

QuarterWatch: 2010 Quarter 4

Monitoring MedWatch Reports

October 6, 2011

Signals for Two Newly Approved Drugs and 2010 Annual Summary

Executive Summary

In this issue we examine signals for two recently approved drugs and report the case totals for the full calendar year. We analyze reports for dabigatran (PRADAXA) involving its effects on blood clotting, examining cases of too much anti-clotting effect (hemorrhages) and too little clot inhibiting effect (reported thromboembolic events). For the new drug for multiple sclerosis, dalfampridine (AMPYRA), we examine case reports that suggest that some patients report it makes it more difficult to walk while the intended benefit was to improve walking speed. In addition we update our reporting on the smoking cessation drug varenicline (CHANTIX) and dronedarone (MULTAQ), a drug for heart rhythm disorders. We also examine patient death reporting for the pulmonary hypertension drug bosentan (TRACLEER).

For the full calendar year of 2010, we identified 141,829 new cases of serious, disabling or fatal adverse drug events reported to the U.S. Food and Drug Administration, a 21% increase over the 117,093 cases in 2009. The increase of 24,736 cases in 2010 was the largest absolute increase since 1998, although the percentage increases were greater in 2002 (26%), 2003 (25%) and 2008 (27%). In the same period, total dispensed outpatient prescriptions increased by 1.1%, from 3.6 to 3.64 billion, according to IMS Health Inc. data.

The annual results also include a ranking of the drugs most frequently associated with reports of serious injury. Prominent were opioid pain medications, blockers of Tumor Necrosis Factor (TNF), acetaminophen, the antibiotic levofloxacin (LEVAQUIN), and the antipsychotic quetiapine (SEROQUEL).

QuarterWatch™ is an independent publication that monitors all domestic, serious adverse drug events reported to the FDA. We analyze computer excerpts which the FDA releases for research use from its Adverse Event Reporting System (AERS). These voluntary reports (best known as MedWatch) are a cornerstone of the nation's system for assuring the safety of prescription drugs after FDA marketing approval.

Findings for Specific Drugs

Dabigatran (PRADAXA) Clotting-related Reports Surge

Within just weeks of its approval in October 2010, this new drug, approved to reduce the risk of stroke in patients with atrial fibrillation, moved to near the top of our adverse event rankings, with more reports than 98.7% of the drugs we regularly monitor. The predominant

reported adverse effects revolved around the drug's central pharmaceutical purpose, inhibiting the body's blood clotting function. However, the events reported were divided among cases indicating too much inhibition of clotting—hemorrhages—and not enough effect, including thromboembolic events such as pulmonary embolism and deep vein thrombosis. In the full report we discuss three drug safety problems raised by these reports: a) Inhibiting blood clotting in an elderly population with a heart problem remains an inherently risky business with a major capacity to cause injury; b) The drug was launched so rapidly that it was generating hundreds of adverse event reports within weeks of approval; and c) This new anti-clotting drug was immediately used off-label where its risks and benefits were less known.

Dalfampridine (AMPYRA) and Walking Problems

Dalfampridine (AMPYRA), a drug for multiple sclerosis (MS) patients, is a new drug with a new indication: an improvement in walking speed, which is a novel clinical measure. Other MS drugs have been shown to reduce disease progression or relapses. After substantial clinical testing and a full FDA evaluation, it replaced at a cost of approximately \$13,000 a year a largely untested drug that was being compounded in pharmacies because some MS patients and their doctors thought it helped. Critics said the benefit—an improvement of about three seconds in walking speed over a 25-foot runway—was not clinically significant. In the 4th quarter of 2010 we identified 217 serious adverse event reports with dalfampridine as suspect. The reported adverse effects fell into three groups: seizures, a known adverse effect of the drug, reports that it created problems walking rather than improving walking speed, and reports of various kinds of altered mental state. The manufacturer, Acorda Therapeutics, told us that report totals may have been higher because it was a new drug, a new kind of indication, and available only from 12 specialty pharmacies. The company also noted that many of the reported side effects were similar to the underlying disease. We discuss the balance of risks and benefits in the full report.

Varenicline (CHANTIX, CHAMPIX) Update

This aid to smoking cessation acquired a warning in July 2010 about increased risk of serious cardiovascular effects following two new studies. While the FDA declared the risks to be “small,” the adverse event data for the 4th quarter of 2010 suggest these studies may have underestimated the overall vascular adverse effects by limiting the focus to only the most serious events. We found seven additional potential vascular effects not included in these studies including hypertension, dizziness, visual and memory impairment and confusional state. All may be potentially linked to vasoconstriction or vasodilation, effects related to the nicotinic receptors that are bound by varenicline. Meanwhile, the Veterans Administration (VA) restricted the use of varenicline, citing risks of suicidal behavior and violence. The VA made varenicline a second-line drug to be used only if bupropion (ZYBAN) or nicotine patches had failed, and mandated a mental status exam to eliminate patients at greatest risk for psychiatric side effects.

