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ISMP Medication Safety Alert!®

Educating the Healthcare Community About Safe Medication Practices

QuarterWatch™ Annual Report Issue

Trends and changes in 2015 that impact medication safety

ISMP's QuarterWatch™ provides an overview of drug safety issues reflected in adverse drug events reported to the US Food and Drug Administration (FDA) during 2015. Based on these data, along with outpatient prescription volume data from IMS Health, this annual report identifies both positive and negative changes in 2015 with significant implications for patient safety.

Reporting totals

In 2015, FDA received 1.2 million adverse drug event reports, including 94,220 deaths. This represents a 32.9% increase in total reports over the previous year and nearly five times the total received 10 years ago. Most of the increase between 2014 and 2015 (73.2%) occurred with non-serious reports. However, a 9.9% increase in reported serious injuries between 2014 and 2015, and a near doubling of reported serious injuries since 2010, provide an approximate measure of either increased reporting or the upward trend in harm caused by the growing use of prescription drugs.

Dangerous gamble with new SGLT2 inhibitors

Sodium-glucose cotransport-2 (SGLT2) inhibitors have gained rapid acceptance into clinical practice. QuarterWatch™ reported safety concerns with **INVOKANA** (canagliflozin) in May 2015 and January 2016. Since then, we observed new signals as well as ample reporting indicating that multiple safety problems have emerged since approval of the three current SGLT2 inhibitors on the market, Invokana (canagliflozin), **FARXIGA** (dapagliflozin), and **JARDIANCE** (empagliflozin), as well as combination products that contain these medications, **INVOKAMET** (canagliflozin and met**FORMIN**), **SYNJARDY** (empagliflozin and met**FORMIN**), and **XIGDUO XR** (dapagliflozin and met**FORMIN** extended-release). By the end of 2015, these products accounted for 2 million outpatient prescriptions, according to IMS Health, representing a nearly six-fold increase since early 2014. (One new combination, **GLYXAMBI** [empagliflozin and linagliptin] was not evaluated).

Table 1. Select SGLT2 inhibitor adverse events reported in 2015

Drug Name	Total Number of Cases	Ketoacidosis		Infections	
		Number	%*	Number	%*
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 met**FORMIN** combinations)

Adverse drug events and emerging clinical trial data provide growing evidence of the adverse events associated with SGLT2 inhibitors. Since May 2015, FDA has issued five drug safety communications about serious adverse events, including life-threatening ketoacidosis, severe electrolyte imbalances, acute kidney injury, possible increased risk of limb

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SAFETY briefs

It's Exelan, not Exelon. It's rare for the name of a drug company to be so close to the name of a drug that it leads to a medication error. But that's exactly what happened in the following case, and it almost led to harm for an elderly patient who nearly got the wrong medication.

After a patient was admitted to the hospital, a family member brought in a prescription bottle that contained meloxicam, a nonsteroidal anti-inflammatory agent that the patient had been taking at home. See **Figure 1** for a photo of the prescription container label. To develop an active medication list for the patient's physician to reconcile, a nurse inadvertently copied down the manufacturer name, Exelan, thinking it was a brand name for meloxicam. The physician then ordered **EXELON**, a brand name for rivastigmine tartrate, along with the meloxicam strength and frequency, "Exelon 7.5 mg one tablet daily." Rivastigmine tartrate is an anticholinesterase inhibitor indicated for patients with mild to moderate dementia of the Alzheimer's type, or mild to moderate dementia associated with Parkinson's disease. Although Exelon isn't available in a tablet, it is available as a patch and capsule. When used orally, the starting dose is just 1.5 mg twice a day with subsequent dose titration after toler-

Figure 1. The drug company name, Exelan, was mistaken as the brand name of a medication, which was then confused with Exelon.

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amputation, and higher risk of bone fracture, sepsis, urogenital infections, and urosepsis. The adverse event data support these communications and show that most adverse effects first reported with canagliflozin are also associated with dapagliflozin and empagliflozin. **Table 1** (on page 1), for example, shows that ketoacidosis and infection cases for the three drugs are roughly similar in proportion to total reports for the drug and patient exposure. Furthermore, there are emerging signals for several other adverse effects, including pancreatitis (n=120) and hypersensitivity (n=877).

