ISMP INSTITUTE FOR SAFE MEDICATION PRACTICES
QuarterWatch
Monitoring FDA MedWatch Reports

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ANNUAL REPORT ISSUE

SGLT2 inhibitors - a health gamble with a new class of drugs for diabetes
Oral anticoagulants linked to nearly 3,000 reported patient deaths, 16,000 hemorrhages
Overall opioid use drops, but oxycodone use grows

Executive Summary

In this annual report issue we outline both positive and negative changes in 2015 with significant implications for patient safety. The year marked the rapid uptake of a new class of diabetes drugs, called sodium-glucose cotransporter-2 (SGLT2) inhibitors, which have unproven clinical benefits and a growing number of safety problems. Use of oral anticoagulants–the highest risk outpatient drug treatment in older patients–increased as novel oral anticoagulants (NOACs) in part replaced the traditional warfarin and also expanded the patient population. In addition, we identified both positive and negative trends in utilization of opioids and sleep medications, and also report on the drugs that accounted for the most adverse event reports in four monitoring categories.

QuarterWatch™ is an independent publication of the Institute for Safe Medication Practices (ISMP) that monitors all adverse drug event reports submitted to the U.S. Food and Drug Administration. 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. We also receive dispensed outpatient prescription data from IMS Health Inc.

In 2015 the FDA received 1.2 million adverse drug event reports, a 32.9% increase over the previous year and nearly five times the total received 10 years ago. The largest share of this increase occurred because of information technology improvements and regulatory changes at the FDA that resulted in adding 354,000 lower-priority reports into its FAERS system that had previously not been accessible for analysis.

Table 1. New case reports received by the FDA, 2014-15

	Year received		Percent
	2014	2015	change
Total	875,186	1,162,860	32.9%
Domestic			
Serious	298,979	328,524	9.9%
Non-serious	328,929	569,760	73.2%
Foreign*			
Serious	231,228	250,146	8.2%

*Manufacturers not required to report foreign, non-serious events

The 9.9% increase in serious injuries reported in the United States (Table 1) in 2015 provides a more realistic but still approximate measure of the trend in harms from the therapeutic use of prescription drugs. Reported serious injuries are increasing because of growing use of drugs with many toxic effects. The introduction of new classes of drugs that move into widespread clinical use also boosted event totals. Increased marketing of brand name drugs can also increase reports because to sell more drugs the manufacturers come into more frequent contact with prescribing physicians and individual patients, and therefore learn more about harms.

Neither the FDA nor the Centers for Disease Control and Prevention (CDC) estimate how many persons are injured or die from the therapeutic use of drugs, nor has either agency established a statistical method by which injuries could be measured systematically. The studies that do exist suggest that from less than 1% to approximately 10% of serious injuries from drug therapy are reported to the FDA, with occasional special cases reaching a reporting rate of 35%. This means that several million individuals experience drug-related injuries every year. The available evidence shows this toll was increasing in 2015.

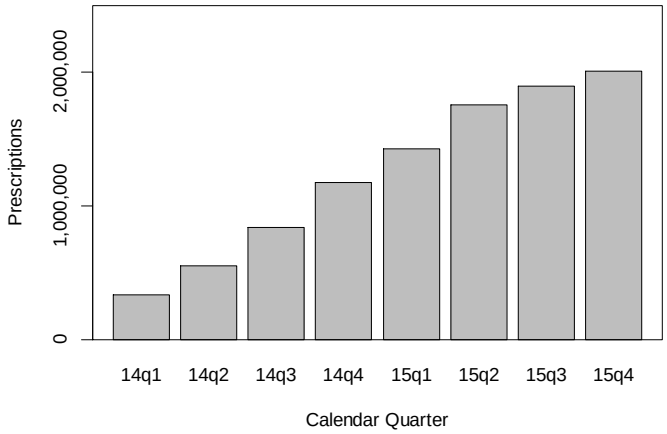
Key Changes in 2015

1) Dangerous Gamble with a New Class of Diabetes Drugs

The nation's gamble in embracing new drugs for long-term use with only short-term clinical testing was most apparent in the rapid acceptance into clinical practice of a new class of oral diabetes drugs called sodium-glucose cotransporter-2 (SGLT2) inhibitors. There are now three such agents, canagliflozin (INVOKANA), dapagliflozin (FARXIGA), and empagliflozin (JARDIANCE). Since approval, evidence of multiple safety problems has emerged.

By 2015 Q4 the three drugs accounted for 2 million dispensed outpatient prescriptions, according to IMS Health, a nearly six-fold increase since 2014 Q1. Canagliflozin captured 64.1% of the market, partly because it was the first in the class to win approval, in March 2013.

Figure 1. SGLT2 prescription growth 2014-2015



Data from IMS Health

Because it takes years of treatment to assess clinical benefit such as limiting the microvascular complications (e.g., damage to the kidneys, nerves, and eyes that can result from diabetes), such drugs need to be low risk. However, both adverse drug events and emerging clinical trial data provide clear evidence of these SGLT2 risks: 1) Life-threatening ketoacidosis; 2) Electrolyte imbalances leading to severe dehydration and other problems; 3) Acute kidney injury; 4) Frequent genital infections, primarily fungal; 5) Increased risk of bone fracture. Furthermore, there are emerging signals of three other adverse effects, possible increased risk of limb amputation, pancreatitis, and hypersensitivity. Questions about the benefit-risk balance are examined in greater detail later in this report.

