Institute for Safe Medication Practices
A Nonprofit Organization Educating the Healthcare Community and Consumers About Safe Medication Practices
A federally certified Patient Safety Organization

QuarterWatch: 2010 Quarter 3

Monitoring MedWatch Reports

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New Signals for Liraglutide, Quetiapine and Varenicline

Executive Summary

In this issue we examine a signal for liraglutide (VICTOZA), a newly approved drug for Type 2 diabetes, explore adverse events reported for ever-widening use of quetiapine (SEROQUEL), and explain why the risks of varenicline (CHANTIX) were underestimated in prior adverse event reporting.

In the third quarter of 2010 the Food and Drug Administration received 36,679 domestic reports of serious, disabling or fatal injuries associated with drug therapy. This represents a 22% increase from the same quarter in the previous year, and up 11% from the previous quarter. In the same period, exposure to prescription drugs increased slightly. Compared to the same quarter in 2009, the number of outpatient dispensed prescriptions increased by 1.3%, according to IMS Health's National Prescription Audit™ 2010. Reports that health care professionals and consumers sent directly to the FDA declined by 17% compared to the previous year while case reports originated by drug manufacturers increased by 33%. The largest single factor in the overall increase was a surge in adverse drug event reports for rosiglitazone (AVANDIA), a drug for Type 2 diabetes that was restricted by the FDA in September 2010 because of its cardiovascular risks, and withdrawn from the market in Europe.

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

Liraglutide (VICTOZA) Launch Spurs Pancreatitis Reports

The approval of the liraglutide injection for Type 2 diabetes in January of 2010 was controversial at the FDA because of uncertainty about its cardiovascular risks, and animal studies showing an increased risk of thyroid cancer. Early adverse event reporting did not speak to these still unresolved issues, but did reveal a marked signal for pancreatitis or inflamed pancreas. This adverse effect was also associated to a lesser extent with another new agent, saxagliptin (ONGLYZA). There are now four marketed drugs that lower blood sugar through their effects on a body enzyme called glucagon-like peptide-1 (GLP-1), and evidence accumulates that all may share an elevated risk of pancreatitis, although possibly to differing degrees. Novo Nordisk, the manufacturer of liraglutide, noted that epidemiological studies show a higher risk of pancreatitis in diabetes patients, independent of treatment. The manufacturer also said it had worked with

the FDA to develop a program to educate patients and doctors about possible risks and safe use of its new drug.

Quetiapine (SEROQUEL) and Irreversible Injury

Quetiapine shares with other antipsychotic drugs the risk that some of its most frequent side effects can be irreversible, notably some cases of diabetes and certain types of movement disorders. In the third quarter we noted hundreds of new reported cases of diabetes associated with quetiapine, together with smaller numbers of reports of three different types of movement disorders, dyskinesia (abnormal involuntary muscle movements), dystonia (spasms or prolonged contractions), and parkinsonism (tremors or muscle rigidity). Because of their side effect profile, these powerful antipsychotic drugs were once largely restricted to the most severe mental illnesses, schizophrenia and psychosis. The adverse event data show quetiapine was being widely used in patient populations outside its core indication, and frequently for off-label uses such as sleep disorders and anxiety. AstraZeneca, the manufacturer, noted that quetiapine is FDA-approved for treatment of depression in combination with antidepressants, for use in bipolar disorder in several different settings, as well as for schizophrenia in adults and adolescents.

New Varenicline (CHANTIX) Suicide Cases

Although psychiatric side effects of varenicline (CHANTIX) are now familiar in adverse event reporting, we were surprised to discover that the manufacturer, Pfizer, had apparently failed to send through the usual channels reports of hundreds of serious psychiatric adverse events that had occurred earlier. Most notable were 150 cases of completed suicides, some of which dated back to 2007. This breakdown in safety surveillance meant that until July 2010 FDA safety analysts were not aware of more than half of the reported suicide cases in which varenicline was the primary suspect drug, and did not have available hundreds of other reported cases of serious psychiatric side effects. In the full report we explain what went wrong and explore the still-unanswered questions.

Drug Safety Perspectives: Cases from Litigation

In this issue we explore a group of reported adverse events that are usually excluded from our analysis: cases that are reported to the FDA in connection with legal claims by patients seeking damage payments from drug manufacturers. Among the brand name drugs that were litigation targets in more than 1000 cases were several estrogens, including the contraceptives Yaz and Yasmin; and Prempro, for post-menopausal hormone replacement. Having an injury attributed to a prescription drug is not enough to justify or trigger a legal claim against the manufacturer. It has to be based on allegations that the drug was either defective, or that the manufacturer knew of risks for which it failed to warn doctors and/or patients. Furthermore, legal claims are allegations, not findings. Legal claims may fail either because of insufficient evidence that the drug caused the event, or because there were other explanations for a specific patient's injury. We identified more than 4000 new case reports associated with litigation in the third quarter.

The Adverse Event Reporting System

Problems with Periodic Reports. The FDA discovered that tens of thousands of periodic reports from several manufacturers had not been submitted to its Adverse Event Reporting Systems (AERS) and therefore were not available for regular safety assessments. While the overwhelming majority of periodic reports were for non-serious adverse events, we found serious adverse event cases that we believe should have been reported promptly and directly into AERS as expedited reports.

