



September 24, 2014 — Data from 2013 Quarters 2 & 3

PERSPECTIVES IN THIS ISSUE

Dimethyl fumarate (TECFIDERA): tolerability problems with a new multiple sclerosis drug
Varenicline (CHANTIX): reports of suicidal/homicidal thoughts surpass all other drugs
Sodium oxybate (XYREM): a restricted drug with severe side effects
Fingolimod (GILENYA): cardiac, vision, and pregnancy risks

Executive Summary

In this issue we analyze severe gastrointestinal toxicity and hypersensitivity reactions reported for the new oral drug for multiple sclerosis (MS), dimethyl fumarate (TECFIDERA). The risks of serious psychiatric side effects are highlighted in a new analysis of varenicline (CHANTIX), an aid to smoking cessation. We also examine the frequent and broad spectrum of serious adverse effects on the brain of sodium oxybate (XYREM), an orphan drug for narcolepsy. Cardiac, ocular, infection, and pregnancy risks are reviewed for a second newer MS drug, fingolimod (GILENYA).

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

Because the FDA has corrected its previously delayed quarterly releases of serious adverse event reports, this issue of QuarterWatch includes data from two calendar quarters of 2013, Q2 and Q3. Totals from the two quarters reveal that after many years of a steady increase in reported fatal, disabling and serious adverse drug events, reports have hit a plateau in 2013. The Q3 total of 47,864 was almost unchanged (+108) from the preceding quarter Q2, and was 8.7% lower than Q3 of the preceding year.

The Safety Profile of Dimethyl Fumarate (TECFIDERA)

Dimethyl fumarate was approved in March 2013 for multiple sclerosis (MS). In the first six months of postmarket data, we observed a signal for tolerability problems involving gastrointestinal (GI) disorders and hypersensitivity reactions. The GI reactions (n = 202) were often severe and required hospitalization. The most common symptoms included nausea, vomiting, diarrhea, fever and dehydration. The hypersensitivity cases (n = 125) involved reports of flushing, urticaria, rash and pruritus. An unusual feature of these reports was that 55% of the hypersensitivity cases also involved GI symptoms. The manufacturer, Biogen Idec, said it was still researching the mechanism causing the GI adverse events.

Important questions about the safety of dimethyl fumarate remained unanswered in premarket testing and from these early adverse event data. Toxic effects on the kidney were so prevalent in animal studies that the FDA toxicology reviewer recommended against approval. However, human clinical studies of two years'

duration did not provide evidence of adverse effects on the kidneys, although the toxicologist noted that the trial surveillance might not have been sensitive enough to detect the slow and gradual deterioration seen in a small study in monkeys. Adverse effects on the testes were also seen in three animal species.

Varenicline (CHANTIX) and Suicidal/Homicidal Thoughts

The FDA has reopened the question of psychiatric side effects of the smoking cessation aid varenicline (CHANTIX) and scheduled a joint meeting of two advisory committees in October 2014 to review the current Boxed Warning and patient Medication Guide mandated in 2009. Thus far, the FDA has revealed little about its reasons for calling this meeting. The first pilot issue of QuarterWatch in 2008 featured an unexpectedly large number of serious adverse drug events for this alternative to nicotine replacement products such as nicotine gum or patch. Therefore, we sought to reassess the adverse event data collected over the seven years since the approval of varenicline. We selected as endpoints three specific and clear psychiatric symptoms: thoughts of suicide, self-injury, and homicide.

These new data show varenicline continues to account for more cases of suicidal, self-injurious or homicidal thoughts than any other therapeutic drug during the period 2007 through 2013 Q3. The ranking is shown in Table 1. The findings were robust and the differences between varenicline and other drugs were large. Varenicline ranked first in both suicidal/self-injurious thoughts as well as homicidal thoughts. Varenicline cases outnumbered those for any other drug by more than 3-fold difference. For homicidal ideation cases the margin was a 5-fold difference. Excluding foreign reports did not alter the findings. Examining the most recent reports since 2011 reduced the margin by which varenicline cases outnumbered all others, but was consistent with a 73% decline in dispensed outpatient prescriptions since the peak in 2008.

Rank	Drug name	Disease target*	Number, pct
1	Varenicline	Smoking cessation	2748 (14.8)
2	Montelukast	Asthma	835 (4.5)
3	Paroxetine	Major depression	714 (3.8)
4	Quetiapine	Schizophrenia	607 (3.3)
5	Venlafaxine	Major depression	565 (3.0)
6	Interferon beta	Multiple sclerosis	540 (2.9)
7	Isotretinoin	Resistant acne	523 (2.8)
8	Duloxetine	Major depression	493 (2.6)
9	Pregabalin	Neuropathic pain	452 (2.4)
10	Bupropion	Major depression	374 (2.0)
*Derived from first listed indication			

High Reporting Rate for Sodium Oxybate (XYREM)

Sodium oxybate (XYREM) is currently approved for symptoms of narcolepsy. It was once famous as an addictive drug of abuse, a colorless, odorless, fast-acting drug capable of inducing euphoria and sexual arousal at lower doses, but confusion, blackout, and memory loss at higher doses or in combination with alcohol. It was one of the first known date rape drugs. Now banned as a Schedule 1 controlled substance under the name gamma hydroxybutyric acid (GHB), it is nevertheless available as an orphan drug for the treatment of two manifestations of narcolepsy under a restricted distribution program.

Although approved in 2002, legal problems involving off-label promotion and a breakdown in manufacturer postmarket surveillance obscured until now the problematic safety profile of this potent central nervous system (CNS) depressant. Sodium oxybate reports described multiple adverse effects on normal brain function, including compromise of motor control (ranging from falls to bedwetting), adverse effects on the extrapyramidal motor system (dystonia, parkinsonism, akathisia), memory and alertness (confusion, blackout, memory loss), and on mood and behavior (anxiety, depression, psychosis, hostility/aggression and suicidal behaviors). With 1,374 reported serious events in the 12 months ending in 2013 Q3, and exposure of an estimated 9,000 patient-years, this amounts to serious injury being reported in approximately 15% of the exposed population. Jazz Pharmaceuticals, the manufacturer of the drug, noted two additional reasons for the large number of reports: a) The company was more likely to discover adverse events because of monthly

pharmacy contact with every patient under its restricted distribution plan, and b) Some events (such as falls) could possibly be attributed to the underlying health disorder of narcolepsy and catalepsy.