2) Good News, Bad News on Opioid Use

Trends measured over 2014-2015 confirm and extend the positive news that overall, opioid use measured by dispensed outpatient prescriptions, has declined substantially, by about 8%, over the eight calendar quarters. However, the change was driven almost entirely by a drop in the leading mid-potency opioid, acetaminophen-hydrocodone (VICODIN). Placing increased restrictions on physician prescribing of this one drug product in 2014 had the effect of reducing its dispensed outpatient prescriptions by 21%, a drop of 6.6 million prescriptions over the period. This is one of the largest known changes in drug utilization, affecting what once was the most widely prescribed therapeutic drug.

However, the trend was not favorable for the higher potency oxycodone (OXYCONTIN) and the oxycodone abuse-resistant combination with acetaminophen (PERCOCET). Over this same period, dispensed outpatient prescriptions for oxycodone products increased 10.9% to reach 15.8 million.

3) Oral Anticoagulant Use and Injuries Increase

In 2015 the FDA received still more evidence of the high risks of oral anticoagulant therapy in the form of 34,765 adverse drug event reports, including 2,997 patient deaths and 9,523 adverse events severe enough to require hospitalization. The major problem reported was hemorrhage, n = 16,222 (46.7%), with the most frequent bleeding sites being the gastrointestinal system (n = 4,828), and the brain and central nervous system (n = 3,711). These totals include foreign reports. The median age was 73 years, with one-quarter 81 years or older, underlining that anticoagulants are the highest risk outpatient drug treatment in older patients. The actual numbers of deaths and injuries associated with anticoagulant therapy are unknown, but thought to be 10 to 100 times higher than those reported.

The year also marked substantial changes in the number and type of anticoagulant drugs to which patients were exposed, according to data from IMS Health. Starting in 2010, a new generation of agents–called novel oral anticoagulants–has been marketed as replacement for warfarin, a standard treatment since the 1950s to prevent ischemic stroke and other dangerous blood-clot-related injuries. Overall, dispensed outpatient prescriptions for oral anticoagulants increased 6.8% to 11.1 million in the fourth quarter of 2015, compared to 2014 Q1. By the fourth quarter of 2015, the four novel anticoagulants had captured 34% of the market, leaving 66% to warfarin. Among the new agents, rivaroxaban (XARELTO) led, with 17.5% of dispensed outpatient prescriptions, but apixaban (ELIQUIS) prescriptions increased four-fold over the time period and now account for 11.8% of dispensed outpatient prescriptions.

In this report we examine the risks of oral anticoagulants in detail, focusing on the problems created when the new generation of agents was developed to be easier to use, rather than for better safety by reducing bleeding risks.

4) Zolpidem (AMBIEN) Prescriptions Drop 9.4%

The most widely used sleep medication, zolpidem (AMBIEN), is a public health concern because a majority of use does not adhere to the safety recommendations. Our previous study showed that 68% of zolpidem patients used it over the long term rather than for a few weeks as recommended; another 22.3% combined zolpidem with opioids, increasing the risk of fatal depression of the central nervous system; a third group combined two drugs active on the same target receptors, also increasing risk of overdose and next-day impairment.

While it seemed a positive safety development to observe that dispensed outpatient prescriptions for zolpidem declined by 9.4% since 2014 Q1, with 8.9 million dispensed outpatient prescription in 2015 Q4, the use of this drug remains very substantial. The year 2015 also marked the launch of a new sleep medication, suvorexant (BELSOMRA), the first orexin neuroreceptor inhibitor. But in the fourth quarter it accounted for only 122,000 dispensed outpatient prescriptions.

Leading Drugs in 4 Monitoring Categories

Adverse drug event reports can be envisioned as different streams of information flowing into the same central system, but originating from different sources, and for different reasons. To capture the full diversity of drug risk information, QuarterWatch also examines the drugs accounting for the most reports of injury in many different monitoring categories–such as all reports directly to the FDA or those originating from legal actions. We selected four different categories for 2015.

Domestic, Serious Events: Rivaroxaban (XARELTO), an oral anticoagulant, accounted for the largest number of reported cases of domestic, serious injury among regularly monitored drugs, a total of 10,674 reports, including 1,121 patient deaths and 4,508 injuries requiring hospitalization. The most frequent side effect was hemorrhage, accounting for 8,643 cases. These events are also included in the totals for all oral anticoagulants.

Direct Reports to the FDA: Adalimumab (HUMIRA), a biological product that suppresses tumor necrosis factor (TNF), was the leading suspect drug in reports submitted directly to the FDA, rather than through drug manufacturers. We regard direct reports as a key indicator of safety risks because these voluntary reports are free from manufacturer marketing and other programs to contact health professionals and consumers that can increase report totals. In 2015, adalimumab accounted for 1,581 direct reports to the FDA, but overall a total of 7,300 domestic serious reports, 34,035 non-serious, and 8,592 foreign reports. Notable were reports of infection, and injection site reactions.

Persistent Adverse Effects: Fluoroquinolone antibiotics accounted for the largest number of reports of persistent adverse effects (n = 855) that became long-term health issues. The total included 489 (57%) for levofloxacin (LEVAQUIN) and 366 (43%) for ciprofloxacin (CIPRO). The persistent adverse effects described most often were painful joint, muscle, and tendon disorders.