About QuarterWatch Data

Our findings should be interpreted in light of the known limitations of a voluntary adverse event reporting system. The FDA's Adverse Event Reporting System (AERS) data combines reports originated by drug manufacturers with cases submitted directly by consumers and health professionals through the agency's MedWatch program. The submission of an individual report does not in itself establish that the suspect drug caused the event described—only that an observer suspected a relationship. However, given numerous reports with credible detail, adverse event data may have important scientific weight in a broader assessment of causality. A substantial fraction of all new warnings, restrictions or other actions to manage the risks of drugs are based on these data. The reporting rate for AERS is unknown, and published estimates range from around 1% to 15% in most cases, and up to 30% in unusual cases of enhanced reporting. We have observed wide variation among specific drugs, for different kinds of adverse events, and over different time periods. We use the term *signal* to mean evidence that, in our judgment, is substantial enough to warrant publication but requires further investigation to determine frequency of occurrence and to establish a causal relationship to the suspect drug. More complete disclaimers and descriptions of our methods are included in the methods section of this report. A new Appendix expands our description of this project and its staff.

Conclusions

Evidence from adverse drug event reporting continues to accumulate showing that the smoking cessation drug varenicline—an alternative to nicotine patches and gum—has an unacceptable safety profile. New data from the third quarter show that the risks of serious psychiatric side effects were previously underestimated because so many of these events were not promptly reported, and were therefore omitted from the FDA's safety analysis. We believe this drug is unsafe for widespread clinical use. In addition, the FDA should investigate why 150 completed suicides and scores of suicide attempts were not reported promptly to the AERS safety monitoring system. It should also reassess the safety profile of varenicline based on this, and other new information.

In the third quarter we traced the substantial increase in overall reported serious adverse drug events to increased awareness or reporting of safety problems relating to a handful of drugs, most notably the now-restricted Type 2 diabetes medication rosiglitazone.

Nevertheless a new chapter of safety uncertainty has opened in the treatment of Type 2 diabetes as we observe signals for pancreatitis and related adverse effects for liraglutide, and other new drugs that are rapidly replacing rosiglitazone. The underlying issue in diabetes treatment has remained unchanged since 1970: drugs that lower blood sugar or increase insulin secretion have never been proven to reduce the risk of heart attack, and stroke and some agents appear to increase it. Because the risks (and health benefits) become apparent only over many years' time, pre-approval testing is simply too short to determine whether the drugs' benefit-risk balance is favorable. Nevertheless the FDA and others feared that if truly rigorous long-term testing were required, the time and costs of developing new agents for diabetes might become prohibitive. As a result, uncertainty about the long-term risks and benefits continues with a new generation of agents for Type 2 diabetes.

We are also concerned that history is repeating itself with the wider use of powerful antipsychotic drugs with numerous serious side effects, some irreversible. The troubling side effect profile of this family of drugs—notably its effect on muscle control—had earlier led to their being restricted to patients with the most severe mental illnesses, schizophrenia and psychosis. Despite the evidence that these risks have never been reduced, and the discovery of new risks such as diabetes, adverse event evidence shows quetiapine is being used as a general purpose psychiatric drug for a wide variety of disorders. The FDA has approved some of this wider use on the basis of 3-6 week tests that cannot assess serious long-term risks. Other medical use remains off label and without clear evidence of benefits that outweigh the risks.

Finally, the FDA needs to clarify its standards and work with industry to insure that appropriate serious adverse event reports are being properly coded as expedited, sent within 15 days, and entered into AERS for immediate safety review. While it appears that part of the problem--failure to submit periodic reports into AERS--has already addressed, the agency still needs to examine whether manufacturers are identifying expedited events correctly.

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Methods

The goal of QuarterWatch is to improve patient safety through regular monitoring and analysis of all serious adverse drug events reported to the FDA. The agency releases computer excerpts for research use on a quarterly basis, [1] and these case reports are our primary data source.

QuarterWatch focuses on domestic case reports of adverse drug events that are coded under federal regulation as "serious," which means events that resulted in death, permanent disability, a birth defect, required hospitalization, were life threatening, required intervention to prevent harm, or had other medically serious consequences.

We exclude reports from foreign sources, cases from clinical studies which have different reporting requirements, and events in which the injuries were not serious. Because of ambiguity in AERS coding and FDA regulation, we exclude reports from manufacturers coded "other" unless they are explicitly identified as expedited serious unlabeled events. Depending on the manufacturer and the year, *other* could mean either *other serious* or *other than serious*. We standardize all drug names to an ingredient name based on the National Library of Medicine RxNorm project. [2] We exclude cases identifying drugs that have been previously withdrawn, or that specifically identify a lawyer as the original report source.

We focus on case reports received by the FDA for the first time in the calendar quarter under study. The actual events may have occurred earlier. When case reports are revised or updated we use the most recent version while retaining the original report date. In two instances an entire year's adverse events may reach the FDA in one calendar quarter. FDA regulations allow drug companies to submit reports annually for older drugs and types of serious adverse events that already had warnings.[3] Because drug manufacturers are required to monitor the medical literature, annual reports and other published summaries may cover an entire year but be submitted in a single quarter. To compensate, our primary comparison is with the same quarter one year earlier, and we check for periodic spikes that affect individual drugs.

In these reports, the adverse event that occurred is described by one or more medical terms selected from the Medical Dictionary for Regulatory Affairs (MedDRA), a terminology developed by the pharmaceutical industry to describe adverse events in clinical studies and post marketing reports. [4] The MedDRA medical dictionary is updated regularly and this report relies on MedDRA Version 13.1. The MedDRA terminology also defines broader categories of adverse events that can include any of a list of more specific and related medical terms. We use these categories, called Standardized MedDRA Queries (SMQs), to identify possible cases of some adverse events. [5] We also group adverse event terms using a MedDRA category called High Level Terms that also combine several related but more specific medical terms.

