

QuarterWatch

Monitoring FDA MedWatch Reports

Signals for Dabigatran and Metoclopramide

January 12, 2012

Data from 2011 Quarter 1

Executive Summary

This issue examines a strong signal for serious bleeding with the new anticoagulant drug dabigatran (PRADAXA) and investigates reports of brain damage associated with metoclopramide (REGLAN), a drug for reflux and other gastrointestinal disorders. In addition, we review the quarterly data for the five most widely prescribed drugs in the United States, revealing results that reflect upon the safety of the most popular and essential drugs as well as providing a perspective on how the monitoring system works.

In the first quarter of 2011, the U.S. Food and Drug Administration (FDA) received 40,151 domestic reports of serious, disabling or fatal injury associated with drug therapy. The total represented a 3% increase over the previous calendar quarter, and a 19.5% increase over the first quarter of 2010. The typical drug we monitor accounted for a median of six reports in a quarter. At the other extreme, 10 drugs each accounted for 500 or more case reports of serious injury in the quarter. Meanwhile, the number of dispensed outpatient prescriptions in the first quarter totaled 938 million, a 1% increase from the previous quarter and a 3% increase from the same quarter of 2010, according to the IMS Health National Prescription Audit™ for 2011.

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 reports) are a cornerstone of the nation's system for monitoring the safety of prescription drugs after FDA marketing approval.

Findings for Specific Drugs

Dabigatran (PRADAXA) and Serious Bleeding in the Elderly

Dabigatran (PRADAXA), a new drug approved to reduce the risk of stroke by inhibiting blood coagulation, generated a strong signal illustrating the substantial bleeding risks of this treatment, with more than 500 reports of fatal, disabling and other severe hemorrhages. Dabigatran is moving rapidly into medical use as an easier-to-use replacement for warfarin

(COUMADIN), first approved in 1954. But with a one-size-fits-all dosing regimen, and without tools to individualize blood levels, and absent a readily available antidote like vitamin K for warfarin overdoses, we saw evidence suggesting that some of the oldest patients may experience severe bleeds, resulting in harm rather than benefit. Underlying causal factors may be overdose, interactions, or altered renal clearance. The manufacturer, Boehringer Ingelheim, noted that the prescribing information warned about the risks of serious bleeding and said it was working with the FDA to provide better guidance to physicians about treating the oldest patients.

Metoclopramide (REGLAN) and Brain Damage

Many would not suspect that a generic drug for acid reflux and digestive complications of diabetes could result in often incurable and disfiguring abnormal movements of the lips, tongue and even entire limbs, a condition called dyskinesia. Despite these risks the drug, metoclopramide (REGLAN), is in widespread use with nearly 1 million dispensed prescriptions in the first quarter. In the same quarter, we identified 63 new cases of reported dyskinesia, along with an additional 1,180 reported cases that originated from lawsuits and are not included in our regular event counts. The abnormal movements reported included drooling, grimacing, tongue protrusion and muscle twitching. In 2009 the FDA required its strongest warnings for both doctors and patients about this risk. While the FDA warnings apparently contributed to a modest decline in prescription volume, a more thorough evaluation is now needed of the drug's place, if any, in clinical practice.

Drug Safety Perspective

The Five Most Widely Dispensed Prescription Drugs

We used data from IMS Health's National Prescription Audit and QuarterWatch to ask two questions: What are the most widely used prescription drugs? What does one quarter of case reports reveal about their risks? The basic results are shown in Table 1.

Table 1. Reported Serious ADEs for the most widely dispensed prescription drugs					
Drug	Medical Use	Millions of RX*	Serious ADEs**	Median Age	Major Adverse Effect
ACETAMINOPHEN-HYDROCODONE	Pain	32.4	390	43	Overdose/Suicide
LEVOTHYROXINE	Hormone replacement	23.8	69	52	Overdose/Suicide
SIMVASTATIN	Lipid-lowering	22.4	132	63	Muscle Damage
LISINOPRIL	Hypertension	20	168	60	Hypersensitivity
AZITHROMYCIN	Antibiotic	18.2	18	51	Severe Cutaneous
Total		116.8	777		

* IMS Health National Prescription Audit. TM ** ADE = Adverse Drug Events.

We noted a large volume of prescriptions for just five drugs—more than 115 million prescriptions for medicationsⁱ dispensed during one calendar quarter in a nation with a total population of 311 million. All of the most widely used medications were generic drugs available for many years, with the newest, simvastatin (ZOCOR), approved in 1991. Two drugs address two of the most widespread of all medical disorders—pain and infection. Two are for prevention of cardiovascular events, and one treats low thyroid hormone levels.

The adverse drug events (ADEs) identified in the reports for these older drugs generally appeared to be genuine and relatively well-known risks. The acetaminophen-hydrocodone (VICODIN) combination poses three substantial overdose risks: liver toxicity from an overdose of acetaminophen, tolerance leading to increasing doses, and respiratory depression from an overdose of the mild opioid. Simvastatin shares with chemically similar lipid-lowering drugs the risk of damaging muscle tissue, sometimes with life-threatening risks. The ACE-inhibitor lisinopril (PRINIVIL) causes angioedema, or swelling, and a distinctive cough. However, the overdose reports for levothyroxine indicated a reporting problem rather than a drug risk. We discuss these and other issues in the full report.