Legal Claims: Pioglitazone (ACTOS) was the most frequent suspect in cases explicitly identified as legal cases, accounting for 3,041 reports. We consider drug problems that spur thousands of legal claims a signal of a notable safety issue, although observing a large number of legal claims does not prove the drug was, in fact, responsible in many cases. For pioglitazone the issue was bladder cancer and the reported cases were among 9,000 that Takeda, the manufacturer, included in a $2.4 billion settlement. We further describe the controversy over the pioglitazone cancer risks in this report.

Adverse Event Reporting System

FDA Changes Boost Non-Serious Report Totals

The FDA informed us of two changes in 2015 that had the effect of substantially increasing the number of non-serious adverse drug event reports submitted into the system. Last year the FDA began requiring mandatory electronic submission of all adverse event reports. Another technical change resulted in the one-time transfer of 354,000 lower priority reports into FAERS that had been previously submitted into a different agency computer system, and were not available for normal postmarket surveillance work at the agency. As a result, these cases from prior years have submission dates in 2015 when they were transferred into FAERS, but may have occurred earlier.

Also in 2015, QuarterWatch began including non-serious reports in its regular monitoring and evaluation. Previously we primarily evaluated domestic reports coded as serious. This change occurred because we observed large numbers of significant adverse drug events that were not classified as serious. While non-serious events such as fatigue and dyspepsia raise limited safety concerns we also found “non-serious” cases that indicated reactions such as hallucinations, sleep walking, tardive dyskinesia, hemorrhage, genital fungal infections, diabetes, and abnormal weight gain.

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 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. While the sheer numbers of case reports have scientific weight, they reveal little about how frequently the events occur in the broader patient population because of variation in reporting rates. 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 risks of introducing new drugs for long-term use without long-term clinical trials are illustrated in the growing safety questions about the SGLT2 inhibitors, the new class of diabetes medications now rapidly moving into clinical practice. Whether the drugs have clinical benefits (such as reduced cardiovascular risks or less kidney or nerve injury) remains unknown, while safety problems grow increasingly apparent. Since May 2015, the FDA has issued Drug Safety Communications about life-threatening ketoacidosis, severe electrolyte imbalances, acute kidney injury, possible increased risk of limb amputation, higher risk of bone fracture, sepsis, and urosepsis. Given that drugs intended for long-term therapy for hyperglycemia in Type 2 diabetes need to be low risk, we conclude that current data provide insufficient evidence that the benefits of SGLT2 inhibitor drugs outweigh their risks. The FDA should re-evaluate its decision to allow unrestricted long-term use of this drug class.

The need to improve the safety of high-risk oral anticoagulants is reinforced by the growing totals of deaths and hemorrhages, mostly in the oldest and most vulnerable patients. A major misstep in patient safety occurred with the approval of a new generation of anticoagulants marketed for ease of use rather than improved safety or efficacy. In addition, two novel anticoagulants have pharmacological problems that render them ill-suited to their current simplified dosing schemes. Dabigatran, with five-fold variability in the anticoagulation achieved in patients getting the one recommended therapeutic dose, is a poor therapeutic choice without adjusting the dose for each patient based on plasma levels, an option not currently available. Rivaroxaban, with a 5-9-hour terminal half-life, is ill suited to its once-daily dosing regimen and results in higher maximum concentrations early, and then potentially sub-therapeutic doses for the second half the 24-hour cycle.

We observed two favorable trends in 2015 in reduced utilization of drugs with notable safety concerns. Dispensed outpatient prescriptions for the most widely used opioid, acetaminophen-hydrocodone, declined 21%, mainly as a result of increased restrictions on prescribing achieved by reclassifying the drugs from Schedule III to Schedule II. Also, the utilization of zolpidem, the most widely used sleep medication, declined almost 10% over the eight quarters beginning in 2014. We have previously reported that the bulk of zolpidem use did not adhere to one or more safety recommendations.

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Methods Summary

QuarterWatch monitors the safety of prescription drugs through analysis of adverse drug events reported to 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.[1] 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 the adverse event was classified as serious under FDA regulation[2] if the case report specified 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 and all new cases were included in this analysis unless indicated otherwise. Earlier QuarterWatch issues have focused primarily on a subset of adverse events, those that are domestic and coded with serious outcomes. We continue to monitor domestic, serious reports as an important subset of the newly released case reports.

In these data, the adverse events reported 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.[3] 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.[4] 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 2015 to MedDRA version 18.1.

To provide a broader public health 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, long-term care, 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 2015 (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."

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 based on the National Library of Medicine's RxNorm terminology.[5] When cited in the text, tables, or charts, the brand name of drugs used is normally the one most frequently indicated on the case reports but the brand identified may account for a small or large share of the actual reports identified. Unless specified, QuarterWatch does not distinguish dose, route of administration, or extended release and other preparations.

Results

Report Trends

In 2015 the FDA received 1,162,860 new adverse drug event reports, including 94,220 (8.1%) reports of patient deaths, 186,554 (16.0%) cases of initial or prolonged hospitalization, and 596,760 (49.0%) cases with an outcome classified as non-serious. These totals included 250,146 (21.5%) cases that were from other countries and were serious injuries. As noted in the executive summary, the 2015 report increase of 32.9% was primarily caused by the artifact of reporting system changes that captured increased numbers of lower priority adverse event reports in the agency's FAERS system. Previously, the agency had not been entering some reports submitted in paper form or as PDFs to another document submission system.

