

QuarterWatch

Monitoring FDA MedWatch Reports

Anticoagulants the Leading Reported Drug Risk in 2011

May 31, 2012

New Data from 2011 Quarters 3 - 4

Executive Summary

Annual Report Issue

For the calendar year of 2011 an estimated 2 to 4 million persons suffered serious, disabling, or fatal injury associated with prescription drug therapy, based on our analysis of a full year of reports to the U.S. Food and Drug Administration. The most frequently identified suspect drugs in direct reports to the FDA were the anticoagulants dabigatran (PRADAXA) and warfarin (COUMADIN), showing that inhibiting clotting ranks among the highest risk of all drug treatments. In addition, we identified nine other drugs associated most frequently with five clinically relevant, drug-related injuries, and show the drugs most frequently the target of lawsuits.

In 2011 the FDA received 179,855 reports of serious, disabling, and fatal adverse drug events in the United States. This was an increase of 15,386 cases, or 9.4% from 2010. We made a minor technical change in our selection criteria that increased the quarterly totals of serious adverse drug event reports, but all historical comparisons use recalculated data. In the same period an estimated 48% of the population was taking a prescription drug in any given month, and an estimated 3.6 billion outpatient prescriptions were dispensed, according to data from IMS Health, a total unchanged from 2010.

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 that the FDA releases for research use from its Adverse Event Reporting System (AERS). 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. Because the FDA has accelerated the release of its data, this report incorporates new information from 2011 Q3 and Q4 not included in previous QuarterWatch reports. Once a year we examine the annual data rather than results from the most recent quarter.

FDA Direct Report Rankings as Risk Index

Reports of serious adverse drug events reach the FDA through two different routes. Among the 179,855 reported cases in 2011, 88% were collected, written, and submitted by drug manufacturers, and only 12% (n = 21,002) were submitted directly to the FDA by health professionals and patients. Many factors influence manufacturer reporting of adverse events. A company actively marketing a brand name drug may learn of adverse events when its sales force calls on physicians, and through consumer hotlines and assistance programs. On the other hand, the multiple manufacturers of a generic drug have little contact with physicians and patients and seldom learn of events to report. This and other variability is avoided with direct reports to the FDA because all events can be reported to a single FDA web site or 800 number.

Thus, direct reports to the FDA constitute one of the most valuable drug safety risk indices: they represent the serious problems that consumers and health professionals are contacting the FDA to report. However, they provide less reliable information from which to determine how frequently any particular adverse event for a specific drug may be occurring. The FDA estimates that less than 1% of all serious adverse events are reported directly to it. Using 2011 report totals, that suggests that there would have been an estimated 2 million cases of serious injury, including 128,000 patient deaths. We explore other injury estimates as high as 4 million in the full report. The five specific drugs with the largest numbers of reports are shown in Table 1; a more comprehensive list appears in the full report.

Rank	Drug Name	Brand Name	Year Approved	Direct Reports
1	DABIGATRAN	PRADAXA	2010	817
2	WARFARIN	COUMADIN	1954	490
3	LEVOFLOXACIN	LEVAQUIN	1996	393
4	CARBOPLATIN	N/A	1989	376
5	LISINOPRIL	ZESTRIL	1988	351
	All other drugs			18,575
	Total (all cases)			21,002

Dabigatran (PRADAXA) and Warfarin (COUMADIN)

Two drugs that inhibit the formation of blood clots ranked first and second among all direct reports to the FDA in 2011, emphasizing that the combination of a vulnerable patient population and a powerful pharmacological action rank among the highest risks in prescription drug therapy. While a therapeutic goal of preventing strokes, pulmonary embolism, and other harm through unwanted blood clots is a worthy objective, these results demonstrate that

treatment is accompanied by substantial risks. We identified both similarities and differences between the two widely used anticoagulant drugs.

Dabigatran (PRADAXA), approved in 2010 for the prevention of stroke in patients with atrial fibrillation, accounted for so many reports of serious adverse drug events that was prominent in several different categories. It accounted for 3,781 domestic, serious adverse events overall in 2011 (both manufacturer and direct reports), including 542 patient deaths. It surpassed all other regularly monitored drugs in reports of hemorrhage (2,367 cases), acute renal failure (291), and stroke (644). It was also suspect in 15 cases of liver failure.

Warfarin (COUMADIN) is the generic drug that since 1954 has been the mainstay of anticoagulation treatment. Its disadvantages are that it requires regular laboratory tests to optimize dosing and interacts with numerous other drugs. It has placed near the top in the rankings of direct reports to the FDA for many years despite being a generic drug with a well-known safety profile. It accounted for 1,106 cases overall in 2011, including 72 deaths.

Litigation as a Risk Index

In 2011, the FDA received almost twice as many adverse event reports in connection with lawsuits against drug manufacturers for alleged patient injuries (n = 43,819) than it did direct reports to MedWatch. Although we monitor litigation-related reports separately from our regular program, these cases reflect patients who believe they have experienced a serious drug related injury and are typically represented by lawyers who find the claims credible enough to fund the costs of litigation hoping for contingency fees if damages are recovered. Table 2 shows the most frequently identified drugs in MedWatch reports indicating lawyers as the report source.

Drug Verbatim Name*	Generic Name	Cases
METOCLOPRAMIDE	METOCLOPRAMIDE	11,450
YAZ/YASMIN	DROSPIRENONE-ETHINYL ESTRADIOL	8,354
AVANDIA	ROSIGLITAZONE	4,105
CHANTIX	VARENICLINE	3,632
ACCUANE	ISOTRETINOIN	3,107
All other drugs		30,648
Total (all cases)		43,819

* Most frequent name given

These cases represent prominent drug safety issues. Metoclopramide (REGLAN), a drug for acid reflux and nausea, is associated with irreversible movement disorders. YAZ and YASMIN are two brands of a combined oral contraceptive containing the synthetic progestin drospirenone, and associated with higher risk of blood clots than other combined products.