Update on Fingolimod (GILENYA)

An example of the risks being taken under FDA policies for promoting innovation and speeding approval of new drugs with less premarket testing came to light two years ago when QuarterWatch reported on early safety signals for fingolimod (GILENYA), then the first oral immunosuppressant treatment for multiple sclerosis. It featured an entirely new mechanism of action, inhibiting lymphocytes from exiting the lymph nodes, and had shown an unacceptable safety profile when administered at several doses higher than that approved (0.5 mg per day). However, the manufacturer, the FDA, and the FDA advisory committee agreed fingolimod should be tested at a lower dose to see if safety could be enhanced without loss of efficacy. This testing could be performed after approval, the FDA concluded, with results now expected in 2016.

Meanwhile, three years of postmarket and new published data highlight four important safety risks of fingolimod. Because fingolimod may disrupt normal heart rhythm, precautions for initiating treatment require that the patient be observed for the first six hours in a medical setting. Adverse event reports for the most recent 12 months showed the cardiac risks were neither rare nor hypothetical. We identified 473 cases of heart rhythm disturbance, primarily bradycardia and heart block. They include 13 patient deaths, 11 cases classified as life-threatening and 141 resulting in hospitalization. Also identified was a large group of cases (n = 348) indicating macular degeneration or less specific adverse effects on the eye. Because of the known risk of macular edema, baseline and follow-up eye exams are recommended, and reminders sent to every patient taking the drug. A third concern was increased infection risk because of the effect of fingolimod on lymphocytes. In the 12-month data we identified 172 cases of reported viral infections, mostly herpes simplex and zoster. Finally, pregnancy risks were a substantial premarketing concern based on animal studies linking the target fingolimod receptor to vascular malformations in rodents and human fetal abnormalities 5/66 (7.6%) of known pregnancies in clinical studies.

We reviewed our preliminary findings with the manufacturer, Novartis. The company said the number of cardiac reports may have been increased because most patients are directly observed in a medical setting for the first six hours. Better surveillance, it noted, results in the discovery and reporting of more adverse effects. Novartis also said two additional factors may have increased reports of vision problems: The mandatory eye exams provided better surveillance, and vision problems are also an early symptom of MS.

Nevertheless, the large volume of reports of serious injury (n = 2,716) equals approximately 17% per patient-year of exposure, showing that fingolimod remains a high-risk drug with multiple toxicities. Additional detail about this calculation and Novartis' views are discussed in the main report.

The Adverse Event Reporting System

An Evolving Adverse Event World

This report focuses on three drugs (dimethyl fumarate, sodium oxybate, fingolimod) that share several characteristics with substantial effects on the total number of adverse event reports submitted. All three are expensive medications (more than \$50,000 per patient-year) for small patient populations (10,000-25,000 patient-years). The high costs and small patient populations lead to marketing and safety surveillance plans that place the manufacturer in contact with every new patient. In the case of sodium oxybate, the central pharmacy calls every patient every month before shipping a refill. For all three drugs, manufacturers have extensive contact with practically all patients as treatment is initiated to assist in navigating insurance coverage for these high-cost specialty drugs. This leads to a different adverse event reporting environment compared with traditional brand name drugs where patient contacts by the manufacturer are limited, but

contacts with physicians are more extensive. Nevertheless, the exact same reporting regulations apply to both quite different settings.

These high-patient-contact settings provide a new opportunity to achieve unprecedented and high-quality postmarket surveillance. It would be especially valuable for orphan drugs with clinical trials for efficacy in patient populations of just 100-200 subjects on the active drugs. Given that patient contact is already occurring for commercial and safety reasons, additional costs would be minimal. But to achieve these benefits, the FDA, manufacturers and stakeholders need to develop regulations, guidances and contact protocols to cover a steadily growing number of drugs.

About QuarterWatch Data

Our findings should be interpreted in light of the known limitations of a reporting system that does not collect data systematically. The FDA Adverse Event Reporting System (FAERS) data combine reports originated by drug manufacturers with cases submitted directly from consumers and health professionals through the agency's MedWatch program. The submission of an individual report does not in itself establish that the suspect drug caused the event described—only that an observer suspected a relationship. More complete disclaimers and descriptions of our criteria are included in the Methods Summary section of this report. A disclosure statement expands our description of this project and its staff.

Conclusions

The signal of frequently reported and severe GI and hypersensitivity reactions associated with early dimethyl fumarate use shows the need to re-evaluate these risks and provide clear warnings for physicians and develop guidelines for optimal treatment.

These new varenicline findings, along with previously published studies, show the need for the FDA to strengthen and clarify the warnings about psychiatric side effects. In particular, the Boxed Warning should include better information about the risk of homicidal ideation, aggression and violence. The indications section should explicitly state that use is not recommended for sensitive occupations such as pilots, air controllers, deployed military personnel, police, fire fighters and emergency medical care professionals. In addition to the psychiatric risks, we have previously reported on other adverse effects of varenicline that would be unacceptable risks to individuals in sensitive occupations, notably blackouts, convulsions and impaired vision. Finally, misleading promotional language about smoking cessation should be removed from the Boxed Warning.

The safety profile of sodium oxybate, now seen in a larger patient population for the first time, establishes the need to reassess whether its benefits justify the risks now being fully reported.

The FDA and the manufacturer should consider reclassifying fingolimod as Pregnancy Category X, clearly identifying it as a drug not suitable for women who may become pregnant.

Both international adverse event reporting standards through the International Conference on Harmonisation and the FDA's regulations for drug manufacturers are built around traditional pharmaceutical marketing practices that may involve intensive marketing to physicians but minimal direct contact with patients. New reporting standards are needed for drugs with manufacturer (or central pharmacy) call center programs. This opportunity to capture important safety data at minimal additional cost to industry should not be overlooked.

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Results

Serious Injury Reports Reach a Plateau

The FDA received 47,864 domestic reports of fatal, disabling and other serious adverse drug events in 2013 Q3, an increase of only 108 reports from the 47,756 reports it received in Q2. The Q3 results are a decline of 8.7% from Q3 a year previously, and 23.6% percent below the all-time peak reached in 2013, Q1. After many quarters of steady increases it appears that reported serious injury from therapeutic drugs has reached at least a short-term plateau. In several subcategories monitored in QuarterWatch, declines were observed. The largest group of reports is called expedited reports, and they are submitted by manufacturers about serious adverse drug events for which adequate warnings may not exist. These expedited reports accounted for 34,631 or 72% of the Q3 total. They also decreased 3.3% from the previous quarter and 14% from the same quarter in 2012. A smaller volume of reports are submitted directly to the FDA through the MedWatch program (<http://www.fda.gov/Safety/MedWatch/>) but are valuable because they represent direct complaints from consumers and health professionals rather than being collected, coded and processed by drug manufacturers. In Q3, direct reports to the FDA totaled 4,743 new cases, or just 9.9% of the total, and a decline of 5.6%. It was the smallest number of direct reports submitted to the FDA since 2007 Q4.