Dronedarone (MULTAQ) Update

For a second time, the heart drug dronedarone (MULTAQ) has been associated with an increased risk of death in a randomized clinical trial. The manufacturer, sanofi-aventis,

announced in July 2011 that a safety monitoring board had halted a clinical trial of dronedarone in patients with permanent atrial fibrillation because of excess mortality. Also seen in that trial was an increased risk or worsening of heart failure, the signal seen most prominently in the adverse event reports as well as in an earlier clinical trial. Dronedarone has also been associated with cases of acute liver failure and reports of potentially lethal heart rhythm disorders, and it interacts with many drugs taken by the target patient population, those with paroxysmal or persistent atrial fibrillation.

The Adverse Event Reporting System Issues

Bosentan (TRACLEER) and 4,133 reported patient deaths. The startling death total of 4,133 patients does not indicate a drug catastrophe, but does reveal an important breakdown in the FDA rules regarding how and when patient deaths should be reported. Because bosentan is a restricted distribution drug for a very specialized and seriously ill patient population, the manufacturer, Actelion Pharmaceuticals, frequently was informed when a patient died. After an inspection, the FDA faulted Actelion for simply assuming the drug had no role in the patient's death rather than investigating each case. This had been going on for at least four years. In response to the FDA warning letter, Actelion reported every patient death it knew of since 2006. But the deaths still had not been investigated, and the reports contained little or no useful information about the event.

The net result of FDA rules and enforcement policies is that its reporting system is being flooded with low quality, uninformative reports of patient deaths in which any drug role was undetermined. We have previously reported on other examples. In the full report we explain why patient deaths, that instead of being the most carefully investigated, are in fact twice as likely to result in vague or uninformative reports.

About QuarterWatch Data

Our findings should be interpreted in light of the known limitations of a voluntary adverse event reporting system. The FDA's Adverse Event Reporting System (AERS) 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 substantial fraction of all new warnings, restrictions or other actions to manage the risks of drugs are based on these data. The reporting rate for AERS is unknown, and published estimates range from around 1% to 15% in most cases, and up to 30% in unusual cases of enhanced reporting. We have observed wide variation among specific drugs, for different kinds of adverse events, and over different time periods. 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 methods are included in the methods section

of this report. An appendix disclosure statement expands our description of this project and its staff.

Conclusions

We urge the FDA to make it a priority to improve the consistency and quality of fatal event reporting by drug manufacturers. The agency needs to develop new adverse event reporting guidelines and enforcement procedures to specify how patient deaths should be investigated by the company and reported. Current programs result in weakened drug safety surveillance because manufacturers, worried about a possible violation, submit large numbers of adverse event reports about patient deaths where the drug was either not a suspect at all, or where any possible drug role is simply unknown. While the quality of investigation and reporting for a patient death in a surveillance system ought to be superior, we find the opposite is true.

The surge in reports for the new anticoagulation drug dabigatran provides a warning about the clinical challenges of altering the blood clotting function in vulnerable, elderly patients with heart problems and other health issues. However, the reports available are insufficient to support a safety comparison between dabigatran and warfarin, the long-used generic drug it is beginning to replace. The substantial volume of reports of serious injury associated with the new MS drug dalfampridine raise the question of whether new guidelines for early discontinuation are needed if patients do not perceive a noticeable improvement in walking speed. Given that a majority of patients in clinical trials did not have evidence of benefit, continuing treatment only exposes them to possible risks.

In the full report we discuss our concern that the FDA is allowing potentially misleading promotional statements to be inserted into the warning sections of the prescribing information for varenicline. For example, the lengthy, 345-word Boxed Warning for varenicline includes two vague benefit claims instead of focusing on a direct and accurate summary of its risks.

The annual standings illustrate that the biggest safety problems during 2010 span the entire spectrum of drug therapy—ranging from acetaminophen, which is nearly universally available but lethal in substantial overdose—to baclofen, a powerful muscle relaxant used in a relatively small and vulnerable population but presenting serious clinical challenges and immediate consequences if problems occur with the device used to administer it.

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Methods

The goal of QuarterWatch is 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, [1] and these case reports are our primary data source.

