



The Institute for Safe Medication Practices

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

QuarterWatch: 2008 Quarter 3

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Executive Summary

The ISMP QuarterWatch pilot 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 postmarket safety surveillance relies on voluntary reports submitted by consumers, doctors, pharmacists and other health professionals. The submission of a report does not in itself prove that the suspect drug caused the event described. There are no reliable estimates of what fraction of serious adverse drug events are ever reported, and small studies show wide variation between drugs and different types of adverse reactions.

Trends in Reported Cases

- In the third quarter of 2008 the FDA received 24,872 serious adverse drug event reports indentifying 854 different drugs. The cases described 2778 patient deaths, 1162 cases of disability and 20,932 cases of other kinds of serious injury.
- The total number of adverse drug events meeting the QuarterWatch criteria was 30.5% higher than the same quarter in the previous year, but little changed from the previous 2 quarters.
- Total reported patient deaths have declined for all three quarters of 2008, with 4724 deaths in the first quarter, 3820 in the second and 2778 in the latest quarter. Nevertheless, reported patient deaths in the third quarter were 41% higher than the same quarter in the previous year.

Specific Drugs

- Digoxin. More than 1000 patient deaths have now been reported in connection with the recall of 800 million digoxin tablets manufactured in New Jersey by the Actavis Group. The tablets were recalled because of the possibility that the strength of tablets was greater than labeled and might provide a potentially lethal overdose to patients taking the drug to aid failing hearts. Nevertheless, one year after the announcement of the recall, no testing of returned tablets has been performed to establish how many of these deaths resulted from a manufacturing defect, and how many might have resulted from other safety problems. Furthermore, a new recall of digoxin tablets in March 2009 from another manufacturer—Caraco Pharmaceutical Laboratories—underlines weaknesses in the U.S. system for insuring quality control in the manufacture of generic drugs.

- Baclofen (LIORESAL INTRATHECAL). Problems with an implantable medical device used to administer drugs continuously into the cerebrospinal fluid were associated with approximately 140 cases of serious injury including one death. Baclofen, a muscle relaxant drug, can be administered with the implantable pump to lessen involuntary muscle contractions in patients with brain injury, cerebral palsy, multiple sclerosis and other conditions that involve damage to nerve cells. Medtronic Neuromodulation, which makes the pump and provides the drug Lioresal intrathecal, issued an urgent alert to doctors that the catheter tubes that deliver the drug to the spine were not being properly attached to the pump, leading to interruption of the drug supply and severe withdrawal symptoms. These confirmed cases were among 872 cases of serious injury reported for all forms of the muscle relaxant drug baclofen.
- Interferon beta (AVONEX, REBIF, BETASERON). These drugs from three manufacturers are used to treat multiple sclerosis and accounted for 1,380 reported serious adverse drug events--more than any other prescription drug in the third quarter. However, we concluded the increase apparently did not signal a new risk to patient safety. The large number of reported cases resulted primarily from intensive company contact with patients on a monthly basis.

Specific Drug Reactions

- Varenicline (CHANTIX, CHAMPIX), a drug to help people stop smoking, continued to account for more reports of serious psychiatric side effects than any other prescription drug. Although the FDA and manufacturer have warned consumers about a possible risk of suicidal behavior, the case reports also suggest a possible link to violence towards others. Since approval, QuarterWatch identified 30 possible cases reporting physical assault, 148 cases mentioning homicidal thoughts and 331 cases of behavior described as aggression.¹
- Kidney dialysis solution (DIANEAL). We noted increasing reports of infection in connection with this product used for kidney dialysis at home. After conferring with the manufacturer, Baxter Healthcare, we agreed that report volume was likely a result of increased vigilance by the company and its extensive direct contact with its patients rather than a signal of a new safety problem.

The Adverse Event Reporting System

- We discovered a system-wide error in how case reports were being coded as “initial” or “follow up.” Numerous reports were coded as “follow up” when

there was no record of an initial report having ever been received. We communicated our findings to the FDA and changed our search strategy so as to capture all new case reports.