To provide a broader perspective on the adverse events reported we assess the patient exposure to drugs on the basis of dispensed prescription data from IMS Health Inc. The data we

rely on are an estimate of total non-governmental prescriptions dispensed through retail and mail channels. Our agreement with IMS includes the following disclaimer:

> "The statements, findings, conclusions, views, and opinions contained and expressed in QuarterWatch are based in part on data obtained under license from an IMS Health Inc. information service called the National Prescription Audit™ for 2010, All Rights Reserved. Such statements, findings, conclusions, views, and opinions are not necessarily those of IMS Health Incorporated or any of its affiliated or subsidiary entities."

The QuarterWatch totals for the quarter include a special category of drugs with reporting requirements or active surveillance programs that result either in a much higher reporting rate, or capture adverse events in which drug involvement is not necessarily suspected. For example, thalidomide and lenalidomide are restricted-use drugs with comprehensive adverse event reporting programs. In other cases the manufacturer engages in regular direct contact with patients to deliver product or monitor care, and therefore maintains active surveillance of the patient population. In many of these special cases patient deaths, relapses and other adverse events are reported, but the drug was not necessarily suspected of causing a side effect. Finally, we group together certain drugs such as insulin and estrogens because of the large number of similar products, and the number of reports with incomplete product names. These special category drugs are included in the total number of reports but are otherwise excluded from comparisons and rankings.

In this issue, QuarterWatch analysis also includes a new data item, the indication or medical use shown for the primary suspect drug. Our analysis is shaped by the limitations of these data. The terminology for indications is not well standardized (e.g. depression, major depression and depressed mood are all possibilities) and so we frequently combine similar terms into one category. In addition, some reports list more than one medical use for the same drug (e.g. mood altered and panic attack). To prevent double counting we establish a priority order to insure each event is listed in only one category.

We frequently use the word *signal* to characterize the evidence we see of a safety issue. The term *signal* as used in QuarterWatch means evidence of sufficient weight to justify an alert to the public and scientific community and to warrant additional investigation to assess a causal relationship to the drug and determine its incidence.

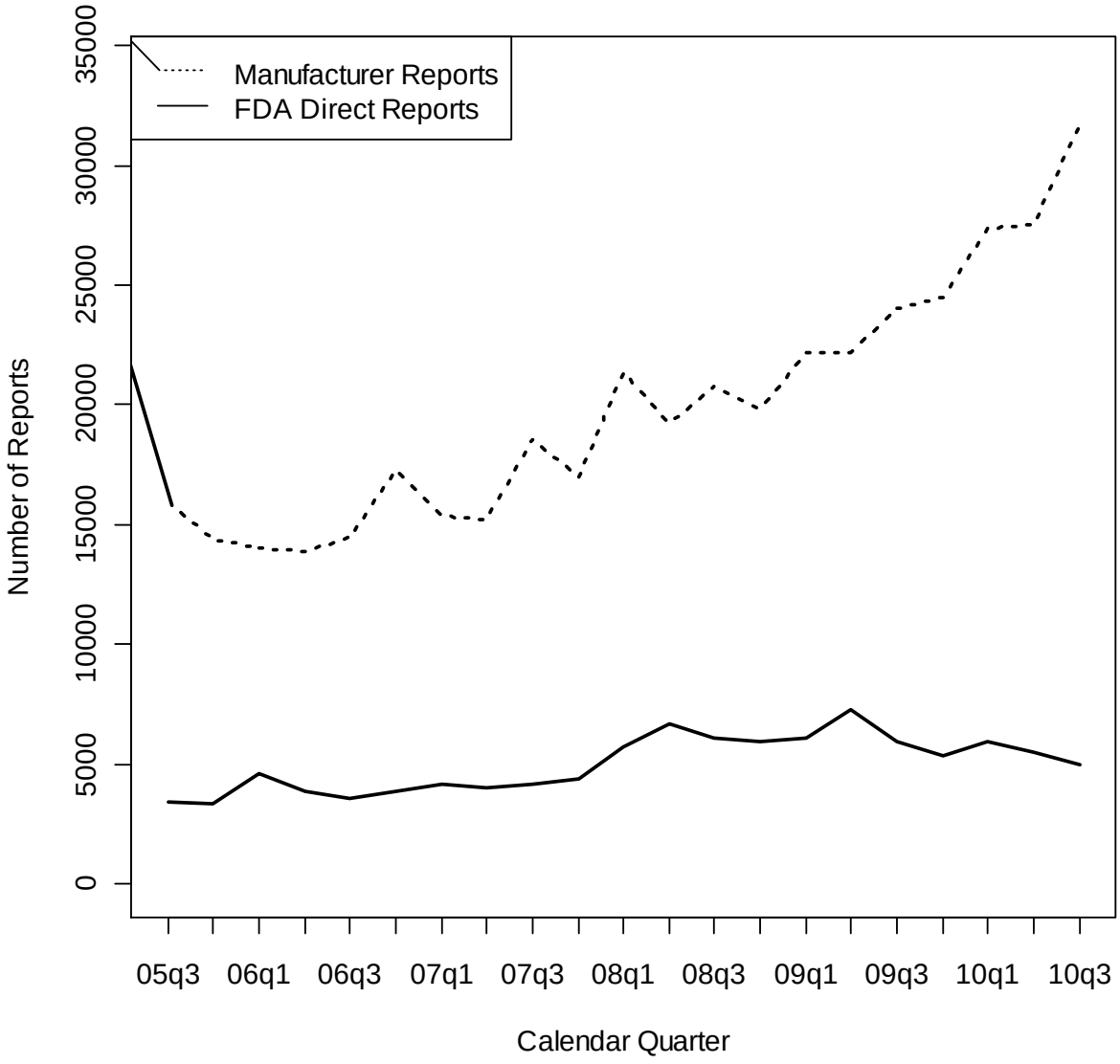
Because thousands of reports are revised, enter the system late, or are updated every quarter, the event totals change slightly over time. To permit accurate comparisons, the historical tables are also revised every quarter.