Adverse Event Reporting System Issues

New Study Underlines System Importance

The essential role of adverse event reporting in drug safety is made clear in a new study published January 9, 2012, in the *Archives of Internal Medicine*. [1] The study of major FDA safety actions in 2009 showed that adverse drug event reports were the predominant source of scientific information used to support 57% of major safety changes overall, and 76% of new Boxed Warnings, the sternest warning for doctors that the FDA can require. (Note: two members of the QuarterWatch project team were coauthors of the report.)

The documentation of the central role of adverse event reporting in drug safety underlines the need for the FDA to assign a higher priority to improving the performance of this system. The FDA has not addressed several important issues raised in QuarterWatch, notably weak, outdated, and inconsistent regulatory guidance for industry; poor quality reporting of patient deaths by drug manufacturers; and low participation by medical professionals in direct reports to the FDA.

ⁱ Dispensed prescriptions don't readily convert to an estimated number of patients because a patient could have had one or more refills in a quarter.

About QuarterWatch Data

Our findings should be interpreted in light of the known limitations of a voluntary reporting system. The FDA's Adverse Event Reporting System (AERS) data combine reports originated by drug manufacturers with cases submitted directly by consumers and health professionals through the agency's MedWatch program. The submission of an individual report does not in itself establish that the suspect drug caused the event described—only that an observer suspected a relationship. However, given numerous reports with credible detail, adverse event data may have important scientific weight in a broader assessment of causality. A majority of new warnings, restrictions or other major 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 disclosure statement at the end of this report expands our description of this project and its staff.

Conclusions

The FDA and the manufacturer should reassess the one-dose-fits-all recommendation for dabigatran, especially for older patients with increased risk of serious bleeding, the most dangerous effect of this drug. In addition, tests of blood levels and kidney functions may be needed at least in the highest risk and most vulnerable patients. In the full report we note evidence that inhibiting formation of blood clots with drugs results in more emergency hospitalizations in the elderly than any other kind of drug therapy. Review of this drug's adverse effects in high risk patients deserves to be a national priority.

On one hand, the FDA should be commended for its 2009 action to require strong warnings that metoclopramide—first approved in 1980—can cause tardive dyskinesia with prolonged use. Nevertheless, the continued widespread medical use of this drug when safer alternatives are available shows that additional restrictions are needed. Among the actions that warrant consideration are outright withdrawal from the market, revoking the drug's first line indications, or a restricted-use program to discourage prolonged use.

Our study of the FDA's major safety decisions in 2009, just published in the *Archives of Internal Medicine*, underlines the fact that after decades of use without major change, the adverse event reporting system remains central to postmarketing safety surveillance. This aging system suffers from management neglect, ambiguous and fragmented guidelines and regulation, and

requirements that dilute the quality of the reporting. The FDA needs to assign a higher priority to improving the performance of this key safety system.

QuarterWatch Project Team

Thomas J. Moore, Senior Scientist, Drug Safety and Policy, ISMP

Michael R. Cohen, RPh, MS, President, ISMP

Curt D. Furberg, MD, PhD, Professor of Public Health Sciences, Wake Forest University School of Medicine.

Media Inquiries

Renee Brehio

ISMP Public Affairs

rbrehio@ismp.org

704-831-8822

Correspondence and Scientific Inquiries

Thomas J. Moore

QuarterWatch Project Director

Institute for Safe Medication Practices

101 N. Columbus Street, Suite 410

Alexandria, VA 22314

tmoore@ismp.org

Contents

Methods Summary	6
Results	8
Dabigatran (Pradaxa)	9
Metoclopramide (Reglan)	12
The Five Mega-Drugs	14
QuarterWatch Team & Funding	17
References	18

Methods

QuarterWatch seeks to improve patient safety through regular monitoring and analysis of serious adverse drug events reported to the FDA. The agency releases computer excerpts for research use on a quarterly basis, and these case reports are our primary data source. [2]

Our reports examine domestic adverse drug events that are specifically coded as “serious,” which means under FDA regulation 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. [3] We exclude reports from foreign sources, cases from clinical studies which have different reporting requirements, and events in which the injuries were not coded as serious. We standardize drug names to an ingredient name based on the National Library of Medicine RxNorm project [4] and do not distinguish between different routes of administration or dosage forms.

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 and in some cases may summarize longer periods of time. When case reports are revised or updated we use the most recent version while retaining the original report date.

In these data, the adverse events that occur are described by 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 postmarketing reports. [5] 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. [6] 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. The QuarterWatch database was updated in November 2011 to MedDRA version 14.1.