One key trend or index of patient harm is for the subset of reports that are of domestic origin and coded with one of the serious outcomes such as hospitalization, disability, or death. In 2015, the agency received 328,524 new reports in this category, a 9.9% increase over 2014, and a near doubling of reported serious injuries since 2010. Five years ago the agency received 164,896 domestic reports of serious injury. Some of this increase is accounted for by newer brand name drugs such as the oral anticoagulants and diabetes drugs reviewed in this issue of QuarterWatch. Another portion of the increase is largely unrelated to safety and primarily a result of new kinds of manufacturer marketing activities such as consumer help lines, health insurance navigators, and instructions for using self-injection products or inhalers. These actions cause companies to learn of adverse events through increased contact with patients and health professionals. Direct reports to the FDA–largely unaffected by pharmaceutical marketing–have increased 20.9% since 2010 and may more accurately reflect increased risks to patients from therapeutic drugs.

Dangerous Gamble with a New Class of Diabetes Drugs

New drugs intended to provide a clinical benefit only measurable over the long term need only be tested for short periods to see if they affect some biomarker. It is hoped that the biomarker–such as blood pressure or tumor regression–predicts benefits that will occur later. The problem is that drugs have many effects–not just on one biomarker such as blood sugar–and it is certain that some of those many effects will cause harm. In 2015 the biggest new gamble evident was in the rapid uptake of the newest class of drugs to treat Type 2 diabetes amidst growing safety concerns.

The new drugs are sodium-glucose cotransporter-2 (SGLT2) inhibitors and they work by causing the kidneys to excrete rather than reabsorb some of the circulating blood glucose and sodium. The first SGLT2 inhibitor to be marketed in the U.S. was canagliflozin (INVOKANA), approved in 2013. It was followed by dapagliflozin (FARXIGA) and empagliflozin (JARDIANCE) in 2014. Combinations with metformin have also been approved for all three drugs.

Table 2. Dispensed prescriptions for SGLT2 inhibitors

	Prescriptions 2015 Q4, pct*	
Total SGLT2	2,009,505	
Canagliflozin (INVOKANA)	1,288,563	64.1%
Dapagliflozin (FARXIGA)	521,746	26.0%
Empagliflozin (JARDIANCE)	199,196	9.9%
SGLT2 = Sodium glucose cotransporter 2.		
Data from IMS Health. Includes combinations with metformin.		

The population being treated for Type 2 diabetes is so large that more than 1 in 5 adults age 65 or older are taking medication to lower blood sugar.[6] Into this large patient population, SGLT2 inhibitors have been marketed with great success over the past two years. From just 336,000 dispensed outpatient prescriptions in 2014 Q1, exposure has grown nearly six-fold to exceed 2 million prescriptions in the last quarter of 2015. Dispensed outpatient prescriptions for the three SGLT2 inhibitors are shown in Table 2. Some early findings from new and ongoing clinical trials provided some limited new perspectives on the health gamble with this new class of drugs

Empagliflozin Trial Claims Benefit

In a rare diabetes study to claim a cardiovascular benefit, a clinical trial of empagliflozin in diabetes patients with serious cardiovascular disease showed a benefit when compared to patients taking combinations of other diabetes medications.[7] The difference (10.5% v 12.1%) was in a combined endpoint of various cardiovascular events. The benefit was also seen for total mortality but little difference was seen in the expected risks of diabetes, myocardial infarction, and stroke.

In addition, the differences in glycemic control were small, the study was short (median 2.6 years), had a high dropout rate (25.4%), and was conducted in an unusually high-risk population. Moreover, the differences were not statistically significant when limited to the subgroup of patients who took the medication for 30 days or more and experienced an event while on treatment. An additional complication was the ongoing adjustment of other medications including diabetes medications (mostly insulin and metformin), hypertension drugs (95%), cholesterol lowering drugs (80%), and blood-clot inhibitors (aspirin, clopidogrel, warfarin) (89%).

Two Warnings from Canagliflozin Trial

The cardiovascular outcomes trial for canagliflozin, CANVAS, is not scheduled for completion until 2017 [8] but interim findings have already generated new safety concerns. In January 2016, the CANVAS sponsors reported that canagliflozin caused a statistically significant increased risk of bone fracture (4.0% v 2.6%) compared to a placebo group treated with other medications.[9] The bone fracture risk was consistent with known effects, reduction in bone mineral density and increases in bone turnover,[10] and was found to increase with the duration of the treatment.

The second potential safety issue was increased risk of foot and toe amputations also reported from the CANVAS study. Both the European Medicines Agency (EMA) and the FDA have reported they are reviewing interim findings from CANVAS, and publicly released the risk data. [11] [12]

The 2015 Adverse Event Data

QuarterWatch first reported our safety concerns about canagliflozin in May 2015 when the first substantial group of adverse event reports became available,[13] and expanded our previous analysis in January 2016.[14] With still more adverse event data, we observed new signals as well as expanded reporting indicating that most adverse effects reported for canagliflozin are also associated with dapagliflozin and empagliflozin. Table 3 shows that ketoacidosis and infection cases for the three drugs are roughly similar in proportion to total reports for the drug and patient exposure.

Table 3. Select SGLT2 inhibitor adverse events reported 2015

Drug name	Cases	Ketoacidosis	pct*	Infections	pct
Canagliflozin	7,458	638	8.6%	1,805	24.2%
Dapagliflozin	1,963	306	15.6%	395	20.1%
Empagliflozin	675	82	12.1%	130	19.3%
Total	10,096	1,026		2,330	

* Percent of reports for that drug (including metformin combinations)

Ketoacidosis or diabetic ketoacidosis PT. Infections = System Organ Class.