Rosiglitazone (AVANDIA), a Type 2 diabetes drug, was restricted because of increased risk of cardiovascular events. The smoking cessation aid varenicline (CHANTIX) has a Boxed Warning for serious psychiatric side effects, and isotretinoin (AC CUTANE), a drug for severe acne, has warnings about birth defects, psychiatric disorders, inflammatory bowel disease, serious skin reactions, and pancreatitis.

Five Severe Side Effects and Most Frequent Suspect Drugs

In the annual data we identify nine suspect drugs most frequently associated with five severe drug side effects resulting in an estimated 179,000 cases of injury based on an assumption of a 5% reporting rate. We explore each of these adverse events in greater detail in the full report. The results are summarized in Table 3.

Table 3. Two most frequent drug suspects for selected severe side effects in 2011

Side effect	Cases	--Suspect Drugs--		Top 2
	all drugs	1st ranked	2d ranked	percent*
Severe liver injury	2,260	INFLIXIMAB	ACETAMINOPHEN	13.2%
Severe cutaneous reactions	2,207	LAMOTRIGINE	VARENICLINE	9.6%
Suicidal/homicidal thoughts	2,030	QUETIAPINE	VARENICLINE	18.9%
Pancreatitis	1,902	LIRAGLUTIDE	EXENATIDE	43.0%
Rhabdomyolysis	516	SIMVASTATIN	ROSUVASTATIN	38.0%

* 1st and 2d ranked percent of all cases

Severe Liver Injury. Because the liver is the most important body organ for metabolizing drugs, it also can be a target organ for drug toxicity. The liver has the capacity to recover from moderate levels of injury, a problem reported for many drugs; a few drugs can overwhelm the organ, leading to severe symptoms and on occasion liver failure. Infliximab (REMICADE), a biological product for rheumatoid arthritis and other autoimmune disorders, accounted for 159 reported cases and the ubiquitous acetaminophen, for 139 cases.

Severe Cutaneous Reactions. When the immune system reacts to a drug, severe skin reactions are one form this adverse reaction may take. In serious cases this can involve exfoliation of large areas of skin, and intensely painful, life-threatening conditions such as Stevens-Johnson syndrome (SJS) and Toxic Epidermal Necrolysis (TEN). In 2011, the two drugs accounting for the most reported cases of severe cutaneous adverse effects were an antiepileptic drug lamotrigine (LAMICTAL), with 119 cases reported, and the smoking cessation aid varenicline (CHANTIX), accounting for 93 cases.

Suicidal/Homicidal Thoughts. Although 58 drugs have FDA-approved warnings or precautions about suicidal behaviors, identifying suspect drugs in adverse event data is challenging. Reports of suicide or attempted suicide may identify a drug that was a *means* of self

injury—an intentional overdose of a toxic drug—without necessarily having a psychiatric role. For this reason we monitored drugs reported to be causing *thoughts* of injury to self or others. The most frequently identified drug in 2011, with 197 reported cases, was quetiapine (SEROQUEL), a drug developed for psychosis but now used for a wide variety of conditions including depression and off label as a sleep aid. Ranked second was the smoking cessation aid varenicline, with 187 cases. Varenicline has a Boxed Warning about psychiatric side effects.

Pancreatitis. The pancreas, with a critical role in producing insulin and other enzymes to digest food, can become swollen and inflamed in the presence of some drugs. In extreme cases, pancreatic tissue is lost. As a new family of drugs to treat Type 2 diabetes—called GLP-1 agents—spread into wider use in recent years, so did reports of acute and chronic pancreatitis. Liraglutide (VICTOZA) was the most frequent suspect, with 413 reported cases, and exenatide (BYETTA) ranked second, with 404 cases. Just these two drugs accounted for 43% of all reported cases of this adverse effect.

Rhabdomyolysis. When skeletal muscle cells are damaged or destroyed, they release a protein into the bloodstream called myoglobin. When the amount is large, it can overwhelm the kidneys' capacity to excrete this protein and lead to renal failure. Awareness has grown that the risk of causing muscle damage caused by the cholesterol lowering drugs known as statins has been underestimated. In 2011 a total of 516 cases of this most severe form of muscle damage were reported. Ranked first with 123 cases was simvastatin (ZOCOR); rosuvastatin (CRESTOR) was second, with 73 cases.

Improving the Adverse Event Reporting System (AERS)

Poor Quality Death Reporting by Manufacturers

In 2011 the most serious weakness in postmarket surveillance that we identified was the frequency of vague, low-quality reports from drug manufacturers about patient deaths. Death reports were submitted in cases where a causal role of the drug was entirely unknown, or not suspected by anyone. For example, we have identified cases where the FDA required reporting of patient deaths that occurred when prescription refill reminder postcards were returned indicating the patient was deceased. FDA enforcement of regulations for reporting any patient death—but without adequate evaluation of a possible causal role—is a prime contributing factor to the volume of low-quality reports. In 2011, a total of 30,385 patient deaths were reported to the FDA. However, of this total, 9,219 death cases (30.3%) were of little or no value for safety assessment because the only description of the event was the single report term, *Death*. Nearly half of these cases were missing age information, and 15.8% omitted gender.