The Safety Profile of Dimethyl Fumarate (TECFIDERA)

Within six months of marketing approval, adverse event reports showed a marked signal of two severe tolerability problems for dimethyl fumarate (TECFIDERA), a new orally administered drug for multiple sclerosis (MS). Approved March 27, 2013, as the third new oral treatment, the drug's product launch was so successful that Biogen Idec reported it "was the leading oral MS therapy in the United States after only six months on the market." The company credited dimethyl fumarate as the leading factor in a 32% revenue gain in the 2013 Q3.[1] In clinical studies dimethyl fumarate demonstrated a beneficial effect in reducing MS relapses, with 17% of treated patients experiencing a relapse in one year compared with 46% of placebo patients.[2] However, the adverse drug event reports since launch highlight two safety problems without adequate warnings: severe gastrointestinal disorders and hypersensitivity.

Issues in Preclinical Toxicology

Dimethyl fumarate--a chemical in use for decades--had an unpromising history as a potential medicine for long-term use in MS. It was a fungicide used agriculturally in Europe, as well as to prevent mold on furniture, clothes and shoes.[3] However, it was banned because of the risk of contact dermatitis. That action in itself might serve as a warning flag about its toxicity. On the positive side, a chemical variant has been approved in Germany since 1994 as a drug for severe psoriasis.

When evaluated for FDA approval, dimethyl fumarate was also unusual because the toxicology reviewer recommended against approval on the basis of animal studies alone.[4] Dimethyl fumarate produced toxic effects in mice, rats, dogs and monkeys in studies ranging from 28 days to 2 years, and at both clinically relevant and higher exposures. The primary target organs were the kidneys, stomach and testes. As often occurs with unfavorable toxicology results, the relevance to humans was debated.

The FDA toxicology reviewer's primary safety concern was adverse effects on the kidney, which were observed in every species tested including monkeys, and at clinically relevant doses. Kidney damage included necrosis, atrophy and tumors. However, the FDA medical reviewer did not report evidence of kidney damage or impairment in a human clinical trial that included 2 years of treatment and surveillance.[5] The toxicology reviewer, however, responded, "It is not clear from the nonclinical data that the monitoring was observed in necropsy after approximately one year of exposure at or near the human dose conducted would

be able to detect the toxicity in humans.”[4] In monkeys, low-level but irreversible kidney damage was observed at one year.

The findings for stomach toxicity were striking, but harder to interpret. In mice and rats, forestomach damage was severe, including ulceration, inflammation, and tumors at all doses tested, including less than equivalent human exposure. However, humans do not have a forestomach where food is stored prior to digestion. Also, in dogs the toxicity was decreased. Further, the company believed GI toxicity would be additionally reduced using a capsule formulation rather than administration by oral gavage. The toxicology reviewer noted, “It is possible that the irritancy could have effects in the exposed portion of the GI tract... especially given the potential for decades of twice-daily exposure in the treatment of this chronic disease.” In this case, the clinical trials did confirm the GI toxicity seen in animals, with 4% discontinuing the drug for gastrointestinal disorders at the recommended dose.[5]

Additional safety concerns involved effects on testes where atrophy, hypospermia or hypoplasia was observed at clinically relevant doses in mice, rats and dogs.[2] Also difficult to assess was cancer risk. A plausible mechanism for fumarate as an oncometabolite has been posited,[6] and squamous cell carcinomas of the forestomach and kidney were observed in mice and rats at doses higher than the recommended human dose.[2]

Finally, the chemistry of dimethyl fumarate shows it is a highly reactive molecule capable of binding to many types of other biomolecules with effects that may not have been determined in toxicology testing.

Adverse Event Results

In the first six months after approval we identified 441 reported serious adverse events, including 9 deaths and 264 cases of hospitalization. The report sources were evenly divided between consumers and health professionals. An unexpectedly large share of these reports was made directly to the FDA rather than through the manufacturers, accounting for 31% of the total compared with 9.9% for all other drugs. We regard a surge of direct reports to the FDA as a separate indicator of safety concerns because the reports are not increased by marketing activities.

Serious GI Toxicity

The largest identifiable subgroup of cases indicated GI toxicity. We identified 202 cases (45%) defined by the Standardized MedDRA Query (SMQ) category for “Gastrointestinal nonspecific inflammation and dysfunctional conditions.” While the category is broad and not specific about likely cause, the reported cases were severe, with 2 deaths, 1 life-threatening reaction, and 119 cases requiring hospitalization. The leading symptoms of GI toxicity were nausea (n = 94), vomiting (n = 83), diarrhea (n = 71) and various abdominal pains (n = 75). However cases were complex and often involved other symptoms, notably dehydration (n = 42), and fever (n = 29). One case could involve several of these symptoms. These data capture only the cases classified as serious under the FDA definition[7] and QuarterWatch criteria. Hundreds of additional cases were reported as non-serious with one or more of the following symptoms: nausea, diarrhea, upper abdominal pain and vomiting.

Hypersensitivity

A second group of serious adverse events was captured by the hypersensitivity SMQ and accounted for 125 cases. The most common hypersensitivity symptoms were flushing (n = 66), urticaria (n = 22), rash (n = 18) and pruritus (n = 17). Each case could account for one or more symptoms. However, many of the hypersensitivity cases involved GI symptoms as well. We found that 69 (55%) of the hypersensitivity cases were also counted among the 202 serious GI cases.

Company Response

We provided a preliminary summary and list of questions to the manufacturer, Biogen Idec. In response the company provided us with information from the current product label. In addition, the company said, “The exact cause of the GI tolerability events is unknown. We are conducting studies to further investigate...” We also asked the company for data that might indicate the time of onset of the GI and hypersensitivity events. Events occurring with the first or second dose might provide important indications of the causal mechanism and enable better focused precautions. The company said, “We are continuing to evaluate the reports and, when warranted, we will communicate the results to the medical community.”

Conclusions

These adverse event data signal a severe tolerability problem that was not adequately captured in premarket clinical trial reporting or in the prescribing information for physicians. In particular this information does not capture the severity of the GI cases that often resulted in fever, dehydration, and hospitalization. Despite more than 100 case of hypersensitivity reported since approval, the prescribing information contains no warning. In addition, these early reports could not be expected to address the three other substantial safety issues identified in animal studies: damage to the kidney or testes and cancer risk. It is also another example of the important unanswered safety questions that remain, despite a demonstration of efficacy in the treatment of MS. As we have written before, caution is indicated when considering prescribing newly approved drugs. [8]

Varenicline (CHANTIX) and Thoughts of Suicide and Homicide

In October 2014 the FDA will move varenicline (CHANTIX) back into the drug safety spotlight. The first pilot issue of QuarterWatch in May 2008 was a special report on varenicline, a smoking cessation aid. It documented that the drug accounted for more serious adverse event reports in 2007 Q4 than any other prescription drug.[9] We thought it troubling that an

alternative to the nicotine patch or gum was the primary suspect in more reported cases of serious injury than inherently toxic cancer treatments, super-potent opioids such as fentanyl, or powerful immunosuppressant drugs that may open the door to infection or cancer. The FDA and other parties reached similar conclusions.