QuarterWatch focuses on domestic case reports of adverse drug events that are specifically coded as “serious,” which means under FDA regulation events that resulted in death, permanent disability, a birth defect, required 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 and in some cases may summarize longer periods of time. When case reports are revised or updated we use the most recent version while retaining the original report date.

In these data, the adverse event that occurred is described by one or more 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. [5] We also group adverse event terms using a MedDRA category called High Level Terms (HLTs) that also combine several related but more specific medical terms.

To provide a broader perspective on the adverse events reported, we assess the patient exposure to drugs on the basis of dispensed prescription data from 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 2010, 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 result either 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 change over time because each quarter thousands of reports are revised, entered the FDA system late, or 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.

We use the word *signal* to characterize the evidence we see of a safety issue. 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 appears on the QuarterWatch web pages (<http://www.ismp.org/quarterwatch/detailedmethods.aspx>).

Results

For the full year of 2010 serious, disabling and fatal adverse drug events reported to the FDA increased 21.1% over 2009, increasing from 117,093 to 141,829 cases. The additional 24,736 cases compared to 2009 represent the largest absolute one-year increase since our records began in 1998. This increase in domestic cases was entirely attributable to a larger number of reports written and submitted by drug manufacturers. Reports submitted directly to the FDA's MedWatch program declined 13.5% in 2010, from 24,730 in 2009 to 21,385 in 2010. In the same period, total dispensed outpatient prescriptions increased by 1.1%, from 3.6 to 3.64 billion, according to IMS Health Inc. data.

In 2010, reports originated by health professionals constituted 51% of the annual total, consumers 38%, with the source of the remaining 11% unknown. The health professional share of all reports declined by 1 percentage point from the previous year, although reports from both sources increased compared to 2009. Both health professionals and consumers can originate the reports by contacting manufacturers, or submit them directly to the FDA.

Adverse event reports indicating patient deaths increased by 42.9% in 2010 to reach a total of 28,456. This seemingly alarming increase, however, was heavily influenced by large numbers of reports from drug manufacturers about deaths in previous years in which a drug product was taken, but not necessarily suspected to be the cause. This trend, which is discussed in this report, primarily reveals regulatory and compliance issues in the FDA's monitoring program rather than a new and catastrophic danger to patient health.

Table 1 lists the drugs most frequently identified as a primary suspect drug in 2010, after excluding the group of special reporting drugs that we have discussed elsewhere.

The drugs on this annual list provide a useful perspective on the most important drug safety problems being reported most frequently in the previous year. Fentanyl (DURAGESIC, FENTORA, ACTIQ) ranked No. 2 on the 2010 list. It is a synthetic opioid drug that is approximately 80-100 times more potent than morphine and administered for chronic pain using several routes of administration, including transdermal patches and tablets that can be slowly dissolved in the mouth. Fentanyl has proven to be an important but difficult to manage pain medication. We have reported problems of accidental exposure to the drug, patient misplacement of patches, adhesive problems, leaking patches, manufacturing quality problems and use of patches that result in an overdose or withdrawal symptoms. Infliximab (REMICADE), etanercept (ENBREL), and adalimumab (HUMIRA) are biological products for rheumatoid arthritis and other auto-immune disorders that block the actions of human Tumor Necrosis Factor (TNF). The frequently reported side effects—notably cancer and opportunistic infections—of these powerful immunosuppressant drugs have resulted in large numbers of serious adverse event reports for many years and a regular stream of new warnings. The nearly universally available acetaminophen (TYLENOL, many others) causes potentially fatal liver toxicity in intentional or accidental overdoses, and QuarterWatch has focused on the problems of managing these risks. [6] Other drugs we have previously studied include: the antipsychotic quetiapine (SEROQUEL) and potentially irreversible side effects, including diabetes and movement

disorders; [7] the antibiotic levofloxacin (LEVAQUIN) and tendon rupture; [8] the smoking cessation aid varenicline (CHANTIX) and psychiatric side effects; [9] and the muscle relaxant baclofen (LIORESAL, KEMSTRO) and issues involving medical devices used to administer it to the spinal area. [10] [11]

Table 1. Primary suspect drugs for reported serious events in 2010

Rank	Ingredient Name	Brand Name**	Cases*
1	BOSENTAN	TRACLEER	4665
2	FENTANYL	DURAGESIC	3035
3	INFLIXIMAB	REMICADE	2500
4	ETANERCEPT	ENBREL	2446
5	TERIPARATIDE	FORTEO	2375
6	VARENICLINE	CHANTIX	2028
7	QUETIAPINE	SEROQUEL	1585
8	ZOLEDRONIC ACID	RECLAST	1542
9	ADALIMUMAB	HUMIRA	1530
10	ACETAMINOPHEN	TYLENOL	1281
11	LEVOFLOXACIN	LEVAQUIN	1123
12	BACLOFEN	LIORESAL	1077
13	PREGABALIN	LYRICA	1077
14	ATORVASTATIN	LIPITOR	1075
15	OXYCODONE	OXYCONTIN	1070

* Excludes special reporting drugs. **Other brand names may exist.