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/).

Results

The sustained and substantial increase in reports of serious injury, disability and death continued in the third quarter of 2010. The case total of 36,679 was 22% higher than the same quarter of 2009 and more than doubled since the same quarter of 2006. The long term trends are shown in Figure 1. The figure also shows that the long-term trends differ for cases reported directly to the FDA, which have declined in recent quarters, and cases reported through manufacturers, which have increased more rapidly. FDA direct reports have ranged from a low of 14% of the total in the most recent quarter to a high of 26% of the total in the second quarter of 2008.

Figure 1. FDA Direct and Manufacturer Reports



Rosiglitazone (AVANDIA)

The largest single contributor to the most recent quarter increase was the rising level of safety concern about a single drug, rosiglitazone (AVANDIA), which is approved for Type 2 or adult onset diabetes. The large volume of cases was spurred by new scientific studies, media publicity, and FDA regulatory actions, and may reflect new potential legal claims from patients who said they were injured by the drug.

After a series of studies pointed to higher risk of heart attack and stroke from a drug administered in hopes it would reduce those same risks, rosiglitazone was withdrawn in Europe in September 2010.[6] However, the manufacturer, GlaxoSmithKline argued that the evidence from six clinical trials "show Avandia does not increase the overall risk of heart attack, stroke or death." [7] The FDA declared that it could not make up its mind: "The evidence pointing to a cardiovascular ischemic risk with rosiglitazone is not robust or consistent. …The cardiovascular safety profile of rosiglitazone is still an open question." [8] As a result, the FDA decided to restrict rosiglitazone [9] rather than withdraw it as did the Europeans.

In the third quarter we identified 3068 reported cases for rosiglitazone, one of the largest quarterly report totals we have observed for any drug. (By comparison 50% of the drugs we monitor account for six or fewer reports in the quarter and only 59 drugs account for more than 100.) In the same quarter in the previous year, rosiglitazone accounted for 1941 cases. While adverse event reports were rising rapidly, total dispensed prescriptions for rosiglitazone were falling, from 585,000 in the third quarter of 2009 to 315,000 one year later. [10]

The rosiglitazone episode illustrates essential lessons about drug safety and post market surveillance. Millions of people were exposed to a drug for Type 2 diabetes for a decade without clear evidence of tangible long-term health benefits amidst a growing body of scientific evidence it might be harmful. Both the FDA and the manufacturer took contradictory positions. The FDA declared that it didn't know whether rosiglitazone was unsafe, but restricted it anyway. GlaxoSmithKline declared its drug was safe while agreeing to pay million of dollars in damage compensation to patients who said they were injured. [11] Meanwhile, we believe the large and increasing case totals did not in this instance reveal a new safety problem, but rather rising public awareness and legal claims that dwarfed the reports for a typical drug.

Rosiglitazone was listed first among a special category of drugs we classify and tabulate separately because of special circumstances. (See the Methods section for additional detail.) The top 10 special reporting drugs are shown in Table 1.

Table 1. Special reporting drugs 2010 Q3.			
Rank	**Drug Name**	**Cases**	**Reason**
1	ROSIGLITAZONE	3068	Restricted
2	INTERFERON BETA	1756	Mfr-Customer Contact
3	DIANEAL	1058	Mfr-Customer Contact
4	ESTROGENS	1017	Combines drugs
5	INSULIN	789	Combines drugs
6	LENALIDOMIDE	671	Special Reporting
7	NATALIZUMAB	670	Special Reporting
8	ROMIPLOSTIM	509	Special Reporting
9	DEFERASIROX	435	Special Reporting
10	AMBRISENTAN	356	Special Reporting

Signal for Liraglutide (VICTOZA)

We identified a prominent signal in the third quarter data for liraglutide (VICTOZA) a new drug for Type 2 diabetes that the FDA approved in January 2010 after an internal debate about its safety profile. In addition, we saw a less prominent signal for another new agent for Type 2 diabetes, saxagliptin (ONGLYZA). For both drugs the signal was for serious cases of pancreatitis and related gastrointestinal symptoms such as nausea, abdominal pain, and vomiting.

Liraglutide and saxagliptin are the two latest entrants into a new group of drugs for Type 2 diabetes. Both drugs modify the natural effects of a body chemical called glucagon-like-peptide-1 (GLP-1). GLP-1 is released by the liver in response to food to increase the secretion of insulin and thereby limit the elevation of blood sugar levels after a meal. Liraglutide and a similar drug, exenatide (BYETTA), consist of daily injections of synthetic GLP-1 designed to have an effect similar to the body's own chemical. Saxagliptin and an earlier approved drug, sitagliptin (JANUVIA), are oral drugs that prolong the action of GLP-1 by slowing the body's ability to break down this same enzyme. The perceived advantage for these drugs is increased insulin secretion in response to food. As a result, patients (who are typically obese) treated with GLP-1 agents tend to lose weight while those treated with rosiglitazone (AVANDIA) and pioglitazone (ACTOS) may gain weight.

