



The Institute for Safe Medication Practices

A Nonprofit Organization Educating the Healthcare
Community and Consumers About Safe Medication Practices

QuarterWatch: 2009 Quarters 1-3

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Did a Cold Remedy Cause Thousands to Lose Their Sense of Smell?

EXECUTIVE SUMMARY

In the third quarter of 2009, the number of serious, disabling and fatal adverse drug events reported to the U.S. Food and Drug Administration continued the steady increase seen for the past two years. The FDA received 29,065 case reports meeting the QuarterWatch criteria in the third quarter, compared to 26,809 in the same quarter one year earlier, an increase of 8.4%. For the first three quarters of 2009 combined, the total number of reports was 8.1% higher than in the same period of 2008.

QuarterWatch monitors all domestic serious adverse drug event reports received by the FDA. Because the FDA has accelerated the release of computer excerpts of adverse drug event reports for research use, this QuarterWatch report will focus on new data from the first through third quarters of 2009, instead of a single quarter.

In the 2009 data we saw a strong signal showing two Zicam brand over-the-counter cold remedies were being blamed for people losing their sense of smell or taste, many permanently. In June 2009 the FDA demanded the immediate withdrawal of two Zicam brand cold remedies, Zicam Cold Remedy Nasal Gel and Zicam Cold Remedy Gel Swabs. The products are manufactured by Matrixx Initiatives of Scottsdale, Arizona. Both contained zinc, which a new study has shown can be toxic to smell receptors in the nose.

Since the June FDA action, new evidence has emerged that the scope, severity and permanence of reported injuries were much larger than originally reported. The case also illustrates that a voluntary reporting system often captures only a fraction of the injuries that have occurred. In seeking the withdrawal of the two Zicam products, the FDA cited 130 adverse event reports received over a period of several years. But in the two weeks after the FDA announcement, the agency received 511 additional reports; in the next quarter another 303 cases. In addition, the company had also received more than 1,000 complaints directly from consumers who said they lost their sense of smell. But the company had not reported any of these cases to the FDA.

We explore the numerous questions raised by the Zicam tragedy in the full report. How many people have permanently lost their sense of smell? Why did it take 11 years to remove Zicam products from the market? How did these products avoid the safety testing normally required for most over-the-counter drugs? Why did the company fail to report a single serious adverse event to the FDA?

Other Signals Observed

- **Rosiglitazone (AVANDIA).** More than 1000 reports of patient deaths were received for rosiglitazone in the first three quarters of 2009, more than any other drug we monitor. Rosiglitazone is an oral medication for treating Type 2 or adult onset diabetes. Most deaths were attributed to cardiovascular causes, a problem for which the FDA has required warnings. While these cases do not appear to signal previously undetected risks of rosiglitazone, the large number of reports alleging serious and fatal injuries associated with rosiglitazone further reinforces concerns about its cardiovascular safety. The company, GlaxoSmithKline, told us it believed most reports were generated by lawsuits. In February 2010 the FDA announced it was conducting an overall safety review of rosiglitazone and would present its findings to a special advisory committee meeting in July.
- **Quetiapine (SEROQUEL, SEROQUEL XR).** In the third quarter of 2009, quetiapine, a drug approved for several severe mental disorders, was the suspect drug in more possible cases of diabetes than all other drugs combined. AstraZeneca, which manufactures this best-selling antipsychotic drug, told us it believed most of the diabetes cases were related to lawsuits. The mandatory Medication Guide to warn patients about the risk of diabetes does not primarily use the word “diabetes” but rather describes the disorder as “high blood sugar (hyperglycemia),” potentially minimizing this serious risk.
- **Testosterone (ANDROGEL, TESTIM).** We observed a signal for adverse events associated with these powerful sex hormone products which are applied to the skin as a gel. Although approved only for use in men, we observed 155 cases of reported injury in women and 22 events in children in the first three quarters of 2009. Despite an FDA warning, it appears accidental exposure and inappropriate off-label use continues to cause injuries.
- **Product quality problems continue.** We observed continued signals for recalled products we have previously described—notably digoxin. In addition we noted reports of bacterial contamination of propofol, an anesthetic, and complaints about recently-approved generic forms of levetiracetam (KEPPRA), a drug for epilepsy. In addition large product recalls have been announced recently for Johnson & Johnson’s Tylenol and Motrin products, all of Neilgen Pharma’s prescription cough and cold products, and millions of infusion needles and insulin syringes manufactured by Nipro Medical Corporation.

The Adverse Event Reporting System

- **Missing age data.** In the third quarter of 2009 the public release age data was missing for 49% of the serious adverse event cases that met the QuarterWatch criteria. We believe that technical problems are causing the deletion of age information from many electronically submitted case reports. Loss of these data seriously limits the capacity to identify and examine vulnerable populations, such children and the elderly.

- **Marked improvements.** The FDA has accelerated the public release of adverse event data, reducing the lag time to around 90 days. While further reductions would be welcome, more timely release of data permits earlier action on any signals detected. In addition, standardized medical terms used in these reports were revised to provide improved detection of product problems and certain medical conditions, such as depression.