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 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 2011 (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 category of drugs with special reporting requirements, restricted distribution or active surveillance programs that either result in a much higher reporting rate or capture adverse events in which drug involvement is not necessarily suspected. These special category drugs are included in the total number of reports but are otherwise excluded from comparisons and rankings. In this report the term “regularly monitored drugs” means those remaining after the special reporting drugs have been excluded.

Reported totals for any calendar quarter, specific drug, or adverse event may change over time because thousands of reports are revised, entered into the FDA system late, or are subject to changes in the QuarterWatch or FDA coding or report criteria. To compensate, all historical comparisons and trends over time are recalculated every quarter and may differ from previously reported totals. 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 further investigation.

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/>). A full technical description of our methodology can be found on the QuarterWatch web pages (<http://www.ismp.org/quarterwatch/detailedmethods.aspx>).

RESULTS

In the first quarter of 2011, longer term trends continued. The totals for reported deaths and serious injuries continued to increase at substantial rates. The 40,151 cases received in the first quarter were 19.5% higher than the 33,602 cases reported in the same quarter of 2011. Compared with the immediately preceding quarter, the total was 1,181 cases higher, or a gain of 3%. The biggest source of the increase was a larger number of reports from consumers submitted through drug manufacturers.

Table 2. Cases received in 2011 Quarter 1		
Category	Cases (%)	
Quarter total	40151	
Event Outcome*		
Death	9721	24.2%
Disability	993	2.5%
Birth defect	268	0.7%
Life threatening	1264	3.1%
Required intervention	596	1.5%
Hospitalization	13580	33.8%
Other serious	12666	31.5%
Not stated	1063	2.6%
How Created		
Written by manufacturers	34768	86.6%
Direct to FDA	5383	13.4%
Occupation of observer**		
Consumer	16765	45.6%
Physician	9963	27.1%
Pharmacist	2873	7.8%
Other health professional	7184	19.5%

*More than one outcome allowed

** Excludes missing data

the FDA in the first quarter. The biggest group of excluded cases were from foreign countries (n = 55,100), followed by adverse drug events that were not coded as serious (n = 53,853). As Table 2 indicates, the cases that meet the FDA standard for a “serious” adverse event involve substantial human harm.

The U.S. adverse event reporting system can be seen as a combination of two different reporting systems. First, the FDA accepts adverse drug event reports directly from consumers and health professionals through mail, fax, an 800 number and an online form (<http://www.fda.gov/Safety/MedWatch/default.htm>). As seen in Table 2, this well-known MedWatch program accounts for relatively few reports—5,383 cases in the first quarter, or 13.4% of the total. The table also shows that the adverse event system receives reports primarily from the pharmaceutical industry, which identified, collected, coded, and submitted 86.6% of the new cases in the first quarter. Drug companies may learn of adverse events through many pathways: its sales force contacts with physicians, telephone complaints, the medical literature, product web sites, consumer hotlines, the news media, and various kinds of marketing programs that include direct patient contact.

The QuarterWatch totals captured only 22% of all adverse event reports that reached

Serious Bleeding With Dabigatran (PRADAXA)

Dabigatran (PRADAXA) is a new entrant into one of the most dangerous of all outpatient drug treatments: anticoagulant drugs that inhibit the cascade of chemical reactions that form blood clots to stop bleeding. Approved to reduce the risk of stroke in patients with atrial fibrillation, dabigatran accounted for 505 reported cases of severe bleeding resulting in death, disability, hospitalization or other serious outcome in the first quarter—more than any other drug we regularly monitor. The hemorrhage cases were occurring in the oldest patients with a median age of 80, and 25% of patients experiencing hemorrhage were 84 years or older, raising the question of whether the oldest patients are getting too high a dose.

One of the most challenging problems in drug therapy begins when, in mostly older patients, the two atria or upper pumping chambers of the heart fail to contract rhythmically, and instead flutter, or fail to contract entirely, a condition called atrial fibrillation. Because the atria are primer pumps for the two large ventricles, atrial fibrillation normally causes only a modest reduction in cardiac output. But in the dead zone of the malfunctioning atria, blood clots may form and then travel to the lungs or brain, where irreversible and potentially life-threatening damage may occur.

For decades, the medical response to this hazard has been to prescribe a generic drug and form of rat poison called warfarin (COUMADIN). [7] The drug blocks the formation of the tiny fibrin threads that help hold together the platelets that collect to form a blood clot. While shown to reduce the risk of strokes caused by blood clots, warfarin triggers serious bleeding at rates so high that it ranks among the greatest risks of outpatient drug therapy. A recent study of emergency hospital admissions for adverse drug reactions for all drugs in patients 65 years of age or older showed that warfarin alone accounted for a startling 33.3% of all such cases, while an antiplatelet agent, clopidogrel (PLAVIX), accounted for another 13.3%. [8] In this study, these two drugs which inhibit the body's capacity to form blood clots accounted for 46.6% of all medical emergencies attributed to drug side effects that required hospital admission. Clearly, the benefits of preventing a stroke or pulmonary embolism have to be carefully balanced against the risk of hemorrhage. Warfarin has two additional limitations. It requires blood tests every 1 to 4 weeks to establish the optimal level of anticoagulation, and it interacts with scores of other drugs, including drugs frequently used in heart patients. [7] However, warfarin also has an important benefit; if an overdose occurs, an antidote (vitamin K) is readily available and highly effective.