We observed three other signals for the SGLT2 inhibitor drugs' adverse effects: 1) renal failure/impairment (n = 257); 2) pancreatitis (n = 120), 3) hypersensitivity (n = 877). In addition, the number of cases grew for other reported adverse effects, notably sepsis and urosepsis, kidney stones, and abnormal weight loss. In June 2016, the FDA, responding to the same adverse events reported in QuarterWatch, strengthened the warning for renal injury. [15] As a further index of how little was known about the adverse effects of these drugs prior to approval, the FDA has had to issue five drug safety communications about serious risks of SGLT2 drugs since May 2015. [12,15–18]

Limitations

We did not systematically compare the safety profiles of the three agents in this analysis. In addition, while the number of reports was large, because of variable reporting rates it remains uncertain how frequently these events are occurring in the overall patient population.

Good News, Bad News on Opioids

The White House, the FDA, the CDC, and Congress have proposed an array of new policies to prevent abuse, dependence, and overdose deaths with opioid drugs. The President proposed measures to increase treatment options for dependence, including lessening restrictions on the opioid buprenorphine in physician supervised treatment.[19] The CDC sought to change clinical practice with a new, more restrictive guideline for physician prescribing of opioids for chronic pain.[20] The FDA announced an eight-point action plan that included promoting abuse-deterrent formulations, increased warnings, and improved access to naloxone, an opioid antagonist useful in treating overdoses.[21] At this writing Congress is still debating actions to improve treatment and how to pay for it.

Complete prescription data for 2015 reinforce one notable, favorable trend. Total dispensed opioid outpatient prescriptions declined 8% from 2014 Q1 through 2015 Q4. In that period, consumption of opioid drug products declined from 65 million dispensed prescriptions to 59.8 million, according to data from IMS Health. However, the reduction was largely driven by changes in the prescribing of one opioid drug–the combination drug acetaminophen-hydrocodone (VICODIN, others). This mid-potency opioid accounted for 40.4% of all opioid consumption, and practically all the reduction in utilization. In our previous analysis [14] we concluded that most of the reduction could be traced to a single 2014 policy decision: Increasing prescribing restrictions on hydrocodone combination products by moving them from Drug Enforcement Administration Schedule III to Schedule II. The additional restrictions require more direct physician interaction for a prescription renewal, and prevent prescribing by non-physicians.

Figure 2. Acetaminophen-hydrocodone

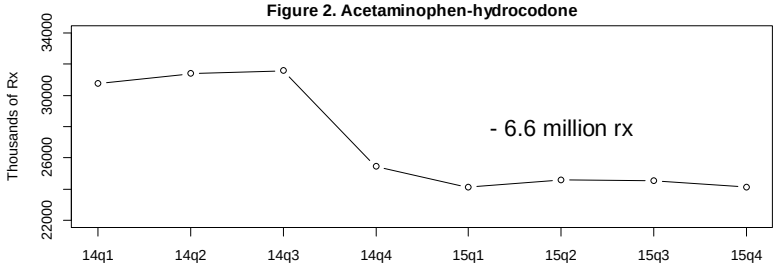
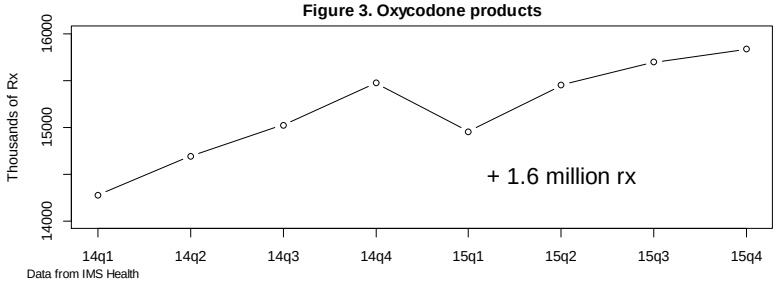


Figure 3. Oxycodone products



On the other hand, the trends were not favorable for oxycodone products (OXYCONTIN, PERCOCET), a higher potency semi-synthetic opioid, and the opioid most frequently linked to abuse and dependence. During the eight calendar quarters we reviewed, oxycodone outpatient prescriptions increased 10.9%, from 14.3 million to 15.8 million. The prescription trends are illustrated in Figures 2 and 3.

Unfortunately, none of these policy changes, or restrictions that may come in the future, address the central medical dilemma: For moderate to severe pain, there are no viable pharmaceutical alternatives without the safety problems of tolerance, withdrawal symptoms, dependence, abuse, and overdose. Fortunately, in many medical settings where pain relief is required, the underlying problem is short term, notably tooth extraction, surgery, or acute injury to bone or joint. In short-term use, the risks of opioids are much lower.

Oral Anticoagulant Use and Injuries Grow

In 2015, important changes could be seen in the utilization of oral anticoagulants, one of the highest risk outpatient drug therapies, with injury rates that can exceed 10% per person-year.[22] [23] Both use and therefore safety risks to patients increased. One of the changes with great impact on safety has been the introduction and growing use of novel oral anticoagulants as easier-to-use alternatives to warfarin. While warfarin requires bi-weekly testing and regular dose adjustments to keep inhibition of blood-clotting within the optimal range, these drugs are prescribed in only one or two dose regimens, with no therapeutic monitoring required or generally available. As outlined in several previous issues of QuarterWatch [13] [24] [25] , we believe that focusing on ease of use over the need to improve the safety profile of these high-risk drugs was a major misstep, a problem compounded by regulatory errors.[26] Five years after the first of the novel anticoagulants was approved, the picture continues to evolve. There are now four novel anticoagulants, dabigatran (PRADAXA), approved in 2010, rivaroxaban (XARELTO), in 2011, apixaban (ELIQUIS) in 2012, and this year the latest entrant, edoxaban (SAVAYSA).

