ISMP INSTITUTE FOR SAFE MEDICATION PRACTICES
QuarterWatch
Monitoring FDA MedWatch Reports

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PERSPECTIVE ON DRUG HYPERSENSITIVITY

Allergic reactions second most frequently reported serious event
Hypersensitivity signals for omalizumab (XOLAIR) and telaprevir (INCIVEK)
Update on anticoagulants, rivaroxaban (XARELTO) and dabigatran (PRADAXA)

Executive Summary

This issue focuses on serious hypersensitivity reactions reported to the US Food and Drug Administration (FDA) for therapeutic drugs using data from the most recent 12 months available. It also surveys the newly released case reports for 2013, Quarter 1, and provides an update on the continuing drug safety issues surrounding anticoagulant drugs.

QuarterWatch™ is an independent publication of the Institute for Safe Medication Practices (ISMP) that monitors all domestic, serious adverse drug events reported to the FDA. We analyze computer excerpts from the FDA Adverse Event Reporting System (FAERS). These reports (best known as MedWatch reports) are a cornerstone of the nation's system for monitoring the safety of therapeutic drugs after FDA marketing approval.

The FDA received 56,165 domestic reports of serious adverse drug events in the calendar quarter ending March 30, 2013. This was an apparent drop of 685 cases (-1.2%) from the previous quarter and a decline of 5,305 reports (-8.6%) from the same quarter in 2012. The total included 12,899 patient deaths and 2,653 cases indicating a possible medication error. The apparent decline is likely exaggerated. Historical records show the new quarter totals are artificially low since the agency typically releases additional reports for the quarter at a later date.

Hypersensitivity Highlights

Cases of reported drug hypersensitivity (mostly drug allergies) were identified using a standardized set of medical terms created by the pharmaceutical industry to classify possible cases of adverse drug events occurring in clinical trials or identified through postmarket surveillance. To identify suspect drugs, we screened 147,318 selected cases of serious adverse drug events from March 2012 through March 2013.

- Hypersensitivity was very common, accounting for 13,042 cases (8.9%), and more than any other among 91 adverse reaction categories except non-specific gastrointestinal symptoms. We classified 4,045 of these cases as severe, involving death, disability, or a medical emergency.

- A large and diverse selection of drugs was implicated, with 234 drugs having 10 or more hypersensitivity reports in one year. However, only 87 drugs fell into the subset of the 4,045 most severe cases.

- A sample of prescribing information for health professionals for 20 drugs with 10 or more reported cases of severe hypersensitivity showed all 20 provided information about these reactions, and 14/20 (70%) had prominent warnings.

Table 1. Hypersensitivity cases in 12 months ending March 31, 2013

Standardized MedDRA Query	Cases	Drugs*	Deaths
Hypersensitivity (narrow scope)	13042	234	
Severe	4045	87	966
Anaphylactic shock**	1196	43	133
Severe cutaneous	891	20	97
Angioedema	894	13	77
Other severe	1316	16	667

*Regularly monitored with 10 or more cases

** Drug cases could fall in more than 1 category

Suspect Drugs

To highlight drugs with the most frequently reported severe hypersensitivity reactions, cases were divided into four categories: *anaphylactic shock*, a rapid onset systemic immune reaction; *severe cutaneous,* widespread skin eruptions that can be life-threatening; *angioedema*, a localized swelling of lips, tongue, eyelids, or other body parts; and *other severe* forms of hypersensitivity. The 10 most frequently reported drugs in each category are identified in the report, constituting useful clinical alert lists

We also examine two drugs where potential hypersensitivity reactions were so frequently reported and severe that this risk should be carefully considered in deciding whether clinical use is appropriate.

- Telaprevir (INCIVEK) won fast track approval in 2011 as a treatment for largely asymptomatic hepatitis C in combination with two other antiviral agents. In previously untreated patients, 60% of treated patients developed skin rashes, with 16% of this group having rashes covering 50% or more of the body surface area. We identified 131 cases of severe hypersensitivity, including 14 patient deaths and 105 cases of severe cutaneous reactions—more than any other drug studied.

- Omalizumab (XOLAIR) is a biological product approved for children and adults who already have documented allergy problems causing asthma or chronic urticaria (hives). However, we identified 59 cases where the drug itself was suspect in potentially life-threatening anaphylactic shock. This drug accounted for more reported cases of anaphylaxis than any other drug in the study.

Anticoagulant Update

Anticoagulant drugs are a high-risk treatment and cause bleeding in approximately 15% of patients with atrial fibrillation exposed for a year. [1] In the latest data we detected a new trend in the numerous serious adverse event reports associated with two newer anticoagulant drugs: dabigatran (PRADAXA) and rivaroxaban (XARELTO). Cases for rivaroxaban (n=680) were steadily increasing and now outnumbered those of dabigatran (n=528), the drug that had been the main focus of safety concerns in QuarterWatch and elsewhere. The trends were mostly explained by a major change in the number of patients exposed to the two drugs. Total dispensed outpatient prescriptions for rivaroxaban have rapidly increased to nearly 1 million prescriptions per quarter, while dabigatran utilization has steadily declined since a peak in early 2012. By the end of 2013, rivaroxaban prescriptions outnumbered dabigatran by almost 2 to 1, according to data from IMS Health, Inc.