- Some drug manufacturers are using many different names to identify the same drug product in reports submitted in the same quarter. For example, we found one company used 11 different names to describe the drug product leuprolide. We believe the problem springs from how manufacturers are setting up software to collect data and report adverse drug events as well as from variation in drug names in different countries.
- We applied the lessons learned through the first three quarters of the QuarterWatch pilot project to edit and correct our master database of adverse events, dating back to November 1997. It may result in slightly different counts than previous reports, but will produce more accurate counts and comparisons in future reports.

Conclusions

It is increasingly clear that the nation is experiencing serious problems in insuring that generic drugs are manufactured with adequate quality control. In the first quarter of 2008, there were large urgent recalls of most of the nation's supply of one form of the drug heparin² and of millions of fentanyl patches from several drug manufacturers.³ In the second quarter, about 50% of the nation's unexpired supply of digoxin was recalled because of potential over strength tablets, and an additional digoxin recall was announced in March 2009. In the third and fourth quarters of 2008, additional urgent recalls were announced for morphine sulfate, propafenone, and isosorbide—all drugs where over or under strength tablets could have significant health consequences.⁴ In addition, two New Jersey plants of the Actavis Group were closed because of manufacturing problems, and all products manufactured there recalled. In December 2008 KV Pharmaceuticals' plants were closed to resolve quality control problems.⁵

This problem has received little public or official notice in part because the FDA does not require that the size of the product recall be disclosed. It can vary from a few thousand tablets to nearly a billion. For example, neither Caraco Pharmaceutical Laboratories nor the FDA would reveal how many digoxin tablets were involved in its March 31, 2009 recall notice.⁶ The FDA's current system for inspecting plants, dealing with violations and managing product recall notices requires systematic independent review.

We continue to be concerned about the safety profile of varenicline (Chantix) which continues to account for more psychiatric side effects reported to the FDA than any other prescription drug. In this report we focus on reports of violence towards others which are not adequately described in the current Medication Guide for patients. In addition, no action has been taken to provide a prominent warning about the potential of varenicline to cause motor vehicle and other types of accidents through its effects on mood, memory, vision and motor control.

The signal seen for the kidney dialysis solution Dianeal illustrates another important trait of the U.S. adverse event reporting system under which the drug manufacturers prepare and submit a majority of the reports. In this case, a substantial increase in reports did not signal a new safety problem, but rather resulted from the company's increased vigilance and high rates of direct contact with a special group of patients.

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Background

QuarterWatch is a pilot program designed to improve patient safety by monitoring serious adverse drug event reports submitted to the Food and Drug Administration. The goals of the program are: 1) To examine overall trends in reported deaths and injury associated with drug therapy, 2) To identify signals for specific drugs that might indicate a new risk to patient safety, 3) To improve the quantity and quality of reports flowing through the voluntary system.

QuarterWatch is based on adverse drug event reports best known to consumers and health professionals as FDA MedWatch reports. These reports are submitted by consumers and health professionals directly to the FDA, or to drug manufacturers who then forward the completed reports to the agency. Approximately 70% of the reports of serious injury originate with drug manufacturers. The FDA publishes computer extracts of all reports for research use after removing personal identifying information. QuarterWatch evaluates these reports on a quarterly basis.

The serious adverse drug event reports analyzed for QuarterWatch have a unique set of strengths and weaknesses that must be considered when interpreting results of this program. The system relies on voluntary reports rather than any form of systematic surveillance. What fraction of all adverse drug events that occur is ever reported has not been determined, and may vary widely over time, between drugs, and among different kinds of adverse events. This means the totals for deaths and injury in this report are a small proportion of those actually occurring. In addition, the submission of an adverse event report does not in itself prove that the suspect drug caused the adverse event--it only shows that an observer suspected a link. In addition, some reports may contain detail suggesting that a causal relationship was unlikely. Other factors, however, may strengthen the evidence of a causal link, and adverse drug event reports form the basis for many official actions by the FDA and drug manufacturers, including major warnings and drug withdrawal.

One strength of the system is its sensitivity. With millions of patients and hundreds of thousands of health professionals as observers, and no restrictive rules for reporting, the system is capable of detecting adverse drug effects that may have been overlooked or underestimated in clinical testing prior to approval. Doctors, pharmacists and patients may also identify an adverse effect overlooked by experts who may have preconceptions about the drug's properties, or were bound by restrictive testing protocols.

We have examined the system in greater depth in previous reports.⁷ Typically the data produce what we describe as signals of a problem that often requires further investigation.