The Federal Aviation Administration banned its use by pilots and air traffic controllers, and the Departments of Defense and Transportation restricted its use in sensitive occupations. In 2009 the FDA, after three escalating warnings about serious psychiatric side effects, required a Boxed Warning and mandatory Medication Guide.[10]

Safety concerns took a major toll on varenicline prescriptions and sales, which peaked at 1.9 million prescriptions in 2008 Q1, but have now declined 73% to 520,000 prescriptions in 2013 Q3, according to data from IMS Health, a health information provider. More than 3,000 patients sued Pfizer Inc., the manufacturer of varenicline, over psychiatric side effects that included suicide, psychosis and violence. On the eve of the first potential trial in open court with batteries of experts on both sides prepared to testify, Pfizer opted to pay most claimants rather than try even a small group of bellwether cases. It is not clear why the FDA opted to convene two advisory committees to reconsider the warnings about suicidal behavior and other psychiatric side effects.

Table 1. Leading suspect drugs in suicidal/self-injurious and homicidal ideation cases, 2007 to 2013 Q3

Rank	Drug name	Disease target*	Number, pct
1	Varenicline	Smoking cessation	2748 (14.8)
2	Montelukast	Asthma	835 (4.5)
3	Paroxetine	Major depression	714 (3.8)
4	Quetiapine	Schizophrenia	607 (3.3)
5	Venlafaxine	Major depression	565 (3.0)
6	Interferon beta	Multiple sclerosis	540 (2.9)
7	Isotretinoin	Resistant acne	523 (2.8)
8	Duloxetine	Major depression	493 (2.6)
9	Pregabalin	Neuropathic pain	452 (2.4)
10	Bupropion	Major depression	374 (2.0)
*Derived from first listed indication			

Psychiatric Side Effects: How Varenicline Compares

For a long-term perspective on the relationship of varenicline to psychiatric side effects we focused on three specific psychiatric symptoms: thoughts (ideation) of suicide, self injury, or homicide. We collected all serious reported foreign and domestic cases for all identifiable therapeutic drugs from 2007 through the most recent data, 2013 Q3. We excluded cases from litigation, clinical studies and withdrawn drugs.

In these data varenicline accounted for more reported cases of suicidal and homicidal thoughts than any other drug, and by a large margin. Our criteria identified 18,610 case reports of serious outcome over the 75-month surveillance period, including 17,920 indicating suicidal/self-injurious ideation and 1,261 for homicidal ideation. Among the cases of homicidal ideation, 571 (45.3%) also involved suicidal ideation. Varenicline ranked first with 2,748 cases, three times the number for the second-ranked drug and a nearly 7-fold difference from the 10th listed drug. Table 1 (reprinted from the Executive Summary section) shows the 10 most frequent suspect drugs.

We also wondered whether homicidal ideation might identify different suspect drugs than did suicidal thoughts. As Table 2 shows, the cases for homicidal ideation are substantially fewer, but the suspect drug list is quite similar. One drug— isotretinoin—drops off the list of most frequent suspects entirely, with only 5 reported cases of homicidal ideation. Varenicline stands out even more prominently in the subset of homicidal ideation, with a 5-fold margin over second-ranked quetiapine. In our previous peer-reviewed study of reported violent acts, varenicline was also ranked higher than any other therapeutic drug.[11] An independent study in the French adverse event database also reported elevated risk for reports of violence associated with varenicline.[12]

These findings were robust. Varenicline continued to rank first on the list when foreign reports were excluded, and still ranked first when limited to the most recent reported cases starting in 2011. (However, in these more recent reports, the difference with other drugs was smaller, but consistent with the 73% decline in patient exposure since 2008.) Varenicline ranked first in both subsets, suicidal/self injurious thoughts, and homicidal thoughts. For varenicline, thoughts of suicide and self-injury also correlated with acts of attempted and completed suicide. Since 2007 varenicline was the primary suspect drug in 293 cases of completed suicide and 490 cases of attempted suicide. While calculating patient exposure of all drugs over 27 months was beyond the scope of this analysis, we did spot check dispensed outpatient prescription data from IMS Health for the 10 highest ranked drugs for 2013 Q3. Only isotretinoin (ACCUTANE, CLARAVIS), had fewer prescriptions (47% of the total for varenicline). The 8 other drugs had much wider patient exposure, ranging from pregabalin (4.2 times higher than varenicline) to montelukast (14.4 times higher than varenicline). Finally, this new assessment confirms and extends the findings of our two peer reviewed studies examining reports of violent acts[11] associated with all drugs, and suicidal behaviors in smoking cessation treatment.[13]

Rank	Drug name	Number, pct
1	Varenicline	306 (24.3)
2	Quetiapine	59 (4.7)
3	Montelukast	51 (4.0)
4	Duloxetine	48 (3.8)
5	Interferon beta	43 (3.4)
6	Sertraline	38 (3.0)
7	Paroxetine	35 (2.8)
8	Venlafaxine	31 (2.5)
9	Atomoxetine	28 (2.2)
10	Pregabalin	26 (2.1)

Limitations of These Data

Thoughts of suicide or homicide are much more common and less severe than suicidal behaviors or violence. Individual case reports themselves do not prove causality, but do indicate that the reporter typically suspected a relationship with the drug. Some of the reported suicidal behavior cases associated with psychiatric drugs such as antidepressants and antipsychotics occurred in patient populations where such behavior might be the result of underlying disease. In addition, we selected suicidal or self-injurious ideation rather than completed suicides or suicide attempts because in adverse event report data, drugs identified in suicidal acts could be either suspect causal agents or the means of suicidal behavior in an intentional overdose that might have involved any drug at hand.

Could These Be Effects of Nicotine Withdrawal?

Both results from earlier reviews[14] and these data show smoking cessation might increase the risk of some psychiatric side effects, notably irritability, anger and possibly depression. Also, some studies suggest the smoking cessation population might have a higher incidence of other psychiatric disorders.[15] But varenicline provides additional increased risk that is substantially more than could be expected from nicotine withdrawal effects alone. Both our previous case series[16] and the FDA's own analysis of varenicline[17] noted that frequently the side effects began during the first week of treatment before new patients reached their smoking quit date. In addition, we observed some similar side effects for nicotine replacement products in a previous study[13] and in these new data, but at a much lower rate. For example, for suicidal/self injurious and homicidal ideation, we identified 78 cases for nicotine replacement products, compared with 2,748 cases for varenicline.