Newly published data also show that the bleeding risks of dabigatran could be substantially reduced if two therapeutic options available in most advanced countries were approved in the United States. Those options are a lower, 110 mg twice daily (BID) dose, and a laboratory test capable of identifying patients who need a dose adjustment because the effect on thrombin inhibition is either excessive, increasing the risk of severe bleeding, or sub-therapeutic, exposing the patient to a higher risk of stroke or other blood-clot related adverse event. ISMP has explained the need for the FDA to make these options available in its February 13, 2014, newsletter, the *ISMP Medication Safety Alert! Acute Care edition*.

Adverse Event Reporting System

Most drug manufacturers appeared to be actively screening and evaluating adverse drug event reports, identifying hypersensitivity reactions, and updating product information for physicians.

The quality of adverse event reports in the FDA's new FAERS system is poor because the agency does not screen incoming electronic submissions for irregular entries and readily detectable errors. For key entries no published data standards exist. The public release version has declined substantially in quality and has been subject recently to the longest delays in many years.

About QuarterWatch Data

Our findings should be interpreted in light of the known limitations of a reporting system that does not collect data systematically. The FDA's adverse event reports 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. More complete disclaimers and descriptions of our criteria are included in the Methods Summary section of this report. A disclosure statement expands our description of this project and its staff.

Conclusions

Clinicians should consider carefully the use of telaprevir to treat hepatitis C, given that its use is not recommended by current treatment guidelines, and drugs with a better safety profile or greater effectiveness are available. They should also be alert to the risk of anaphylactic shock with omalizumab.

The safety of anticoagulant drugs remains a major concern given the high risks of bleeding and increasing use as newer agents replace the generic, warfarin. For all the newer agents, marketing the drug for ease of use, rather than providing tools to reduce bleeding risk, constitutes a substantial wrong turn for an important medical treatment. In particular, the FDA should reconsider its decision to prohibit a lower dose of dabigatran that is recommended for older patients in almost all other advanced countries, and establish a therapeutic range so that plasma level tests can identify patients with excessive or suboptimal effects.

We are concerned about the deteriorating quality and slow release of adverse event reports submitted to the FDA. Both our own and FDA studies demonstrate that these reports remain the most important source of information for detecting new risks of drugs already approved and marketed. The most recent two data releases had notable quality control problems. The key problem is a rising volume of electronic submissions that are not being screened for irregular entries that compromise data integrity. The FDA needs to create screening software to isolate and return for revision adverse event reports with flawed data—as do most web sites that accept electronic data input.

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Results

The FDA received 56,165 domestic, serious reports of adverse drug events in the first quarter of 2013. These included 4,896 case reports (8.7%) submitted directly to the FDA by consumers and health professionals, with the remainder submitted by drug manufacturers. Individuals who observe a drug adverse event can either report it directly to the FDA or contact a drug manufacturer, which is then required to complete, analyze, and forward the report to the FDA. The quarterly total was a slight decline (n=685) from the previous quarter, and a larger decline (n=5,305) from the same quarter one year previously. However, the FDA is unable to process for release all the reports it receives in a calendar quarter. For example, in its latest release, the FDA included 7,448 cases (15%) that should have been counted in the previous quarter, 2012 Quarter 4. The long-term trends demonstrate steady increases in reports from drug manufacturers but a largely stable or slightly declining number of reports submitted directly to the FDA.

Perspective on Hypersensitivity

Overview

Hypersensitivity and other allergic reactions to therapeutic drugs range from mild rashes to fatal hypotension occurring within minutes of administering the first dose. These reactions have been observed among many antibiotics, analgesics, psychotropic drugs, cancer treatments, biological products, anti-epileptics, blood pressure and cholesterol lowering drugs—even topical preparations. The incidence ranges from so rare that estimates have not been calculated to as high as 10%. This issue of QuarterWatch used the most recently available 12 months of adverse drug event reports to identify the drugs most frequently implicated in the most severe hypersensitivity reactions, and to explore three different clinical presentations. The population screened for possible cases (n=147,318) excluded foreign and certain other reports. (For details, see Methods Summary.)

We used four Standardized MedDRA Queries (SMQs) [2] to identify possible hypersensitivity reactions. The most inclusive category, “hypersensitivity,” narrow scope, captured 13,042 cases of reported serious injury. Among the 91 different level-1 SMQs, only one other type of reaction, non-specific disorders of the gastrointestinal tract, accounted for more cases meeting our criteria. In addition, this category included three more specific types of hypersensitivity reactions: anaphylactic shock, an immune system over-reaction that is life threatening; severe cutaneous reactions; and angioedema, a category that included urticaria (hives) as well as swelling of the lips, tongue, eyelids, airway, and other localized tissues.

Since hypersensitivity reactions may be triggered by many different kinds of allergens besides drugs, we defined a drug-specific hypersensitivity signal as 10 or more reported cases in the 12-month period, and probability of < 0.01 that hypersensitivity was reported by chance. Our primary analysis and tables narrowed the focus to severe hypersensitivity cases. These were defined as those resulting in death or disability, were life-threatening, or required intervention to prevent harm. In addition, all anaphylactic shock and severe cutaneous cases were classified as severe. The overall results are shown in Table 1 in the Executive Summary.

As a group, the hypersensitivity reactions had some differences and many similarities to other types of adverse drug events reported among regularly monitored drugs. In the overall hypersensitivity group, the outcome was less likely to result in death (7% vs 15%) compared with other types of adverse events, but more likely to be life-threatening or require intervention to prevent harm (9% vs 4%). The cases were similar to all other types of adverse drug events in age (median 56, interquartile range (IQR) 43-66) and gender (62% female).