Good news, bad news on opioid use

Trends measured between early 2014 and the fourth quarter of 2015 confirm the positive news that, overall, opioid use, measured by dispensed outpatient prescriptions, has declined by about 8% over the 2 years. However, the decline was driven almost entirely by a drop in **HYDRO**codone with acetaminophen. Placing increased restrictions on prescribing of this drug product in 2014 had the effect of reducing dispensed outpatient prescriptions by 21%, or 6.6 million fewer prescriptions during the 2-year 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 oxy**CODONE** and the oxy**CODONE** with acetaminophen combinations. Over the same 8 calendar quarters, outpatient prescriptions dispensed for oxy**CODONE** increased by 10.9%, reaching 15.8 million. Unfortunately, despite recent policy changes, the central medical dilemma remains: For moderate to severe pain, there are insufficient viable pharmaceutical alternatives without the risks of tolerance, dependence, abuse, and overdose.

Oral anticoagulant use and injuries increase

In 2015, FDA received 34,765 adverse drug event reports for oral anticoagulants, including 2,997 patient deaths and 9,523 adverse events severe enough to require hospitalization. The major problem reported was hemorrhage (n=16,222; 47%), with the most frequent bleeding sites being gastrointestinal (n=4,828), and the brain and central nervous system (n=3,711). These totals include foreign reports. The median age of patients in the reports was 73 years, with one-quarter of patients 81 years or older, underscoring that anticoagulants are among the highest risk outpatient drug treatments in older adults. 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.

In 2015, important changes could also be seen in the utilization of oral anticoagulants, particularly with the novel oral anticoagulants. There are now four novel oral anticoagulants on the market: **PRADAXA** (dabigatran), **XARELTO** (rivaroxaban), **ELIQUIS** (apixaban), and **SAVAYSA** (edoxaban, just approved in 2015). Dispensed prescriptions for novel oral anticoagulants rose 73.6% from early 2014 through the end of 2015, while warfarin use decreased by 10.9% during the same time period.

Zolpidem prescriptions decline

The most widely used sleep medication, zolpidem, has led to a public health concern because the majority of use does not adhere to the published 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 the risk of overdose and next-day impairment. Only 5% of women and 10% of older persons were then taking the newly recommended lower dose of 5 mg (or 6.25 mg extended release). While it seemed a positive safety development to observe that dispensed outpatient prescriptions for zolpi-

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ating that dose for 2-4 weeks, then additional dose titration, again after 2-4 weeks, until a maximum dose of 12 mg daily is tolerated. Among the capsule strengths available are 1.5 mg, 3 mg, 4.5 mg, and 6 mg, so a 7.5 mg oral dose could be ordered and dispensed as two capsules (6 mg and 1.5 mg, or 3 mg and 4.5 mg). Fortunately, a pharmacist noticed the unusual Exelon dose and recognized the error.

Perhaps the pharmacy label would have been a bit less error prone if the manufacturer name was listed far away from the drug name—a recommendation we made to the mail order pharmacy that displayed the manufacturer's name above the directions for use. This type of error also demonstrates the importance of including the drug indication with prescription communications. We have also notified Novartis, Exelan, and the US Food and Drug Administration (FDA). Exelon, a Novartis product, initially received FDA-approval in 2000. Exelan, the company, was incorporated in 2010. Neither ISMP nor FDA have any similar reports of mix-ups between Exelan and Exelon in our databases. We plan on following up with the mail order pharmacy to find out if a change has been made in their labeling. In the meantime, let us know if you or your patients have experienced confusion with drug company names being mistaken with product names.

Opioid mix-ups. A pharmacist recently reported a mix-up between oxy**CODONE** and oxy**MOR**phone. A patient was prescribed oxy**CODONE** 10 mg tablets. A pharmacist retrieved one bottle of oxy**CODONE** from a locked controlled substances drawer and handed it to a pharmacy technician. However, the bottle did not contain enough tablets to fill the prescription. The pharmacist accessed the drawer a second time for another bottle. This time, the pharmacist inadvertently selected a bottle of oxy**MOR**phone 10 mg tablets. Thankfully, the technician caught

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dem declined by 9.4% since early 2014, the use of this drug remains very substantial with 8.9 million dispensed outpatient prescriptions just in the last quarter of 2015.

Leading drugs in four monitoring categories

For the 2015 annual report, QuarterWatch™ also examined the drugs accounting for the most reports of injury in four different safety monitoring categories.