Conclusions

The 2011 annual results emphasize that anticoagulant drugs used in a vulnerable older population are resulting in thousands of serious injuries and death, and these must rank among the highest risk of all outpatient drug therapies. Additional steps to achieve safer use of these drugs—especially dabigatran—should be an important priority.

Among the drugs identified as leading suspects in severe side effects, most carry some form of FDA-approved warnings, often prominent ones. On one hand, this shows that FDA and manufacturer safety surveillance programs have identified these significant safety risks. On the other, it illustrates that placing warnings in product information documents only begins the process of managing the risks of prescription drugs. The nine drugs identified provide a good starting point for developing programs to use drugs more safely.

Numerous tools are available to address the drug risks identified in this report. For example, given there are many alternative anticonvulsants, the FDA should consider restricting to second line use the epilepsy drug lamotrigine, which has an acknowledged risk of severe and fatal cutaneous adverse reactions. We have previously concluded that the smoking cessation drug varenicline, with psychiatric, cardiovascular, and accident risks, is unsuitable for first line use.

In other cases, comparative safety studies are needed to document the safest agents and more clearly identify high-risk groups. For HMG-CoA reductase inhibitors (statins), the emerging information about their risks—notably rhabdomyolysis and diabetes—provides an example of a drug class deserving priority attention to determine optimal dosages, target populations for treatment, and identify the safer drugs within this class of medications.

In addition, some regulatory decisions now warrant critical reconsideration. The approval of dabigatran—with a single primary dose and no readily available laboratory test to guide dose optimization—is a prime example of a decision that should now be reassessed to determine whether additional measures can facilitate safer use.

Finally, for the FDA to require manufacturers to submit so many essentially worthless reports of patient deaths into the AERS system without follow-up or useful detail is simply unacceptable. We describe a straightforward solution in the full report.

With an estimated 2 to 4 million serious injuries each year, drug therapy stands as one of the most significant perils to health resulting from human activity. Major health benefits can be achieved through safer medication use, which should be a much higher priority for medicine, government, and the public.

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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.

Starting with this 2011 Q 3-4 issue we made a technical change in our definition of serious adverse drug events that resulted in capturing an additional 1,000-2,000 events each quarter. Some events from drug manufacturers are coded with an outcome of *Other*. Previously we had assumed that this code might mean “other than serious” rather than “other medically serious” unless the report had other indications the event was serious. However, the FDA has clarified its guidance to industry to indicate that “Other” means a medically serious event. Inspection of reports shows industry is complying with this guidance. As a result, we are now counting these events as serious under the QuarterWatch definition and revised the historical data starting with 2006 to permit accurate comparisons.

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 initial 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. [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. The QuarterWatch database was updated in November 2011 to MedDRA version 14.1.

To assess some adverse drug events, we calculate a proportional reporting ratio (PRR), which shows whether an unexpectedly large number of cases of a specific adverse event (e.g. depression, pancreatitis) was reported for the suspect drug, compared with the expected number based on the totals for all other drugs. The PRR adjusts for background noise levels and the possibility that different drugs have different reporting rates. A full technical description and example appear in the Detailed Methods section of the QuarterWatch web page (<http://www.ismp.org/QuarterWatch/detailedmethods.aspx>).

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.”

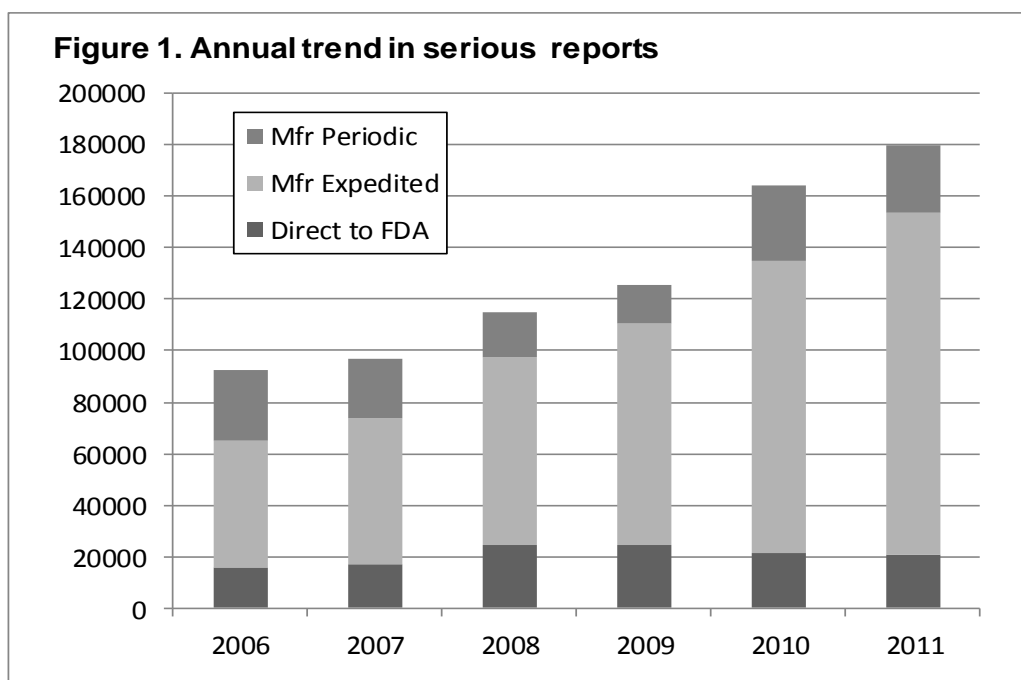
The QuarterWatch totals include a category of drugs with special reporting requirements, restricted distribution, or active surveillance programs that either result in a much higher reporting rate or capture adverse events in which drug involvement is not necessarily suspected. These special category 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, entered into 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. 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>).