Conclusions

These findings provide additional strong support and extend the evidence from our own previous studies as well as earlier analysis by the FDA's Office of Surveillance and Epidemiology. They also show that seven years after approval, no other therapeutic drug approaches varenicline in the number of reported cases of suicidal, self-injurious or homicidal ideation. The Boxed Warning for varenicline should be clarified and strengthened to indicate more clearly the risk of homicidal ideation, aggression and violence. Promotional language about smoking cessation benefits should be removed from the Boxed Warning. In addition, the indications section should include specific instructions that use of varenicline is not recommended for people in sensitive occupations such pilots, air traffic controllers, missile crews, armed military personnel, police, fire and emergency medical care professionals. The risk to patients in sensitive occupations includes not only the psychiatric effects, but neurological or cardiac effects such as blackout, convulsions and impaired vision.[9]

Sodium Oxybate (XYREM): Adverse Effects on the Brain

Our assessment of sodium oxybate (XYREM) began when this orphan drug for narcolepsy, a rare sleep disorder, accounted for more reported serious adverse drug events than other drugs taken by hundreds of thousands or even millions of patients. There were more reported adverse events than with high-alert drugs such as the super-potent synthetic opioid, fentanyl (DURAGESIC), and many inherently toxic cancer drugs. Jazz Pharmaceuticals, the drug's manufacturer, was the beneficiary of special policies to provide incentives to develop treatments for rare diseases, and to make available high-risk drugs with special restrictions. The drug had also produced hundreds of millions in pharmaceutical sales since approval in 2002. Nevertheless, 12 years later serious questions remain whether its benefits justify its unusually high risks and whether off-label use has been controlled.

Sodium oxybate, also known as gamma hydroxybutyric acid or GHB, is an active metabolite of gamma-aminobutyric acid (GABA), principal inhibitory chemical messenger of the brain. Benzodiazepines and barbiturates are agonists of GABA receptors, and calm and depress the central nervous system.[18] However, GABA itself is not useful orally because it does not pass the blood-brain barrier; however, GHB, a metabolite, does. GHB is an extremely fast acting sedative and CNS depressant; it acts so fast that narcolepsy patients are warned not to take the evening dose of GHB (sodium oxybate) unless they are in or near bed.[19] It is also eliminated rapidly, and sodium oxybate patients are instructed to set an alarm to take a second dose 2.5 to 4 hours later. The second dose should be taken while sitting in bed. Its effects on the CNS are so rapid and potent that injectable GHB is approved as an adjuvant anesthetic in Germany and France. Other adverse events linked to its effects on the nervous system are bed-wetting and fecal incontinence.[20]

The Date Rape Drug

The first major safety concerns about GHB arose in the 1980s when it became widely available as an unregulated dietary supplement.[21] It was used by body builders for reasons not clear pharmacologically, and taken for weight loss, but it became better known as a date rape drug used at concerts and parties. It is a colorless, odorless powder and especially combined with alcohol, another CNS depressant, could induce euphoria and sexual arousal; but as the dose increased it induced confusion, loss of consciousness, and amnesia. It was classified in 2000 as a Schedule I controlled substance, a designation reserved for the most dangerous drugs with potentially severe psychological effects or physical dependence.[22]

FDA Approves Sodium Oxybate for Restricted Use

GHB soon came back to life as sodium oxybate or Xyrem, benefiting from two special FDA policies. To control its potential for diversion and abuse, it was one of the first drugs approved under a restricted distribution scheme with one central pharmacy and a required education program for both prescribing doctors and patients. Also, it benefited from incentives enacted by Congress to promote development of treatments for rare diseases. The rare disease in this case, affecting approximately 150,000 patients, was narcolepsy. This sleep disorder is characterized by excessive daytime sleepiness, suddenly falling asleep without warning, and cataplexy, an attack of sudden muscle weakness usually triggered by strong emotions. Cataplexy attacks can involve a sagging jaw, drooping shoulders or buckling of the knees. Most attacks last less than 2 minutes.[23]

The FDA approved sodium oxybate in 2002 after a divided advisory committee vote, a problem-plagued New Drug Application, and limited long-term safety data. The approval letter noted that only 141 patients had received the 9 g/day effective dose.[24] In the key trial for assessing its effect on cataplexy attacks only 35 patients received the effective dose. However, despite the small trial size and 4-week duration, the 9 g dose demonstrated a beneficial effect on cataplexy attacks, reducing them from a median of 24 per week to 9 per week.[25] It was also clear that sodium oxybate in medical use remained a toxic drug. In trials of just 4 weeks 6/35 (17%) of subjects discontinued the drug for adverse effects at the 9 g dose in the cataplexy trial, and 15/47 (32%) in a later trial to assess effects on daytime sleepiness, and 40/190 (21%) with 6 g/day in a trial for patients with fibromyalgia.[26] Among the adverse drug events identified were bed-wetting, fecal incontinence, hypertension, suicidal behaviors, psychosis, anxiety, life-threatening respiratory depression, confusion, falls, and compromised mental alertness.[20]

Off-Label Use

The orphan drug designation provided the manufacturer, Orphan Medical, with tax credits for the development costs, and an extended treatment monopoly, but a small patient population. Precautions intended to restrain off-label uses were not effective, in part because of company actions.

In 2007 Jazz Pharmaceuticals (which had purchased Orphan Medical) pleaded guilty to a felony charge for off-label promotion and paid \$20 million to settle a whistleblower complaint later joined by the Justice Department.[27] According to the whistleblower, a sales representative, the company sponsored events to promote off-label use, gave unrestricted medical grants to induce physicians to prescribe the drug for off-label uses, and paid tens of thousands of dollars in speaker fees to doctors to promote the use of sodium oxybate for insomnia and various psychiatric disorders. The company sales manager and one outside psychiatrist also pleaded guilty to criminal misdemeanor charges.