Methodology

We limit our analysis to adverse drug events that are serious, fatal or disabling, that occurred in the United States, and that were not part of a clinical study or subject to other mandatory reporting rules. We standardize drug names using our own dictionary and classify adverse event types using terms from the Medical Dictionary for Regulatory Affairs (MedDRA) and Standardized MedDRA Queries (SMQs), a tool developed by the pharmaceutical industry to identify possible cases for further evaluation. We have previously described our methodology in greater detail.

In this pilot project, our methodology continues to evolve through technical changes that improve the accuracy of the drug event counts. To improve historical comparisons since the current FDA Adverse Event Reporting System (AERS) was created in November 1997, we conducted a complete edit and revision of the entire database to reflect new information about adverse event data reporting discovered in our previous reports. In this revision, we were able to clarify the drug names on confusing reports, reducing the number of case reports excluded because of an unidentifiable drug. In addition, we developed a more accurate method for identifying reports that were new in the current quarter, rather than updates of reports previously submitted. In doing so, we discovered that some manufacturers were coding as “follow up” reports some cases that were in fact new to the AERS system and should be counted in each quarterly total. We have previously reported that some manufacturers were also miscoding as cases that were already in the system as new, initial reports. As a result of these improvements, quarterly event totals for previous quarters will differ slightly from previously published results. In addition we reclassified ambrisentan (Letairis), an orphan drug for pulmonary hypertension, as an excluded study drug because it has become subject to special mandatory reporting requirements, as are thalidomide (Thalomid) and lenalidomide (Revlimid).

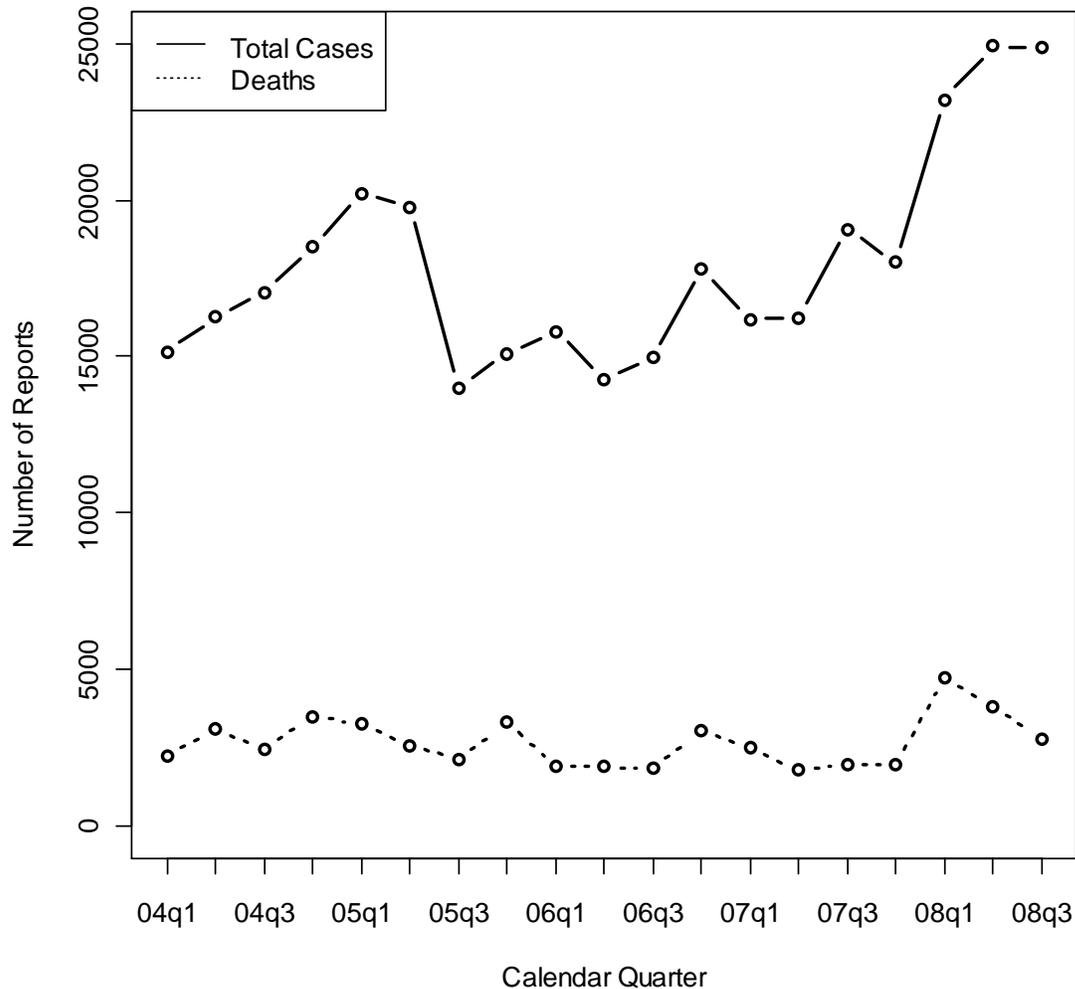
Computer excerpts of all adverse event reports received by the FDA since November 1997 are maintained with open-source database software MySQL (www.mysql.com), and analyzed with an open-source statistical program, the R Package for Statistical Computing (www.r-project.org).