The FDA's approval of liraglutide was controversial. Both the FDA's unit that reviews animal studies and the clinical safety reviewer recommended against approving liraglutide and the FDA advisory committee vote was divided.[12] The two most critical issues were that a) the risk of thyroid cancer seen clearly in animal studies could not be ruled out in humans and b) the testing of liraglutide was not extensive enough to rule out an increased risk of heart attack and stroke.[12] The safety review also noted an increased risk for pancreatitis. The FDA

compromised, and approved liraglutide with a boxed warning about thyroid cancer risk, and a second-line indication, meaning that other drugs should be preferred. [13]

Liraglutide accounted for 70 cases of acute and chronic pancreatitis in the third quarter of 2010, and 105 cases since approval nine months earlier. This result was surpassed only by its most similar but more widely prescribed counterpart, exenatide, with 78 cases. The other new drug, oral saxagliptin, accounted for 14 cases of pancreatitis in the third quarter of 2010. Sitagliptin accounted for 18 cases. It appeared that the two injectable GLP-1 analogs were triggering far more reports of pancreatitis than the oral products with a different mechanism. We saw an additional safety signal for liraglutide in the third quarter, 13 cases of possible kidney failure or impairment, a concern because the FDA safety review cited laboratory test evidence of a possible adverse effect on kidney function. [14] The full results are shown in Table 2.

Table 2. Pancreatitis and GLP-1 agents in 2010 Q3.

Drug	Pancreatitis Cases Reported*	Dispensed Prescriptions**
Injectable synthetic GLP-1		
Exenatide	78	449,000
Liraglutide	70	192,000
Oral DPP-4 inhibitors		
Sitagliptin	18	1,664,000
Saxagliptin	14	203,000

* Acute and chronic pancreatitis High Level Term (HLT)

** IMS Health National Prescription Audit ™ 2010

We discussed our results with Novo Nordisk, the Danish manufacturer of liraglutide. The company noted that the FDA's own list of new signals did not include liraglutide. Also, the company said epidemiological studies showed that the risk of pancreatitis was 2.8-4.2 times higher in the diabetes population, compared to those without diabetes. Finally, it noted it has an FDA-approved plan to educate doctors and patients about the possible risks of liraglutide, including pancreatitis.

These new data also confirm and extend a recently published analysis that found increased risk of pancreatitis for sitagliptin and exenatide [15] and showed the odds ratio for the injectable exenatide (OR 11.76) was nearly double that for the oral sitagliptin (OR 6.86) when compared to other Type 2 diabetes medications. Because this analysis compared medications within the same diabetes population, it adjusted for the possible higher risk of pancreatitis in this patient group.

In approving liraglutide despite the safety controversy, senior FDA officials said they hoped second-line therapy status might slow its introduction into clinical practice "giving us an opportunity to gain clinical experience gradually." [14] However, gradual introduction did not occur. As indicated in Table 2, liraglutide accounted for nearly 200,000 dispensed prescriptions just nine months after approval. These data show that while it may take years to resolve the

uncertainties about liraglutide's safety profile, it has become widely dispensed in a matter of months.

In scientific terms these GLP-1 agents represent a promising new approach to treating Type 2 diabetes whose clinical use is expanding rapidly. But it is unknown whether any of these agents reduce or increase the most important health consequences of Type 2 diabetes, the danger of heart attack and stroke. Evidence is accumulating that these agents increase the risk of pancreatitis, and that risk might be higher with the injectable agents, compared to the oral products. But studies to determine the incidence, identify differences between drugs and provide the basis to weigh these risks against possible benefits have not been performed. In addition, pancreatitis, in turn, is a risk factor for pancreatic cancer, [16] and animal data suggests a thyroid cancer risk for liraglutide.

The results from the previous "new" class of diabetes drugs—the thiazolidinediones—were not encouraging. The first agent in this class, troglitazone (REZULIN) was withdrawn in 2000 for fatal liver toxicity. At the time Rezulin was withdrawn, the FDA cited as one reason for withdrawal the availability of a chemically similar agent, rosiglitazone, which did not demonstrate comparable adverse effects on the liver. [17] However, rosiglitazone, as noted elsewhere, had other adverse effects that led to its withdrawal in Europe and severe restrictions in the United States.

Quetiapine (SEROQUEL) and Irreversible Injury

In the third quarter of 2010 we identified two issues of concern for quetiapine, which remains the most frequently dispensed antipsychotic drug in the United States. We observed hundreds of newly reported cases of diabetes—which in some cases may indicate irreversible damage to the body's ability to regulate blood sugar levels. In addition, we discovered that the adverse event data show quetiapine has become a general purpose psychiatric drug with most reported injuries occurring outside its core indication for treatment of the most severe mental disorders, schizophrenia and psychosis.