In October 2010 the FDA approved dabigatran, the first new treatment alternative to warfarin in 57 years. [9] Pre-approval testing showed that dabigatran had approximately the same risks and benefits as warfarin, technically called “non-inferiority.” Furthermore, bleeding with dabigatran remained a frequent and serious risk. In the major clinical trial comparing the

drug to warfarin, 32.5% of dabigatran patients experienced bleeding over the 2-year trial period, and 6.2% experienced major or life-threatening bleeds. [10] The rates were similar for warfarin, with dabigatran appearing safer in some bleeding categories and higher risk in others.

But dabigatran had fewer drug interactions than warfarin, and the frequent laboratory tests needed to manage warfarin blood levels were not recommended. In fact, the familiar test for warfarin, International Normalized Ratio (INR), did not provide an accurate measure of how much inhibition of normal blood coagulation had been achieved in each individual dabigatran patient.[9] The idea of an easier-to-use anticoagulant apparently appealed to physicians, and the German manufacturer, Boehringer Ingelheim, had an effective launch. By the end of the first quarter of 2011, IMS Health data showed 272,119 dispensed outpatient prescriptions. But reports of serious adverse drug events also surged.

In the first quarter of 2011 dabigatran produced two different kinds of signals of major drug risk: a large volume of total serious reports, and large numbers of reports for a specific adverse event, hemorrhage. Overall we identified 932 serious adverse drug events of all types in which dabigatran was the primary suspect drug, including 120 patient deaths, 25 cases of permanent disability, and 543 cases requiring hospitalization. For the quarter, this was a higher total than for any drug we monitor with one exception.ⁱ In the Standardized MedDRA Query (SMQ) for Hemorrhage, dabigatran accounted for 505 cases, more than any other drug. (Warfarin ranked second with 176 cases.)

The 932 overall dabigatran cases in the first quarter included 293 cases that were also classified in the narrower gastrointestinal hemorrhage SMQ, more than any other regularly monitored drug. An additional 120 cases contained event terms in the Hemorrhagic stroke SMQ.ⁱⁱ The strokes are of particular concern because if treatment intended to prevent ischemic strokes then causes hemorrhagic strokes the risk/benefit balance is called into fundamental question. In 65 hemorrhage cases overall, the patients died. These data apparently were also noticed by the FDA which announced in early December 2011 that a safety review of adverse event reports of serious bleeding was being conducted. [11] In the MedDRA terminology, one case may be classified in several different SMQ categories.

Patient age was the most notable feature of the hemorrhage cases. The median age was 80 years (compared to a median age of 56 for all other drugs). In one quarter of the bleeding cases

ⁱ It was surpassed by treprostinil (REMODULIN), a drug for pulmonary arterial hypertension, a rare and frequently fatal lung disorder.

ⁱⁱ In the MedDRA system the gastrointestinal stroke and hemorrhagic stroke categories are not exact subsets of the larger hemorrhage SMQ, but the overall category captured most cases.

the patients were 84 years old or older. This safety profile raises the question of whether the oldest patients are being overdosed with dabigatran with potentially fatal consequences.

Unlike warfarin, which is adjusted for individual patient blood levels on an ongoing basis, dabigatran was approved in a “one size fits all” dose of 150 mg twice a day. The FDA explicitly rejected a lower dose of 110 mg, which had been sought by the company. [12] However, the lower dose was approved and is available in Canada, Japan, and European countries. This means that not only is this lower dose unavailable, patients are not routinely monitored to see if they are getting too much drug.

Declining or impaired kidney function—which also occurs in older patients—is a second and potentially related safety issue associated with possible overdose and bleeding. In pharmacologic studies of dabigatran, patients with mild kidney impairment had dabigatran blood levels that were 50% higher than patients with normal kidney function, and moderately impaired kidney function could result in blood levels that were three times higher. Nevertheless, the prescribing information does not recommend a dosage adjustment except in cases of severe renal impairment and does not recommend regular testing of renal function.

We discussed our findings and concerns with Boehringer Ingelheim, the manufacturer of dabigatran. The company said it had also observed the large volume of serious adverse event reports for its new drug, but noted that bleeding was a known risk of anticoagulant drugs, and substantial warnings were in place. The company attributed the report volume in part to the rapid acceptance of the drug into the market and an active sales force with extensive contact with physicians, resulting in more frequent reports. The company said it was working with the FDA to provide better guidance to physicians about treating older patients, especially those with impaired kidney function, even transient episodes such as those occurring after use of contrast media for diagnostic testing. The company declined to comment on whether it was again seeking FDA approval for the lower 110 mg dose approved in many other countries.