Results

From July-September 2008 the FDA received 24,872 reports of serious injury, disability or death associated with prescription and over-the-counter drug therapy. This total represented a 30.5% increase from the same quarter in the previous year, when the agency received 19,062 reports. However, total events meeting the QuarterWatch criteria were little changed from the previous calendar quarter, 24,872 reports versus 24,900 reports. Analyzed separately, the 2778 reported patient deaths were 41% higher than the

same quarter one year earlier, but marked a steady decline over the first three quarters of 2008. In 2008, approximately 5,400 additional serious injuries are being reported each quarter, compared to the previous year. Trends over time in overall domestic cases are shown in Figure 1. The totals reflect the revision of historical data.

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



Findings for Specific Drugs

In the third quarter we identified 854 drug products accounting for one or more case reports of serious, disabling or fatal adverse events. Half of these drugs or 427 accounted for six or fewer adverse event reports each. In addition, QuarterWatch tracked an additional 1086 drug products which had no reported cases meeting our criteria in the current quarter. At the other extreme, 53 drugs accounted for 100 or more reported cases each in the current quarter. The leading 15 drug in this quarter are shown in Table 1. Just

these 15 drugs shown in Table 1 accounted for 33.3% of all QuarterWatch cases in the current quarter.

Table 1. Serious, disabling and fatal events in 2008 Q3

Drug Name	Cases	Rank
INTERFERON BETA	1380	1
DIGOXIN	1023	2
BACLOFEN	872	3
VARENICLINE	659	4
ESTROGENS	586	5
ROSIGLITAZONE	494	6
ETANERCEPT	412	7
INSULIN	399	8
EXENATIDE	399	9
INFLIXIMAB	369	10
FENTANYL	369	11
QUETIAPINE	339	12
ADALIMUMAB	336	13
DIANEAL	335	14
NATALIZUMAB	319	15

Digoxin (DIGITEK) Recall

For the six months of April through September 2008, the FDA received reports of 1094 patient deaths associated with digoxin—most linked to the April 2008 recall of approximately 800 million digoxin tablets manufactured by the Actavis Group, a generic drug manufacturer based in Iceland. The tablets had a brand name of Digitek and were distributed through another company—Mylan Pharmaceutucials—and packaged and sold under the names “Bertek” and “UDL Laboratories.” Two of Actavis’s New Jersey plants were closed to address quality control problems and all products manufactured there were recalled because of quality assurance problems.

Digoxin is a generic drug discovered more than a century ago and widely used in patients whose hearts are sufficiently damaged that declining cardiac output is causing serious health consequences. It is used to increase cardiac output, and to manage irregular heart rhythms.

Both digoxin recalls were classified as Class I recalls, which means defects in the product with a “reasonable probability that use of, or exposure to, a violative product will cause serious adverse health consequences or death.”⁸ In both recalls the most important manufacturing defect issue was that some tablets might provide an overdose. Digoxin is a narrow therapeutic index drug, meaning that a small overdose can cause serious health consequences or death. Because of the potential health consequences, these recalls were

conducted to the consumer level, rather than being limited to distributors, wholesalers or pharmacies.

