Focus on new sleep medication, changing opioid use, and new diabetes medications

The latest edition of ISMP’s QuarterWatch™ (see Box below) provides an overview of drug safety issues reflected in adverse drug events reported to the US Food and Drug Administration (FDA) in the first two quarters of 2015 (the latest data available for research). The report is based on combined FDA MedWatch data, but trends focus on 2015 quarter 2 reports. Based on these data, the report identifies:

- Signals for the new sleep medication suvorexant (BELSOMRA)
- Changes in opioid use, specifically a decline in HYDROCodone exposure and an increase in exposure to higher potency opioids
- Update on new diabetes drugs that block the protein sodium-glucose cotransporter 2 (SGLT2)—canagliflozin (INVOKANA), dapagliflozin (FARXIGA), and empagliflozin (JARDIANE)

Signals for suvorexant

Sleep medication targets newly discovered neurotransmitters. Suvorexant is a novel sleep medication prescribed for chronic insomnia, which affects 1 out of 3 adults worldwide. The drug, first marketed in 2015, blocks the effects of two recently discovered neurotransmitters called orexins that are active in the complex sleep-awake process. Orexin receptors receive wakefulness signals and interact with many other neurotransmitters (e.g., histamine, dopamine, norepinephrine, acetylcholine, serotonin).

Most sedative-hypnotics, such as zolpidem (AMBIEN) and ALPRAZolam (XANAX), target gamma-aminobutyric acid (GABA) receptors to enhance their depressant effects on the central nervous system (CNS). Suvorexant blocks orexin receptors that receive wakefulness signals. An absence of all or most orexin-producing neurons has been closely linked to narcolepsy, a condition leading to severe daytime sleepiness. The manufacturer of suvorexant, Merck, expected the new drug would help people sleep at night by blocking orexin receptors without the complications of impairing other elements of the CNS, as seen with sedative-hypnotic medications targeting GABA receptors.

What is QuarterWatch™?

QuarterWatch™ is an independent ISMP surveillance program that monitors adverse drug events reported to FDA by manufacturers, health professionals, and the public. The agency releases for research excerpts of all reports it receives into its adverse event reporting system (FAERS). The goal of QuarterWatch™ is to identify signals that may represent important drug safety issues. The term signal means evidence judged to be substantial enough to warrant publication but which requires further investigation to determine its frequency and establish a causal relationship to the suspect drug.

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Clinical trials and FDA approval. During clinical trials, suvorexant demonstrated a half-life of 12 hours, meaning many patients would still have a therapeutic effect upon awakening after 8 hours. Unlike many other sleep medications, suvorexant also accumulated with repeated daily dosing. For example, after 7 days of administration, the half-life of 40 mg of suvorexant had grown from 12 to 17 hours in older men and to 20 hours in older women. Many patients on a 40 mg dose might experience a therapeutic effect for the entire 24-hour period, potentially leading to daytime sleepiness. But the effects of a lower 10 mg dose would fall below the expected therapeutic range within a few hours of taking the evening dose, potentially leading to early awakening.

Merck sought approval of the highest dose tested (40 mg), which showed the greatest effect on total sleep time—an increase of 46 minutes (but only 23 minutes longer than the placebo). The trials also demonstrated secondary benefits including a decrease in the time to fall asleep and the number and duration of awakenings during the night. However, the clinical trials had limitations, including small numbers of carefully selected patients studied for short durations. The trials excluded patients taking antidepressants, antipsychotics, stimulants for attention deficit hyperactivity disorder (ADHD), mood stabilizers, and anxiolytics. More than 20% of the adult population takes these psychoactive drugs. Thus, it was a challenge to draw valid conclusions about what might happen when this new kind of sleeping medication with a different mechanism of action was marketed to large patient populations.

The FDA, concerned about potential impairment of next-day driving and alertness, insisted on a 10 mg initial dose, which Merck had abandoned after preliminary studies showed marginal efficacy; it prolonged sleep by only 5 minutes (not statistically significant) longer than the placebo. An optional increase to 20 mg was also approved, which prolonged sleep by 23 minutes longer than the placebo.

