

# Community/Ambulatory Care

## ISMP Medication Safety Alert!®

Educating the Healthcare Community About Safe Medication Practices

### QuarterWatch™ 2016 Annual Report: Signals for oral anticoagulants and drugs with withdrawal effects



The latest issue of ISMP's **QuarterWatch™** (see box below) is an annual report that focuses on drugs and specific adverse events that affect large populations and involve substantial numbers of serious injuries reflected in 1.2 million reports submitted to the US Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS) during 2016. Two critical topics in the 2016 annual report are injury from oral anticoagulants and drugs with withdrawal effects.

#### Adverse Drug Event Reporting for 2016

Exposure of the US population to therapeutic drugs is extensive. In 2016, a total of 4.5 billion outpatient prescriptions were dispensed, a 1.9% increase over 2015, according to QuintilesIMS. Of that total, 89.5% were for generic drugs, the remainder for brand name drugs.

In calendar year 2016, FDA received 1,165,073 new reports of adverse events from the therapeutic use of prescription and over-the-counter drugs, a 1.9% decline from the previous year. This marks the first annual decline since the year 2000. Event reporting is voluntary for consumers and health professionals, who can report suspected events either directly to FDA (n = 50,878 reports) or to drug manufacturers (n = 1.1 million reports). A few drugs have special restrictions and reporting requirements that generate much larger numbers of reports than for drugs prescribed and distributed through normal pharmacy channels.

One indicator of drug risks to the US public is the subtotal of new adverse event reports that are domestic in origin and are fatal, disabling, or serious enough to result in hospitalization or have other severe medical consequences. In 2016, FDA received 311,790 reports in this category, a decline of 8.4% from the previous year. The annual toll included 45,255 (14.5%) patient deaths, and 110,179 (35.3%) cases requiring hospitalization. For 8.1% of the 2016 cases, a medication error was shown as contributing to the injury reported. These annual totals include the new data released for 2016 Q4. The FAERS report totals underestimate the extent of drug-related injuries actually occurring, with wide variation among drugs and events. Published estimates show that between 1% and 34% of all serious events are reported, including approximately 8-10% for brand name drugs.

The types of injuries reported affected every body system and include severe damage  
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#### What is QuarterWatch™?

**QuarterWatch™** is the publication of 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 and data analysis, excerpts of all domestic and foreign reports it receives into the FDA Adverse Event Reporting System (FAERS). The goal is to identify signals that may represent important drug safety issues which often require further investigation to determine their frequency and establish a causal relationship to the suspect drug.

#### 20th Annual ISMP Cheers Awards

Each year, ISMP celebrates individuals and organizations that have set a standard of excellence in the prevention of medication errors during the previous 12 months. Nominations for this year's **Cheers Awards** will be accepted through **September 9**. ISMP accepts outside nominations, including self-nominations. The prestigious awards spotlight efforts from all healthcare disciplines, including nursing, medicine, and pharmacy, and winners have represented all practice areas, including acute care, long-term care, ambulatory care, and community pharmacy settings. To submit a nomination, visit: [www.ismp.org/sc?id=1777](http://www.ismp.org/sc?id=1777).

### SAFETY briefs



**Name mix-up: rifAMPin and rifapentine.** A patient was started on outpatient therapy with a weekly dose of rifapentine (**PRIFTIN**) and isoniazid for 12 weeks to treat a latent *Mycobacterium tuberculosis* infection ([www.ismp.org/sc?id=2963](http://www.ismp.org/sc?id=2963)). The initial prescriptions covered the first 8 weeks of therapy, and the patient was adherent to the prescribed regimen. A problem occurred when a prescription for the final 4 weeks of rifapentine therapy was sent electronically to a pharmacy, and rifAMPin was dispensed in error. Apparently, the dispensing pharmacist had not compared the new prescription with the original prescription and dispensed the wrong medication.

A persistent clinical pharmacist at the patient's health plan, who was monitoring the therapy, discovered the error. He first contacted the dispensing pharmacy to confirm that the treatment had been changed to rifAMPin. He then contacted the patient's provider for clarification, but  
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to the kidneys and liver, fatal cardiac events, cancer, potentially life-threatening allergic/immune-mediated reactions, as well as neuropsychiatric effects such as depression, suicidal thoughts, and aggressive and violent acts. Although these largely voluntary reports capture only a fraction of the severe injuries that occur, the therapeutic use of drugs constitutes a major public health risk of the same order of magnitude as illicit use of drugs or violent crime.