This is the largest Class I recall of prescription drugs that we know of, with more than one million heart patients affected. The recall also triggered large numbers of reported serious injuries and deaths. In the last two quarters, digoxin accounted for 2,912 reports of serious injury, including 1,094 deaths. The digoxin case total in the second quarter was higher than for any prescription drug since January 2004.

One year after the Actavis digoxin recall, the most important patient safety questions remain unanswered. While we noted in the previous report that 82% of the cases were definitely or probably linked to digoxin tablets recalled by Actavis, this was still not direct and definitive evidence that the injury resulted from a defective tablet. Without testing the recalled tablets, it would be difficult to distinguish cases in which the overdose resulted from a defective tablet or for other medical reasons. Digoxin overdose is a well documented complication of drug treatment and can result from declining kidney function in patients with failing hearts along with failure to monitor patient drug levels.

Despite reports of more than 1000 patient deaths, no testing of the returned tablets has been undertaken, according to the company. Regardless of the ultimate testing result, the findings have important implications for patient safety. If many of these cases prove to be linked to manufacturing problems, then the nation has experienced a little-noted drug disaster of major proportions. Even if the reported adverse events resulted from other causes, it nevertheless dramatizes how many patients are being injured by this hard-to-use drug that is sensitive to the correct dose. Whatever the underlying reason, these reports show digoxin patients are being injured in substantial numbers.

The company told us that no testing had been performed because it had not reached an agreement about how to test the returned drugs with lawyers who had brought more than 400 lawsuits. The cases concerned patients who had taken the Digitek brand digoxin and suffered injury. The company told ISMP that because the matter was in court it did not believe it was appropriate to initiate testing on its own.

In addition, another generic pharmaceutical manufacturer—Caraco Pharmaceutical Laboratories—announced on March 31, 2009, that it was recalling its entire unexpired production of digoxin tablets.⁹ The same shortcomings we noted in our previous report about the Actavis Group recall occurred with the new digoxin recall. Once again, the FDA allowed Caraco, the recalling company, to manage publicity about the recall, merely reproducing the company's one-page statement. As in the previous recall, the company recall notice was brief, technically worded, and did not disclose how many tablets were affected.

Baclofen (LIORESAL INTRATHECAL)

Baclofen is a muscle relaxant available in several dosage forms. Under the brand name Lioresal, the product is primarily used with an implanted pump to infuse the drug directly into the cerebrospinal fluid.¹⁰ Many drugs are not capable of passing through the blood-brain barrier and therefore do not circulate in fluid that surrounds the nerve

cells of the brain and spinal cord. In other cases direct infusion into the cerebrospinal fluid permits higher doses for nerve cells without toxic effects on other organs.

Lioresal intrathecal is primarily used to relieve uncontrolled muscle spasms in patients with brain injury, cerebral palsy, muscular dystrophy and multiple sclerosis. It is continuously infused with battery-driven pumps surgically implanted in the abdomen. A catheter (delivery tube) is also implanted, with one end connecting to the cerebrospinal fluid surrounding the spine, and the other end to the implanted pump. The pumps, catheters and Lioresal brand baclofen are marketed by Medtronic, a large medical device manufacturer. The company reported that approximately 15,000 patients in the United States are administered drugs through the implantable pumps, primarily Lioresal.

Despite a relatively small patient population, Lioresal ranked third among all prescription drugs for reported serious, fatal and disabling injuries in the third quarter of 2008. Of the 872 cases identifying baclofen, we traced 855 cases to the Lioresal brand used in Medtronic implanted pumps or for direct injection into the spinal fluid.

In June 2008 Medtronic issued an urgent safety alert to physicians and patients warning that the delivery of this drug could be interrupted because the catheter delivering the drug could become either blocked or disconnected entirely at the junction where it connected to the pump.¹¹ The problem was crucial because abrupt discontinuation of baclofen can lead to severe injury and death, according to the FDA-approved product information.¹² The alert was part of a program to alert patients and doctors to the signs and symptoms of a device problem, and to provide instructions for checking device function, and education on the proper implantation and connection of the components.¹³

We discussed this signal with Medtronic Neuromodulation, the device manufacturer and distributor of intrathecal baclofen for use in its drug delivery system. The company said that as of April 2009 it had received approximately 140 confirmed reports involving the blockage or disconnection of the pump from the catheter that delivered the drug into the cerebrospinal fluid. The company noted that the large total of Lioresal reports in the third quarter partly resulted because the company was permitted to submit some kinds of serious adverse event reports on an annual rather than quarterly basis.