Reported adverse events. Given this pre-approval trial data, it’s not surprising that, among the 1,016 adverse events reported during the first 2 quarters of 2015, the most frequent reports (42%) were associated with a lack of effect (e.g., “drug ineffective”), although there was no statistical difference between lower (10 mg) and higher (20 mg) doses. The next largest group of adverse events involved sleep disturbances (32%), including nightmares, abnormal dreams, hallucinations, sleep paralysis, and sleep walking. Impaired alertness involving somnolence, headache, dizziness, fatigue, amnesia, memory impairment, or confusion, comprised 28% of the adverse event cases. A few case reports (n = 5) indicated the consequences of impairment, including traffic accidents, falls, and head injuries. Our evaluation did not detect any relationship between a higher dose (greater than 10 mg) and more frequent reports of impaired alertness.

Another group of patients (22%) described paradoxical reactions: instead of becoming sleepy, they reported agitation, anxiety, irritability, nervousness, tremors, restless legs syndrome, and muscle spasms. Many of these paradoxical effects have also occurred during withdrawal of a benzodiazepine sleep aid. Thus, it is conceivable that some of these cases might be occurring because patients switched from benzodiazepine sleep aids to suvorexant and experienced withdrawal symptoms from the benzodiazepine. About 5% of the adverse event reports indicated depression, suicidal ideation, and suicidal behaviors, although reports could include more than one of these terms. We also observed numerous cardiac symptoms, including palpitations, chest pains, and other arrhythmias.

SAFETY briefs

Label characteristic contributes to errors. The way the manufacturer’s strength is oriented on a product container label is an important safety consideration, especially for pharmacists, pharmacy purchasers, and medication safety officers. The Apotex brand of ARIPiprazole tablets is a case in point. Take a look at the bottles in Figure 1. Bottle size, shape, label, and container colors are all similar. Still, you would certainly be able to identify what the medication is. It is the way the product strength appears that is troubling. Since most drug containers are round, when strengths appear to the far right of the label, they may easily be missed if the container is turned just slightly (Figure 1). The drug name may be readily visible but not the strength. Continued on page 3—SAFETY brief >

Figure 1. Strength may easily be missed if the bottle is slightly turned to the right in the photo.
Conclusion. Suvorexant is the first drug to affect a new kind of neurotransmitter that interacts with many other neurotransmitters. Although approved for long-term use, the drug was evaluated only in small numbers of patients in short duration trials of a few months. This means that tens of thousands of patients will be exposed to a drug about which both scientific knowledge and ongoing safety surveillance are limited. Specific safety concerns about suvorexant include whether the warnings against taking the drug with alcohol (CNS depressant effects are additive) and not to drive or engage in any dangerous activity the next day are realistic. In addition, little information exists about the extent of accumulation and other adverse effects with prolonged use.

Changes in Opioid Use

HYDROcodone exposure decreases. For many years, HYDROcodone with acetaminophen (VICODIN, LORTAB, others) has been the most widely used opioid, and also the most frequently dispensed outpatient prescription drug of any kind, according to data from IMS Health. Until August 2014, HYDROcodone was classified as a US Drug Enforcement Administration (DEA) Schedule III controlled substance.

Figure 1. Opioid prescription trends, 2008-2015 Q2

Given its potential for abuse, the opioid was reclassified in 2014, after years of study, as a Schedule II controlled substance, which requires substantial, additional safeguards associated with record-keeping, storage, and prescribing—in no telephone prescriptions or refills are allowed, for example.

Because of the new prescribing and dispensing restrictions, HYDROcodone with acetaminophen has fallen from first to third place as the most widely prescribed therapeutic drug—a decline of 8 million prescriptions from levels in 2011 (Figure 1, graph A). The decline in utilization is so substantial that it reduced overall usage across the entire opioid drug class (Figure 1, graph B). Given that most illicit use of opioids begins when individuals get the drug from family or friends, this substantial reduction in availability could have long-term benefits.

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Confirmation bias could lead to a mix-up. In this case, the font size used to express the strength is also much smaller than the font size used for the drug name, which may add to the confusion. A pharmacist told us that he recently picked up the wrong bottle and nearly dispensed the wrong strength.