About QuarterWatch Data

The ISMP QuarterWatch monitoring program evaluates computer excerpts of all serious, disabling and fatal adverse drug events reported to the FDA for patients in the United States. The U.S. system for postmarketing safety surveillance relies on voluntary reports submitted by consumers, doctors, pharmacists and other health professionals. The submission of a single report does not in itself prove that the suspect drug caused the event described. But these reports also form the basis of a majority of regulatory actions and warnings. There are no reliable estimates of what fraction of serious adverse drug events are ever reported, and small studies and our own investigations show wide variation in reporting rates for different drugs and among different types of adverse reactions. Although we have occasionally documented instances where injuries for a drug may be overstated, the events reported to the FDA are believed to be a relatively small fraction of the drug-related injuries actually occurring.

Conclusions

While many important questions remain unanswered, thousands of people are reporting they have lost their sense of smell after using Zicam Nasal Gel and Swab products that contained zinc. Although millions of people purchased these products for years, these Zicam products did not undergo the FDA premarket safety review required for most over-the-counter products. The manufacturer received numerous complaints about loss of the sense of smell but did not submit them to the FDA. Further study is required to determine how many people permanently lost their sense of smell as a result of these withdrawn products. We recommend that the FDA Commissioner's office conduct an independent review of the Zicam products episode for its implications for regulatory law, enforcement policy, and the possibility that other dangerous compounds may still be in widespread use.

We believe that the warning about the diabetes risk of quetiapine needs to be strengthened and clarified in both the Medication Guide that is required for every patient, and the prescribing information for physicians.

As product recalls continue into 2010, we again call on the FDA to reassess its inspectional and enforcement programs intended to assure product quality. As we mentioned in prior QuarterWatch reports, the FDA often allows the companies associated with recalled drugs to handle even consumer-level announcements; it does not require disclosure of the size of the recall, and it may assesses the level of risk to the public after long delays.

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Contents

Methodology.....	5
Results.....	6
Zicam Nasal Products.....	11
Rosiglitazone.....	13
Quetiapine.....	15
Testosterone Gel.....	17
Product Problems Continue.....	18
References.....	21

METHODOLOGY

We have previously described our program for monitoring serious adverse drug events reported to the FDA.^{1,2} The agency publishes for research use computer excerpts of all adverse drug event reports it receives directly, or through drug manufacturers, who collect the information and forward the report. Reporting of adverse effects of drugs is voluntary for consumers and healthcare professionals, who may elect to report an event to the FDA or the drug company. The companies, in turn, are required to collect the information and forward to the FDA complete reports of any adverse drug event of which they are informed. Reports are also collected from the scientific literature and from a drug company's foreign safety surveillance activities.

QuarterWatch focuses on domestic case reports of adverse drug events that are classified under the regulation as "serious," which means events that resulted in death, permanent disability, a birth defect, required hospitalization, was life threatening, required intervention to prevent harm or had other medically serious consequences. We exclude reports from foreign sources, cases from clinical studies which have different reporting requirements, and events in which the injuries were not serious.

In the third quarter of 2009, the FDA received a total of 129,992 adverse drug event or "MedWatch" reports of all types of which 29,065 (22.3%) met the QuarterWatch criteria. The most common exclusions were reports from foreign sources, 43,206 cases, or events that were not serious, 37,012 cases.

We have learned that our case totals change over time for previous calendar quarters already evaluated and reported. This occurs for three reasons. Some quarterly releases from the FDA include late filed cases that belonged in the previous quarter. Also, in any given quarter, pharmaceutical companies revise or update thousands of reports from previous quarters. Finally, minor changes or improvements in our selection criteria may alter quarterly event totals. As a result, we recalculate the historical comparisons for each quarter to insure that we apply exactly the same criteria to all of our data, and are utilizing the most recent available versions of case reports that have been revised. While comparisons within any QuarterWatch report are accurate and consistent, event totals may vary slightly between various quarterly reports.

We typically describe our findings as signals, meaning we have seen enough information to generate a safety concern that warrants additional investigation. A single report in itself does not prove that the drug caused the event. However, depending on the content of the report, and the number of reports received, these cases may bear substantial weight in a full scientific assessment of causal relationship.

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/>).

Changes this Quarter

Two new revisions in our selection criteria have had a measurable effect on event totals. We had been excluding a small group of drugs which had special mandatory reporting requirements similar to those for clinical studies. Over time, we have discovered an increasing number of drugs with special reporting schemes and are therefore adding them to this special category. To provide more accurate accounts, we will no longer exclude these drugs, but will list them in a separate table in the Results section of this report. In addition we slightly revised our drug dictionary, which has had a small effect on the number of drugs we track.

RESULTS

Volume of Reports

In the third quarter of 2009 the steady increase continued in reported serious, disabling and fatal adverse drug events. Cases meeting the QuarterWatch criteria totaled 29,065 cases, an increase of 2,256 cases (8.4%) from the same quarter in the previous year. For the first three quarters of 2009, combined case reports increased by 8.1% from the first three quarters of 2009. The increases in 2009 occurred at a slower rate than in 2008, when cases increased by 25%.³ The trend over time is illustrated in Figure 1.