Results for the 4th Quarter

For the 4th quarter alone, reports meeting the QuarterWatch criteria totaled 38,733, an increase of 5.5% compared to the previous quarter and an increase of 8,852 cases (29.6%) compared to the 4th quarter of 2009. The largest single factor in the one-quarter increase was the startling spike of more than 5,000 patient deaths involving three treatments for pulmonary arterial hypertension, bosentan (TRACLEER), treprostinil (REMODULIN) and iloprost (VENTAVIS). These reports are discussed in the section on adverse event reporting issues. Other contributors to the increase include the recently approved drugs examined in this report and previous reports including dabigatran (307 cases), dalfampridine (217), and dronedarone (164).

Adverse Event Reporting System Issues

4,133 Reported Patient Deaths for Bosentan (TRACLEER)

In one of the most startling signals yet seen, we observed 4,133 reported patient deaths for bosentan (TRACLEER), a restricted-distribution drug approved to treat pulmonary arterial hypertension, a rare, severe, progressive, and frequently fatal lung disease. Total patient deaths of this magnitude are roughly comparable to total U.S. military losses in the Iraq war or one year's deaths from all workplace injuries. These reports also moved bosentan to the No. 1 position in our quarterly ranking of serious injuries for regularly monitored drugs, and the No. 1 position for reported deaths. However, on investigation we discovered a new and dramatic example of an adverse event reporting issue that was troubling, but by no means signaled an emerging drug disaster.

A vital feature of adverse drug event reporting is the inference that the suspect drug may have caused the event reported. The FDA and the pharmaceutical industry frequently note that the submission of an adverse event report does not prove that the drug was responsible. But under normal circumstances some observer suspected that the drug may have been responsible. In the case of patient deaths the FDA requires reporting when "there is a reasonable probability that the drug caused the adverse effect." [12]

Bosentan, meanwhile, is marketed by a Swiss specialty pharmaceutical company called Actelion Pharmaceuticals. After an inspection of Actelion's U.S. facility in South San Francisco, the FDA alleged that the company was not investigating patient deaths of which it learned. [12] But because of a rare disease, a restricted distribution program, and a patient support program, this company was learning of literally thousands of patient deaths from this progressively fatal disease. According to the FDA, the company was assuming that patient deaths in this seriously ill population were not caused by the drug and did no further investigation. (The manufacturer did not respond to our queries.)

In response to the FDA's warning letter threatening additional legal enforcement, the company submitted the 4,133 patient death reports into the AERS system. The death cases dated back to 2006 and contained little or no useful information about the event, most containing a single MedDRA term "Death." The company also submitted an additional 228 patient death reports for another drug product for pulmonary arterial hypertension, iloprost (VENTAVIS). In addition, another manufacturer of a third drug for this disorder, which may have noted the published warning letter to Actelion, suddenly submitted 458 patient reports for treprostinil (REMODULIN).

The net result of this enforcement program was to inject into the agency's vital Adverse Event Reporting System thousands of death reports of low quality and without any investigation or information about whether the drug might have played a role in the patient death. Not only do the reports have no value in postmarket safety surveillance, they obstruct the assessment of genuine potential threats to the public health by diminishing report quality.

Overall, 6,361/10,317 (61.7%) of patient death reports in the 4th quarter were limited-value reports containing the single event term “Death.” In addition, 81% of these cases were also missing patient gender, patient age or both. In the previous quarter, we found fewer but still significant numbers of these cases, 1509/5120 (29.5%) of patient deaths were these limited-value reports.