Sometimes graphic designers and reviewers view sample label print-outs on a flat surface, without considering how the label will look when applied to a round container, or how the product will be stored and later used. When we checked label graphics from other US ARIPiprazole generic manufacturers, they all had the strength either immediately following the drug name on the same line or had the strength centered immediately beneath the drug name, as it should be. When there’s a choice of brands for specific products, avoid labels that separate the dose/strength from the product name. A good reference to check for container label appearance is DailyMed, a service provided by the US National Library of Medicine (http://dailymed.nlm.nih.gov/dailymed/index.cfm). Whenever possible, use barcode scanning when selecting products and/or draw an arrow from the drug name pointing to the strength, to call attention to it. Also, make sure labels are facing forward when bottles are stored on a shelf.

IV fat emulsion needs a filter. A change in the package insert for intravenous fat emulsions used in nutrition (e.g., INTRALIPID, NUTRILIPID LIPOSYN III from Hospira is currently out of stock) indicates a 1.2 micron filter should be used when administering these products. This is also a change from some product labeling that stated filters are not recommended, or if filtration is used, then a filter of less than 1.2 micron pore size must not be used. Newer fat emulsion labeling states: “Use a 1.2 micron filter with Intralipid (strength). Filters of less than 1.2 micron pore size must not be used.” There may be confusion about this change. For example, when Fresenius Kabi went from EXCEL to BIOFINE containers last year, the product label was simultaneously updated (June 2015) to reflect the new filter requirement.
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**OxyCODONE exposure increases.** On the other hand, higher potency oxyCODONE (OXYSYMPTON, others) prescriptions, alone or in combination with acetaminophen (PERCOCET, others), have continued to increase steadily. From 2008 through the first quarter of 2015, exposure to oxyCODONE alone nearly doubled, from 3.4 million to 6.2 million prescriptions per calendar quarter. Although oxyCODONE prescription numbers are only one-third of those of HYDROcodone products, oxyCODONE accounted for more than twice as many overdose cases in emergency departments, according to the Drug Abuse Warning Network (DAWN). Thus, oxyCODONE use has been a target of many regulatory policies including abuse-resistant formulations of extended-release oxyCODONE, a risk management program, strengthened warnings for long-acting opioids, and physician education to urge compliance with prescribing instructions.

**Growth most rapid for high-potency opioids used to treat dependence.** The most rapidly growing group of prescribed opioids are long-acting, higher potency drugs including methadone and buprenorphine, which are used for the treatment of dependence and are intended to block withdrawal effects without producing euphoric mood changes. Products with buprenorphine were the fastest growing among the 13 most frequently prescribed opioids—an increase of 67% since early 2011 to reach 3 million prescriptions in the second quarter of 2015. These data do not show whether the increase reflects greater numbers of patients with opioid addiction, a higher rate of addiction treatment, or both.

**Growth with low-potency opioids.** Low-potency opioid use—primarily cough medications—also grew moderately. The saw-tooth pattern in Figure 1 (graph C on page 3) indicates seasonal use during the winter quarters.

**Conclusion.** Our analysis shows that additional DEA restrictions on the most widely used opioid—HYDROcodone with acetaminophen—greatly reduced exposure to the drug. Less reassuring was the steady increase in the use of higher potency opioids (Figure 1, graph D on page 3) such as oxyCODONE. Therapeutic drugs containing opioids have been a major safety problem for more than a century. The Centers for Disease Control and Prevention (CDC) reported 18,893 overdose deaths in 2014 from licit and illicit use of opioids, a 14% increase from the previous year, emphasizing again the public health risks of these drugs. The sheer numbers rank it among the most important causes of accidental death. By comparison, other deaths in 2013 included 19,974 homicides and 35,369 motor vehicle accident deaths. Controlling the use of opioids is greatly complicated by the lack of alternatives for treating moderate to severe pain, and the widespread need for this treatment. Managing the risks of a product that has substantial hazards but needs to be widely available for legitimate use is a safety challenge of the first magnitude.

