaroxaban, with 104,000 dispensed outpatient prescriptions in the first quarter, trailed far behind dabigatran, with 716,000 prescriptions, according to data from IMS Health.

Company Assessment

We discussed these findings with the manufacturer, the Janssen Pharmaceuticals subsidiary of Johnson & Johnson. The company told us that it had reviewed the same data and saw no signal of a safety issue that needed to be addressed. It noted that direct comparisons with dabigatran were not necessarily valid because the drugs were being used differently in different populations: long-term therapy for atrial fibrillation for dabigatran vs. short-term therapy after hip and knee replacement for rivaroxaban. It attributed the large and rising volume of reports to the company's success in launching the drug, which it said had captured 22.5% of the market for anticoagulation after hip and knee surgery by the first quarter of 2012. It noted that in preapproval and postmarketing clinical trials for hip and knee replacement surgery rivaroxaban was associated with fewer thromboembolic events than comparators.

Conclusions

We agree with the company that direct comparisons between the anticoagulants are complicated by the different patient populations. Although more quarters of data are required to confirm these findings, the rapid increase in reports may also be related in part to an aggressive and successful product launch. QuarterWatch defines an adverse event signal as data sufficiently convincing to require further investigation. In this case, the predominance of reports for thromboembolic events not seen for other anticoagulants constitute a signal of possible sub-therapeutic doses or some other form of unexpected lack of efficacy, and this signal should be investigated further.

Waivers for Non-Serious Adverse Events

We contacted Abbott Laboratories to ask about a large spike in adverse event reports for adalimumab (HUMIRA) received by the FDA in the first quarter of 2012. It included 1,801 domestic serious reports—more than any other regularly monitored drug—and 19,043 non-serious reports. (Botulinum Toxin A was in a distant second place with 2,721 non-serious cases.) Adalimumab, a biological product that blocks Tumor Necrosis Factor (TNF) in the immune system, has long been a high-alert drug that along with other drugs in the class accounts for a disproportionate number of serious adverse events. [6] The company told us that the large number resulted from two factors. Because adalimumab was an older drug, the company was permitted to report on an annual rather than quarterly basis serious adverse events with existing warnings in the prescribing information. Second, it said increasing sales of the drug had

generated more reports. But the non-serious reports resulted from a company policy to report all non-serious adverse events rather than seeking an FDA waiver. Instead of 19,043 reports, the company could have obtained a waiver and submitted zero reports.

An Obsolete FDA Policy

In its 12-year-old but still valid 2001 adverse event reporting guidance for industry [42] the FDA makes it clear that it would rather not know about non-serious adverse events—those that did not involve a death, disability, hospitalization, were life threatening, required intervention to prevent harm or some "other" medically serious event: "Applicants are encouraged to request a waiver of the requirement to submit individual case safety reports of non-serious, expected adverse experiences." The company still had to collect the non-serious case reports, and submit them promptly if requested.

The policy dates back to the time when the FAERS system was new and required a large data entry staff that was burdened with a major backlog of serious reports. It was understandable that the agency, overwhelmed by the data flow, was looking for a practical solution to reduce the workload. Unfortunately, a waiver policy had problems from the start. It added an entirely new element of unpredictability to the reporting system. Some drugs would have waivers from the requirement to submit reports, but a similar drug might not, undermining comparisons between drugs. A uniform requirement (for example, applying to all drugs marketed for three years or more) would have been better, but would still have raised problems. We have previously described the large gray area between "other medically serious" events and non-serious events. The distinction is not clear, and an important side effect might become invisible because the company classified it as non-serious rather than "other medically serious."

Waivers Could Be Eliminated

The FDA need not grant waivers for submission of non-serious reports. It would be hard to find a drug safety problem with a simpler and cheaper solution. Pharmaceutical companies are required to have the case reports in their computer systems, ready to produce within five days. They usually transmit the reports electronically, requiring no data entry by the FDA. In an era where data storage is so cheap that large companies give it away gratis, costs to the FDA would be vanishingly low.

The benefit would be a more complete and balanced safety profile for each drug. It would eliminate ambiguity over whether an event was serious or not, and could provide key links between serious events and non-serious signs and symptoms.

QuarterWatch Team and Funding Sources

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Thomas J. Moore serves as a part-time project director for QuarterWatch. He has developed and maintains the master adverse event database that serves as the primary data source for the publication and conducts the primary analysis for each issue. Mr. Moore receives an honorarium from ISMP for each issue, with the remaining work being on a volunteer basis. Mr. Moore also conducts and publishes other independent studies in the peer-reviewed scientific literature and works as a consultant on drug safety issues, doing business under the name Drug Safety Research. He was a consulting expert to the Attorney General of the State of Texas in a Medicaid fraud lawsuit against Johnson & Johnson regarding the antipsychotic drug Risperdal (risperidone), and was an expert witness for the United States Army in connection with a criminal case involving Chantix (varenicline). In 2011 he was a consulting expert for plaintiffs in the civil litigation regarding Chantix, and examined the completeness and accuracy of adverse drug event reports for biological products for Amgen. He has also conducted confidential assessments for attorneys inquiring about the safety profiles of bisphosphonates, antipsychotic drugs, and proton pump inhibitors.

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