We believe the strong signal for dabigatran leads to the following conclusions. First, the surge in bleeding reports for this new drug underscore the problem that inhibiting blood coagulation in older patients with a renally-cleared drug without a readily available antidote is a risky business, requiring the highest level of medical vigilance. An FDA analysis showed that with dabigatran treatment, life-threatening bleeds (a drug adverse effect) occurred at a higher rate than strokes or systemic embolism (1.5% per year versus 1.1% a year), suggesting a razor thin margin between benefit and risk. [13] While further study is needed, we see indications that the “one size fits all” dosing regime may be resulting in overdoses in some patients, leading to serious and fatal hemorrhages. A drug that is easier to use because it doesn’t require weekly or monthly laboratory tests to individualize doses may be appealing to physicians and patients but less safe for some. Finally, we believe the FDA and the manufacturer should revisit

recommended dosing in older individuals or in those with renal insufficiency, as well as whether the most vulnerable patients require blood level tests to determine optimal dosage.

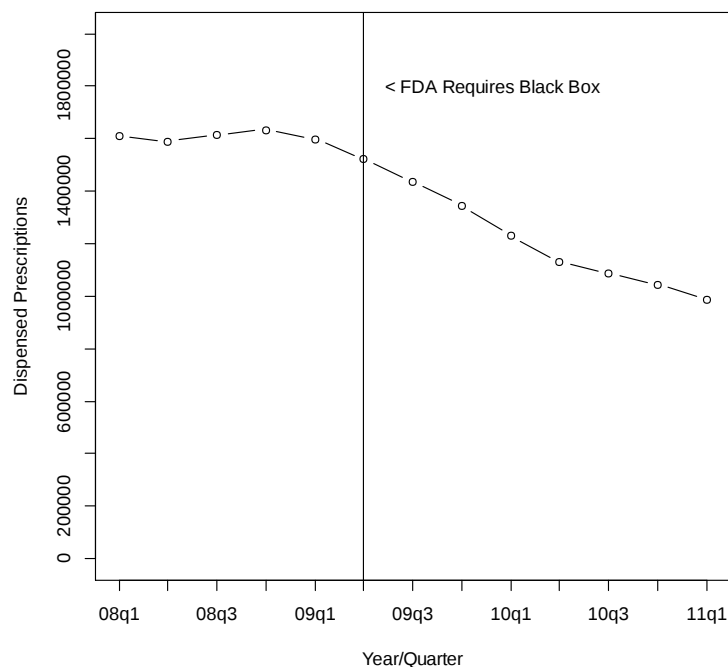
Brain Damage Caused by Metoclopramide (REGLAN)

A drug for nausea and gastroesophageal reflux that can cause irreversible brain damage challenges the core concept that a drug's benefits must outweigh its risks. Metoclopramide (REGLAN) is a widely prescribed generic drug available in tablets and by injection for nausea, gastric reflux, and for stomach disorders related to nerve damage in patients with diabetes (called gastroparesis). [14][15] Its most troubling side effects are abnormal, often disfiguring movement disorders called dyskinesias. The movements may involve protruding tongue, lip smacking, eye rolling, and even repetitive movements of entire limbs. In time, the movements may become untreatable and irreversible, a condition called tardive dyskinesia. In the first quarter of 2011 we observed 63 cases of dyskinesia (or abnormal movements) meeting the standing QuarterWatch criteria, and identified an additional 1,180 dyskinesia cases arising from lawsuits against the drug manufacturers for events that likely occurred over a longer period of time.

The possibility that metoclopramide could damage the brain is evident from its mechanism of action. While intended to improve emptying of the stomach, the drug targets dopamine receptors in the brain. Dopamine, in turn, is central to control of muscle movement, mood, behavior, sexual development, and weight regulation. In addition to blocking D₂ dopamine receptors, metoclopramide also blocks serotonin receptors, which are also involved in mood as well as the regulation of the digestive system. Its mechanism of action is similar to that of the most powerful drugs for psychosis and schizophrenia. And it shares the same risks. Over a year's treatment, antipsychotic drugs are believed to cause irreversible brain damage in 5% to 10% of those treated. [16] [17] Data are less clear for metoclopramide, but there are published estimates of 1% to 10%, depending on the length of exposure. [18]

It can be argued that risk of brain damage has to be accepted to treat the most severe mental disorders such as schizophrenia when other drugs are not effective. However, it is not clear why nearly 1 million prescriptions were dispensed in the first quarter of 2011 for metoclopramide, a drug with related risks of brain damage but used for nausea, reflux or gastroparesis. Worse yet, patients have been exposed to this drug risk since its approval 1980.