Drugs Implicated

Hypersensitivity reactions were reported among practically every category of therapeutic drug ranging from topical preparations to tyrosine kinase inhibitors used to treat metastatic cancer. In just four quarters, 234 (33.5%) drugs were implicated among 698 drugs with 10 or more serious reports in the 12-month period. Using a more restricted category of severe hypersensitivity, 87 drugs (12.5%) were the primary suspect in 10 or more cases. However, the diversity of therapeutic uses remained. This means that in almost all medical settings health professionals must be alert to the dangers of hypersensitivity reactions. The probability was < 0.01 that any of the drugs with 10 or more cases were identified by chance.

Survey of Hypersensitivity Warnings

To assess whether drugs with signals for severe hypersensitivity had appropriate warnings for physicians and other health professionals, we surveyed the prescribing information for a random sample of 20 of the 87 drugs associated with 10 or more reported cases. Any information identified was ranked by prominence. A *Boxed Warning* is the most conspicuous warning, and appears first in the prescribing information. The next most prominent display was the appearance of the hypersensitivity information in the official *Warnings* section that identifies important adverse effects probably associated with the drug. All other references to hypersensitivity appeared in either the *Precautions* or the *Adverse Events* section.

All 20 drugs surveyed provided accurate information about hypersensitivity reactions somewhere in the prescribing information. This included 3 drugs with the most prominent, Boxed Warnings, and 11 with information in the Warnings section. The remainder provided information in the Precautions or Adverse Events section. The survey included ibuprofen, a widely used over-the-counter analgesic, with a different and simpler information format. It was classed as a warning because the information for consumers and health professionals included a prominent “Allergy Alert.”

Limitations

With a single year’s data, this analysis identified only the most prominent signals and may have excluded drugs otherwise associated with hypersensitivity. The underlying SMQs also had significant drawbacks. The most important was that except for one medical term, the SMQs did not identify cases of Type II hypersensitivity such as agranulocytosis, hemolytic anemia, and thrombocytopenia. SMQs exist for these adverse effects, but it was not feasible to separate hypersensitivity from other mechanisms with adverse effects on blood forming cells. Overlap occurred between the angioedema and anaphylaxis categories, with 174 (4%) of angioedema cases also classified as anaphylaxis. This analysis could not capture the characteristics of exposure, a relevant feature given that Type I hypersensitivity typically occurs in a second exposure.

Anaphylactic Shock

Anaphylactic shock ranks among the most feared drug hypersensitivity reactions because it may occur within minutes of the first dose and is potentially fatal absent a prompt and effective medical intervention. The first symptoms are effects on the skin and mucosal tissue as generalized urticaria (hives), flushing, itching, and swelling of the lips, tongue, and uvula.[3] It can be fatal because it may progress to respiratory collapse and sharply reduced blood pressure. The primary treatments—airway management and injection of epinephrine—are dramatically effective provided they occur within minutes. Other common causes of anaphylaxis include allergies to food, insect bites, and insect venom.

We identified possible cases of anaphylactic shock if a case report contained any of eight Preferred Terms in Level-2 SMQ, “Anaphylactic/anaphylactoid shock conditions,” narrow scope. All of the cases also fell within the hypersensitivity category and, by definition, were classified as severe.

Anaphylactic shock accounted for 1,196 (30%) of the severe hypersensitivity cases and 133 (14%) of reported patient deaths. The 44 drugs with 10 or more cases included antibiotics, allergy drugs, blood pressure medications, radiological contrast agents, and two of the most widely used analgesics, ibuprofen (n=18) and naproxen (n=17). The 10 most frequently reported drugs are shown in Table 2.

Table 2. Anaphylactic shock and overall severe hypersensitivity—most frequently reported drugs

Rank	Drug name	Trade name	Anaphylactic shock, pct*		Hypersensitivity, pct**		All Causes
1	Omalizumab	Xolair	59	(9.4)	65	(10.4)	627
2	Moxifloxacin	Avelox	39	(17.5)	57	(25.6)	223
3	Infliximab	Remicade	35	(1.2)	64	(2.3)	2830
4	Gadopentetate dimeglumine	Magnevist	29	(19.1)	32	(21.1)	152
5	Cetuximab	Erbitux	23	(4.7)	33	(6.7)	492
6	Glatiramer	Copaxone	22	(2.8)	26	(3.2)	800
7	Amlodipine	Norvasc	20	(3.9)	28	(5.4)	518
8	Ibuprofen	Advil	18	(2.2)	34	(4.1)	834
9	Lisinopril	Prinivil	17	(2.4)	146	(20.9)	697
10	Naproxen	Aleve	17	(1.8)	26	(2.7)	966

*Standardized MedDRA Query, level 2, narrow scope, percent of all cause drug total

** Severe hypersensitivity, percent of all cause total

Omalizumab (XOLAIR) – Unusual Anaphylaxis Risk

Omalizumab (XOLAIR) is a humanized monoclonal antibody produced from hamster ovary cells that targets Immunoglobulin E (IgE) – the immune factor that is the primary effector of Type I hypersensitivity. [4] Circulating IgE binds to mast cells and basophils throughout the body. In the presence of a recognized allergen these cells immediately release stored histamine, heparin, and other mediators of inflammation and allergic reactions.