Domestic, serious events. Xarelto (rivaroxaban) accounted for the largest number of reported cases of domestic, serious injury among the regularly monitored drugs, with a total of 10,674 reports, including 1,121 patient deaths and 4,508 injuries requiring hospitalization. The most frequent side effect with rivaroxaban was hemorrhage (n=8,643).

Direct reports to FDA. HUMIRA (adalimumab) was the leading suspect drug in reports submitted directly to FDA rather than through drug manufacturers. We regard direct reports as a key indicator of risks as these reports are not increased due to manufacturers' contacting consumers. In 2015, adalimumab accounted for 1,581 direct reports to FDA. Overall, the drug accounted for 7,300 domestic serious reports, 34,035 non-serious reports, 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 (57.2%) reports for levo**FLOX**acin and 366 (42.8%) for ciprofloxacin. The persistent adverse effects described most often were painful joint, muscle, and tendon disorders. In 65% of the cases the person affected was reported to be disabled by the event. Ciprofloxacin and levo**FLOX**acin are the two most widely used fluoroquinolones, accounting for 5.9 million and 3.5 million outpatient prescriptions, respectively, in the last quarter of 2015. These data suggest that injuries from fluoroquinolones could be much larger than indicated by these case totals (see ***Sidebar*** on page 4).

Legal claims. ACTOS (pioglitazone) was the most frequent (n=3,041) suspect drug in cases identified as legal cases. Drug problems that spur thousands of legal claims often signal a safety issue, although observing a large number of legal claims does not prove the drug was responsible. For pioglitazone the issue was bladder cancer. Pioglitazone illustrates the challenges in assessing cancer risks. A signal in lifetime animal studies raises questions whether the findings are applicable to humans, and clinical trials are typically too short to provide an adequate period of surveillance. The latest company-sponsored epidemiological study claimed to see no association of the drug with bladder cancer.

The full report with references can be found at: www.ismp.org/sc?id=1702.

"Use as directed," whatever that means

The phrase "use as directed" is ambiguous and does not constitute adequate dosing instructions for patients or practitioners (e.g., when conducting medication reconciliation). Pharmacists cannot assume that the prescriber has educated the patient on how to properly take the medication or that the patient will remember the instructions if told. Explicit directions including the strength, frequency of administration, route of administration, and duration of therapy are needed in order for pharmacists to effectively counsel patients. Furthermore, certain elements of a prescription (e.g., route, frequency, dosage form) may help pharmacists differentiate between two drug names that look or sound similar. Several events reported to ISMP illustrate errors that have occurred, at least in part, due to the prescription being written as "use as directed."

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the mistake before counting the tablets. It is because of mix-ups between these two drugs that we recently added oxy**MOR**phone to our list of tall man letters (www.ismp.org/sc?id=1746) to differentiate it from oxy**CODONE**, **OXYCONTIN** (oxy**CODONE** extended release), and **HYDRO**morphone. We encourage voluntary use of these tall man letter schemes by healthcare practitioners, drug information vendors, and medication technology vendors. Any product label changes by manufacturers require approval by the US Food and Drug Administration (FDA).

ISMP releases List of High-Alert Medications in Long-Term Care (LTC) Settings. High-alert medications are drugs that bear a heightened risk of causing significant patient or resident harm when they are used in error (e.g., wrong drug, wrong dose, wrong route). Although mistakes may or may not be more common with these drugs, the consequences of an error with these medications are clearly more devastating to patients or residents. ISMP has maintained lists of high-alert medications for hospitals and community pharmacies for many years, and we are excited to provide an important list of high-alert medications specific to the LTC setting. Based on the results of a survey and review by ISMP and other medication safety experts in the LTC field, the list for LTC facilities has been finalized and is available on our website at: www.ismp.org/sc?id=624.

The purpose of the high-alert medication list is to focus the limited resources in LTC settings on the implementation of robust error-prevention strategies that will help prevent errors with this limited number of drugs that could cause the most harm to residents if an error occurs. Pharmacies and pharmacists that provide services to LTC facilities should review the *ISMP List of High-Alert Medications in Long-Term Care (LTC) Settings* and work with facility staff to develop and implement effective risk-reduction strategies.