Results

In 2011 the FDA received 179,855 reports of domestic, serious, disabling, or fatal adverse events that identified a therapeutic drug as a primary suspect. This was an increase of 15,386 cases (9.4%) from the 2010 total, 164,469. As noted, case reports reach the FDA through two mechanisms: reports from health professionals and consumers directly to the FDA MedWatch program and reports prepared and submitted by drug manufacturers for any adverse event of which they learn. In 2011 the trends were different for the two kinds of reports. A total of 21,002 cases (11.7%) were direct reports to the FDA, a decline of 1.8% from 2010. On the other hand, reports from manufacturers totaled 158,853 (88.3% of the total) and increased by 9.9% over 2010. The longer term trends are illustrated in Figure 1.



Reports from manufacturers, in turn, are divided into two classes. Expedited reports describe serious adverse events for which adequate warnings do not exist, and must be submitted to the FDA within 15 days. Periodic reports are events for which warnings already exist, and are submitted on a quarterly or annual basis.ⁱ As Figure 1 indicates, the growth in reported serious adverse events is entirely explained by increases in Expedited reports from manufacturers. The

ⁱ Periodic reports also include non-serious events, but these cases are excluded under QuarterWatch selection criteria.

increase, we believe, is largely explained by marketing activities for newer brand name drugs that cause the industry to learn of more adverse events. In addition, some recently approved drugs are generating substantial numbers of new reports. Examples include dabigatran (PRADAXA), dronedarone (MULTAQ), fingolimod (GILENYA) and liraglutide (VICTOZA). Since 2008, our earliest data, patient exposure as measured by dispensed outpatient prescriptions from IMS Health has changed little.

FDA Direct Report Rankings as Risk Index

In searching for data to help set an agenda for drug safety risk management, we have found that an annual listing of direct (rather than manufacturer) reports to the FDA provides important insights not available anywhere else. The defining characteristics of the FDA's direct reports are that they are spontaneous and voluntary. Consumers and health professionals identify a possible drug side effect and become concerned enough to contact the FDA and fill out a MedWatch form. The person reporting doesn't need to identify the manufacturer or know how to contact the company. They contact the FDA. Drug companies also collect important drug safety information through their safety surveillance programs, but there are many more factors influencing what events a company learns about, and how it processes that information. The FDA direct reports share other limitations of spontaneous reports, the most significant being that, particularly for individual drugs, the data provide only clues to incidence—how frequently the reported event is occurring. Also, the volume of direct reports is small—just 21,002 case reports in 2011 to describe events occurring in a patient population numbering in the hundreds of millions. Nevertheless, in a field with a limited research base, it remains one of the best measures available.

Injury Estimates

It is a consensus view [6] but supported by limited research data that less than 1% of all serious adverse events are reported directly to the FDA. Thus, the 21,002 cases reported directly to the FDA in 2011 produce an estimate of 2.1 million serious injuries, including 128,000 patient deaths. When including manufacturer reports, the total reaches 179,855 cases, and the estimates of overall reporting rates range from 1% to 15%. Our previous estimate of around 5% of all cases being reported [7] produces a midpoint estimate of 3.6 million serious, disabling, or fatal injuries, with a broad range of 1.8 million (10% reporting) to 18 million (1%). Taken together, these data result in a conservative estimate of 2 to 4 million drug-induced serious injuries in 2011. While these estimates are large, the definition of a serious adverse drug event includes many events that might not result in hospitalization such as accidents, suicide, sexual dysfunction, depression, elevated blood sugar, weight gain, or angioedema. Most estimates in the range of 1 to 2 million were based on hospitalization rates. [8] [9]

Most Frequent Suspect Drugs

Table 4 below lists the 15 drugs most frequently identified as primary suspects in direct reports to the FDA during 2011. (For reference, the number of manufacturer reports is also shown.) Rather than evaluating the exact numbers of reports, we believe the list is most useful to show rank order, meaning that in priority order these were the drugs that health professionals and consumers told the FDA were causing serious and fatal side effects. Also, the year-of-approval results show that major drug safety issues are hardly confined to recently approved drugs. Just 3 of these 15 suspect drugs were approved in the last decade and only one in the previous year.

Rank	Drug Name	Brand Name	Year Approved	Report Type	
				Direct	Mfr
1	DABIGATRAN	PRADAXA	2010	817	2,964
2	WARFARIN	COUMADIN	1954	490	616
3	LEVOFLOXACIN	LEVAQUIN	1996	393	583
4	CARBOPLATIN	N/A	1989	376	140
5	LISINOPRIL	ZESTRIL	1988	351	274
6	CISPLATIN	N/A	1978	343	105
7	SIMVASTATIN	ZOCOR	1991	312	244
8	DULOXETINE	CYMBALTA	2004	278	789
9	CIPROFLOXACIN	CIPRO	1987	264	201
10	SULFAMETHOXAZOLE-TRIMETHOPRIM	BACTRIM	1973	200	85
11	ALENDRONATE	FOSAMAX	1995	195	982
12	CYCLOPHOSPHAMIDE	CYTOXAN	1959	176	502
13	ZOLEDRONIC ACID	ZOMETA	2001	173	1,520
14	BEVACIZUMAB	AVASTIN	2004	170	590
15	LAMOTRIGINE	LAMICTAL	1994	166	585

Anticoagulant Drugs Most Frequently Reported Risk

Dabigatran (PRADAXA) and Warfarin (COUMADIN)

In the sobering arithmetic of anticoagulation, treatment with warfarin prevents ischemic strokes in approximately 1% of high-risk patients a year, but causes major bleeding in an estimated 3%, and minor bleeding in another 15%. [10] [11] [12] Some analyses note that stroke damage is disabling and largely irreversible, while many bleeding cases can be treated, although some are fatal, and hemorrhages in the brain and CNS are just as harmful as ischemic strokes.