A Profit Center

The legal problems of sodium oxybate did not prevent it from becoming the primary profit center for Jazz Pharmaceuticals, a specialty pharmaceutical company based in Dublin, Ireland, and Palo Alto, CA. Jazz purchased Orphan Medical (and sodium oxybate) for a reported \$122 million in 2005.[28] By 2013 the company reported \$569 million net sales for sodium oxybate, accounting for 65.8% of the company's total

revenue.[29] Boosting sodium oxybate revenue by 50% was a component in the \$1 million bonus awarded to the chief executive officer. The company reported that a dedicated sales force of approximately 100 had increased bottle volume by 12%. Current pharmacy price, the company said, was \$3,000 per bottle of medication; depending on the dose taken, the per-patient revenue could total approximately \$50,000 a year. The orphan drug status that permitted these high costs, however, expired in 2009 and three generic manufacturers applied to market less expensive generic versions. As of 2014, the company has thus far blocked FDA approval of generics through litigation and patent claims for its restricted distribution program.[29] Despite the \$50,000-a-year patient cost, one guide warning about date rape drugs said “GHB can be manufactured with inexpensive ingredients and using recipes on the Internet.”[30]

Postmarket Adverse Events Not Reported

In 2009, Jazz Pharmaceuticals published an optimistic safety overview of sodium oxybate indicating “a very low risk” of abuse/misuse, dependence, accident and suicide risk. The company summarized its safety surveillance database from 2002-2008.[31] In particular, it cited only 21 patient deaths reported since approval. In 2010, it gave a similarly benign portrayal of the adverse event experience to an FDA advisory committee then considering whether to expand the medical use of sodium oxybate to fibromyalgia, a much larger patient population (5 million versus 150,000).[32] The committee voted 20-2 against approval for this indication, and this expanded use was not approved.[33]

However, in 2011 Jazz revealed that it had not been properly reporting most serious adverse drug event deaths to the FDA for many years. For example, its safety overview paper had included only 21 of 103 patient deaths.[34] Further investigation and FDA inspections disclosed a large-scale breakdown that included other types of adverse events[35]. The problem was traced to adverse event reporting procedures at the single central pharmacy that distributed all sodium oxybate bottles and was in monthly communication with patients. The company blamed the pharmacy, but the FDA cited Jazz for lack of adequate written procedures for the events for which it should be informed and noted previous violations in 2007. The result was that for almost a decade, the true adverse event profile of sodium oxybate was not known to the company, the medical community, or the FDA. This QuarterWatch issue provides the first published overview of a fully reported adverse event profile.

Sodium Oxybate Safety Profile

The first safety signal for sodium oxybate is the unexpectedly high total of reported serious adverse events, given the small patient population. In the 12 months ending in 2013 Q3 we identified 1,374 serious adverse events reported in an exposure the company estimated at approximately 9,000 patient-years. This total shows that 15.3% of patients treated for a year suffered a reported serious, disabling or fatal injury. Relatively few drugs (notably anticoagulants and antipsychotic drugs) injure 10% or

Table 3. Selected reported serious adverse events reported for sodium oxybate for 12 months ending Sept. 30, 2013

Adverse event category, source	Cases
Psychiatric disorders (SOC)*	416
Depression (SMQ)	214
Anxiety symptoms (HLT)	117
Hostility - aggression (SMQ)	103
Psychosis (SMQ)	92
Suicide - self injury (SMQ)**	56
Accidents and Injuries (SMQ)*	227
Fall (PT)	129
Head injury (PT)	32
Contusion (PT)	26
Road traffic accident (PT)	21
Effects on alertness	
Dizziness (PT)	59
Loss of consciousness (PT)#	45
Memory impairment (PT)	35
Confusional state (PT)	35
Extrapyramidal Motor System (SMQ)*	112
Dystonia (SMQ)	50
Dyskinesia (SMQ)	17
Parkinson-like (SMQ)	74
Other Categories	
Hypertension (SMQ)	113
Insomnia (PT)	113
Drug abuse-dependence-withdrawal (SMQ)	84
Somnambulism (PT)	30

* Subcategories indicate selected terms. Also, one case could include terms in several categories or subcategories.

** includes suicidal behaviors and ideation

includes syncope

Abbreviations: SMQ = Standardized MedDRA Query. HLT = High Level Term. PT = Preferred Term. SOC = System Organ Class.

more of patients exposed for a year. However, the overall estimate should be interpreted with caution as outlined below.

Effects on the Nervous System

The adverse event profile of sodium oxybate shows a wide spectrum of harmful and disruptive effects on the nervous system. See Table 3, which includes a selection of specific adverse events that illustrate the primary safety concerns. The drug appears to disrupt motor control (depressing respiration, causing bedwetting and fecal incontinence), the extrapyramidal motor system (abnormal movement disorders), normal function of memory and attention (memory impairment, confusional state, loss of consciousness). In addition to these systems, sodium oxybate reports indicate a wide spectrum of adverse effects on mood and behavior, notably anxiety, depression, aggression, psychosis and suicidal behavior. Given that GABA receptors are among the most numerous and widely distributed throughout the CNS, these adverse effects are biologically plausible. Sodium oxybate induces sleep abnormalities, including sleepwalking actions (n = 30) with the potential to result in injury. Another frequent side effect—accidents and injury—are a likely consequence of the capacity of sodium oxybate to impair motor systems, memory and attention, indicating how severe and unexpected its effects were to patients, despite warnings.

Hypertension Cases

Sodium oxybate had another, possibly related effect, reports of hypertension. We identified 113 cases in the hypertension SMQ, more than any other monitored drug in 2013 Q3. The prescribing information warns of salt sensitivity and hypertension and notes the 9 g nightly dose, a sodium salt, would provide 1640 mg of sodium, about 70% of the recommended daily intake of 2300 mg. This certainly is one possibility, but effects of sodium oxybate on the CNS are so broad and disruptive that other mechanisms should be investigated.

Abuse and Dependence

Compared with other adverse effects, case reports suggesting abuse and dependence were less frequent, even though fears about these characteristics led to GHB being classified as a Schedule I controlled substance, except for its approved use in narcolepsy. The restricted distribution program was intended to prevent diversion and abuse. We identified 84 cases in the drug dependence/abuse/withdrawal SMQ of which 15 indicated drug withdrawal. When opioids are available at a fraction of the \$3,000-per-bottle cost, it may be that high cost as much as the restricted distribution program restrains diversion and abuse. However, insomnia, the first listed withdrawal effect, was the second most frequently reported adverse event PT term (n = 113).

Given earlier civil and criminal proceedings about off-label promotion of sodium oxybate, we were concerned that the adverse event reports still indicate off-label use in 19% of reported adverse events. In another 20% of reports, the indication could not be determined. Reports prepared by the company indicated that 811 (59%) appeared to be a labeled indication. Among the 19% of cases with irregular entries or off-label use were fibromyalgia (n = 63), insomnia (n = 74) and unspecified sleep disorder (n = 54).

Reporting Rate Evaluated

Without a control group, it is not possible to distinguish drug effects from those that might be related to the underlying disease. On the other hand, the 15.3% rate of reported serious injury could also be a substantial underestimate because the events count included only patients who volunteered the information to pharmacy technicians when contacted about the monthly refill. Patient education materials showed that program nurses repeatedly telephone all patients on several occasions to discuss doses, therapy programs and safety. However, our safety concerns remain, even assuming that the adverse event data were capturing a large share of all events occurring. In addition, many of these events such as suicidal behavior, psychosis and road traffic accidents, are severe and potentially life changing. Finally, 56% of reports came

from health professionals. These totals also do not include another 9,000 adverse drug event reports that the company collected but classified as not serious.