Better or Worse Than Warfarin?

The clinical testing of novel oral anticoagulants was riddled with serious flaws. Comparisons between these agents and warfarin were established in four of the largest international clinical trials in recent history, together providing more than 120,000 person-years of observation. The unprecedented trial size was mandated by the need to measure very small differences with the long-established, but high-risk warfarin. Despite the large size and numerous prespecified safety endpoints, the pivotal trials for all for these drugs were characterized by flaws that raise questions about the relevance of the small differences identified. The dabigatran results were partially corrected after reanalysis disclosed unreported cases of major bleeding and acute myocardial infarction. [27] The accuracy of the rivaroxaban ROCKET-AF trial was challenged by FDA reviewers; later reviews showed the warfarin comparison group was flawed because the point-of-care devices underestimated warfarin anticoagulation effects,[28] raising questions about the entire trial.[29] The apixaban claim of a mortality benefit was not supported if the results of a clinical site in China are excluded after an FDA inspection disclosed fabricated data.[30] In the edoxaban trial (ENGAGE-AF), the FDA reviewers were concerned with weak results in patients with normal renal function,[31] resulting in a major limitation not to use the drug in this large patient group. [32] Despite the large and very expensive testing–costing billions of dollars–the best that can be concluded is that the treatments are about the same as warfarin in terms of benefits and risks in most settings. And warfarin retains the advantage of widely available laboratory tests to assess and manage the bleeding risks.

Suitable Without Dose Adjustment?

At least two of the four novel oral anticoagulants have pharmacological properties that render them a poor choice as a warfarin substitute without anticoagulation monitoring, or better individualized dosing. Dabigatran, because of low bioavailability (3-7%) and a single renal route of elimination, was revealed to have a five-fold variability in patients receiving the same dose.[33] One simulation model showed that at the standard therapeutic dose 18% would receive a sub-therapeutic dose and more than 40% would receive a higher dose than needed, increasing bleeding risk.[26] In a previous analysis of rivaroxaban, we raised questions about its suitability for use under the current dosing regimen. [34] The problem is that a drug with a 5-9 hour terminal half-life was tested and marketed for once-a-day dosing (unlike the other novel agents, with twice-a-day regimens and longer half-lives). For rivaroxaban, this mean higher initial maximum concentrations soon after dosing to get enough drug on board in a single dose, but low trough concentrations for 12 hours of the 24-hour treatment cycle because of its rapid elimination.

Changes in Utilization

We identified four important changes in anticoagulant prescribing in 2015 using dispensed outpatient prescription data from IMS Health. 1) Novel oral anticoagulant dispensed prescriptions rose 73.6% from

2014 Q1 through 2015 Q4. 2) The growth was roughly divided between an expanded patient population and use as a substitute for warfarin, for which prescription volume declined 10.9% over the same period. 3) The market share for apixaban, the third entrant into the market, grew more than four-fold, and looked poised to overtake rivaroxaban. 4) Prescriptions for dabigatran, first to win approval, continued to decline (-18.4%) because of safety concerns and possibly as a result of marketing competition. The newest novel anticoagulant, edoxaban, was approved only in January 2015, had a restrictive indication, and as yet had little market impact. Warfarin continued to dominate the oral anticoagulant market, but was reduced to about 66% of dispensed outpatient prescriptions. See Table 4.

Table 4. Changes in oral anticoagulant prescriptions, 2014 Q1 - 2015 Q4

Drug	2015 Q4	Year	Market	Percent
Novel Oral Anticoagulants (NOAC)		approved	share	change 14q1
Apixaban (ELIQUIS)	1,315,075	12/2012	11.8%	446.2%
Dabigatran (PRADAXA)	488,169	10/2010	4.4%	-18.4%
Edoxaban (SAVAYSA)	23,563	1/2015	0.2%	
Rivaroxaban (XARELTO)	1,948,303	7/2011	17.5%	45.8%
Class total	3,775,110		34.0%	73.6%
Warfarin (COUMADIN)	7,330,265	6/1956	66.0%	-10.9%
Oral anticoagulant total	11,105,375			6.8%
Data from IMS Health				

Adverse Events Summary

In 2015 the five anticoagulant drugs accounted for 34,765 adverse drug event reports, including 2,997 patient deaths, 9,523 cases requiring hospitalization, and 10,815 cases classified as not having a serious outcome. The report total included 8,796 (26%) cases that were of foreign origin. The reports were, as expected from the anticoagulant mechanism of action, dominated by 16,222 (46.7%) reports of hemorrhage. The most frequently reported bleeding sites were gastrointestinal (n = 4,828), followed by cerebral hemorrhages and other bleeding in the central nervous system (n = 3,711). The anticoagulant adverse events were occurring primarily in older patients: the median age was 73 years, and one-quarter were 81 years or older. Rivaroxaban also accounted for the largest number of domestic, serious adverse event reports that the FDA received in 2015, and is further discussed in the report section on leading drugs in four monitoring categories.