Figure 1. Total Cases Reported (Serious, Disabling, Fatal)

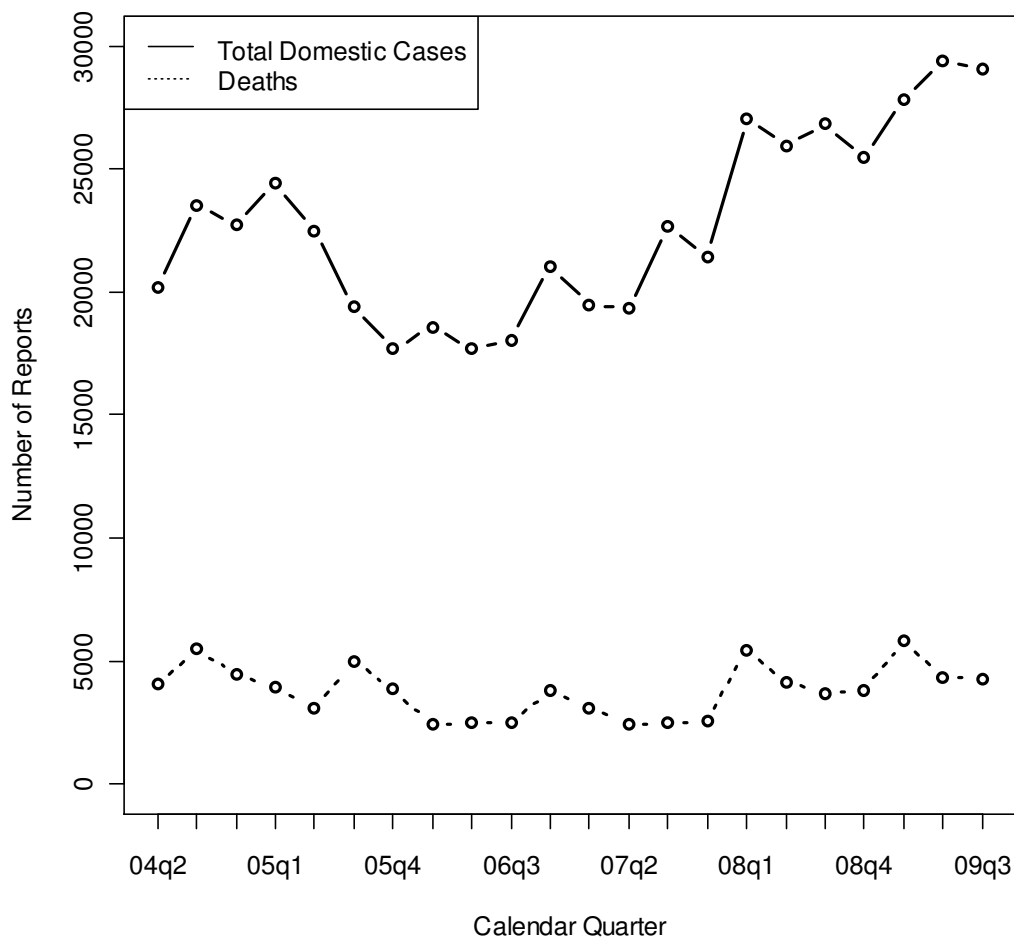


Figure 1 also illustrates that reported deaths associated with prescription drug therapy were more stable than the combined total of serious, disabling and fatal reports. In 2009 we observed a spike in reported deaths in the first quarter, similar to what we also reported for the first quarter of 2008. In both years, we believe the spike in deaths is a result of the annual report of the American Association of Poison Control Centers, which is published in December. In the next quarter these cases—primarily from intentional and accidental drug overdoses—are reported in the system as adverse drug events.

Drugs Most Frequently Reported

After an update in the list of drugs that we monitor, we now track 1,949 identifiable drug products. Of the drugs we monitor, 1,116 (57%) had zero reports in the third quarter of 2009 of a serious, disabling or fatal injury that met the QuarterWatch criteria. Among the remaining 833 drugs for which adverse drug events were reported, the median or typical number of cases for each drug was 7 reports. At the other extreme, a total of 57 drugs had 100 or more cases reported in the third quarter. The 15 most frequently reported drugs are shown in Table 1. As noted in the methodology section of this report we tabulate and list

separately a small group of drugs with special reporting requirements or procedures. We discuss adverse events associated with rosiglitazone and quetiapine later in this report.

Table 1. Most frequently reported drugs in 2009 Q3 from all sources

Drug Name*	Brand Name	Cases	Rank
ROSIGLITAZONE	AVANDIA	1218	1
QUETIAPINE	SEROQUEL	977	2
BACLOFEN	LIORESAL	796	3
FENTANYL		688	4
ETANERCEPT	ENBREL	495	5
INFLIXIMAB	REMICADE	395	6
ADALIMUMAB	HUMIRA	353	7
DEFERASIROX	EXJADE	294	8
ZOLEDRONIC ACID		287	9
TERIPARATIDE	FORTEO	278	10
ACETAMINOPHEN		276	11
DULOXETINE	CYMBALTA	266	12
IBANDRONATE	BONIVA	249	13
LEVOFLOXACIN		242	14
IMATINIB	GLEEVEC	239	15

*Generic drugs shown in bold face

Direct Reports to the FDA

Reports of serious adverse drug events reach the FDA through two markedly different routes. Health professionals or consumers may voluntarily report adverse drug events directly to the FDA by telephone (800-332-1088), mail, fax or online (<https://www.accessdata.fda.gov/scripts/medwatch/medwatch-online.htm>). In the third quarter of 2009, the FDA received 5,963 case reports meeting the QuarterWatch criteria directly from consumers of health professionals, or only 21% of the report total. The overwhelming majority of the reports, therefore, were submitted by drug manufacturers, who are required to forward every reports of every case of which they become aware. For this issue of QuarterWatch we explored the question of whether the FDA was receiving reports for different drugs than was industry. The evidence shows that in fact, they were. The top ranked direct reports to the FDA from consumers and health professionals are shown in Table 2.