**Update on new diabetes drugs**

**Rapid growth of new diabetes drugs.** Both prescription volume and adverse drug event reports are increasing rapidly for canagliflozin (Invokana), dapagliflozin (Farxiga), and empagliflozin (Jardiance). These medications belong to a new class of drugs used for treating type 2 diabetes that blocks the SGLT2 protein, which binds to sugar and transports it back into circulation. The drugs lower blood sugar by causing the kidneys to excrete some of the glucose rather than returning it to circulation. Despite the lack of long-term data on safety and benefits, these new drugs have moved rapidly into widespread clinical use. Canagliflozin, approved in 2013, reached 1.1 million dispensed outpatient prescriptions in the second quarter of 2015 according to data from IMS Health, followed by dapagliflozin with 411,000 and empagliflozin with 136,000, both approved in 2015.

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Reported adverse events. Adverse drug event reports over the last 12 months increased roughly in line with patient exposure, with 5,484 new cases for canagliflozin, 1,805 for dapagliflozin, and 455 for empagliflozin. The most frequently reported side effects of all three drugs are genital fungal or bacterial infections. For canagliflozin, 1,464 infection cases (27% of all cases) were reported in 12 months; 379 (21%) for dapagliflozin, and 93 cases (20%) for empagliflozin. While these infections are normally treatable and occur frequently without SGLT2 inhibitor drug treatment, the relative risk in clinical trials was 3- to 4-fold. The presence of glucose in the urine and bladder creates a favorable environment for infections, and FDA also warned of bacterial infections that spread to the urine or kidneys with potentially life-threatening consequences. In December 2015, FDA warned that it had identified 19 cases of urosepsis or kidney infections, all of which required hospitalization, including two that required hemodialysis because of acute kidney failure.

We also observed increasing numbers of reports of metabolic acidosis—a potentially life-threatening disorder not understood prior to approval that has been the focus of two FDA Drug Safety Communications. In its May 2015 communication, the FDA identified 20 cases. In a December 2015 update, the agency identified 73 cases. Our most recent adverse event data identifies many additional possible cases, including a total 168 cases for canagliflozin, 80 cases for dapagliflozin, and 12 cases for empagliflozin. Because it is not known how many cases go unreported, it is not possible to estimate the incidence of this adverse effect.

Conclusion. There are reasons to ask whether many of the mechanisms for lowering blood sugar still make sense biologically. The earliest oral diabetes medications—sulfonylureas—work by stimulating the pancreas to secrete more insulin. But is this a good idea in patients whose insulin-secreting cells are already impaired? A second group of agents—thiazolidinediones—lower blood sugar by inducing fat cells to absorb more circulating glucose. But is it a good idea in mostly obese patients to induce their fat cells to absorb more sugar, thereby causing additional weight gain? Similar questions could be asked about this new class of drugs—SGLT2 inhibitors that cause some of the circulating glucose to flow into the bladder and urinary tract, which normally do not have substantial glucose concentrations.

The rapid market uptake of SGLT2 inhibitors brings new uncertainties about the effects of treatment on the health of patients with type 2 diabetes. Postmarket surveillance data indicate thousands of cases of genital fungal and bacterial infections, mostly in women, mirroring the results of clinical trials (11% of women and 4% of men). To these well-characterized risks are added many fewer but more severe cases of metabolic acidosis and other adverse effects on the kidneys. Whether the long-term clinical benefits of these drugs outweigh the increasing evidence of their risks remains uncertain.

The full QuarterWatch™ report with references can be viewed at: www.ismp.org/quarterwatch/default.aspx.
ISMP Safe Medication Management Fellowship

**Location and Term:** The 12-month Fellowship commences summer 2016 at the Pennsylvania (near Philadelphia) office of ISMP. Relocation to the Philadelphia area is required.

**Description:** The Fellowship offers a nurse, pharmacist, or physician with at least 1 year of postgraduate clinical experience an unparalleled opportunity to learn from and work with some of the nation’s experts in medication safety. Now in its 24th year, the Fellowship allows the candidate to work collaboratively with practitioners in various healthcare settings to assess and develop interdisciplinary medication error-prevention strategies.

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Information and applications can be found at: [www.ismp.org/profdevelopment/](http://www.ismp.org/profdevelopment/).

Applications can also be requested by calling 215-947-7797.

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The application deadline for all Fellowship Programs is **March 31, 2016**.