The FDA approved omalizumab in 2003. In pivotal clinical trials it was tested in children and adults with asthma triggered by allergies documented with skin tests, and with high levels of circulating IgE. Over a 12-week trial phase, 86% of treated patients had no asthma exacerbations, compared to 77% of untreated patients in the control group. [4] The medical reviewer noted “the number of exacerbations in these trials was small” in both treatment and placebo groups. [5] In 2014, it was approved for chronic urticaria of idiopathic or unknown origin.

After four cases of anaphylaxis were observed in clinical trials,[6] omalizumab was approved with a warning. Four years later, in 2007, the FDA required a Boxed Warning and a strongly and clearly worded Medication Guide for patients listing the risk of anaphylaxis, symptoms, and actions to take. [7] The 2007 FDA safety analysis was detailed and complete, noting 124 reported cases from 2003 to 2006 in an estimated patient population of 57,300. It showed that 39% of the reactions occurred after the first dose and 19% after the second, but reactions could occur at any time, even after a year of treatment.

The 12-month adverse drug event data included 64 new cases of severe hypersensitivity with omalizumab, including 59 cases (92%) of anaphylactic shock and 8 cases (13%) of the related but less severe angioedema. (Some cases involved symptoms of both categories.) Despite a small patient population, omalizumab accounted for more reported cases of severe anaphylaxis than any other monitored drug in the study.

Given a drug with a strong signal for a life-threatening drug reaction, it appeared the risk was being managed through prominent warnings, and the requirement that the drug injection be administered in a

physician's office, a setting where emergency treatment should be immediately available. However, almost half the cases in the FDA study occurred more than an hour after drug administration. This may explain why reported hypersensitivity cases still resulted in 2 reported patient deaths, 3 cases of permanent disability, and 9 hospitalizations. Some patients were paying a substantial price for a drug with a modest effect on allergic asthma exacerbations and chronic urticaria.

Severe Cutaneous Reactions

Skin eruptions caused by drugs can be mild but frequent (10% prevalence of reported rash for lamotrigine (LAMICTAL) [8] and 7% for fluoxetine (PROZAC) [9]). Less frequently drugs trigger a potentially life-threatening spectrum of cutaneous reactions that in order of increasing severity include target-shaped lesions of erythema multiforme, Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN). In the most severe variants, SJS/TEN, widespread exfoliation and skin detachment occurs over 5-30% of the body, leading to life-threatening complications comparable to the most severe burn cases. Annual incidence of the three conditions has been reported as approximately 7 per million in the general population [10] but for specific drugs was as high as 20 per 100,000 for phenobarbital and 7 per 100,000 for sulfamethoxazole/ trimethoprim (BACTRIM). [11] A separate but also severe form of hypersensitivity is called drug reaction with eosinophilia with systemic symptoms (DRESS).[12] It may involve edema and skin eruptions covering 50% or more of body surface area and include fever, enlarged lymph glands, multi-organ involvement, and hematological abnormalities.

Possible cases were selected using the Level-1 SMQ "Severe cutaneous adverse reactions," narrow scope, which included 14 Preferred Terms, all indicating the more severe skin reactions. By the study definition all cases were classified as severe.

In the 12 months ending March 31, 2013, we identified 891 possible cases, or 22% of the total severe hypersensitivity cases. The total included 97 patient deaths and 35 cases of permanent disability. The reactions identified included 387 (43%) cases of SJS/TEN and 291 cases (32.7%) of DRESS. The 10 most frequently identified primary suspect drugs are shown in Table 3.

Table 3. Severe cutaneous reactions and overall severe hypersensitivity—most frequently reported drugs

Rank	Drug name	Trade name	Severe cutaneous, pct*		Hypersensitivity, pct		All Causes
1	Telaprevir	Incivek	105	(5.6)	131	(7.0)	1868
2	Lamotrigine	Lamictal	55	(10.3)	83	(15.5)	534
3	Allopurinol	Zyloprim	48	(43.6)	55	(50.0)	110
4	Duloxetine	Cymbalta	37	(3.2)	52	(4.5)	1157
5	Vancomycin	n/a	26	(10.0)	55	(21.1)	261
6	Levetiracetam	Keppra	25	(5.8)	27	(6.3)	431
7	Sulfamethoxazole; trimethoprim	Bactrim	25	(10.4)	57	(23.7)	241
8	Phenytoin	Dilantin	24	(5.9)	27	(6.7)	406
9	Bendamustine	Treanda	23	(5.1)	32	(7.2)	447
10	Clindamycin	Cleocin	20	(12.5)	34	(21.2)	160

*Standardized MedDRA Query, level 2, narrow scope, percent of all cause drug total

Unresolved Questions

For several suspect drugs, including telaprevir combination therapy and lamotrigine (LAMICTAL), milder skin rashes are common. Does a mild rash predict the more severe, potentially life-threatening forms of

severe cutaneous reactions, or is a different mechanism or unknown patient genotype involved? But does the alternative—waiting for progression or more severe symptoms—mean waiting until it is too late to arrest the development of a catastrophic adverse drug event? More research is needed to identify effective clinical strategies for discontinuation of high-risk drugs.

Telaprevir (INCIVEK) – Severe Cutaneous Reactions

Telaprevir (INCIVEK) received fast track approval in May 2011 for treatment of hepatitis C, a largely asymptomatic viral disease that may not be recognized for decades. Over time the disease can lead to cirrhosis and liver cancer. An estimated 3 million persons in the United States are infected. The drug was approved for genotype 1 (of 7 known genotypes) in combination with two other antiviral agents, peginterferon alfa and ribavirin. Approval was based on a reduction in virus detected in laboratory assays.