In previous QuarterWatch reports we have observed other cases where the FDA’s enforcement policy—at least as interpreted by the pharmaceutical companies—has resulted in large numbers of poor quality, uninformative reports of patient deaths. We have also examined death and other reports for DIANEAL, a peritoneal kidney dialysis solution that can be used at home. Because the manufacturer, Baxter International, delivered the product directly to customer homes, it learned of patient deaths. [10] We also reported on a surge of deaths for ibandronate (BONIVA) that occurred because the manufacturer, Roche Therapeutics, had a postcard and email reminder program for its monthly osteoporosis treatment and learned of and reported cases when reminders were returned indicating a patient death. [13] Finally, we have previously reported on hundreds of duplicative reports submitted each year when different generic manufacturers send in all the cases in a single published annual report of drug overdose related deaths from the American Association of Poison Control Centers. Companies reported patient deaths even when their drug product was not a leading suspect, but merely appeared somewhere in published listing as having been taken. [6]

We believe the FDA should make it a priority to evaluate and remedy the unintended effects of its reporting program inspections on drug manufacturers with extensive patient contact through restricted distribution, direct distribution or other patient contact schemes. The net result currently weakens postmarket surveillance.

Several solutions are possible. Through regulations or published guidance the FDA can set standards for how drug companies should investigate and assess causality of patient deaths detected through these special reporting mechanisms (technically called solicited reports). A second approach is to create a reporting category for patient deaths that were not investigated but identified through solicited reports.

Every regulatory step involves weighing costs and benefits. But the current FDA practices impose substantial costs and provide no benefits whatsoever, and likely harm the system.

Dabigatran (PRADAXA) Clotting-related Reports Surge

Within 12 weeks of initial marketing approval in October 2010, dabigatran (PRADAXA) was the suspect drug in 307 reported serious adverse events, outstripping 98.7% of the drugs we regularly monitor, as well as the drug it was intended to replace, warfarin (COUMADIN), with 202 reported cases. The cases—primarily serious bleeding or blood clots in the elderly—underline the inherently high risks of this new anticoagulation treatment.

Dabigatran was approved to reduce the risk of stroke in patients with atrial fibrillation, a heart rhythm disorder of the two upper pumping chambers of the heart. When the small upper pumping chambers stop working normally, it increases the risk that blood clots will form; if the clots reach the brain they may cause a stroke, and can also cause serious injury elsewhere. For decades the accepted treatment strategy was to administer warfarin—which powerfully inhibits the formation of blood clots. The treatment has two major drawbacks. First, warfarin is hard to dose, and requires frequent laboratory tests to insure that the clotting function is inhibited enough to reduce the risk of stroke without undue risk of hemorrhages or serious bleeding. Warfarin also interacts with scores of other drugs as well as some dietary supplements and foods. Second, even with careful testing and patient monitoring, serious bleeding still occurs and is a significant cause of hospitalization.

Clinical testing showed dabigatran appeared to have solved two of the problems of anticoagulation with warfarin: constant monitoring of anticoagulation was not recommended, and it did not have extensive drug interactions as does warfarin. However, a large scale clinical trial that compared dabigatran to warfarin showed that the risk of bleeding remained extremely high with both treatments. [14] In that trial 1977/6076 (32.5%) of the patients treated with dabigatran had a bleeding event, of which 375 (19%) were major or life-threatening. The results for warfarin were similar, with 2142/6022 (35.6%) experiencing bleeding, of which 397 (18.5%) were major or life threatening. If dabigatran solved one long-term drug safety issue (an easier-to-manage drug), it created a new one. If warfarin does cause bleeding severe enough to require treatment, its effects can be readily reversed with an antidote. This is not the case with dabigatran, and the FDA review noted little information yet existed on whether dabigatran bleeding episodes might raise new problems for treatment. [15]

Data from the 4th Quarter

The 4th quarter of 2010 results showed that paradoxically large numbers of reports were being received indicating both adverse effects of imposing a change on blood clotting—hemorrhages that indicated harmful inhibition of clotting, and thromboembolic events indicating the drug might not have been effective in preventing clot-related adverse events. Among the 307 reports, 133 cases (43%) had terms indicating a possible hemorrhage event, and 108 cases (35%) indicated blood-clot related thromboembolic events.

The new reports had two other significant features. First the serious injuries were occurring in a markedly aged patient population, median age of 75 years of age with 25% of the cases over age 83. The data showed that despite a relatively narrow indication (prevention of stroke in patients with atrial fibrillation) the drug was being used extensively off-label, or for general but unspecified purposes of inhibiting blood clotting. For the cases reporting the indication, only 36% specifically reported that it was being used for the approved use of atrial fibrillation. Another 46% indicated the drug was being used to prevent blood clots or stroke in general terms and other cases included clearly off label uses, hip arthroplasty, knee arthroplasty, deep vein thrombosis, surgery and post operative care. The indications data suggest that physicians were substituting dabigatran for warfarin across a wide spectrum of conditions.