Table 2. Drugs most frequently reported directly to FDA in 2009 Q3

Drug Name	Cases	Rank
LEVOFLOXACIN*	175	1
WARFARIN	112	2
TOPIRAMATE	111	3
LAMOTRIGINE	105	4
VARENICLINE	101	5
AMPHETAMINES	96	6
CIPROFLOXACIN	90	7
DULOXETINE	89	8
LISINOPRIL	87	9
RISEDRONATE	74	10
BUPROPION	72	11
MONTELUKAST	66	12
LEVETIRACETAM	66	13
LENALIDOMIDE	65	14
VALPROIC ACID	64	15

* Generic drugs shown in bold face

Table 2 shows that reports submitted directly to the FDA are dominated by generic drugs, while the list overall is dominated by industry reports about brand name drugs that typically are promoted intensively. Among those drugs reported to the FDA directly 11/15 (73%) are generic drugs. Similarly 11/15 drugs (73%) in Table 1 (reports from all sources) are brand-name drugs from a single manufacturer.

While a definitive answer requires more systematic study, we believe this evidence suggests that adverse events for brand name drugs may be reported more frequently in this voluntary system than are those for generic drugs. Put another way, adverse events for generic drugs are more likely to be underreported than are problems with brand name drugs.

The reason for the difference likely resides with the purpose of drug brand names: to create awareness of the product in the minds of consumers and healthcare professionals. The company's name as well as the product brand name typically are prominently featured in promotional materials. This makes it easy to find the drug company and report an event. On the other hand, the manufacturer of a generic drug is not always obvious from the materials that a consumer receives. Most are made by multiple manufacturers and we have identified numerous cases in which drugs are manufactured by one company but distributed to consumers under the name of another company.

The consequence is that a much smaller number of direct reports involving generic products should be considered a signal and warrant further investigation by the FDA and the generic drug manufacturers.

Special Reporting Drugs

At the other end of the scale, unusually large numbers of case reports are received for certain drugs which the FDA approves with special requirements for intensive adverse event reporting. Examples of these drugs included thalidomide (THALOMID) and lenalidomide (REVLIMID), highly specialized drugs with severe risks for birth defects, and natalizumab (TYSARBI) a drug for multiple sclerosis associated with a rare and potentially fatal brain infection called progressive multifocal leukoencephalopathy.

To this list of drugs with FDA requirements we have added additional drugs where we have confirmed that the drug company maintains contact with literally every single patient who has been prescribed the drug. We have previously reported on DIANEAL, a product for kidney dialysis at home.⁴ In this case, the company delivers the product on a monthly basis to each consumer and therefore learns of adverse events. Similar intensive patient contact occurs with the interferon beta product AVONEX.⁴ The special reporting drugs are shown in Table 3.

Drug Name	Cases
INTERFERON BETA	1716
NATALIZUMAB	805
ESTROGENS	679
INSULIN	646
LENALIDOMIDE	526
DIANEAL	287
AMBRISANTAN	194
THALIDOMIDE	110

In addition to the cases described above, the expanded special reporting category now also includes two drug groups—estrogens and insulin—that are combinations of many different similar products. In the third quarter of 2009, the most frequently reported specific estrogen products were MIRENA, an intrauterine birth control device with estrogens (177 cases), YAZ, an oral contraceptive product (133 cases), and PROVERA, an estrogenic product containing medroxyprogesterone (104 reports). The insulin cases were spread among various products which were difficult to identify specifically.

SPECIFIC DRUGS

ZICAM Nasal Gel and Nasal Swab Products

Background

In June of 2009 the FDA demanded that Matrixx Initiatives of Scottsdale, AZ immediately withdraw two over-the-counter drug products, ZicamNasal Gel and Zicam Nasal Swabs.⁵ The agency said it was acting on the basis of 130 adverse event reports in which users of the two products said they had lost their sense of smell, some permanently.

Matrixx Initiatives (formerly Gum Tech) is a publicly traded company with 34 employees that sells millions of ZICAM brand cold products every year mainly through Wal-Mart, Walgreens and CVS.⁶ In response to the FDA action, William J. Hemelt, the president and CEO of Matrixx, told investors that the company was taken completely by surprise by the FDA actions.⁷ The company agreed to comply with the FDA demand, but said its scientific evidence showed the product was safe and effective for treating the symptoms of the common cold. Other reasons for loss of smell, he said, were colds (which can affect sense of smell), a nose injury, natural aging or other drugs. The products withdrawn constituted 40% of the company's net sales.⁸ The company reported that its profit margins were 79% of the gross sales price. Other Zicam products remain on the market.

Both the risks and claimed benefits of the two Zicam products are traced to the same ingredient: zinc. Two small clinical studies of zinc nasal gels reported that the products shortened the duration and severity of cold symptoms.^{9,10} But in October 2009 a new independent study conducted at the University of Washington reported that Zicam products "irreversibly damage mouse and human nasal tissue."¹¹ The company told us that it no longer sold any product intended for use in the nose that contained zinc, although it continued to sell various oral preparations with that ingredient.