Limitations

Although previous QuarterWatch reports have compared the anticoagulant drugs, this analysis does not distinguish among the five drugs in this class. Marketing competition between the four novel oral anticoagulants seeking to replace warfarin could increase the reporting of bleeding and other serious adverse drug events. The newly approved edoxaban accounted for only 402 reports, or 1.2% of the total.

Zolpidem (AMBIEN) Prescriptions Drop 9.4%

Sleep medications are of safety interest because an estimated 1 in 4 adults have chronic sleep and wakefulness problems, [35] and medication is frequently the therapeutic approach chosen. Sleep disorders have many causes, including shift work, mental disorders such as depression and anxiety, chronic pain, and direct medical issues such as sleep apnea and narcolepsy. We identified two changes in sleep medication utilization with safety implications.

Dispensed outpatient prescriptions for the most widely used sleep medication–zolpidem (AMBIEN, others)–declined substantially from the first quarter of 2014 through the end of 2015. The first new sleep medication in several years–suvorexant (BELSOMRA)–was launched in early 2015 with only moderate uptake into the large market, and raising new kinds of safety issues and unanswered questions.

Evidence of widespread potentially unsafe use of zolpidem emerged from our previous review [6] using a major national health survey called the National Medical Expenditure Panel Survey. Although zolpidem is intended for short-term use, we found 68% of all prescriptions in 2012 were for long-term use, meaning 3 or more prescriptions with a mean of 228 days' supply. Only 5% of women and 10% of older persons were then using the newly recommended lower dose of 5 mg (or 6.25 mg extended release.) At least 22.3% were also taking opioids, risking potentially fatal depression of the central nervous system. Another 23% were taking two drugs active on the same gamma aminobutyric acid (GABA) receptors, which also increases the risk of overdose and next day impairment.

Given a drug where most use appeared to be inconsistent with safety recommendations, it was a net positive for safety to observe that dispensed outpatient prescriptions for zolpidem declined by a substantial 9.4% from 2014 Q1 through 2015 Q4. This represented a large amount of reduced exposure, a drop of 925,000 prescriptions, according to data from IMS Health. Nevertheless, in Q4 2015, exposure remained substantial, with 8.9 million dispensed outpatient prescriptions.

Enter Suvorexant (BELSOMRA)

In many instances, a drop in utilization of off-patent generic drugs (zolpidem was approved in 1992) is offset by the uptake of a new brand name drug. In this case the new entrant was suvorexant (BELSOMRA), the first sleep medication explicitly developed for chronic rather than short-term use, and with a new mechanism of action. It worked by blocking recently discovered neurotransmitters–called orexins–with a key role in the complex sleep-wakefulness process. It was developed by Merck. However, despite the enormous potential market, Merck's launch of suvorexant has been only a modest success. In Q4 2015, dispensed outpatient prescriptions totaled 122,000, according to IMS Health data.

By the end of 2015, the suvorexant adverse event safety profile contained twice as many events (2,378 v 1,016) as our previous review, [14] which included the first two quarters for 2015. But the major issues raised by consumers and health professionals were similar. The most frequent problem cited was that the drug was ineffective (n = 905, 38% of cases). The next most frequently reported issues were sleep disturbances (n = 639, 26.9%), a total that included abnormal dreams (n = 211), hallucinations (n = 112), and sleep paralysis (n = 59). There was more evidence to support an additional concern–that the 12-hour half-life of suvorexant would lead to next-day impairment. (It also led the FDA to reduce the starting dose from the 40 mg sought by Merck to 10 mg.) The full year data identified impairment that included somnolence (n = 159), dizziness (n = 58), fatigue (n = 52), and hangover (n = 23). Each case report could include terms indicating problems in more than one of the categories above. In addition, these data do not provide a basis to estimate how frequently these adverse effects might have been occurring.

Continuing safety concerns about suvorexant also include the limited information about the long-term effects on orexin receptors, and whether prolonged treatment might lead to narcolepsy. Also, it is worth questioning whether the recommendations not to drink alcohol or drive the next day are, in fact, realistic.

Leading Drugs in 4 Monitoring Categories

For the 2015 annual report, we review the therapeutic drugs that accounted for the most adverse drug event reports in four different safety monitoring categories. Although the event report totals are large–indicating hundreds to thousands of serious injuries–they are only a fraction of those occurring, and the fraction that are reported varies among drugs, for different kinds of injuries, and over time.

Domestic, Serious Adverse Drug Events: Rivaroxaban (XARELTO)

The anticoagulant rivaroxaban (XARELTO) accounted for 10,674 reports of fatal, disabling, and serious injury in the U.S., more than any other of the 1,395 identifiable drugs we regularly monitor in this category. For comparison, the median number of reports per drug was 7 cases, with 25% of drugs accounting for 4 or fewer serious cases in 2015, and 25% accounting for 103 cases or more. The rivaroxaban total also included 1,121 reported patient deaths. Rivaroxaban is one of the novel oral anticoagulants examined in a separate section of this report.

The primary hazards of oral anticoagulants are twofold: with too much inhibition of the body's ability to form blood clots the result is hemorrhage. Not enough anticoagulation foils the drug's intended purpose of preventing thrombotic strokes and pulmonary and venous embolism. The adverse event reports mirror these risks, with 8,643 (80.9%) indicating a hemorrhage, and 1,611 (10.9%) an embolic-thrombotic or clot-related event.