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- An elderly man experienced a severe hypoglycemic event requiring hospital admission after the man's son accidentally administered 100 units of **NOVOLOG** (insulin aspart). The insulin vial was labeled with the following directions: "insulin aspart 100 units/mL. Give three times a day before meals as directed." The man's son did not receive any teaching when his father was discharged from the skilled nursing facility the day prior to the event.
- A mix-up occurred between **CLINDESSE** (clindamycin vaginal cream) used for bacterial vaginosis and **CLINDETS** (clindamycin pledgets) used for acne. A prescriber left a prescription on a pharmacy's voice mail for Clindesse, with instructions "use as directed." Upon playback, the order sounded like Clindets and was processed and dispensed as such. The error was discovered when the patient called the pharmacy to ask how to use the pledgets vaginally.
- Three errors involved mix-ups between the intended colonoscopy preparation drug **VISICOL** (sodium phosphate dibasic and sodium phosphate monobasic) and the opioid **VICODIN** (**HYDRO**codone and acetaminophen). In all three instances the prescription for Visicol was written as "take as directed." Two of the errors resulted in severe harm after the patients took over a dozen Vicodin tablets over the course of a day. (Note: The brand name product Visicol is no longer available.)

Survey. An online outpatient pharmacy survey was conducted between May 19 and June 19, 2016. The survey was comprised of 6 questions, 2 related to respondent demographics and the remaining 4 questions related to the prevalence of the sig "use as directed" on prescriptions, medications commonly prescribed as "use as directed," and how pharmacists address these prescriptions.

Results. Despite the wide uptake of electronic prescribing and repayment penalties for discrepancies over the correct days' supply, the results of the survey indicate that many drugs are still prescribed and dispensed with the directions "use as directed." A total of 434 participants responded to the survey, 92.4% of which indicated their country of practice as the US. The majority of participants (55.7%) indicated that between 1-5% of the prescriptions that they receive are written with a sig of "use as directed" and less than 10% of participants indicated that they *never* receive prescriptions written as "use as directed." A majority of respondents indicated that they receive electronic (84.4%), handwritten (74.6%), and facsimile (55.6%) prescriptions that include the sig "use as directed." Respondents indicated that they most frequently verify the directions with the prescriber (74.7%) when they receive prescriptions written as "use as directed," provide the usual and customary directions for the medication if they exist (59.3%), or simply place "use as directed" on the bottle (43%). Many respondents noted that they confirm the days' supply or maximum daily dose with the prescriber for billing purposes. Respondents also identified medications for which they have received prescriptions with the directions "use as directed" (**Table 1**, available exclusively online with this article at www.ismp.org/sc?id=2779). "Other" identified medications include: colonoscopy/bowel preparations, diabetic testing supplies, ophthalmic products, and inhalers.

Safe Practice Recommendations. In order to better safeguard the correct and appropriate use of medications and help minimize errors between medications that look or sound alike, ISMP and the National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) (www.ismp.org/sc?id=1778) recommend prescribers include explicit directions for use on prescriptions. Pharmacists should avoid dispensing medications labeled as "use as directed." Verify the directions with the prescriber prior to dispensing the medication and counsel the patient to ensure that he or she knows how to take the medication properly.

Sidebar: Harm from fluoroquinolones

ISMP's QuarterWatch™ report notes that fluoroquinolone antibiotics accounted for the largest number of reports of persistent, long-term adverse effects. Just this week, the US Food and Drug Administration (FDA) published a drug safety communication stating that fluoroquinolones used systemically (i.e., tablets, capsules, injectable) are associated with disabling and potentially permanent serious side effects that can occur together (www.ismp.org/sc?id=1779). These adverse effects can involve the tendons, muscles, joints, nerves, and also the central nervous system, and again, they can be permanent! As a result, FDA is updating the *Boxed Warnings* for these products and now recommends fluoroquinolones be reserved for use in patients who have no other treatment options for acute bacterial sinusitis (ABS), acute bacterial exacerbation of chronic bronchitis (ABECB), and uncomplicated urinary tract infections (UTI) because the risk of these serious side effects generally outweighs the benefits in these patients. Healthcare practitioners should not prescribe systemic fluoroquinolones to patients who have other treatment options for these infections. **Therapy should be stopped** if a patient reports serious side effects, and the patient should be switched to a non-fluoroquinolone antibacterial drug to complete the treatment course. Safe and judicious use of fluoroquinolones should be part of every antibiotic stewardship program.

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