Signal in Adverse Drug Events

The serious adverse event reports for Zicam cold products were unusual in several ways. We identified 1,402 serious adverse event reports for these products dating back to 2004. A total of 1,327 (95%) of the reports contained medical terms indicating a single kind of adverse event: loss of smell or taste. The reports were unusual in that until the warning letter in June 2009, not a single adverse event report was submitted by the drug manufacturer, Matrixx Initiatives. An FDA inspection report stated that the company did not regard loss of the sense of smell as a serious adverse event.¹²

The Zicam products reports shared a drawback with numerous other reports of over-the-counter drugs: the identification of the implicated product was not clear. Although we know of at least 23 different products in the Zicam line of remedies, only 2 were withdrawn

in the FDA action. A total of 249 reports simply indicated “Zicam” while others indicated “Zicam cold remedy.” While both brand name and generic drugs have distinctive and unique names, over-the-counter drug products do not.

The timing of the Zicam reports also shows the extent to which previous cases were likely underreported. In the second quarter of 2009 the FDA received 11 case reports of loss of sense of smell for Zicam products prior to the recall, bringing to overall total to 130 cases since 1999. However, in just two weeks after the recall, the company received 511 more reports. In the next quarter, the FDA received an additional 303 case reports.

Complaints for More Than a Decade

Both the nasal gel and swabs had drawn complaints about consumers losing their sense of smell since the first of the related products was introduced in 1999. In a media briefing in June, the FDA noted that its first adverse event report dated back to 1999.¹³ A few years later the news media were targeting these products and the consumer complaints, including the ABC News program “Good Morning America” and Consumer Reports, which advised against using the nasal products. In 2005, the FDA inspected the company’s offices in Scottsdale and found the company had received 36 consumer complaints of loss of smell in the month of March 2005 alone.¹² The company reported recently it had received more than 1,000 complaints of impaired sense of smell and had paid or expected to pay damages to 510 people.¹⁴ The company reported that 340 of those claimants were paid a total of \$12 million, or an average of \$35,000 each. The remaining claims were being settled for approximately \$4,500 each. The company disclosures about the settlement figures did not include any additional claims—expected to be numerous—following the products’ withdrawal.

Discussion: A Regulatory Breakdown

Since 1932 companies selling drug products for the mitigation or cure of disease have been required to conduct scientific studies demonstrating these products are safe and submit these studies to the FDA for independent review. However, there are exceptions, and Matrixx claimed that its Zicam products fell under one of them. Beginning in the 18th century a form of alternative medicine called homeopathy developed treatments based on administering minute quantities of toxic substances which were believed to stimulate a protective effect from the immune system of the body. While the FDA claims the legal authority to regulate homeopathic products, it states that it will not act on products produced in accordance with the Homeopathic Pharmacopeia of the United States.¹⁵ The zinc in the Zicam nasal products was among those listed in this compendium. While the theoretical purpose of homeopathy is to stimulate an immune response from minute quantities of a toxin, the two clinical trials of Zicam nasal gel indicated the investigators believed it likely had a direct pharmacological effect on the protein coating of cold viruses. The animal and human tissue study noted above suggested a risk: If the zinc came in contact with smell receptors, it might irreversibly damage them.¹¹ In demanding the withdrawal of the Matrixx Zicam products, the FDA asserted that these products were a drug, which required the full spectrum

of testing for safety and efficacy—none of which had been performed prior to millions of people being exposed to these products.

The company’s response to the FDA is also revealing. In November, the company petitioned the FDA to reverse its decision and permit the two Zicam products to return to the market. The company maintained that neither the FDA nor anyone else had “valid scientific evidence that these Zicam products are unsafe.”¹⁴

The company, therefore, wants to shift the burden of proof, and demands that the FDA prove its products are not safe. The FDA’s position is that, because of safety concerns about these products, it is placing the burden of proof on the company to conduct the necessary scientific studies to demonstrate that its products are safe and effective. We believe this case illustrates the importance of a safety system that since 1932 has placed the burden of proof for safety studies on those who offer drugs for sale, and for those drugs for which safety studies disclose potential risks, additional studies to demonstrate that its benefits outweigh its risks. This lapse in the system associated with the two Zicam products may have resulted in uncounted thousands of people suffering from loss of sense of smell, possibly permanently.

Is it possible that intranasal zinc might shorten the symptoms or duration of the common cold? Two small studies are not conclusive, but the possibility certainly cannot be ruled out. Is it also possible that if the zinc penetrates deeply enough into the nasal cavity to come into contact with the receptors for the sense of smell, that it impairs or possibly destroys those receptors? The University of Washington study supports this proposition. If the Zicam products do irreversibly impair the sense of smell, how many such injuries have occurred among the millions of people who took the drug over a decade’s time? The answer is also unknown, although thousands of consumers have complained that this occurred.