We believe this large surge of reports so soon after approval illustrates important drug safety issues, likely to grow in importance as use of dabigatran grows and as additional alternatives to warfarin are approved. First, it shows that inhibiting blood clotting in an elderly population with a heart problem remains an inherently risky business with a major capacity to cause injury. Next, an easier-to-use drug that reaches the blood clotting target range more accurately does not significantly reduce the risk of serious bleeding that is an inherent hazard of the drug's intended effect. In addition, the data show the speed with which a new treatment can spread into wide clinical use, generating reports of hundreds of serious injuries in a matter of weeks. Finally we are troubled that this new anti-clotting drug was immediately used off-label where its risks and benefits had not yet been systematically studied.

Reporting Rates Vary Widely

The reports for dabigatran and warfarin, when combined with dispensed prescription data from IMS Health, powerfully illustrate the large differences that can occur with reporting rates, especially between an older generic drug and a new brand name drug being introduced with extensive promotion. In the 4th quarter, warfarin ranked No. 25 among all prescribed drugs with 6.9 million dispensed prescriptions—and 202 serious adverse event reports. The just-approved brand name drug dabigatran accounted for only 68,000 prescriptions in the 4th quarter (only 1% of the warfarin total) but spurred 307 adverse event reports. Nevertheless, a large clinical trial showed the risk of injury from treatment was roughly comparable for the two drugs. These stark contrasts illustrate that while adverse event reports may provide strong evidence of an association of a particular adverse drug event and a suspect drug, they are markedly less useful for estimating how frequently such events might be occurring.

Dalfampridine (AMPYRA) and Walking Problems

Dalfampridine (AMPYRA), a new drug approved to improve walking speed in multiple sclerosis (MS) patients, accounted for 217 reported serious adverse drug events in the 4th quarter of 2010, which were more cases than hundreds of drugs used in much larger patient populations. Among 869 drugs regularly monitored, the median number of cases per drug was 6 and approximately 50-60 drugs accounted for 100 or more cases in a quarter.

Because all drugs involve a balance of benefits and risks, the large total of reported cases identifying dalfampridine as the primary suspect drug were also notable given the pre-approval debate about whether its benefits were clinically meaningful. Multiple sclerosis is a nerve disorder that involves damage to the myelin sheath that insulates brain and spinal cord nerve fibers. As the myelin sheath is compromised, MS patients may experience tremors, difficulty walking, or other problems involving motor control. Dalfampridine is a broad spectrum potassium channel blocker with complex effects on nerve signal conduction, and the reasons for a therapeutic effect are unknown. The drug is a sustained release version of fampridine, which is also a powerful bird poison for pigeons and other pest birds—where it triggers seizures, erratic flying and vocalizing alarm cries. [16]

For the past 50 years the bedrock foundation of prescription drug approval has been the legal requirement that to be marketed a drug must demonstrate a benefit in rigorous, well controlled clinical trials in human subjects. Over the years literally hundreds of seemingly promising drugs based on novel mechanisms of action or enthusiastic endorsements from doctors or patients who perceived positive results have nevertheless been found to have no measurable benefits when subjected to the rigors of randomized clinical trials. However, the law, FDA regulation, and historical practice do not clearly specify or define what a “benefit” might be. The debate about the efficacy of dalfampridine broke new ground on that issue.

The proposed beneficial effect of dalfampridine was not an effect on MS progression, relapse, or overall functioning. The theory tested was that it could increase walking speed of MS patients—who may have difficulty walking as one symptom of their disease. In the pre-approval trials this was measured by clocking MS patients who were timed with a stopwatch as they walked down a 25-foot runway. The FDA medical reviewer pooled the two clinical trials and reported that, on the average, the dalfampridine patients moved during treatment at 2.36 feet/per second and the placebo patients at 2.29 feet/per sec, a difference that by this yardstick that was not statistically significant. [17] Measured as the change from baseline, the treatment advantage in walking speed amounted to approximately 3 seconds over the 25-foot runway, and was statistically significant. By still another measure, the patients’ own global impression about whether the drug had helped overall, there was also no difference.

However, the dalfampridine trials provide an object lesson in the number of possible ways the progress of a patient moving down a 25-foot runway can be measured. [18] The manufacturer of dalfampridine, Acorda Therapeutics, had set a different measurement metric. It declared that patients who walked *any* faster down the runway during 3 of 4 treatment visits were “responders” if this speed exceeded the fastest non-treatment visit. By this measure, 34.8% of dalfampridine patients were responders compared to 8.3% of the placebo patients, in one trial, and the results were similar in a second, similar trial.