Quetiapine, along with risperidone (RISPERDAL), aripiprazole (ABILIFY), ziprasidone (GEODON), and numerous generics share the common property of blocking dopamine receptors in the brain. Dopamine, in turn, is a vital neurotransmitter that regulates a vast variety of body functions, including muscle movements, body weight, sexual hormones, sleep, pleasure/rewards, and mood and other behavior. While dopamine blocking may have beneficial effects on psychosis and some kinds of abnormal moods, it frequently impacts other body functions. Many antipsychotics cause substantial and rapid weight gain; its effects on sex hormones can cause breast development in males and unexpected lactation in females. The drugs are associated with pancreatitis and Type 1 and Type 2 diabetes. Among the most troubling adverse effects of dopamine-blocking drugs are on movement. They cause parkinsonism, which can include tremors, a shuffling gait and loss of facial expression. They also cause dystonias, which are abnormal muscle spasms, often of the neck or shoulders. The most severe and often irreversible movement disorders are called tardive dyskinesia—these are repetitive, uncontrollable, movements of the lips, tongue, fingers and even entire limbs. While some dyskinesia cases

resolve, with continued exposure many become irreversible and untreatable and are known as tardive dyskinesia. Landmark studies of this problem show that with one year's continuous exposure to antipsychotic drugs from 5% to 10% of patients will get tardive dyskinesia, and that rates increase over time.[18] [19] For many years this side effect profile led antipsychotic drugs to be reserved for the most severe forms of mental illness and to be prescribed for the shortest feasible periods of time. However, both new FDA-approved indications and off label use have led to their use in a wider variety of mental disorders.

Third Quarter Results

We identified 717 cases of serious injury, disability or death in the third quarter in which quetiapine was the suspect drug. The large total was partly a result of a periodic report of 383 cases that had occurred over the previous four quarters. Nevertheless, the third quarter results display the full spectrum of antipsychotic side effects including 396 possible cases of diabetes, 109 possible cases of suicidal/self-injurious behavior, 23 possible cases of dyskinesia, 20 of dystonia and 17 of parkinsonism

Indications

We also analyzed the indication or medical use associated with the reported adverse events for quetiapine. In the third quarter this information was available for 368/717 (51%) of the reported cases, and for 5657 cases since 2004. We combined the indications into four groups in this priority order: schizophrenia/psychosis, all forms of bipolar disorder, depression and all other off-label uses. The results are shown in Table 3.

Table 3. Quetiapine indications in ADRs.

Indication	10Q3	Pct	All*	Pct
Bipolar	132	36%	1832	32%
Depression	83	23%	1211	21%
Off label	94	26%	1464	26%
Schiz/Psychosis	59	16%	1150	20%

*2004-2010q3

In the off label category more than half the cases were for sleep disorders and insomnia. The next largest group was anxiety, and the remainder was divided among many other medical uses including autism, panic attack, headache, restlessness, nervousness, dementia and agitation. We agree with the conclusion of a 2009 study of antipsychotics in the Veterans Administration health system that reported that 60.2% of prescriptions were for off-label use. "Given that these drugs are expensive, have potentially severe side effects, and have limited evidence supporting their effectiveness for off-label usage, they should be used with greater caution." [20]

Varenicline (CHANTIX) Risks Underestimated

While reported serious psychiatric side effects of varenicline prompted the FDA to require a boxed warning and mandatory Medication Guide for patients in 2009, we discovered the FDA had been unaware of hundreds of serious psychiatric adverse event reports that were originated by Pfizer and dated back as far as 2006. These reports had not been promptly submitted into the agency's AERS safety database as the FDA had expected. Thus, FDA analysts could not evaluate 150 completed suicides reported to the company, along with hundreds of other cases indicating psychosis, depression, or attempted suicide. We explain this significant breakdown in safety surveillance below, and recommend the FDA investigate why Pfizer was reporting suicide deaths as "expected adverse events."

Varenicline, an aid to smoking cessation, was approved in 2006, and by 2008 was being taken by hundreds of thousands of smokers who wanted to quit. But as patient exposure increased, the FDA adverse event reporting system received hundreds of reports of psychiatric side effects and other potential safety problems. When we first examined quarterly data for varenicline in May 2008, adverse event reports for the drug outnumbered those for other prescription drugs on the U.S. market including inherently toxic cancer chemotherapy agents, high-alert drugs that suppress the immune system, and extremely potent synthetic opioids. [21] Pfizer told the FDA that it thought stronger warnings were not necessary, and said "it was not unexpected" to see psychiatric side effects among smokers, and in particular those who might be experiencing nicotine withdrawal. [22] The FDA disagreed after completing its own analysis of the adverse event data [23] [24] and in July 2009 required strong warnings for both doctors and patients. [25] Even these warnings, we have now learned, were based on significantly incomplete data about psychiatric side effects.

Results for Third Quarter 2010

We began a new investigation into a signal for varenicline after observing the drug was again setting records. After peaking in 2008, both dispensed prescriptions and reports of serious injury then declined modestly. With a new spike totaling 1055 serious adverse drug events meeting QuarterWatch criteria for the third quarter of 2010, it again surpassed all other drugs we regularly monitor.* It also ranked first in reported deaths, more than twice as many as any other drug we regularly monitor. Varenicline cases also outnumbered all regularly monitored drugs for specific conditions as measured by Standardized MedDRA Queries (SMQs). It accounted for more possible cases than any other drug for suicidal/self-injurious behavior, depression, psychosis, hostility/aggression, and convulsions.

Further analysis uncovered the reason for the sudden spike in varenicline reports. The third quarter totals for 2010 had been boosted by 589 reports about serious and fatal adverse events that had occurred in prior years but were not entered into the FDA AERS monitoring

* Excludes 226 cases linked to legal claims. See Table 4.

system until July 2010. We found 12 newly entered cases with manufacturer dates from 2006, the year varenicline was first approved, 119 from 2007, and 176 additional cases from 2008. The rest of the 589 cases were for 2009 and early 2010, but also not entered into the reporting system until July 2010 or later.