The Jazz Pharmaceuticals Response

We provided a summary of our preliminary data to Jazz Pharmaceuticals along with a list of questions. In a letter responding, Jazz did not dispute the overall data totals but concluded, “There is not a new safety signal for Xyrem [sodium oxybate].” The company noted that the reports had increased for two reasons. First, the company noted an increase in patient-years on therapy from 6,488 in 2009 to 9,241 in 2013. Second, it said it discovered “the central pharmacy had not reported to Jazz Pharmaceuticals all the events observed between 2002 and 2011 and said the 2012 and 2013 data contained some catch-up reports from previous years. The company also said that psychosis, anxiety and other mood disorders were known to occur at higher rates among narcolepsy patients.

Conclusions

The updated safety profile of sodium oxybate—12 years after approval—raises the question of whether its benefits outweigh its risks, especially at the 9 g/day dose. The postmarket surveillance reporting on thousands of patients reveals a spectrum of risks not seen clearly in more limited premarket testing. The overall impression is that the effects of this drug are consistent with a large overdose of CNS depressants such as benzodiazepines or alcohol. Onset of sedation is so rapid that patients are advised to drink the solution only while at or near the bed. In addition, its rapid disappearance from the body makes it unsuitable as a sedative. It was unusual to discover a treatment for a sleep disorder that requires each patient to set an alarm to wake up after 2.5 to 4 hours to take a second dose. We recommend the FDA conduct a thorough re-evaluation of the risks and benefits of sodium oxybate. Randomized clinical trials have never been conducted to compare or measure the benefits of alternative treatments for narcolepsy, including antidepressants and optimal use of stimulants.

In addition, physicians who are considering prescribing sodium oxybate for on-label or off-label use will receive a misleading impression of the safety of sodium oxybate from the published scientific literature. Although Jazz Pharmaceuticals published a correction to its 2009 adverse event assessment, the paper was not retracted, and patient deaths were the only outcome updated in the 2011 correction.

Update on Fingolimod (GILENYA)

When fingolimod (GILENYA) was approved in 2010 it met almost any reasonable definition of an innovative new drug. It had an entirely new mechanism of action in the immune system, acting on a ubiquitous but poorly understood family of receptors, sphingosine 1-phosphate (S1P). Its effect on many of these receptors was also unusual because first it activated the cellular process, but over time caused these receptors to be down-regulated, thus blocking cellular activation.[36] The most readily characterized immunological effect was to bind to activated lymphocytes, and thus obstruct their exit from the lymph nodes, causing white blood cell counts to plunge. But S1P receptors could also be found in the heart, blood vessels, eyes and elsewhere. Fingolimod was also innovative in clinical terms when it became the first oral MS drug with a claim to be modifying the disease process. As another indicator of its innovative properties, the FDA granted a more rapid priority review, a designation reserved for drugs potentially offering a significant improvement in treatment of a serious disease.

However, the preapproval testing of fingolimod also revealed a lengthy catalog of potentially serious safety concerns that could not be fully characterized before thousands more patients were exposed to this new drug. We reported on these risks in 2012.[37] This update examines those risks and what has been subsequently learned from adverse drug events and other relevant scientific sources.

Risks in Pregnancy

Fingolimod failed its animal teratogenicity tests prior to approval.[33] In rats, fetal vascular malformations were seen at less than the human dose and linked to S1P receptors active in vascular formation in the embryo. In rabbits fetal mortality and growth retardation were observed, but at much higher than recommended human doses. In preclinical testing abnormal babies were born to women taking fingolimod. Nevertheless, fingolimod was approved as Pregnancy Category C (negative effects in animal studies but use in pregnant women may be justified). As part of the evolving policy of testing drugs after approval, the FDA mandated a pregnancy registry. In February 2014 Novartis, the manufacturer, published updated information from its completed and ongoing clinical studies, indicating fetal abnormalities in 5/66 (7.6%) exposures.[38] Three cases indicated vascular malformations, one was a spontaneous uterine death, and one was failure of fetal development. We disagree with Novartis' conclusion that these data "do not permit firm conclusions to be drawn about the fetal safety of fingolimod." In the 12 months of adverse event data reviewed for this issue, we identified 3 reported additional cases in postmarket surveillance with an outcome of birth defect.

Cardiac Rhythm Risks

Severe and fatal cardiac rhythm disturbances were observed during preapproval testing of fingolimod, primarily bradycardia and heart block occurring soon after initiating treatment.[39] Several fatalities in testing occurred at higher than the currently approved dose. In response to this risk fingolimod was approved with a recommendation that the first dose be administered with monitoring and observation for the first 6 hours. In the QuarterWatch adverse event data, cardiac arrhythmias were the largest subcategory of reported serious adverse drug events. We identified 473 cases in the cardiac arrhythmia SMQ, including 13 patient deaths, 11 cases classified as life threatening and 141 resulting in hospitalization. While "decreased heart rate" was the most common manifestation reported (n = 175) other cases indicated loss of consciousness or syncope (n = 58) and various heart blocks (n = 62). One case could have report terms in multiple categories. Adverse event data show that cardiac adverse events proved to be a major hazard of this drug in clinical practice.

Risk of Infection

Given that fingolimod obstructs the egress of activated lymphocytes from the lymph nodes with both known and unknown effects on the immune response, viral infection was a significant post-approval concern requiring further investigation. We identified 172 cases in the viral infection High Level Group Term (HLGT) category, including 4 reported deaths. The largest group of reported cases were herpes viral infections, both simplex and zoster, but it also included 36 cases of influenza, which would be difficult to attribute to a drug treatment. One concern during preapproval assessment was that fingolimod might share the risk of even more feared and severe opportunistic viral infections such as progressive multifocal leukoencephalopathy (PML), an often-fatal brain infection. PML cases led to withdrawal of natalizumab (TYSABRI) from the market and its later reinstatement as a restricted drug for second-line use in MS. Because the first case of PML associated with fingolimod occurred in Europe, we asked Novartis for an analysis of PML risk. The company told us that it currently had identified 11 total cases of PML in fingolimod patients, but said 10 had previously been treated with natalizumab.