The FDA’s medical reviewer recommended against approval. “The clinical meaningfulness of the benefit is unclear. The responder variable is limited by its ignoring the extent of improvement.” [17] In addition, the reviewer cited the risks: a known risk of seizures, and the possibility not yet fully investigated that it might cause MS relapses and other neurological side effects. The medical reviewer, Kachi Illloh, also concluded the drug should be tested at lower doses with the idea the efficacy might be retained but seizure and other risks reduced.

However, FDA senior management and an advisory committee of outside experts disagreed, and concluded that an adequate benefit had been demonstrated to warrant marketing approval. [19]

Meanwhile, the 217 serious adverse event reports the FDA received in the 4th quarter indicated that potential risks identified in pre-market testing were now being reported in a broader patient population. The adverse events fell into three broad groups: seizures, symptoms that indicated impaired walking or movement, and symptoms of various forms of mental

impairment. We noted 29 cases mentioning seizures. Among the terms appearing indicating walking problems were dizziness (29 mentions), balance disorder (25), gait disturbance (23), fall (20), muscular weakness (13), and muscle spasms (11). The third group of adverse events indicated an altered mental state and included the terms memory impairment (14 mentions), loss of consciousness (14 cases), confusional state (13 cases), and feeling abnormal (11 mentions). More than one of these terms could appear in a single report. These events were reported in a comparatively small patient population of approximately 50,000 patients according to the manufacturer, Acorda Therapeutics.

The manufacturer provided several additional perspectives on the fourth quarter reporting. First the company said it expected larger numbers of case reports because this was a new drug for a new indication. Also, dalfampridine was available only through 12 specialty pharmacies—which often sent follow up queries to patients if the prescription was not renewed. This practice, the company said, could lead to a higher reporting rate. Finally the company noted that many of the reported events were difficult to distinguish from the underlying symptoms of the progressing MS disease. In addition a senior company scientist told us that walking speed was chosen as an endpoint because FDA approval required a benefit that could be measured and the theoretical drug effect—improved nerve conduction in some patients—could not be measured directly.

While the company observed that many of the reported events resembled symptoms of MS, the FDA reviewer concluded that the clinical testing had not been capable of measuring the possibility that at least in some patients, dalfampridine could worsen the disease. These reports do not resolve the question, but show some patients believed that to be the case and reported it. However, the specialized pharmacy contacts with patients could also have increased report totals.

We believe these reports provide a signal that shows that the neurological adverse effects potentially identified in clinical testing are now resulting in reported patient injuries that are serious, including those requiring hospitalization or counted as life-threatening. With benefits as limited as those observed, it does not take much to tip the benefit-risk balance in an unfavorable direction. At a minimum, guidelines for early discontinuation should be considered in patients who do not perceive a marked subjective improvement in walking or other movement within the first month of treatment.

Varenicline (CHANTIX, CHAMPIX) Update

After both the FDA and an independent meta-analysis found increased risks of serious cardiovascular events, a new section about this risk was added to the prescribing information for varenicline (CHANTIX, CHAMPIX). New data from the 4th quarter and previous case reports suggest that both studies may have underestimated the overall cardiovascular risks of varenicline because they were limited to serious cardiac events such as strokes, unstable angina, heart attacks and coronary bypass surgery. The reported adverse events for varenicline included at least seven other possible vascular adverse effects that could be a result of either vasoconstriction or sudden vasodilation. Meanwhile, the Veterans Administration substantially restricted the use of varenicline because of its increased risks of suicide and violence. Nevertheless, the FDA allowed

additional promotional statements into the prescribing information warning sections that dilute the logic and force of the warnings.

While the main focus on safety has involved psychiatric side effects and severe skin reactions, the possibility of cardiac adverse events was noted in our first report in May 2008. [20] The issue was largely resolved in July 2011 when a widely-noticed meta-analysis of 14 clinical trial data [21] showed a 72% increased risk of serious cardiovascular events. At the same time the FDA released its own analysis of a single clinical trial in higher risk cardiovascular patients, and reached similar conclusions. [22]

The FDA, however, minimized the risks in its public announcement. It described it as “a small increased risk” and said “the absolute risk in relation to its efficacy is small.” While it is reasonable to focus a safety analysis on the most serious risks, a broader look shows that varenicline’s cardiovascular effects may be more widespread. Because varenicline binds many of the same nerve cell receptors as nicotine, it should share with cigarettes some of the same effects on vasoconstriction or vasodilatation.