However, using anticoagulants in patients with atrial fibrillation and other conditions where blood clot injury risk is high is standard practice in medical care.

With these high rates of drug-induced injury, it is not surprising to find anticoagulants dabigatran (PRADAXA) and warfarin (COUMADIN) leading the rankings that identify the drug safety problems most frequently reported directly to the FDA. Both were also prominent in the overall totals that include drug manufacturer reports. In overall reports, the most frequently reported side effect of the two anticoagulant drugs was bleeding. Hemorrhage cases totaled 2,367/3,781 or 62.6% of all cases for dabigatran, and 731/1,106 (66%) for warfarin. And the reported cases overall were frequently lethal, with deaths totaling 542 (14%) for dabigatran and 72 (7%) for warfarin.

Similarities Between Drugs

Although in the overall event count dabigatran cases outnumbered warfarin injuries more than threefold (3,781 v. 1,106), these data alone are insufficient to conclude that dabigatran has a higher risk of bleeding than warfarin. In the large comparative trial, rates of major and minor bleeding were similar for the two drugs, although gastrointestinal hemorrhages were more frequent with dabigatran. [12] The difference could be at least partly explained by differences in the reporting rate for an older generic drug with many manufacturers, and a newly launched brand name drug being promoted by a large sales force. What is clear, however, is that the FDA's system is receiving a strong signal about this safety issue. A large share of dabigatran reports (79%) come from health professionals, suggesting that despite this well-known drug risk the bleeding was unexpected or unusually severe.

Differences

The primary feature of dabigatran that has helped its rapid uptake into the market has been the perception that it is easier to use than warfarin. Its use does not require frequent laboratory tests to adjust the dose—as does warfarin—and it has fewer drug interactions. It is approved in one primary dose of 150 mg. However, as previously reported, this one-dose-fits-all strategy may be leading to excessive doses in the oldest patients, especially those with declining kidney function. [13] As of January 2012, a new manufacturer recommendation now says physicians should “assess renal function during therapy as clinically indicated.” But it is not clear whether this modest language will lead to safer use. Whether anticoagulation can be managed safely without individualizing the dose remains an unanswered question.

The Future

A new trial comparing warfarin and low-dose aspirin in heart failure patients illustrates the difficult balance between ischemic stroke prevention and bleeding risk. [10] As in previous

studies, warfarin was more effective than aspirin in preventing ischemic strokes, but that benefit was offset entirely by an increase in major bleeding, hemorrhagic strokes, and deaths. The need to achieve greater safety in anticoagulant treatment should be a drug safety priority. While dabigatran is replacing warfarin in the market as a drug that is easier to use, the priority need is for stroke prevention treatments that are safer. We think the FDA, the medical community, and the manufacturer need to reassess the single primary dose recommendation for dabigatran. Among the possibilities warranting study are making the 110 mg dose used outside the U.S. available here for the oldest patients, more specific monitoring of kidney function, regular testing of anticoagulation effect, and identification of patient subgroups where safer alternatives may provide adequate stroke prevention.

Litigation as a Risk Index

Lawsuits brought on behalf of patients claiming a serious drug-induced injury are another measure of prominent drug safety problems being reported. In 2011, the FDA received almost twice as many adverse drug event reports connected with lawsuits against drug manufacturers for alleged patient injuries (n = 43,819) as it did direct reports to MedWatch. On one hand, if tens of millions of dollars are being spent in litigation on behalf of thousands of patients, it is often a signal of a major drug safety issue. On the other hand, the filing of a lawsuit claiming that a drug caused harm is not proof that a drug-induced injury occurred. It is not uncommon for thousands of lawsuits to be later dismissed without any damage award. This is because the legal burdens on patients making claims are substantial. The plaintiffs must present convincing scientific evidence that the drug was capable of causing the particular side effect; they must prove that the drug and not some other medical problem caused the side effect in each patient; in addition the claimants must prove that the drug was unsafe and defective, or that the company knew of risks and failed to warn doctors and patients.

We monitor litigation-related reports separately from our major program for several reasons. Because these reports are typically filed by the legal departments of pharmaceutical companies that have received newly filed lawsuits, they often represent events that occurred years before and may have already been reported by patients or providers. Also, the initial lawsuit documents often contain limited detail and may arrive in large clusters for specific drugs. Nevertheless, these case reports provide another form of signal meriting examination.

Table 2 (reprinted from the Executive Summary for reference) shows the drugs most frequently the target of personal injury lawsuits. Metoclopramide (REGLAN) led the 2011 rankings. QuarterWatch has previously reported that this drug for acid reflux is capable of causing irreversible nerve damage that results in disfiguring involuntary movements. [14] Combined oral contraceptives containing drospirenone acquired strong new FDA warnings about increased risk of blood clots, but were not withdrawn even though safer alternatives with lower

risk are available. [15] Rosiglitazone (AVANDIA) was withdrawn in Europe in 2010 but the FDA has permitted its continued sale with severe restrictions. Varenicline and isotretinoin have had numerous safety issues and acquired prominent warnings over many years.