The case of Lioresal intrathecal baclofen illustrated that serious patient injury can result from complex interactions between a device, a drug and the implantation of the device. We believe this case warrants additional study to determine what went wrong: Was the connector too hard to use? Were the instructions for implanting the device and its catheter inadequate? Was more training needed? In any event the result was tragic as in more than 100 confirmed cases serious injury resulted when vulnerable patients experienced abrupt discontinuation of a vital drug.

Interferon beta (AVONEX, REBIF, BETASERON)

Interferon beta is one a special class of drug products that are genetically engineered versions of components of the human immune system. Interferon beta is similar to a specialized protein manufactured by human cells of the immune system as

part of the response to viral infection. By mechanisms that are not completely understood, interferon beta was found to reduce the damage to nerve cells that occurs in multiple sclerosis. Avonex, Rebif, and Betaseron are similar products consisting of genetically engineered interferon beta and all are FDA-approved for reducing relapses and slowing the progression of multiple sclerosis.

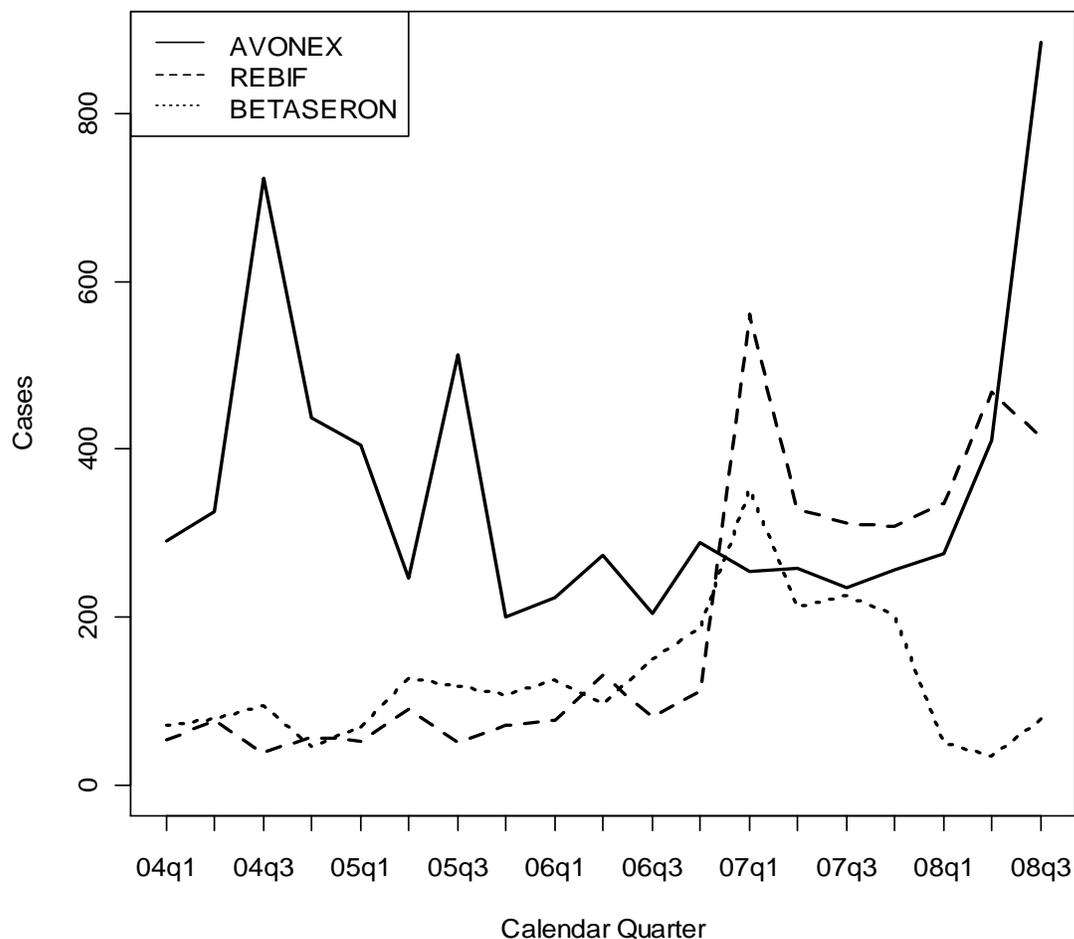
Since first introduced more than 10 years ago, interferon beta products have produced numerous reports of serious adverse drug events. In a previous study of all serious and fatal adverse drug events from 1998 through 2005, interferon beta products ranked fourth among all drugs in serious and disabling adverse events, and eighth for patient deaths.¹⁴ The product information contains warnings about the possibility of depression and suicidal behavior, allergic reactions, and reduced blood counts. In addition, caution is recommended for use in pregnant women.