150 Completed Suicides

Prominent among these newly available cases were 150 completed suicides identifying varenicline as the primary suspect drug. These additional cases more than doubled the total suicides that were in the AERS system and available to the FDA and others for safety analysis. Here is our breakdown:

- Prior to July 2010 the AERS system had 37 completed suicide cases submitted by the manufacturer identifying varenicline as primary suspect drug.

- Another 85 suicides associated with varenicline were reported directly to the FDA by health professionals or consumers, and entered into the system without manufacturer involvement.

- In July 2010, these additional 150 suicide cases from the manufacturer first become available.

The newly available completed suicides were not the only reporting and coding problems we detected. These suicides numbered among the 589 cases that met the regular QuarterWatch criteria. This group also included 102 possible cases of hostility/aggression, 156 cases of depression, and 56 cases of possible psychosis. (A case could be classified into more than one of these categories.) In addition, the manufacturer submitted in July 2010 more than 26,000 additional varenicline adverse event cases that did not meet the standing QuarterWatch criteria for serious, domestic adverse events. While we have not fully analyzed this larger group of 26,000 cases, a preliminary survey indicates this group includes numerous additional cases of psychiatric side effects that affect the safety profile of varenicline. Having discovered this large body of significant new safety information submitted in July 2010, we sought to learn how this had occurred.

Comments Sought

We communicated our preliminary findings to the manufacturer, Pfizer, and sought an explanation of these delayed case reports. As has been the case since 2008, Pfizer declined to respond to our questions about varenicline or any other of its products. In a minor policy change, Pfizer said that this time, it could not respond because QuarterWatch data or one of the QuarterWatch project team members might be involved in the future in legal cases involving the safety of varenicline. Previously Pfizer had not indicated why it chose not to respond to ISMP's offer to discuss its findings in advance.

In addition, we communicated our preliminary findings to the FDA. The agency provided a useful and detailed response that resolved some of our questions, but left others unanswered. Based on the information available, a review of the FDA's adverse event reporting regulation and other industry guidance, here is our understanding of what went wrong.

What Went Wrong

Since 1998 the FDA's primary tool for postmarket safety surveillance has been its computer database called the Adverse Event Reporting System (AERS) into which hundreds of thousands of case reports flow each year. Safety analysts at the FDA search this data base routinely to identify reports that might signal a safety issue for additional study. For new, serious adverse events (called expedited reports) the manufacturer is required to report within 15 days, and today most submissions are electronic and flow automatically into the agency safety database. For the less important non-serious events and a few serious adverse effects that are well-characterized, the updates take place on a quarterly basis and are called Periodic Reports. However, the 26,000 cases described above had not been previously submitted to this key safety data system as the FDA expected.

In addition, the FDA requires manufacturers to submit a text report and analysis on a quarterly basis for the less important periodic cases. Listings of the 26,000 case reports were included in these quarterly text documents, the FDA said. Until 2010, the FDA said, it had not been fully aware that some manufacturers were not submitting the case reports into both systems. The agency also said the problem was not limited to varenicline or to Pfizer alone.

Unanswered Questions

We still do not understand why Pfizer grouped hundreds of cases of suicide, suicide attempt, and psychosis among more than 26,000 mostly non-serious adverse events submitted in an inaccessible text report format—especially prior to July 2009 while these safety issues were being actively evaluated by the FDA. To classify a suicide or suicide attempt as an "expected adverse event" rather than submitting it promptly as a 15-day report where it would have been immediately available is troubling in our view. Additional questions arise about how Pfizer coded hundreds of reports of depression and suicidal ideation. When the FDA surveillance system did not include more than half the reported suicide deaths in which varenicline was primary suspect drug, it is a safety lapse that warrants careful investigation.

FDA Warning Letter Sent

In addition, the agency has raised other concerns found in an inspection of Pfizer's adverse event reporting program. The FDA's Inspections, Compliance, Enforcement and Criminal Investigations unit sent Pfizer a six-page warning letter on May 26, 2010 indicating the agency had found deficiencies in the company's adverse event reporting program dating back to 2004. [26] Among the violations the FDA alleged had occurred were failure to submit serious adverse event reports for cases already in company files until identified by an inspector, misclassifying and downgrading events without reasonable justification, and failing to submit

expedited reports within 15 days as required. The agency also alleged Pfizer had failed to keep prior commitments to improve training and performance for adverse event reporting. The specific cases cited as examples in the letter did not include varenicline but applied broadly to Pfizer's safety surveillance program.

Need for FDA Clarification

Avoiding problems such as this in the future will require a substantial FDA effort to consolidate and simplify its requirements for adverse event reporting by industry. In researching the question of what should have happened with these serious adverse events we discovered procedures that were variously prescribed by federal regulation [3] (useful but too brief), a formal Guidance for Industry [27] (Much more detailed procedures but dating to 1992), a major Clarification of What to Report [28] (dated 1997) , a new Draft Guidance for Industry [29] (dated 2001, but never finalized) and finally a current web page with instructions to industry [30] about how to fill out the reporting form, but with no indication of its formal regulatory status. Nowhere could be found clear and consistent requirements about what should be reported in today's electronic age.

Drug Safety Perspectives:

Adverse Event Reports and Legal Claims

In the current report quarter, the FDA received 4468 initial serious adverse drug event reports that explicitly indicated that the injury was associated with lawsuits filed against drug manufacturers by patients who allege they were injured by a drug and seek compensation. It is possible that hundreds to thousands of additional case reports might become linked to a legal claim in the future, or were already part of a legal claim but could not be clearly identified. While we exclude these cases from our main analysis, they nevertheless provide a valuable and different drug safety perspective.