We identified other factors that contributed to the large report total for rivaroxaban. In 2015 an intense marketing competition was underway among four novel anticoagulants to replace warfarin, an off-patent generic available since 1957. Marketing and promotion increase manufacturer contact with health professionals and consumers, which causes companies to learn about more adverse events. In addition, while these reports of serious injury were first received by the FDA in 2015, we found 36% had occurred in previous years and were being reported for the first time in 2015, also increasing the total. It is also possible that some of these reports were included among the group of 354,000 reports the FDA transferred into FAERS in 2015. On the other hand, it means that in prior years, injury reports were understated.

Thus, several factors combined to create the exceptionally large total of reported serious injuries for rivaroxaban. However, it remains a strong signal that improving the safety of oral anticoagulant treatments should be a major priority in drug safety.

Direct Reports to the FDA: Adalimumab (HUMIRA)

The anti-tumor necrosis factor (anti-TNF) blocker adalimumab (HUMIRA) accounted for the largest number of reports directly to the FDA, rather than through drug manufacturers. Even though direct reports accounted for only 4% of reports received by the FDA in 2015, we monitor this category separately. While report totals are small, it is an informative index of concerns health professionals and consumers are taking the initiative to bring directly to the FDA's attention, independent of marketing and other influences on reporting. In 2015, the FDA received 1,581 reports identifying adalimumab as the primary suspect, more than any other drug. But this was only a fraction of 49,923 reports for adalimumab overall when foreign, manufacturer serious, and non-serious reports are included.

Anti-TNF biological products have been available since 1998. Approved uses of adalimumab include rheumatoid arthritis, some forms of psoriasis, ulcerative colitis, and Crohn's disease. The most serious adverse events are related to the immunosuppressant effects of these products, including risk of serious infection and malignancy. However, the subset of direct reports to the FDA in 2015 most frequently involved hypersensitivity, injection site reactions, and pain.

Adalimumab emerged in 2015 as the most widely prescribed anti-TNF agent, accounting for 634,000 dispensed outpatient prescriptions in the fourth quarter of 2015. In terms of non-discounted spending, IMS Health ranked adalimumab second among all drug products in the U.S. at $10.6 billion. [31] However, total exposure to adalimumab is comparatively modest; 266 other drugs had higher dispensed prescription totals in 2015 Q4.

As reported previously, these anti-TNF products have accounted for disproportionate numbers of adverse drug event reports for more than a decade.[36] We suspect that the high costs (~ $3-$4,000 per prescription) and self-injection route of administration increased patient interaction with pharmacists, who reported the subset of adverse reactions they learned about from patients.

Persistent Side Effects: Fluoroquinolone Antibiotics

Many drug adverse effects resolve when the suspect drug is discontinued; one key indicator in establishing causality is evidence that that the problem disappears when the drug is stopped. However, some drug effects are persistent. We monitor this category by examining the suspect drugs in reports where the respondent, when asked if the problem stopped after the product was discontinued, specifically answered “No.” In 2015, two similar fluoroquinolone antibiotics accounted for the most reports of persistent adverse effects: levofloxacin (LEVAQUIN) with 489 cases, and ciprofloxacin (CIPRO) with 366 cases. In 65% of the cases the person affected was reported to be disabled by the event. Almost all (99%) were direct reports to the FDA.

The primary persistent injuries reported were joint, muscle, and tendon disorders and pain and discomfort associated with those conditions. This included pain in extremity (n = 200), unspecified pain (n = 162), and tendon pain (n = 119).

These two fluoroquinolone antibiotics are widely used, with ciprofloxacin accounting for 5.9 million dispensed outpatient prescriptions in Q4 2015, and levofloxacin 3.5 million. Because antibiotics are typically used in short-term treatment, it means literally millions are exposed each year.

Generic versions of fluoroquinolones are available, but adverse event reporting rates are much lower for generics than for brand name drugs still on patent. The lower generic reporting rate was illustrated by the fact that that FDA direct reports account for 4% of cases overall but 99% of the persistent fluoroquinolone cases. These data suggest the health problem of persistent injury from fluoroquinolones could be much larger than indicated by these case totals.

Most Legal Cases: Pioglitazone (ACTOS)

Adverse drug events that emerge after FDA approval, had no prior warning, and are seen to involve severe injuries that might warrant substantial compensation often end up as mass torts with thousands of lawsuits combined under the supervision of a single judge. Manufacturers are also required to report legal cases as adverse drug events, and we monitor this distinctive category. In 2015, the legal category was led by 3,041 cases involving pioglitazone (ACTOS), an oral drug for Type 2 diabetes.

The pioglitazone legal cases involved the heavily debated question of whether the drug increases the risk of bladder cancer. Increased risk was seen in some animal carcinogenic studies and in 5-year results of an epidemiological study.[37] Unfavorable trends were seen in some clinical trials but the numbers were small. The result of the litigation was that in April 2015, Takeda Pharmaceuticals, the manufacturer, agreed to pay $2.4 billion to settle 9,000 legal cases.[38]

Pioglitazone illustrates the significant challenges inherent in assessing the cancer risks of therapeutic drugs. An unfavorable signal in lifetime animal studies of the drug raises questions whether the findings are applicable to humans. Clinical trials are typically too short to provide an adequate period of surveillance. Studies in electronic health records that find no association with cancer may simply be flawed. In this case millions of dollars were spent to test the conflicting claims in open court. After five of the first eight cases resulted in verdicts against the company, Takeda settled the remaining cases. But most of the scientific evidence remains under seal. The latest company-sponsored epidemiological study claimed to see no association. [39] But the unanswered question of studies that find no association between a drug and a suspected adverse effect is whether their design was capable of detecting an association if one existed.

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