When interferon beta products ranked first among all prescription drugs for the third quarter, we investigated possible reasons for the increased prominence. (Table 1). We learned that the increase in 2008 was accounted for primarily by just one of the three interferon beta products, Avonex, manufactured by Biogen Idec. (Figure 2)

We also examined the types of serious adverse events reported for interferon beta. The largest number of cases for Avonex, Rebif and Betaseron involved complaints about relapse or exacerbation of multiple sclerosis. These reports were difficult to interpret since both events would be expected to occur despite treatment, which slows rather than eliminates the disease. Although there is a warning about possible suicidal behavior on the product information for doctors, in the third quarter we identified only 16 possible cases in the suicide/self injury category. Depression, about which patients were also warned, was much more common.

We contacted Biogen Idec, the manufacturer of Avonex, to inquire into the reasons for the large volume of reports. The company said it had a special staff of case managers who were in direct contact on a monthly basis with the company's 68,000 U.S. patients currently using Avonex. If the case managers learned of a relapse or exacerbation of the patient's multiple sclerosis, it was company policy to report that as an adverse event even if no drug role was suspected. The Avonex total in the third quarter was further boosted by an authorized company practice of reporting some kinds of serious adverse events on a semi-annual basis rather than quarterly.

Figure 2. Cases for Interferon Beta Products



The interferon beta case reports for all three drugs, however, did suggest a possible additional risk of cancer—an adverse effect for which warnings do not currently exist. The latest quarter of data included 131 possible cases of cancer, including reports of cancers of breast, lung, prostate, ovary, thyroid, esophagus, colon, rectum, kidneys, brain, liver, kidneys, bladder and skin. Since the drugs were first approved we noted 1,338 reported cases of possible malignancies. Biogen Idec stated it had previously evaluated reported cancers and had not found any signal. Reported cases did not exceed the background rate based on National Cancer Institute statistics, the company said. However, unusual feature of the reported cases was numerous different kinds of cancers. Cancers associated with drug therapy normally tend to be of a limited number of types. These data do not provide definitive evidence of cancer risk but do signal a possibility of a more generalized increase in cancer risk that warrants further investigation.

Varenicline (CHANTIX) Update

In the third quarter, we observed a decline the number of serious, disabling and fatal adverse drug events in which varenicline (Chantix, Champix) was the principal suspect drug. Using our revised criteria, the number of cases totaled 1311, 1031 and 659 in the first to third quarters of 2008. We believe the decline in reports was primarily a result of a 49% decline in sales compared to the previous year as a result of safety concerns.¹⁵ The risks of varenicline, a drug to help people stop smoking, have been examined in two previous QuarterWatch reports.^{7 16} Despite the reduced number of reports in the third quarter, varenicline nevertheless ranked fourth among all prescribed drugs in the number of reported cases of serious injury. (Table 1)

In the third quarter evidence also accumulated that varenicline might be associated with acts of violence towards others. We identified 1568 cases since 2006 classified as “hostility/aggression” using Standardized MedDRA Queries (SMQs) a tool developed by the pharmaceutical industry to identify possible cases of various drug-related adverse events. To see the kinds of events causing cases to be classified as possibly involving hostility or aggression, we examined which specific medical terms were causing a reported case to fall into this category. These are the results for medical terms with 15 or more mentions:

Table 2. Report terms linked to possible hostility-aggression cases since 2006

MedDRA report term	Mentions
Anger	383
Aggression	331
Irritability	291
Abnormal behavior	268
Agitation	263
Paranoia	164
Homicidal ideation	148
Psychotic disorder	108
Mania	96
Personality change	94
Bipolar disorder	76
Violence-related symptom	49
Screaming	45
Hostility	37
Psychomotor hyperactivity	37
Physical assault	30
Injury	18
Affect lability	16
Gun shot wound	15

It seemed likely that some of these symptoms (irritability, anger) might be associated with nicotine withdrawal effects that might occur when people stop smoking. But others suggested a possible side effect that could pose a risk to other persons, notably physical assault (30 mentions), homicidal ideation (148 mentions), and aggression (331 mentions). Note that more than one of these terms could appear in the same report, and some, such as gun shot wound, could include violent acts towards either self or others.

The current FDA-approved medication guide does not appear to describe adequately this potential adverse effect and appears limited to suicidal behaviors and agitation:

“Some patients have had changes in behavior, agitation, depressed mood and suicidal thoughts or actions while using CHANTIX to help them quit smoking.”¹⁷

In addition, ISMP continues to be concerned that varenicline may contribute to vehicle and other accidents because of its effect on mood, motor control and vision and other senses. We observed additional evidence of this drug risk in the new data available for the third quarter of 2008.

We noted eight additional reports of road traffic accidents, bringing the total to 55 cases. Additional reports described possible adverse events that could lead to accidents, notably loss of consciousness (17 new mentions), convulsions (20 cases), muscle spasms (11 cases), memory impairment (21 cases), blindness (3 cases), and impaired vision (5 cases).

As we have noted previously, the Federal Aviation Administration (FAA) and the Department of Defense acted immediately to ban use of varenicline by pilots, aircraft crews and missile crews. However, one year later neither the FDA nor the manufacturer of varenicline, Pfizer Inc., has acted to strengthen the accident warning on information for patients and doctors.

Solution for kidney dialysis (DIANEAL)

We investigated a signal for Dianeal, a solution used for kidney dialysis, which accounted for 335 cases in the latest quarter, and ranked 14th among all drugs. In addition, we observed a steady increase since 2007 when only 50 cases were reported. The most frequently reported reaction terms included various types of bacterial and fungal infection in the abdomen. The volume of reports appeared especially large when considering the size of the patient population. Approximately 500,000 patients in the United States have failing kidneys that can no longer remove toxins from the blood, a condition known as end stage renal disease.¹⁸ Failing kidneys can be replaced through organ transplants; alternatively toxins can be filtered out through two treatment strategies: through hemodialysis, where the blood is circulated through special machines, or peritoneal dialysis, through infusing about 2 quarts of dialysis solution directly into the abdominal cavity and then removing it. This latter form of dialysis can be performed by the patient, who either manually infuses the solution several times a day through a surgically implanted portal, or using machines which circulate the dialysis solution

overnight. However approximately 320,000 patients are receiving hemodialysis at special centers and only 25,000 receive peritoneal dialysis at home.

We contacted the manufacturer of the solution and equipment used to administer it, Baxter Healthcare. The company originated all but one of the reports in the quarter, the one remaining case being reported directly to the FDA. The company said it too had noted the increase in reports but said it had concluded that the signal did not indicate a new or growing safety problem with the Dianeal product.

The company said that the relatively large number of reports was a result of two factors. First, the company was in direct telephone contact with its end stage renal disease patients on a monthly or quarterly basis to provide the dialysis supplies and equipment for use at home. Therefore the company customer service representatives would learn of patient hospitalizations and other serious medical problems. In addition, the company said it had conducted a training program with its customer service staff to make them more aware of their obligations to initiate an adverse event report when they had an indication of a problem from a customer. The company said it had no indication of a product problem or contamination of the solution that might account for the frequently reported abdominal infections. The risk of infection is the major recognized complication of this form of kidney dialysis.

Under most circumstances, patients obtain their drugs through pharmacies or managed care providers and have limited direct contact with the company that manufactures and markets the drug. We were persuaded that the relatively large volume of reports were primarily a result of the company's extensive direct contact with its patients.

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- ¹² Full Prescribing Information about IBT Therapy. Lioresal Intrathecal (baclofen injection). Medtronic, December 2008. <http://www.medtronic.com/your-health/stroke/full-prescribing-information/>
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