Drug Verbatim Name*	Generic Name	Cases
METOCLOPRAMIDE	METOCLOPRAMIDE	11,450
YAZ/YASMIN	DROSPIRENONE-ETHINYL ESTRADIOL	8,354
AVANDIA	ROSIGLITAZONE	4,105
CHANTIX	VARENICLINE	3,632
ACUTANE	ISOTRETINOIN	3,107
All other drugs		30,648
Total (all cases)		43,819

* Most frequent name given

Five Severe Side Effects and Most Frequent Suspect Drugs

The primary objective of QuarterWatch is not to flag “dangerous” drugs, but rather to provide data and analysis to support better programs to manage their risks. Such efforts must necessarily begin with understanding the number and nature of drug-induced injuries and the specific drugs suspected of causing them. Tools available to lower the risk of injury include better information for health professionals and patients, restrictions on use of high-risk drugs, preferences for safer alternatives, and better identification of vulnerable patient subgroups.

In this next section we report the data for five severe side effects with substantial evidence linking them to drugs. The two most frequently identified suspect drugs and three estimates of possible incidence rates are shown in Table 5. The incidence estimates show that while these side effects are considered “rare,” they likely result in tens of thousands of serious injuries every year.

Side effect	All cases	---Suspect Drugs---		Top 2 percent*	Reporting Rate/Incidence Estimate**		
		1st ranked	2d ranked		1%	5%	10%
Severe liver injury	2,260	INFLIXIMAB	ACETAMINOPHEN	13.2%	226,000	45,200	22,600
Severe cutaneous reactions	2,207	LAMOTRIGINE	VARENICLINE	9.6%	220,700	44,140	22,070
Suicidal/homicidal thoughts	2,030	QUETIAPINE	VARENICLINE	18.9%	203,000	40,600	20,300
Pancreatitis	1,902	LIRAGLUTIDE	EXENATIDE	43.0%	190,200	38,040	19,020
Rhabdomyolysis	516	SIMVASTATIN	ROSUVASTATIN	38.0%	51,600	10,320	5,160
Total (all drugs)					891,500	178,300	89,150

* 1st and 2d ranked percent of all cases

**Estimated incidence for all drugs based on reporting rate assumptions shown

Severe Liver Damage

The liver not only plays a key role in metabolizing many drugs, it is also highly vulnerable to damage by them. In fact, many drugs can have some toxic effects on the liver, and this can be assessed by measuring serum levels of two enzymes released by liver cells when they are damaged—alanine transaminase (ALT) and aspartate transaminase (AST). The normal liver has substantial capacity to regenerate, and in many cases health consequences of drug-induced hepatotoxicity are limited. Some drugs, however, are capable of causing severe liver damage. When the liver is damaged beyond its capacity to recover, the result is acute liver failure, a life-threatening condition. In the most severe cases, a liver transplant may be the only option.

We measured severe liver damage using the Standardized MedDRA Query (SMQ) called *Drug related hepatic disorders - severe events only*. The category includes outright liver failure, hepatitis, and liver cancers. We also conducted a separate analysis to identify suspect drugs reported in association with the most severe and life-threatening liver toxicity, identified by any of the MedDRA terms *Acute hepatic failure*, *Hepatic failure*, *Hepatorenal failure*, or *Liver transplant*.

In 2011, the largest number of cases of severe liver injury, a total of 159, was reported for infliximab (REMICADE) a biological product that blocks a component of the immune system called Tumor Necrosis Factor (TNF). It is approved to treat eight autoimmune disorders, including rheumatoid arthritis and plaque psoriasis. The drug has two potential mechanisms of liver toxicity.[16] Because of its immunosuppressant effects, a pre-existing hepatitis B infection could be reactivated. In addition, direct toxicity and liver failure have been reported. Among these cases of liver injury, 10 indicated the most severe variant, acute liver failure.

Acetaminophen is toxic to liver cells in a substantial overdose, and under some circumstances liver damage occurs at lower doses, particularly with chronic use. In 2011 it ranked second, with 139 cases of severe liver toxicity, and ranked first in acute liver failure, with 69 cases. An FDA study of acetaminophen said it was the leading cause of acute liver failure in studies dating back nearly a decade. [17]

Other drugs identified in the most serious category of acute liver failure included dabigatran (PRADAXA) with 15 cases, amoxicillin-clavulanate (AUGMENTIN) with 15 cases, dronedarone (MULTAQ) with 11 cases, and duloxetine (CYMBALTA) with 10 cases.

Severe Cutaneous Reactions

Mild drug-induced skin reactions such as a rash are relatively common for many drugs. Severe skin reactions may involve exfoliation and necrosis of substantial areas of skin, blisters, painful ulcers in the mouth, or exfoliation of the lips. The most severe and life-threatening of these skin reactions are Stevens-Johnson syndrome (SJS) and Toxic Epidermal Necrolysis (TEN). The limited studies available show that SJS/TEN cases are rare, occurring in 5 per 1 million patients or less [13] and are observed in only a small number of drugs.

Serious skin hypersensitivity was identified using the SMQ called “Severe cutaneous adverse reactions,” which groups 46 different terms describing skin reactions. The majority of the terms unambiguously describe severe skin conditions (lip exfoliation, toxic skin eruption) but a few are milder (blister, skin erosion). We also examined separately reports that specifically identified Stevens-Johnson syndrome and Toxic Epidermal Necrolysis.