In the 4th quarter we identified seven additional adverse effects that could be related to blood pressure regulation, but were not as serious as heart attacks or strokes. These included hypertension (13 mentions), increased blood pressure (12 mentions), dizziness (9) visual impairment (9), memory impairment (9), confusional state (9) and speech disorder (5). These same effects (especially dizziness, visual impairment, confusional state) may also contribute to the risk of accidents. We believe a broader and more complete assessment of the cardiovascular risks of varenicline is now needed, focusing on blood pressure regulation and vasoconstriction. Given that a primary immediate benefit of smoking cessation is supposed to be a reduction in cardiovascular risks, this emerging safety profile of increased vascular risk is troubling.

Meanwhile, the flow of reports of serious psychiatric side effects continued unabated. In the 4th quarter, varenicline ranked high among all drugs we regularly monitor for following Standardized MedDRA Queries (SMQs): depression (74 mentions, ranked No. 1), hostility-aggression (64 cases, ranked No. 1), psychosis (46 cases, ranked No. 1), and suicidal/self injurious behavior (26 cases, ranked No. 2).

Promotional Statements Dilute Important Warnings

The varenicline prescribing information (or package insert) continued to acquire additional promotional statements in what are normally sections devoted to safety. The Boxed Warning (a.k.a. black box warning) for varenicline—normally reserved for the most essential risk information—contains the statement. “The health benefits of quitting smoking are immediate and substantial.” To our knowledge, varenicline has not been proven to have immediate health benefits, and in fact demonstrated immediate health risks. Similarly, the cardiovascular events paragraph in the *Warnings and Precautions* section concludes with another promotional statement: “CHANTIX has been demonstrated to increase the likelihood of abstinence from smoking for as long as one year compared to placebo.” While technically true this promotional statement omits the fact that at one year smoking cessation rates were low (around 20%) and not

statistically significantly different from nicotine patches. [23] A similar third promotional statement occurred in the separate section, *Neuropsychiatric Symptoms and Suicidality*. This is the only instance we know of in which the FDA has allowed promotional messages in sections intended to provide warnings and precautions, including its highest priority warning, the Boxed Warning at the beginning of the label.

Veterans Administration Restricts Varenicline

Meanwhile, because of psychiatric side effects, the Veterans Administration has substantially restricted varenicline, moving it to a second-line medication to be used only after the patient had failed on bupropion (ZYBAN), nicotine replacement or a combination. [24] In addition, the VA required that before starting varenicline, patients should receive a mental health screening. “Patients with suicidal or assaultive thoughts, ideation or behaviors within the past 12 months are not candidates for varenicline,” the VA stated.

Dronedarone (MULTAQ) Update

Evidence is accumulating from multiple sources, including reported adverse events, that the heart drug dronedarone (MULTAQ) may trigger or worsen heart failure and may cause potentially lethal heart rhythm disturbances, raising the fundamental question of whether this treatment is beneficial or harmful. Dronedarone is an antiarrhythmic drug approved to “reduce the risk of cardiovascular hospitalization” in patients with episodic or “persistent” atrial fibrillation, a heart rhythm disorder of the two small upper pumping chambers of the heart. In July 2011 the manufacturer, sanofi-aventis, terminated a clinical trial with dronedarone after interim data showed an increased risk of death, stroke and hospitalization for heart failure. [25]

The main difference between the clearly harmed patient population in the terminated trial (called PALLAS) and the approved patient population was that the PALLAS patients had “permanent” atrial fibrillation and currently approved patients may have “persistent” atrial fibrillation. The company stated, however, “The risk benefit of Multaq remains unchanged in its approved indication in non-permanent AF.” [26] In addition, increased risk of death and worsened heart failure was seen in an earlier clinical trial in patients recently hospitalized for heart failure.

The adverse event reports for the 4th quarter for dronedarone mirror the more authoritative findings of the PALLAS trial. Of special concern were 26 case reports of heart failure and 16 possible cases of fatal and life threatening disruption of the two ventricles, the main pumping chambers of the hearts. Also seen in the adverse event reports were indications of the other safety questions, including possible liver toxicity, interaction with warfarin, and possible cases of kidney failure and impairment.

As noted in the original QuarterWatch report on dronedarone, its limited clinical benefits and numerous safety issues raise serious doubts about its suitability for widespread clinical use. [6] The later discovery of a risk of life-threatening liver toxicity and an additional clinical trial with excess deaths raise the fundamental question of whether this drug is, overall, harmful or beneficial.

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 is currently 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 in 2009 was an expert witness for the United States Army in connection with a criminal case involving Chantix (varenicline). In February 2011 he agreed to serve as a consulting expert for the plaintiffs in the civil litigation regarding Chantix. In 2011 Moore examined the completeness and accuracy of adverse drug event reports for biological products for Amgen.

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