In testing prior to approval, telaprevir was observed to have cutaneous toxicity rarely seen outside of cancer treatments. In a 12-week dosing period in treatment naïve patients, 60% had a rash, including 10% of patients whose drug therapy had to be discontinued.[13] In the comparison group receiving the other two antiviral agents, rashes were also common (32%) but mild, with only 1 patient discontinuing. For the most severe skin eruptions involving 50% or more of body surface area, 38 cases (4%) were identified in telaprevir patients, compared to 2 patients on the other antiviral agents (0.6%). Compared to the antiviral controls, telaprevir patients were approximately 10 times more likely to discontinue treatment or experience the most severe skin eruptions. A review panel identified 3 cases “suggestive” of SJS and 11 cases of DRESS in pre-approval testing. All were in the telaprevir treatment group. In addition, 36% suffered from indications of anemia, and telaprevir interacted with more than 50 other drugs, some with the potential for causing serious adverse drug events.

Telaprevir was approved without a Boxed Warning, and with a less prominent warning stating that patients with mild to moderate rash should be monitored for progression and that the drug should be discontinued only if the symptoms became severe. The FDA press release issued on approval did not mention adverse effects. In December 2012 the FDA issued a Drug Safety Communication noting that it had received reports of patient deaths from serious skin reactions that occurred because their therapy was not discontinued after symptoms progressed. [14] A Boxed Warning was added to the prescribing information for physicians and a strongly worded Medication Guide for patients was created. However, the prescribing information continued to retain the recommendation that treatment should be continued despite a rash occurring until the point of “systemic symptoms or a progressive severe rash.” The Medication Guide further told patients if a rash occurred, “Never stop taking INCIVEK combination treatment without talking to your healthcare provider first.”

In the QuarterWatch study period telaprevir was primary suspect in 131 cases of severe hypersensitivity reactions, including 14 patient deaths. (Another 83 patient deaths were reported but were linked to other causes or contained insufficient detail.) The hypersensitivity group included 105 cases of severe cutaneous reactions, more than any other study drug. Reported severe hypersensitivity cases included 72 suspected cases of DRESS and 27 cases of SJS.

The use of a drug with this toxicity profile for an asymptomatic viral disease seems questionable. Whether discontinuing treatment only when the skin symptoms become “severe” is a viable safety strategy remains unknown.

Recommendations from the Infectious Diseases Society of America said treatment with telaprevir was “markedly inferior to the preferred and alternative treatments” and “associated with higher rates of serious adverse events” and was not recommended for genotype 1 patients. [15]

Angioedema

Angioedema is typically the mildest of the hypersensitivity reactions in this study, and usually involves urticaria (hives) or swelling of the eyelids, lips, tongue, or extremities. However, it can be life threatening if it occurs in the upper airway, blocking respiration. It also can affect the intestinal tract, causing nausea, abdominal pain, vomiting, and diarrhea. It is very common and estimated with a lifetime risk of 15% to 25% of individuals. While the cause of angioedema is never identified in a majority of cases, the leading causes are drugs, foods, and insect bites.[16]

Possible cases of angioedema were identified using the SMQ "Angioedema," narrow scope, which includes 37 different Preferred Terms, with most referring to edema of different body parts. Severe angioedema cases were limited to those with an outcome of death, disability, life-threatening, or that required intervention to prevent harm. Among 4,231 cases of angioedema, 894 (21%) were classified as severe. The most frequent suspects among the severe angioedema cases are shown in Table 4.

Table 4. Severe angioedema and overall severe hypersensitivity—most frequently reported drugs

Rank	Drug name	Trade name	Severe angioedema, pct*		Hypersensitivity, pct**		All Causes
1	Lisinopril	Prinivil	131	(18.8)	146	(20.9)	697
2	Hydrochlorothiazide; lisinopril	Zestoretic	27	(27.8)	30	(30.9)	97
3	Sulfamethoxazole; trimethoprim	Bactrim	20	(8.3)	57	(23.7)	241
4	Alendronate	Fosamax	18	(1.1)	107	(6.5)	1648
5	Levofloxacin	Levaquin	18	(2.4)	47	(6.4)	740
6	Moxifloxacin	Avelox	18	(8.1)	57	(25.6)	223
7	Enalapril	Vasotec	15	(36.6)	15	(36.6)	41
8	Telaprevir	Incivek	15	(0.8)	131	(7.0)	1868
9	Ciprofloxacin	Cipro	12	(2.6)	38	(8.2)	461
10	Benzoyl peroxide	Proactiv	11	(26.2)	17	(40.5)	42

*Standardized MedDRA Query, level 2, narrow scope, percent of all cause drug total

** Severe hypersensitivity, percent of all cause total

The most notable signal was for lisinopril (PRINIVIL), an angiotensin-converting-enzyme inhibitor (ACE inhibitor), both as monotherapy and in combination with hydrochlorothiazide. A second ACE inhibitor, enalapril (VASOTEC) was also a frequent suspect, as were three fluoroquinolone antibiotics, levofloxacin (LEVAQUIN), moxifloxacin (AVELOX), and ciprofloxacin (CIPRO). Lisinopril and moxifloxacin were also prominent suspects in the more life-threatening form of hypersensitivity, anaphylactic shock.