Rosiglitazone (AVANDIA)

Background

Rosiglitazone (AVANDIA) is used to treat Type 2 or adult onset diabetes, and since its approval in 1999 has been at the center of important questions about the measurement of drug risks and benefits. In Type 2 diabetes the body’s ability to control levels of blood sugar is impaired and declines over time—often in association with obesity. Typically there are few or no symptoms, but over many years’ time, those with Type 2 diabetes are at greater risks for heart attacks and strokes (called macrovascular complications) and impaired sight and damage to the kidneys through damage to minute blood vessels (also called microvascular complications). The body’s ability to manage its blood sugar levels may be measured through a laboratory test of a special type of hemoglobin in red blood cells, HbA1c. Higher levels of HbA1c indicate that blood glucose levels have been elevated in the recent past. But the health benefit of a drug to lower HbA1c levels is, at present, theoretical, as no oral medication that lowers this laboratory measure has yet been proven to produce tangible health benefits such as fewer heart attacks, or less deterioration of vision or kidney

function.¹⁶ But many experts in the field believe improving the laboratory measure of HbA1c is sufficient to justify treatment.

But what if a drug with a beneficial effect on an important laboratory measure, also has tangible adverse effects on health? This is a question which has weighed on rosiglitazone. In addition to improving glycemic control, the drug is also associated with weight gain, edema (swelling and fluid retention), macular edema (blurred vision from fluid retention in the eye), and increased rate of bone fractures in women.¹⁶ But in addition, longer studies of rosiglitazone have also shown it increases the risk of heart failure. In addition, several analyses that combined smaller clinical studies concluded that rosiglitazone may increase the risk of heart attack rather than lowering it.¹⁶⁻¹⁸ In 2009, the manufacturer, GlaxoSmithKline, reported the results of a large clinical trial monitoring patients over five years. The study showed that treatment with rosiglitazone doubled the risk of heart failure, was inconclusive about heart attack risk, and showed increased risk of bone fractures.¹⁹ In February 2010 the FDA announced that it was conducting a safety review of all safety data about rosiglitazone and would present its analysis at a special advisory committee in July.

Adverse Event Signals

In the third quarter of 2009, rosiglitazone accounted for more serious, disabling and fatal adverse event reports than any other drug we regularly monitor, a total of 1,218 cases. Rosiglitazone also ranked first among the drugs we monitor in patient deaths, with a total of 304 reported. Among 400 drugs with case reports indicating a patient death, the median number of deaths reported was two. Over the first three quarters of 2009 combined, rosiglitazone was the suspect drug in 1,028 reported patient deaths, approximately three times higher than the second – and third-ranked drugs, acetaminophen with 343 cases and digoxin with 330.

The events reported in association with rosiglitazone were primarily cardiovascular in nature with 613 cases mentioning myocardial infarction (heart attack), 278 cases noting congestive heart failure and 206 identifying strokes.

Discussion

While these cases do not appear to signal the possibility of a previously undetected risk of rosiglitazone, the large volume of reports alleging serious and fatal injury associated with rosiglitazone further reinforces concerns about its cardiovascular safety. GlaxoSmithKline told us that the company also had noted an increase in fatal rosiglitazone outcomes since mid 2007, but it attributed the increase largely to media publicity and to lawsuits against the company. GSK also said its new study noted above showed the drug did not increase the overall risk of hospitalization or death from cardiovascular causes.

Enough questions have arisen about the risks and benefits of rosiglitazone that we agree with the American Diabetes Association and European Association for the Study of Diabetes report, which “unanimously advised against using rosiglitazone.”²⁰

Quetiapine (SEROQUEL)

Background

Quetiapine (SEROQUEL, SEROQUEL XR) is an antipsychotic drug, a class of drugs used to treat schizophrenia. Its use has expanded to other mental illness including bipolar disorder and major depression. The hallmark of drugs in this class is that they block dopamine receptors in the brain. Dopamine is a chemical in the brain with an important role in muscle movement, mood, behavior, sleep and psychological rewards. Two kinds of side effects of are typically of greatest concern. Quetiapine may cause involuntary muscle movements called tardive dyskinesia, which can be incurable. In a landmark clinical trial of quetiapine and four other drugs for schizophrenia all five drugs tested triggered tardive dyskinesia in about 13% of the patients during 18 months of treatment.²¹ A second major risk of antipsychotics such as quetiapine involves impairing the normal regulation of blood sugar, resulting in weight gain and diabetes. In the same clinical trial, 17% of quetiapine patients experienced clinically significant weight gain, which was similar to three of the comparison drugs but less than olanzapine (ZYPREXA). Quetiapine also has warnings or precautions about suicide risk, increased mortality in elderly patients with dementia, and increased risks of elevated cholesterol and blood pressure in adolescents.²² The manufacturer, AstraZeneca, reported that quetiapine was the market-leading product in its class in the third quarter of 2009 with a 31% market share²³ With the approval in December of 2009²⁴ of a major new medical use—adjunctive treatment in depression—it seems likely that the sales of quetiapine will expand still further.

Adverse Event Signals

In the third quarter of 2009, quetiapine ranked second among monitored drugs with 977 reports of serious, disabling or fatal adverse drug events in which it was the principal suspect drug. Reported cases have risen steadily from 261 cases in the fourth quarter of 2008, but we have identified higher spikes in previous years.

Although quetiapine and other antipsychotic drugs have a wide array of side effects as previously noted, the surge in new case reports was caused almost entirely by potential cases of diabetes. We identified potential cases of diabetes using the industry Standardized MedDRA query for diabetes, narrow scope.²⁵ In the third quarter of 2009, we identified 669/977 (68%) of all quetiapine adverse drug events as possible cases of diabetes.