In the 2011 data the antiepileptic drug lamotrigine (LAMICTAL) ranked first in reported severe cutaneous reactions with 119 cases, including 5 patient deaths. This total included the more specific and severe SJS/TEN with 86 cases, also ranked first. In a published study of all AERS data from 1968 through 2009 Q3, lamotrigine accounted for more reported cases of SJS/TEN than any other drug studied even though it was not approved until 1994.[18] A case control study identified lamotrigine with a 14-fold increased risk for SJS/TEN compared with matched controls from a hospitalized population. [19]

The smoking cessation aid varenicline (CHANTIX) ranked second in reported severe cutaneous events with 93 cases, including 2 patient deaths. However, formally diagnosed cases of SJS/TEN were far fewer than for lamotrigine with 5 cases. However, the other reactions were still severe, including mentions of skin exfoliation (28 cases), oropharyngeal blistering (29 cases) and blister (26 cases). It was possible for more than one of these terms to appear in a single case report.

Other drugs with SJS/TEN reports had been identified in previously published studies and included phenytoin (DILANTIN) (68 cases), sulfamethoxazole-trimethoprim (BACTRIM) with 22 cases, and ibuprofen with 21 cases.

For lamotrigine, these data confirm and extend other published reports indicating that this drug accounts for a disproportionate share of severe cutaneous adverse reactions. These results raise the question of whether lamotrigine should be used only when other epilepsy drugs have failed. Also the risks of lamotrigine warrant additional educational efforts to warn parents, patients, and physicians to discontinue this drug at the first sign of a rash.

Suicidal/Homicidal Thoughts

For more than 20 years a controversy has raged over the capacity of psychiatric and other drugs to cause suicidal behaviors and violence. Although the first landmark paper associating fluoxetine (PROZAC) with suicidality was published in 1990 [20] it was not until 2004 that the FDA mandated a suicidal behavior warning for antidepressant drugs, and not until 2009 that a warning was mandated for all anti-epileptic drugs. A recent count showed 58 drugs had warnings or precautions about suicidal behavior [21] and one study linked 31 drugs to reports of violent thoughts and actions. [22]

Our goal was to identify drugs most frequently associated with reports of an increased risk of injury to self and others. To identify cases we used three MedDRA Preferred Terms, *Suicidal ideation*, *Homicidal ideation*, and *Self-injurious ideation*. We used thoughts rather than acts of injury to avoid the problem that drugs identified in intentional overdose reports are widely available in medicine cabinets and toxic in large doses. Acetaminophen, which is highly toxic to the liver in an overdose, is a prime example of a drug not suspected of having psychiatric side effects but commonly reported in intentional overdoses. However, all of the five most frequently reported drugs for suicidal/homicidal thoughts also had a substantial number of reported cases of suicide or suicide attempt. It was possible for some reports to include both thoughts and acts involving injury to self and others.

In 2011 quetiapine (SEROQUEL) ranked first with 197 cases of suicidal, self-injurious, or homicidal thoughts and 203 cases of completed suicide or suicide attempt. Quetiapine was developed as an antipsychotic drug but was also approved as adjunctive treatment for depression and bipolar disorder and was used off label for sleep disorders.

Varenicline (CHANTIX) ranked second in 2011 with 187 cases of suicidal or homicidal thoughts and 58 cases of suicides or suicide attempts. This smoking cessation aid carries a Boxed Warning about suicidal behavior, hostility, and other neuropsychiatric adverse effects.

Other drugs with frequent reports of suicidal/homicidal thoughts and reported events include buprenorphine-naloxone (SUBOXONE) with 83 cases of suicidal/homicidal thoughts and 20 completed suicides or attempts, and isotretinoin (ACCUTANE) with 59 cases of suicidal/homicidal thoughts and 17 cases of suicide or attempt.

Pancreatitis and GLP-1 Drugs

The past five years have seen the rise of a class of drugs for Type 2 diabetes that directly or indirectly affect a hormone called glucagon-like-peptide-1 (GLP-1). This hormone stimulates the pancreas to secrete more insulin when blood sugar levels rise. [23] Given a frequently obese patient population, these agents had the advantage of inducing modest weight loss while some

other diabetes medications cause weight gain. While these drugs affect laboratory measures indicating better body regulation of blood sugar levels, they have no effect on symptoms or quality of life, and tangible long-term health benefits of these treatments have not been established for these or other Type 2 drug treatments. The FDA-required disclaimer states “There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction.” [24] Because it would take years of treatment to demonstrate the assumed small but unproven tangible health benefits, it means such treatments should not represent significant risks. However, in this class of diabetes drugs, signals are emerging that some may be toxic to the pancreas, with serious and sometimes fatal outcomes. The 2011 data provide additional evidence that several of these agents may cause pancreatitis.

Cases of pancreatitis were selected using the MedDRA High Level Term (HLT) called *Acute and chronic pancreatitis*. The grouping includes 22 MedDRA terms with direct variants of the medical term *pancreatitis*. Based on a 5% reporting rate, we estimate that overall, drugs accounted for an estimated 38,040 cases of pancreatitis, but possibly as many as 190,200 cases if the reporting rate were only 1% and as few as 19,020 if the reporting rate were at the top of the expected range, or 10%. Additional comparisons between diabetes drugs are shown in Table 6.

Table 6. Reported cases of acute/chronic pancreatitis 2011			
Drug Name	PRR*	Cases	Rx 11q4**
Liraglutide	53.4	413	418,226
Exenatide	48.8	404	350,893
Sitagliptin	46.0	179	1,905,144
Saxagliptin	14.6	23	404,324
Metformin	3.2	19	13,958,392

*Proportional reporting ratio

** Dispensed outpatient prescriptions, IMS Health

It is noteworthy that pancreatitis as a drug adverse effect is rarely reported except for this group of diabetes drugs. The three most frequently suspected drugs—liraglutide (VICTOZA), exenatide (BYETTA), and sitagliptin (JANUVIA)—accounted for 52.4% of all such cases reported in 2011. The strong association of pancreatitis with these drugs is also seen in the high proportional reporting ratios (PRR) shown in Table 6. For liraglutide, for example, it means that pancreatitis is 53 times more likely to be reported compared to all other drugs.