Other Severe Reactions

The final subset includes atypical reactions where numerous case reports were captured through the study criteria, but the characteristics of the cases did fit into the other categories where the adverse reactions were mediated primarily through the immune system or the more general criteria for drug allergies. The most frequent suspect drugs are shown in Table 5. It was notable that 5 of the 10 most frequently reported suspects were biological products rather than small molecule drugs.

Table 5. Frequently reported drugs with other severe hypersensitivity reactions

Rank	Drug name	Trade name	Other severe, pct*		All causes
1	Erlotinib	Tarceva	453	(15.5)	2917
2	Alendronate	Fosamax	85	(5.2)	1648
3	Heparin	n/a	26	(11.9)	218
4	Digoxin	n/a	20	(6.8)	296
5	Bevacizumab	Avastin	19	(1.2)	1637
6	Vemurafenib	Zelboraf	18	(4.4)	407
7	Infliximab	Remicade	16	(0.6)	2830
8	Interferon alfa	n/a	16	(1.2)	1286
9	Rituximab	Rituximab	16	(2.2)	741
10	Sulfamethoxazole; trimethoprim	Bactrim	15	(6.2)	241

*Cases of severe hypersensitivity not included in anaphylaxis, angioedema, or severe cutaneous SMQs.

Erlotinib (TARCEVA) accounted for more severe hypersensitivity cases overall than any other drug. Because this drug is indicated for metastatic non-small cell lung cancer and pancreatic cancer where long-term survival is rare, patient deaths were numerous (n=461), as were reports of rash, which in clinical trials occurred 85% of patients, with rashes covering 50% or more of the body in 14%. [17]

Alendronate (FOSAMAX) accounted for numerous reactions because of reports of osteonecrosis of the jaw, a well-documented reaction of a different type that often included symptoms diverse enough to meet the criteria for hypersensitivity reaction.

Heparin-induced thrombocytopenia is a well-documented example of Type II hypersensitivity. As noted in the methods section, Type II hypersensitivity cases were generally not captured by the study criteria except for one Preferred Term, “Type II hypersensitivity.”

Anticoagulant Update: Contrasting Trends Observed

Since 2012 QuarterWatch has reported prominent signals for the bleeding risks of three anticoagulant drugs, dabigatran (PRADAXA), rivaroxaban (XARELTO), and warfarin (COUMADIN). The concerns arose in a setting of a race to market replacements for warfarin, a generic drug first approved in 1956. Both dabigatran and rivaroxaban were marketed as providing the same or slightly better results than warfarin in preventing strokes and other blood clot-related events, but were easier to use because weekly or monthly blood level tests were not required or available. Dabigatran was first to win approval in October 2010 for use in non-valvular atrial fibrillation, followed by rivaroxaban for this population, in November 2011. In December 2012, the FDA approved an additional contender, apixaban (ELIQUIS), but no data are yet available for review.

Soon after dabigatran entered the market, QuarterWatch reported a signal for serious and fatal bleeding, primarily in older patients with a median age of 80.[18] When rivaroxaban was marketed approximately a year later, we observed numerous but fewer reports than with dabigatran, but observed unexpectedly large numbers of thromboembolic events in rivaroxaban patients getting the lower 10 mg dose after surgery, suggesting an insufficient dose this setting. [19]

Rivaroxaban Overtakes Dabigatran

According to IMS Health data, dispensed outpatient prescription data (available through the end of 2013) show that rivaroxaban utilization has rapidly and continuously increased, mostly at the expense of

dabigatran. By the fourth quarter of 2013, rivaroxaban accounted for 989,000 prescriptions, almost double that of dabigatran, with 550,000 dispensed prescriptions. Also notable was the steady decline in dabigatran prescriptions, which peaked at 716,000 in early 2012, and then declined every quarter since. Warfarin, however, continued to account for most anticoagulant dispensed prescriptions, declining 11.3% from 6,502,000 in 2010 Quarter 1 to 5,766,000 in 2013 Quarter 4.

Adverse Events Track Utilization

Serious adverse event reports largely mirror the prescribing trends. In the most recent available adverse event data, the first quarter of 2013, rivaroxaban has also overtaken dabigatran in volume of reported serious adverse events. The quarterly trends in reported adverse events are shown in Figure 1. Dispensed outpatient volume from IMS Health appears in Figure 2. Rivaroxaban reports rose with prescribing volume and dabigatran case totals fell as prescription volume declined. These trends do not support the FDA explanation for the surge in dabigatran reports, which it dismissed as "stimulated reporting." [20]