Figure 1. Dispensed Prescriptions for Metoclopramide



Years later, this problem drew the attention of the FDA. The FDA's Office of Surveillance and Epidemiology had conducted a study in a health insurance database in 2007 and discovered that doctors were frequently disregarding the principal safety measure for this drug—limiting the use of the drug to 12 weeks or less. [19] The FDA study showed 20% of the prescriptions were for longer periods. Two years later, the agency acted, escalating the warning for tardive dyskinesia to a prominent, bluntly worded Boxed Warning at the beginning of the prescribing information. [20] The FDA also required that a plain-

language Medication Guide be given to patients warning of the dangers of prolonged use. As Figure 1 shows, the FDA warning may have contributed to a slow decline in dispensed prescriptions. Nevertheless the volume of dispensed prescriptions for the tablet product is more than 986,000 per quarter and within the top 200 most frequently prescribed prescription drugs, according to IMS Health data. These totals do not include the injected version of metoclopramide.

The problem has not gone away. In the first quarter of 2011, we identified 77 serious adverse drug events for metoclopramide, including 18 patient deaths—a higher toll than for 88% of the drugs we regularly monitor. Among these cases, 63 contained terms indicating dyskinesia. We also identified an additional 1,208 case reports that indicated they originated from lawsuits and are not included in the regular QuarterWatch totals. These cases included 180 patient deaths and 1,180 cases indicating dyskinesia. Notable was that 566/1,208 (47%) of the cases indicated “Incorrect drug administration duration.” It is likely that the lawsuit cases came from events that originated over a longer period of time than a calendar quarter.

Safer alternatives exist for all but one of the FDA approved indications for metoclopramide. For gastrointestinal reflux, there are numerous proton pump inhibitors and H₂ antagonists available. Metoclopramide is also approved for the treatment of gastroparesis, a condition in which the nerves that control muscles in the stomach are impaired and the stomach

does not empty normally. Apparently, metoclopramide is the only drug approved for this condition. However, a recent review of this drug noted that the studies of this effect were small, short term, and showed only modest benefit. [18] No benefit was recorded after one month. Given that gastroparesis is a chronic or long-term disorder, such meager, short-term benefits do not appear to justify the risk.

We believe substantial additional action should be taken to reduce brain damage caused by this widely used drug. The first step is a more systematic assessment of its risks, benefits and alternatives given current therapeutic choices. Possible steps to be considered include outright safety withdrawal, highly restricted availability limited to a few weeks, and repeal of all its first-line indications. Its use in injectable form for nausea from surgery and chemotherapy should also be reassessed, given the presence of numerous safer alternatives.

Drug Safety Perspective

The Five Most Widely Dispensed Prescription Drugs

QuarterWatch usually focuses on drugs that account for unexpectedly large numbers of serious adverse drug event reports, either for a specific drug, or for particular adverse reactions. Sometimes the suspect drug is regularly used by millions of patients—for example, levofloxacin (LEVAQUIN) and reports of tendon rupture.[21] However, hundreds of adverse event reports may be generated in one quarter by drugs with small patient populations—for example, our report on dalfampridine (AMPYRA), a drug for multiple sclerosis that was used by approximately 50,000 patients. For this analysis, however, the starting point is the mega-drugs, the five most widely dispensed outpatient drugs, as shown in the IMS Health National Prescription Audit for 2011. Our analysis provides insights into the drugs most often taken, the varying risks of those most popular drugs, and what is revealed about their safety profile in a one calendar quarter of reports. The overall results are shown in Table 1 (reprinted here from the Executive Summary).

Table 1. Reported Serious ADEs for the most widely dispensed prescription drugs					
Drug	Medical Use	Millions of RX*	Serious ADEs**	Median Age	Major Adverse Effect
ACETAMINOPHEN-HYDROCODONE	Pain	32.4	390	43	Overdose/Suicide
LEVOTHYROXINE	Hormone replacement	23.8	69	52	Overdose/Suicide
SIMVASTATIN	Lipid-lowering	22.4	132	63	Muscle Damage
LISINOPRIL	Hypertension	20	168	60	Hypersensitivity
AZITHROMYCIN	Antibiotic	18.2	18	51	Severe Cutaneous
Total		116.8	777		

* IMS Health National Prescription Audit. TM ** ADE = Adverse Drug Events.

Medical Uses of the Mega-Drugs

The opioid painkiller acetaminophen-hydrocodone (VICODIN) towers over all other drugs in number of dispensed prescriptions. Its 32 million prescriptions for a calendar quarter are 40% more than its nearest competitor, levothyroxine, the thyroid hormone replacement. Use of mild opioids has been a mainstay of medical practice for more than a century.

Laboratory testing and replacement of low thyroid hormone has been another widespread medical practice for decades. However, the U.S. Preventive Services Task Force guidelines state that it doesn't have enough scientific evidence to recommend either for or against screening, suggesting the medical benefits of thyroid hormone replacement are uncertain, or at least unproven. [22]

The generic cholesterol-lowering drug simvastatin ranks third. This total understates how extensively these drugs are used because other cholesterol-lowering drugs also have large patient populations: atorvastatin (LIPITOR) ranks second in the class, with 10 million prescriptions, followed by rosuvastatin (CRESTOR) with 6 million, and pravastatin (PRAVACHOL) with 5 million prescriptions.