The overall toll of injury associated with drug therapy is crudely estimated at approximately 100,000 deaths per year, and approximately 5.5% of hospitalizations (or about 1.9 million); and causes an estimated 700,000 emergency room visits. [31] [32] [33] [34] The total that conforms to the FDA's formal definition of serious, disabling and fatal adverse drug events is not estimated regularly by any established methodology or authoritative source, but must number in the low millions. The QuarterWatch count of reported events totaled 133,000 cases over the previous four quarters, suggesting that possibly 5% of serious, disabling or fatal adverse events that occur are reported to the FDA.

Legal claims against drug companies form an unusual special case in drug safety reporting. The U.S. legal system treats drug-associated injuries in largely the same way it treats auto accident injuries. The claimant has to prove the drug (or automobile) was defective in a significant way that led to the injury. Thus a drug-induced injury does not automatically generate a legal claim any more than an auto accident would automatically result in a lawsuit against the manufacturer. Typically drug-associated injuries involve a claim that the manufacturer knew or

should have known about certain risks of its product and failed to warn doctors and/or patients. A withdrawal of a drug for safety reasons frequently triggers lawsuits that can number in thousands or occasionally tens of thousands of cases. The pattern we see is that a relatively few drug safety problems generate hundreds of claims each, but many, many drug side effects generate few if any claims.

In this QuarterWatch we provide two perspectives on the specific kinds of drug injuries that are generating large number of legal claims. In Table 4 we list the brand name drug products that indicated a legal claim in 2010 Q3. In Table 5 we list the brand name drugs with 1,000 or more lawsuits now pending in the U.S. federal court system. (Large numbers of additional lawsuits could be pending in state courts). We have listed in the tables whatever product name was supplied in the adverse event report.

Table 4. Legal case reports in 2010 Q3.

Drug Name	Reports
YAZ	976
YASMIN	568
CELEBREX	474
METOCLOPRAMIDE	471
PROVERA	245
CHANTIX	226
PREMPRO	170
PAMIDRONATE DISODIUM	160
PREMARIN	150
PAXIL	114
AVANDIA	100

Table 5. Drug injury claims pending in federal court.*

Product	Indication	Pending Cases
PREMPRO	Hormone replacement	7,543
SEROQUEL	Antipsychotic	6,203
YASMIN/YAZ	Contraceptive	5,310
AVANDIA	Type 2 diabetes	2,051
CHANTIX	Smoking cessation	1,545

* More than 1000 cases as of March 15, 2011 for still-marketed drugs

These legal claims provide a novel perspective on drug safety because they represent a count of injured individuals seeking compensation for an injury for which a drug is allegedly responsible. However, these data have a unique set of limitations. First, these are allegations not proven claims. In later legal proceedings the court and/or juries could absolve the drug entirely,

or find injuries of some claimants were not caused by the drug while finding in favor of other claimants. Also, this group of uniquely coded adverse event reports (occupation = lawyer) does not capture the full scope of adverse event reports that may be linked to a present or future legal claim. Law firms may collect hundreds (or even thousands) of potential claims which might generate adverse event reports, but then file a much smaller number of the strongest claims as formal lawsuits. While we think legal claims can provide valid safety information, the cases we exclude appear to come primarily from the legal departments of pharmaceutical companies and are likely to duplicate case reports already submitted by the patients. Nevertheless, it is important to note that even a flood of cases into the legal system may underestimate the true scope of injury caused by a major breakdown in drug safety. Our regular monitoring and these legal claims data merely expose different parts of the iceberg.

Appendix: QuarterWatch Funding Sources and Team

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. Mr. Moore also conducts and publishes other independent studies in the peer-reviewed scientific literature, and works as a consultant on drug safety issues, doing business under the name Drug Safety Research. He is currently a consulting expert to the Attorney General of the State of Texas in a Medicaid fraud lawsuit against Johnson & Johnson regarding the antipsychotic drug Risperdal (risperidone), and in 2009 was an expert witness for the United States Army in connection with a criminal case involving Chantix (varenicline). In February 2011 he agreed to serve as a consulting expert in the civil litigation regarding Chantix.

Curt D. Furberg, MD, PhD is a Professor of Public Health Sciences at Wake Forest University School of Medicine and serves as senior medical adviser to QuarterWatch. He receives no compensation for work in assessing scientific evidence, defining safety issues, shaping the written report and communicating with the FDA and others about QuarterWatch findings. He has a research and academic role at Wake Forest and has published more than 400 peer-reviewed scientific articles. An expert on clinical trials of drug treatments, Dr. Furberg, is author of a major textbook on that subject, and has worked for the National Institutes of Health and the pharmaceutical industry as an investigator in clinical drug research. He has recently given expert testimony or depositions in cases involving COX-2 inhibitors, a gadolinium contrast agent, and Fosamax (alendronate).

Michael R. Cohen, RPh, MS, ScD is founder and president of ISMP and guides the overall policies and content of QuarterWatch. He also edits the other ISMP newsletters and is author of the textbook *Medication Errors*. He has served as an advisor and consultant to the FDA, and for his work in medication safety was recognized as a MacArthur Fellow by the John D. and Catherine T. MacArthur Foundation. Dr. Cohen receives a regular salary as president of ISMP and does not engage in outside consulting or legal testimony.

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