The signal for diabetes was also striking because quetiapine accounted for 669/1147 (58%) of possible cases of diabetes associated with all prescription drugs in the third quarter. Not only did quetiapine account for a majority of all cases reported to the FDA, it also accounted for more reported cases than all the other drugs combined, more than 10 times more cases than the next ranked drug, exenatide (BYETTA) with 61 reported cases.

We also examined what specific medical terms included in the diabetes category. Most medical terms in the reports were unambiguous descriptions of diabetes: Diabetes mellitus (513 mentions), Type 2 diabetes mellitus (363), Diabetes mellitus inadequate control

(145 mentions). More than one of the terms listed above could have appeared in the same report.

We contacted the manufacturer—AstraZeneca—about the diabetes reports. The company responded that it believed 98% of the reports involved lawsuits from patients who believed the drug had caused diabetes. But the company said it did not believe these reports proved a causal relationship.

Discussion

We believe the FDA and the manufacturer should restructure and simplify the patient Medication Guide for quetiapine²² and clarify the statement of diabetes risk for physicians.

It is surprising that a mandatory Medication Guide to warn patients about the risk of diabetes from quetiapine does not use the word “diabetes” but rather calls it “high blood sugar (hyperglycemia)” as if that were some separate medical condition. Then the guide lists common symptoms of diabetes such as thirst, frequent urination, hunger or fatigue, but calls them “symptoms of high blood sugar.”

The diabetes section of the prescribing information for physicians is complex, equivocal and difficult to understand. The first paragraph is filled with qualifications instead of information, referring to the issue being “complicated,” the presence of “confounders,” and a relationship that is “not completely understood.” This is followed by two difficult to interpret tables. The advice to physicians (monitor patients who already have diabetes, and alert all patients to symptoms) follows this densely worded mass of complex technical language.

The key purpose of drug testing required by law is to define with reasonable precision the risks and benefits of a drug to assist doctors and patients in determining its safe and appropriate use.

Quetiapine was first approved 1997, and has been administered to many millions of patients and is now approved for use in a wider spectrum of mental disorders than any other drug in its class. If prominent diabetes risk of this drug cannot be stated clearly and the patient monitoring necessary to manage this risk cannot be simply stated to patients and prescribing physicians, then some kind of breakdown in the system has occurred and we can expect increasing reports of this serious adverse drug effect.

Whether this breakdown was yielding to industry pressure to minimize the diabetes warning for fear of reducing sales, or failure to require appropriate clinical testing to measure this risk cannot be determined here.

Testosterone (ANDROGEL, TESTIM)

Background

The male sex hormone testosterone typically is administered through injection, a transdermal patch or a gel that is spread on the skin. When administered orally it is rapidly broken down by the liver. ANDROGEL and TESTIM are topical gels that are applied to the shoulders, arm or abdomen, and are FDA approved for replacement therapy in adult males with a deficiency or absence of the hormone. In May of 2009, the FDA warned that children were being inadvertently exposed to the gel products through contact with adults who had applied it.²⁶ The agency said that in a few cases children had enlarged genitalia inappropriate for their age. The FDA said it believed that in 2007 there were 27,000 prescriptions off label for women—in whom the drug has not been tested.

Adverse Event Signal

In the first three quarters of 2009 we identified 220 adverse drug events associated with testosterone products of which 155 (70%) were reported in women. The female cases mainly involved adult women, with a mean age of 44.5 years; approximately 10% of these cases occurred in children. Among all the 175 cases in women, the exposure was explicitly identified as accidental in 25 (14%) of cases. The most frequently appearing medical terms in these events involved acne and abnormal hair growth or loss.

Discussion

Although only 14% of the cases explicitly identified the exposure in women as accidental, we suspect the true total is higher. The computer excerpts which QuarterWatch analyzes are much simpler and less detailed than are the full reports, which contain detailed narratives. The FDA warning and a new requirement for a Medication Guide to provide patients with a warning about accidental exposure appears to be warranted and an appropriate step. In addition, the FDA warning itself may have motivated affected consumers to report additional cases.

Product Problems Continue

Background

Product problems involve deficiencies in the manufacturing or packaging of drugs that create the potential for injury, most often through contaminants, or products that do not contain the correct dose, or dissolve too slowly or too quickly. Typically, when product problems are discovered through FDA inspections or complaints, the products are recalled. Adverse drug event reports play numerous roles in the process. Sometimes the adverse event reports provide the first evidence that a product problem is occurring. Also, a public announcement by the FDA or the manufacturer of a recall may contribute to additional reporting as consumers and health professionals realize this issue may have been responsible for a medical problem that was not previously linked to the drug. Finally, large scale product recalls may trigger legal claims from persons who believe that a defective product was responsible for an injury. QuarterWatch has previously reported on major signals seen in connection with the recall of heparin in vial form, digoxin, morphine, isosorbide, propafenone, and baclofen.^{1, 4}

Adverse Event Signals

In the first three quarters of 2009 we observed two new signals, identified continuing cases from previously reported issues, and noted important public announcements of additional major recalls likely to lead to future reports. One new signal concerned levetiracetam (KEPPRA), a drug for epilepsy seizures intended for use in combination with other epilepsy medication. In 2009 generic drugs from several manufacturers became available in addition to the brand name product manufactured by UCB, a biopharmaceutical company based in Belgium. We identified 168 reports for levetiracetam alleging that seizures were occurring as a result of problems identified as product quality issues, product substitution issues and “therapeutic response unexpected with drug substitution.” A total of 78% of the product quality reports came from health professionals rather than consumers, and 90% were made directly to the FDA rather than to any specific drug manufacturer. The computer excerpts did not permit us to identify what manufacturers’ products might be identified. We asked the FDA about this signal, and the agency responded that it too had observed the signal and was continuing to investigate it. However, the FDA told us they had yet to uncover any safety issues in the generic versions.