The generic ACE-inhibitor lisinopril (PRINIVIL) for hypertension ranks highest among more than 30 approved drugs to lower blood pressure. Azithromycin ranks first among scores of antibiotics. To the extent that the medical marketplace identifies superior drugs, those identified here have risen to the top of the class of painkillers, antibiotics, and blood pressure medications, and cholesterol-lowering drugs. In the case of levothyroxine, it is the only thyroid hormone in widespread use.

It is also notable that the top five are all generic drugs of long standing. The newest is simvastatin, approved 20 years ago for cholesterol lowering. It is also of interest that only two out of the five drugs—the painkiller and antibiotic—are used short-term to treat diseases with symptoms. The other three are used long-term in patients typically without symptoms but with what are believed to be risk factors for heart disease or other disorders.

Side Effects of the Five Mega-Drugs

One would hope that the most time-proven and widely used drugs—especially those prescribed for long-term use—would rank among the safest, with the lowest risk of serious injury. There is some evidence of low risk here—with just 708 cases of serious injury and death reported for 116.7 million dispensed prescriptions. That equals about 7 cases per million prescriptions per quarter. However, we suspect adverse events with these generic drugs may also

share an extremely low reporting rate in a voluntary reporting system. They are older drugs with a familiar safety profile. Also, we believe that generic drugs have lower reporting rates than brand name drugs. Pharmaceutical companies that actively promote brand name drugs have large sales forces, extensive contact with physicians, consumer hotlines, web sites and other marketing programs that cause them to learn of adverse drug events, which they must report under FDA regulations. To determine the rate at which these popular drugs are injuring patients would require other sources of data.

Even when reporting rates are low, a single quarter of adverse event data still reveals important information about the risks of these prescription drugs. Starting at No. 1, the acetaminophen-hydrocodone combination drug provides multiple overdose risks. Acetaminophen can cause fatal liver damage at approximately four times the daily labeled dose. Hydrocodone shares with other opioid drugs three properties that lead to overdose. Over time patients develop tolerance to opioids and seek to increase the dose to maintain the same level of pain relief. Like other narcotics, it can cause withdrawal or rebound symptoms leading to dependency. Finally, an overdose of sufficient size leads to respiratory depression and death.

Simvastatin shares with chemically similar cholesterol-lowering drugs the possibility of causing muscle weakness and damage, which can be painful when the damage is mild and life-threatening when the proteins released by damaged muscle cells overwhelm the kidney's ability process them, a condition called rhabdomyolysis. The quarterly results for simvastatin include 34 reported cases of rhabdomyolysis and additional mentions of muscle weakness and muscle pain. In June 2011 the FDA also recommended strict limitations on the highest dose of simvastatin, 80 mg. [23]

The ACE-inhibitor lisinopril is well known for causing hypersensitivity reactions, and the data showed 50 cases of angioedema, 12 mentions of lip swelling and 9 mentions of swollen tongue. (A case can fall in more than one category.) These data also included 11 cases of the widely known ACE-inhibitor cough, almost surely a serious underestimate, since a cough would not normally be classified as a serious adverse event.

The antibiotic azithromycin included a few cases of allergic reactions, including two cases of Stevens-Johnson Syndrome, a life-threatening autoimmune skin reaction. However, for levothyroxine, we noted an unexpected signal for suicidal and self-injurious behavior, with 20 completed suicides reported for the drug in the quarter. In a problem we have noted before, [24] three different drug companies reported the same overdose suicide cases that were listed in the 2010 Annual Report of the American Association of Poison Control Centers. Furthermore, the 203-page report did not in fact list even one case in which levothyroxine was the primary suspect drug.[25] Instead, levothyroxine was one of a long list of drugs identified in the bloodstream of some overdose victims. In each case another drug with a known suicidal behavior risk and

warning also had been taken, and in many cases several such drugs. In a vivid example of unintended consequences, the FDA requires that drug manufacturers check the medical literature for published case reports. It happens that the poison control group published in the journal *Clinical Toxicology* a summary of each of more than 1,000 cases it reviewed.

QuarterWatch Team and Funding Sources

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

Thomas J. Moore serves as a part-time project director for QuarterWatch. He has developed and maintains the master adverse event database that serves as the primary data source for the publication and conducts the primary analysis for each issue. Mr. Moore receives an honorarium from ISMP for each issue, with the remaining work being on a volunteer basis. 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. In 2011 Moore examined the completeness and accuracy of adverse drug event reports for biological products for Amgen.

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 his 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 given expert testimony or depositions in cases involving COX-2 inhibitors, a gadolinium contrast agent, and

Fosamax (alendronate), and recently became a testifying expert in the litigation involving Chantix (varenicline).

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.