Figure 1. Serious adverse event reports

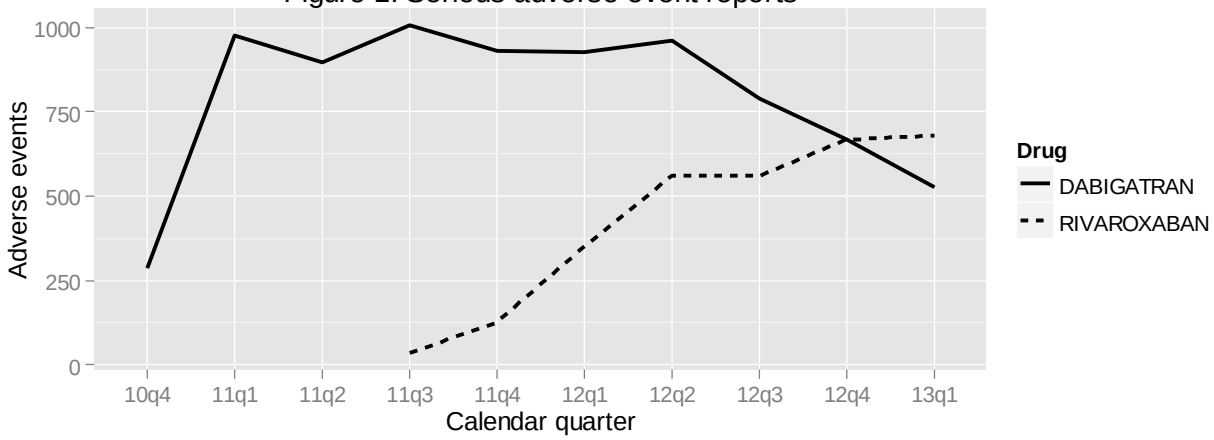
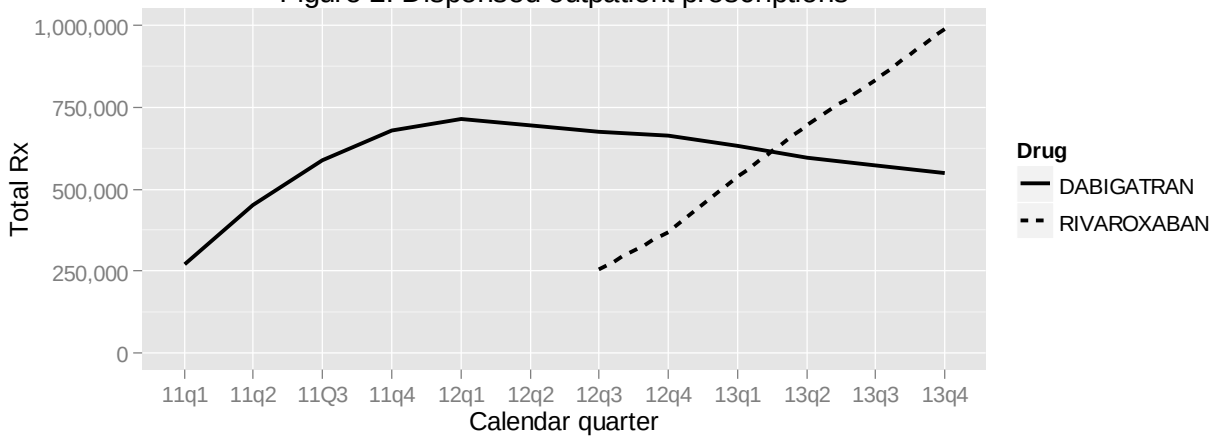


Figure 2. Dispensed outpatient prescriptions



Dispensed prescriptions source: IMS National Prescription Audit®, Jan 2011, Mar 2013, IMS Health Inc. All rights reserved.

Safer Dabigatran Use Possible

Newly published data show that thousands of bleeding events with dabigatran could be prevented through use of two therapeutic options not currently available in the United States: 1) a lower, 110 mg strength, so that a 110 mg twice daily (BID) dose could be prescribed, and 2) a Hemoclot thrombin assay to detect dangerously high or low dabigatran plasma levels. Both the lower strength capsules (110 mg) and test are available in Canada and 30 European countries, but not in the United States. [21] Except in cases of severe kidney impairment, dabigatran is approved at only a single dose, 150 mg BID. Although the manufacturer, Boehringer Ingelheim, sought a lower dose for older patients, the FDA declined.[22] The FDA's stated reason was that although severe bleeding would be increased in older patients, so would the drug's ability to prevent strokes. Two published studies using blood level data now show the lower dose could be used in many older patients without increasing the risk of stroke. [23] [24]

These same studies revealed that dabigatran was an extremely poor candidate for a one-dose-fits-all strategy. That is because the single dose can result in plasma levels and inhibition of blood clotting that varies more than 5-fold in different individuals.[24] Those with higher plasma levels are at high risk of potentially life-threatening hemorrhages; those with sub-therapeutic plasma levels will get little drug benefit and may suffer a stroke. The safety of this high-risk treatment can be improved through individualizing the dose for drug effect on thrombin time, as is routinely done with warfarin through a different test, the International Normalization Ratio (INR). However, that important safety option is not available here for three reasons: 1) Neither the company nor the FDA has specified therapeutic plasma levels, despite the availability of extensive data. 2) The Hemoclot thrombin inhibitor kit is not approved in the United States except for research use. 3) The lower, 110 mg strength capsule is not available, should a lower dose be indicated.

Adverse Event Reporting System

Success in Detecting Hypersensitivity

Our survey of drugs with 10 or more reported cases of severe hypersensitivity showed the postmarket surveillance system was performing well in detecting these reactions and providing this information to health professionals. As noted above, all 20 randomly sampled drugs included hypersensitivity information. This suggests that drug manufacturers were screening and evaluating the adverse event cases they received and updating the prescribing information as required. In addition, the drugs with larger numbers of severe reactions reported generally had stronger or more prominent warnings

Quality Assurance Problems Notable

The FDA's Adverse Event Reporting System (FAERS), which QuarterWatch independently monitors, remains the cornerstone of postmarket safety surveillance. It is the system through which most substantial drug risks are detected, once a drug is approved for marketing.[25] While Congress mandated a new kind of monitoring system based on electronic health data in 2007, and the FDA has invested millions in developing it, the new Sentinel System has yet to detect a substantial new drug risk that resulted in a safety withdrawal, a contraindication, or a warning. According to a recent FDA workshop presentation, it did provide supporting information last year for a digestive disorder associated with olmesartan (BENICAR), although the problem was originally detected with the FAERS data. [26]

Over a decade's time the FDA has transitioned from a system depending on massive amounts of paper records to an electronic system. The FAERS system has followed, and in 2013 Quarter 1, a total of 86% of all case reports received were electronic submissions. In September 2012 the FDA initiated a new internal computer system to manage the growing volume of reports.