Adverse Effects on the Eye

Preclinical testing of fingolimod established an increased risk of macular edema and reported a risk of 0.5%. This resulted in a recommendation that patients receive an eye exam before treatment and after 3-4 months on the drug.[40] In the adverse event data we identified a large group (n = 348) of cases indicating adverse effects on the eye, generally, and 79 cases indicating macular or retinal edema. The remaining adverse events were less specific or did not indicate a causal mechanism, such as visual impairment (n = 102), vision blurred (n = 84) and blindness (n = 22). Novartis told us that it believed that many of the vague or less specific reports of visual disturbances should be attributed to underlying disease, especially because

optic neuritis and blurred vision are often the first symptoms of MS. In addition, the company said that because of the recommendation for an eye exam, both physicians and patients would be more aware of vision issues and therefore more likely to report such symptoms. However, many of the eye problem cases could also have been poorly described episodes of macular edema.

Additional Risks

Because of the immunosuppressive effects of fingolimod, FDA reviewers expressed concern about increased cancer risk, a problem seen with other kinds of immunosuppressant products such as anti-TNF agents. Although adverse drug event reporting has limitations in detecting cancer risk, we detected no signal for fingolimod in these data. In addition, preapproval testing of fingolimod also disclosed impairment of lung function as revealed in specific tests. We identified 107 cases of dyspnea and 62 cases of chest discomfort among 261 cases classified as respiratory disorders in the 12-month data. Early concerns about liver toxicity were also confirmed in postmarket data, with 104 cases in the hepatic disorder SMQ, including 23 rated as severe.

Overall Report Totals

Our update of fingolimod was also triggered by a different kind of safety signal—an unexpectedly large overall total of serious adverse event reports in a patient population of approximately 15,300. For the year ending 2013 Q3 we estimate that serious injuries (n = 2,716) were reported at a rate of approximately 17% per patient-year of exposure, based on prescription data from IMS Health and an estimate of 15,300 patient-years of exposure. Even if patient and physician contact were so extensive that these data captured 100% of adverse events, this would still amount to a substantial safety concern. As with sodium oxybate, this high rate should be interpreted with caution, since on one hand some cases could be attributed to the underlying disease, while others could occur but were not reported. Novartis disagrees with our estimate of patient exposure. Using its estimate of 23,000 patient-years of exposure, the rate of serious injury reports would be reduced to 12% per patient-year of exposure.

Is the Dose Too High?

Prior to approval, the FDA advisory committee reviewing fingolimod voted unanimously that the drug should be studied at a lower dose to see if safety could be improved without loss of efficacy. The logic was compelling because clinical trials at three doses higher than the approved 0.5 mg daily had to be halted for safety, and the drug had never been studied at dose below 0.5 mg. Despite not knowing the optimum dose, the FDA approved fingolimod on the condition that a lower dose be studied. The Phase IV study of a lower dose is now under way and scheduled for completion in 2016, one year after the date specified at the time of approval.

Conclusion

The new adverse event data underline the importance of observing two critical precautions when initiating fingolimod treatment: First dose monitoring to observe all patients for abnormal heart rhythms, and conducting initial and follow-up eye exams at treatment initiation and at 3-4 months to detect macular edema. The large number of overall serious injury reports given a small patient population emphasizes that this is a high-risk treatment. Whether safety can be enhanced with a lower dose will remain unknown for several more years.

Adverse Event Reporting System

As described in the executive summary, a growing number of high-cost drugs for small patient populations create an environment of extensive direct patient contact that was not common when the current system was devised. But this level of extensive patient contact also creates an opportunity for much-

improved postmarket surveillance not possible with more conventional brand name drugs marketed to large patient populations.

The FDA needs to set a higher priority on updating its decades-old adverse event reporting system, including the global standards, regulations, and more detailed guidances. Adverse event basic guidance dates to the 1960s, and the most recent revision is 13 years old. The international standard dates from the early 1990s. While the FDA has invested millions in its Sentinel System based on insurance claims and electronic health information, it has yet to produce notable new warning information.

Methods Summary

QuarterWatch monitors the safety of prescription drugs through analysis of adverse drug events reported to the FDA by consumers and health professionals, either directly to the agency or through drug manufacturers. The agency releases computer excerpts for research use on a quarterly basis, and these case reports are our primary data source.[41] A full description of our methodology is available on the QuarterWatch pages of the ISMP web site (<http://www.ismp.org/QuarterWatch/detailedMethods.aspx>).

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

To provide a broader perspective on the adverse events reported, we assess the patient exposure to drugs on the basis of dispensed outpatient prescription data provided by IMS Health Inc. The data we rely on are an estimate of total non-governmental prescriptions dispensed through retail and mail channels. Our agreement with IMS includes the following disclaimer:

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In these data, the adverse events that occur are described by medical terms selected from the Medical Dictionary for Regulatory Activities (MedDRA), a terminology developed by the pharmaceutical industry to describe adverse events in clinical studies and postmarketing reports.[42] 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.[43] We also group adverse event terms using a MedDRA category called High Level Terms (HLTs) that also combine several related but more specific medical terms. High Level Group Terms (HLGTs) combine several related HLTs, and System Organ Classes combine the terms into 26 categories. The QuarterWatch database was updated in November 2013 to MedDRA version 16.1.

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

Events in QuarterWatch are attributed to the product identified as the primary suspect drug in the case report. The drug names are standardized to drug ingredient names base on the National Library of Medicine’s RxNorm terminology.[44] When cited in the text, tables or charts, the brand name used for a drug is the one most frequently indicated on the case reports. Unless specified, QuarterWatch does not distinguish dose, route of administration, or extended release and other preparations.

We measured exposure to therapeutic drugs in patient-years, based on dispensed outpatient prescriptions from IMS Health. In any quarter or year, the number of patients exposed to a therapeutic drug

for any portion of the period is higher than patient-years, because of medication starts and stops. The patient-year calculation estimates the total exposure as if all patients were exposed through the entire period.

QuarterWatch Team and Funding Sources

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Thomas J. Moore serves as a part-time project director for QuarterWatch. He has developed and maintains the master adverse event database that serves as the data source for the publication and conducts the primary analysis for each issue. Mr. Moore receives an honorarium from ISMP, with the remaining work being on a volunteer basis. He is also a lecturer in the Department of Epidemiology and Biostatistics in The Milken Institute of Public Health at The George Washington University. Mr. Moore also publishes other research works as a consultant doing business under the name Drug Safety Research. He was a consulting expert to the Attorney General of the State of Texas in a Medicaid fraud lawsuit against Johnson & Johnson regarding the antipsychotic drug Risperdal (risperidone), and was an expert witness for the United States Army in connection with a criminal case involving Chantix (varenicline). He also worked as a consulting expert for plaintiffs in the civil litigation regarding Chantix. In 2013 he was a consulting expert for the plaintiffs in the Celexa and Lexapro Marketing and Sales Practices Litigation. He has also conducted confidential assessments for attorneys inquiring about the safety profiles of bisphosphonates, antipsychotic drugs, and proton pump inhibitors.

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