References

1. Moore TJ, Singh S, Furberg CD (2012) The FDA and New Safety Warnings. *Arch Intern Med* 172: 78–80.
2. Adverse Event Reporting System (AERS) (2011). Food and Drug Administration Web site. Available:<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm>. Accessed 7 February 2011.
3. Code of Federal Regulations Title 21 314.80 Postmarketing reporting of adverse drug experiences (2011). Food and Drug Administration. Available:<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=314.80>. Accessed 3 March 2010.
4. Unified Medical Language System: RxNorm (2010). National Library of Medicine. Available:<http://www.nlm.nih.gov/research/umls/rxnorm/>. Accessed 22 December 2011.
5. MedDRA MSSO (2010) Introductory Guide MedDRA Version 14.1. Chantilly, VA: MedDRA Maintenance and Support Services Organization. 84 p.
6. MedDRA MSSO (2010) Introductory Guide for Standardised MedDRA Queries (SMQs) Version 14.1. Chantilly, VA: MedDRA Maintenance and Support Services Organization. 244 p.
7. COUMADIN (warfarin sodium) tablets, for oral use [Package Insert] (2011). Princeton, NJ: Bristol-Myers Squibb.
8. Budnitz DS, Lovegrove MC, Shehab N, Richards CL (2011) Emergency hospitalizations for adverse drug events in older americans. *N Engl J Med* 365: 2002–2012. doi:10.1056/NEJMsa1103053.
9. PRADAXA (dabigatran etexilate mesylate) capsules for oral use [package insert] (2011). Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc.
10. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, et al. (2009) Dabigatran versus Warfarin in Patients with Atrial Fibrillation. *N Engl J Med* 361: 1139–1151. doi:10.1056/NEJMoa0905561.

11. FDA Drug Safety Communication: Safety review of post-market reports of serious bleeding events with the anticoagulant Pradaxa (dabigatran etexilate mesylate) (2011). Food and Drug Administration Web site. Available:<http://www.fda.gov/Drugs/DrugSafety/ucm282724.htm>. Accessed 20 December 2011.
12. Beasley H, Thompson A (2010) Clinical Review: NDA 022-512: Dabigatran (Pradaxa). Silver Spring, MD: Food and Drug Administration, Center for Drug Evaluation and Research.
13. Beasley BN, Unger EF, Temple R (2011) Anticoagulant options--why the FDA approved a higher but not a lower dose of dabigatran. *N Engl J Med* 364: 1788–1790. doi:10.1056/NEJMp1103050.
14. REGLAN (metoclopramide hydrochloride) injection, solution [Package Insert] (2010). Deerfield, IL: Baxter Healthcare Corporation.
15. REGLAN (metoclopramide hydrochloride) tablet [Package Insert] (2009) Marietta, GA: Alaven Pharmaceuticals LLC.
16. American Psychiatric Association Task Force on Late Neurological Effects of Antipsychotic Drugs (1980). Washington, DC: American Psychiatric Association. p.
17. Schooler N, Rabinowitz J, Davidson M, Emsley R, Harvey PD, et al. (2005) Risperidone and haloperidol in first-episode psychosis: a long-term randomized trial. *Am J Psychiatry* 162: 947–953. doi:10.1176/appi.ajp.162.5.947.
18. Lee A, Kuo B (2010) Metoclopramide in the treatment of diabetic gastroparesis. *Expert Review of Endocrinology & Metabolism* 5: 653–662.
19. Kaplan S, Staffa JA, Dal Pan GJ (2007) Duration of therapy with metoclopramide: a prescription claims data study. *Pharmacoepidemiol Drug Saf* 16: 878–881. doi:10.1002/pds.1397.
20. Safety Information - Reglan (metoclopramide) tablets, ODT (Orally Disintegrating Tablets), and injection (2009). Food and Drug Administration Web site. Available:<http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm170934.htm>. Accessed 1 December 2011.
21. Moore TJ, Cohen MR, Furberg CD (2011) QuarterWatch: 2010 Quarter 2: Signals for Varenicline, Levofloxacin and Fentanyl. Institute for Safe Medication Practices. Available:<http://www.ismp.org/QuarterWatch/2010Q2.pdf>.
22. Screening for Thyroid Disease: Recommendation Statement (2004). US Preventive Services Task Force. Available:<http://www.uspreventiveservicestaskforce.org/3rduspstf/thyroid/thyrrs.htm>. Accessed 16 December 2011.
23. FDA Drug Safety Communication: New restrictions, contraindications, and dose limitations for Zocor (simvastatin) to reduce the risk of muscle injury. Food and Drug Administration Web site. Available:<http://www.fda.gov/Drugs/DrugSafety/ucm256581.htm>. Accessed 2 January 2012.

24. Moore TJ, Cohen MR, Furberg CD (2010) QuarterWatch: 2010 Quarter 1: Acetaminophen, Dronedarone and Botulinum Toxin Products. Institute for Safe Medication Practices. Available:<http://www.ismp.org/QuarterWatch/2010Q1.pdf>.
25. Bronstein AC, Spyker DA, Cantilena LR, Green JL, Rumack BH, et al. (2011) 2010 Annual Report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 28th Annual Report. Clin Toxicol (Phila) 49: 910–941. doi:10.3109/15563650.2011.635149.