Typically, electronic records systems lead to quality improvements because they can filter, collect, or reject irregular entries. This has not proved to be the case with the FDA's electronically submitted adverse

drug event reports. Our regular screening of the reports, even after months of FDA processing, shows that the report quality is poor. In thousands of reports each quarter, the drug names are irregular, and the FDA has not published a standard for drug identification. (QuarterWatch uses the publicly available ingredient names of the National Library of Medicine RxNorm terminology). Dates in the reports may be plainly implausible. Drug therapy is reported as being stopped before the therapy start date. Dose data are irregular and appear in different fields. Irregular computer codes are embedded in the submissions. The FDA specifies codes and abbreviations to denote key features of the adverse event reported. But the system does not reject records with improper or unreadable codes. Report integrity is sometimes compromised because a case is missing the name of the primary suspect drug, or contains more than one primary suspect.

The problem at the FDA appears to be twofold. For some key information (such as drug names) the FDA has not published a clear and useful standard. Second, the FDA does not screen incoming submissions to reject/return inappropriate entries (as happens whenever consumers try to enter data on most web sites). Finally, when the FDA releases the data for public use, the staff does not want to alter the original data in the FDA system, even if it is incorrect. Where clear standards do exist, compliance and quality have been relatively good. MedDRA, the international dictionary of medical terminology, has been standardized for more than a decade, and it is rare to encounter a non-standard term.

Methods Summary

QuarterWatch monitors the safety of prescription drugs through analysis of adverse drug events reported to the FDA by consumers and health professionals, either directly to the agency or through drug manufacturers. The agency releases computer excerpts for research use on a quarterly basis, and these case reports are our primary data source. [27] A full description of our methodology is available on the QuarterWatch pages of the ISMP web site. (http://www.ismp.org/QuarterWatch/detailedMethods.aspx)

The severity of the adverse event was classified as serious if the case indicated an outcome of death, disability, hospitalization, required intervention to prevent harm, was life threatening or had other medically serious consequences. Cases without these specific outcomes were classified as not serious.

In these data, the adverse events that occur are described by medical terms selected from the Medical Dictionary for Regulatory Activities (MedDRA), a terminology developed by the pharmaceutical industry to describe adverse events in clinical studies and postmarketing reports.[28] 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.[2] 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. High Level Group Terms (HLGTs) combine several related HLTs and System Organ Classes combine the terms into 26 categories. The QuarterWatch database was updated in November 2013 to MedDRA version 16.1.

The MedDRA terminology was used to create two additional report categories: product quality complaints and medication errors, both identified by HLGTs of that name. An event was classified as occurring in normal medical use if the report contained no indication of either a medication error (including intentional overdoses) or a product quality complaint.

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 Health 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 2014 (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.”

Events in QuarterWatch are attributed to the product identified as the primary suspect drug in the case report. The drug names are standardized to drug ingredient names base on the National Library of Medicine’s RxNorm terminology. [29] When cited in the text, tables, or charts, the brand name selected for the drugs is the one most frequently indicated on the case reports but may account for a small or large share of the actual reports identified. Unless specified, QuarterWatch does not distinguish dose, route of administration, or extended release and other preparations.

The hypersensitivity section focused on a specific subset of adverse event reports received by the FDA in the 12-month study period ending March 31, 2013. It excluded foreign reports, cases identified as resulting from litigation, and group of drugs we classify as special reporting drugs because of special circumstances that lead to unusual kinds of reporting. In addition, it excluded reports that indicated a patient death, but had no information indicating that a possible role of the drug had been evaluated. The population of cases screened for the hypersensitivity analysis included 147,318 / 216,026 (68.2%) domestic cases with a serious outcome.

QuarterWatch Team and Funding Sources

QuarterWatch is published by the Institute for Safe Medication Practices as a public service. It has no regular income, foundation grant, or other dedicated financial support and is provided to the public and health professions without charge. We seek outside peer reviewers for each issue but their identities are not disclosed. QuarterWatch's essential costs are funded from the general budget of ISMP, a non-profit organization dedicated solely to promoting the safe use of medication. ISMP, in turn, is supported by charitable donations, volunteer efforts, foundation grants, and subscription income from its four other medication safety newsletters, for pharmacists in the acute care and ambulatory care settings, for nurses, and for consumers.

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. He is also a lecturer in the Department of Epidemiology and Biostatistics in The George Washington University Milken Institute of Public Health. 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 and for a civil defendant in connection with criminal cases involving Chantix (varenicline). He also worked as 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. In 2012 he was a consulting expert for the plaintiffs in the Celexa and Lexapro Marketing and Sales Practices Litigation. In 2014 he was a consulting expert for the plaintiffs in federal whistleblower litigation involving Elidel (pimecrolimus).

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