We also saw a new signal for the anesthetic propofol--45 reports suggesting bacterial contamination in units manufactured by Teva Pharmaceuticals, a generic drug manufacturer based in Israel. The signal also drew the attention of the Centers for Disease Control and Prevention, the FDA and the manufacturer. In July 2009 Teva announced the recall of an unspecified number of propofol vials because of “elevated endotoxin levels.”²⁷ Endotoxins are poisons released when bacteria die. In November 2009 another manufacturer of propofol, Hospira Inc., announced it was withdrawing an unspecified amount of propofol because the containers “may contain particulate matter.”²⁸ The company stated it had not

received any reports of adverse drug events, and we found no such cases that met the QuarterWatch criteria through September 2009.

We continued to see large numbers of reported adverse drug events associated with another large product recall—the heart drug digoxin. In 2008 more than 50% of the nation’s supply of digoxin tablets—more than 800 million tablets--were recalled to the consumer level because of the possibility of over strength tablets.¹ An overdose of this heart medicine posed potentially life threatening risks because of small margin between a therapeutic and toxic effect. The recalled tablets were manufactured by the Actavis Group, a generic drug manufacturer based in Iceland, but distributed by other drug companies. In March 2009 another generic manufacturer—Caraco Pharmaceutical Laboratories of Detroit—also withdrew its entire production of digoxin tablets due to similar problems the company described as “size variability.”²⁹ In the first three quarters of 2009 we identified 841 serious adverse event reports for digoxin including 443 cases from Actavis and 166 cases from Caraco. In June 2009 the FDA had U.S. Marshals seize 33 products manufactured at Caraco’s Detroit area plants because of failure to address manufacturing problems.³⁰

In addition to these signals, we observed large scale recalls that may generate many more adverse event reports in the future. In November 2009 American Regent recalled all 15 mg vials for injection of ketorolac, a painkiller, because it might contain particles that could obstruct blood vessels.³¹ In April 2009 Neilgen Pharma and Advent Pharmaceutical recalled all their prescription cough and cold products because they were unapproved drugs.³² In November and December of 2009 and January 2010 Johnson & Johnson’s subsidiary McNeil Consumer Healthcare recalled large numbers of Tylenol, Motrin, Benadryl, Roloids, and St. Joseph’s Aspirin products because they might be contaminated with a chemical 2,4,6-tribromoanisole or TBA.^{33, 34} The main defect, the company said, was an unpleasant odor, but cases of nausea, diarrhea and vomiting had also been reported. The company stated it believed the products may have absorbed trace amounts of chemical preservative on the wooden pallets on which the products were stored for shipment. In January Nipro Medical Corporation announced the withdrawal of millions of defective insulin syringes and infusion needles.^{35, 36}

Discussion

While the numerous drug recalls reflect in part a vigorous FDA program of inspection and enforcement, we believe that the inspection and recall system needs a complete independent review. These are some of the topics that need to be studied:

The full scope of the product quality problems is being minimized by both the FDA and industry through the device of failing to disclose the size of the product recall. The Johnson & Johnson recall of Tylenol, Motrin, Benadryl and other over-the-counter drugs in late 2009 and early 2010 may be the largest drug recall in history. The company press statement stated it was recalling “certain lots of OTC products.” At the time of the recall, the company responded to a question from the Associated Press by stating it did not know how many products were being recalled. Typically, recalls are described as numbered “lots” which can be of practically any size. We did determine independently that the 2008 Actavis

recall involved 800 million digoxin tablets or 50% of the nation's supply; however the public statement from the company released through the FDA merely stated that "166" lots were being withdrawn. When ISMP sought to determine the size of the second digoxin recall in 2009, neither the manufacturer, Caraco, nor the FDA would tell us the size of the recall.

The second problem occurs because the FDA usually allows the companies to write and publish the recall announcements, even when recalls are directly or indirectly a result of FDA enforcement action. In addition, the FDA has a classification system to indicate relative risk to health. Class I indicates a potential for serious injury or death; Class II indicates the possibility of irreversible damage to health; and Class III indicates a chance of health consequences.³⁷ We have noted that at the time of some recalls, the FDA had not yet determined the recall classification.

The third potential issue is the many months that elapse between an initial unsatisfactory inspection and increasingly forceful enforcement. In the cases of Caraco, Actavis and KV Pharmaceuticals, initial recalls escalated over a period of months to involve scores of products, and a broader manufacturing shutdown.

Finally, we know of no publicly available assessments of how many people were exposed to defective drug products capable of adverse effects on health, how many individuals might have been injured as a result, and how effective the efforts were to retrieve the recalled products. Without these basic facts about important individual recalls or the overall performance of the system, it is difficult to assess the dangers to which consumers are being exposed.

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