In these data it appears that the two injectable agents, liraglutide and exenatide, may have a higher risk of reported events than the two oral agents, sitagliptin and saxagliptin. The data for metformin, which is not suspected of causing pancreatitis, is provided for comparative purposes. Adverse event data signals sometimes suggest possible safety benefits. These data suggest the

possibility that saxagliptin (ONGLYZA) might have safety advantages over the other agents for risk of pancreatitis.

Rhabdomyolysis

The cholesterol-lowering drugs known as statins are so widely used that 22% of adults over age 45 have a prescription at a total annual cost of \$14 billion. By age 60 the prescription exposure includes 45% of all adults. [25] In addition to reducing the risk of heart attack, these drugs, HMG-CoA reductase inhibitors, also have the capacity to damage skeletal muscle. In mild cases the result is muscle weakness and pain. In the most severe cases the damaged muscle cells leak myoglobin into the blood and overwhelm the kidneys' capacity to remove this protein, leading to kidney failure. In clinical trials, severe myopathy and rhabdomyolysis developed in about 1% of patients observed for 6.5 years. [26] A case serious enough to warrant hospitalization, according to the FDA, occurs in about 4 in 100,000 people treated with statins. [27] The risk of rhabdomyolysis is dose dependent and one cholesterol drug, cerivastatin (BAYCOL), was withdrawn in 2001 because of excess risk of this injury.

To identify cases of severe muscle damage we used a single and intentionally restrictive MedDRA Preferred Term, *Rhabdomyolysis*, and identified 516 cases. The MedDRA terminology also provides a much broader category with 44 different terms that captured 8,680 possible cases. In our judgment, the broader category included too many terms not necessarily linked to rhabdomyolysis, such as “renal failure” and “muscle fatigue.”

In 2011 the leading drug associated with rhabdomyolysis was simvastatin (ZOCOR) with 123 cases. It was also the third most widely prescribed drug and the most widely prescribed cholesterol lowering drug in the United States in the fourth quarter of 2011 with 21 million prescriptions, according to IMS Health's National Prescription Audit. In June 2011 the FDA recommended restricting the use of the highest dose, 80 mg, to reduce the risk of muscle damage. [27]

Rosuvastatin (CRESTOR) ranked second with 73 cases reported. Atorvastatin (LIPITOR) accounted for only 15 reported cases. In addition, rhabdomyolysis was reported for two other drugs, daptomycin (CUBICIN), an intravenous antibiotic with 27 cases, and tramadol (ULTRAM), an analgesic with 11 reported cases.

The likelihood that complications involving muscle injury are greatly underreported is illustrated by a unique study performed at the University of California at San Diego. [28] Golumb *et al.* studied how doctors responded to patients complaining about statin adverse effects. Among those patients complaining of muscle pain, only 29% of doctors endorsed the

possibility of a link to the drug, 49% dismissed the possibility entirely, and 24% did not respond either way.

Improving the Adverse Event Reporting System

Poor Quality Manufacturer Death Reports

With death as the most serious possible health outcome of an adverse event, one would imagine quality reporting would be a priority. In fact, the 2011 data illustrate that many of the reports of patient deaths from drug manufacturers are of such low quality as to be nearly useless.

When a patient dies and a drug is suspected as being causally related, it is critical to know what condition(s) developed and what is thought to be the proximal cause of death. Did the patient develop a heart attack, liver failure, a severe skin eruption, symptoms of anaphylaxis? As in clinical trials, this detail is provided in the MedDRA event terms selected to describe the event. In 2011 a total of 30,385 patient deaths were reported to the FDA. However, of this total, 9,219 reports (30%) were nearly useless because they contained the single event term, *Death*. What's more, these low-quality case reports omitted other key patient information. A total of 4,384/9,219 (47.6%) had no patient age and another 1,456 (15.8%) did not indicate gender. Of these low-quality reports, 99% were written by drug manufacturers, and just 136 defective reports (1%) were sent directly to the FDA's MedWatch program. We categorize as *vague* any report that contained a single adverse event term and was missing either age or gender information. Overall, 24% of all death outcome reports were classified as vague, compared with 13% of other serious outcomes, and just 4.5% of disability or birth defect cases.

These data do not capture an additional weakness of death reporting in the AERS system. Manufacturers also "learn" of and report numerous patient deaths in which the drug was not suspected of contributing, or that were never evaluated to determine a possible drug role. We have previously described deaths reported because medication refill reminder postcards were returned marked "deceased" and another instance where medication delivery drivers were required to report patient deaths when a monthly delivery was refused for this reason.

One solution to this problem is straightforward. The FDA can continue to require manufacturers to report all patient deaths of which they become aware through any source even when a drug role is not suspected or evaluated. This information can be added to one of the existing periodic or annual reports, but not submitted into the AERS system. The FDA can also set standards for how such death cases should be evaluated, and establish guidelines to determine when a drug role in a patient death should be reported as suspected. But it is not acceptable for the agency to permit the system to be flooded with thousands of vague patient death reports of little or no value.

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 February 2011 he became a consulting expert for plaintiffs in the civil litigation regarding Chantix. In 2011 Mr. Moore 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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