### Oral Anticoagulant Drugs

Anticoagulant drugs—led by rivaroxaban (**XARELTO**)—accounted for 21,996 reports of severe injuries in the US, including 3,018 reported deaths, according to our analysis of 2016 FDA adverse event data. Practically all these injuries ( $n = 17,218$ ) were from hemorrhages, making bleeding one of the most frequently reported serious adverse drug effects of all types. This class of drugs also includes warfarin (**COUMADIN**), apixaban (**ELIQUIS**), dabigatran (**PRADAXA**), and edoxaban (**SAVAYSA**).

A separate US Centers for Disease Control and Prevention (CDC) study released in late 2016 showed that anticoagulant drugs accounted for more emergency department (ED) visits for outpatient adverse effects than any other class of drugs in therapeutic use, including opioids (non-abuse visits), antibiotics, and diabetes drugs (Shehab N, Lovegrove MC, Geller AI, et al. US emergency department visits for outpatient adverse drug events, 2013-2014. *JAMA*. 2016;316[20]:2115–25). The anticoagulant events were severe, with 48.8% requiring a hospital stay. Further, using these data, **QuarterWatch™** estimates 6.3% of patients exposed to an anticoagulant for one year will need to visit the emergency room. According to the CDC study, ED visits for anticoagulant adverse drug effects increased more than 2-fold between 2005-2006 and 2013-2014. The CDC data also illustrate that FAERS voluntary reporting underestimates the drug-related injuries actually occurring. While not strictly comparable, the CDC's systematic study shows an estimated 228,600 annual visits to the ED for anticoagulants, or more than 10 times the FAERS total number of voluntary reports.

### Drugs with Withdrawal Effects

Nausea, dizziness, electric shock-like sensations, insomnia, and anxiety—based on the 2016 **QuarterWatch™** data, these are the leading symptoms reported by patients who stopped taking a wide variety of psychoactive drugs. While issues involving opioid withdrawal are well known, the safety issue extends to drugs with even larger patient populations, most notably antidepressants and a large group of pain and anti-anxiety drugs. For many of these drug classes, the severity, duration, and likelihood of withdrawal effects is underestimated in prescribing information for physicians and *Medication Guides* for patients. In other cases, withdrawal effects were too poorly studied to support adequate estimates of injury rates.

We analyzed 4,016 reports of drug withdrawal effects in 2016 and identified 42 drugs with signals for withdrawal effects (see Table 2 in the full **QuarterWatch™** report at: [www.ismp.org/sc?id=1702](http://www.ismp.org/sc?id=1702)). When the drugs are withdrawn, especially abruptly, a wide array of symptoms occur as neurotransmitter or receptor circuits seek to readjust. The population at risk is very large. For example, one study showed that about 1 in 6 adults were taking a psychiatric drug of which 84.3% were long-term users where withdrawal effects are more likely. The four neurotransmitters or receptors associated with withdrawal effects are:

**Serotonin.** Although they have multiple effects, most antidepressants inhibit the reuptake of serotonin. The largest number of withdrawal reports in 2016 ( $n = 888$ ) was for **DULoxetine (CYMBALTA)** which is active on serotonin, norepinephrine,

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for some unknown reason, an office staff member incorrectly verified that the prescription had been changed due to gastrointestinal (GI) issues. Then, the clinical pharmacist contacted the local public health officer to inquire if the use of weekly rifAMPin in place of rifapentine was appropriate therapy in this case. The public health officer confirmed that this was not appropriate therapy and suggested having the health plan medical director contact the provider. The conversation between the health plan medical director and the provider confirmed that the regimen should not have been changed to rifAMPin, that the office staff had misspoken regarding the change in therapy due to GI issues, and that the pharmacy had made a dispensing error.

It is easy to see how this error could occur, as both rifapentine tablets and rifAMPin capsules are available in 150 mg doses, and both are rifamycin-class antibiotics with a US Food and Drug Administration (FDA)-approved indication to treat tuberculosis (TB). Additionally, most practitioners are likely more familiar with rifAMPin which may contribute to confirmation bias. While there was no immediate harm to the patient, it is possible that left undiscovered, the patient would have been inadequately treated and may have eventually developed active TB. RifAMPin has also been confused with rifAXIMin, a name pair that is included on *ISMP's List of Confused Drug Names* ([www.ismp.org/sc?id=492](http://www.ismp.org/sc?id=492)).



**Elavil OTC Sleep—not a drug!** A supplement known as **ELAVIL OTC SLEEP** (Figure 1, on page 3) contains melatonin, valerian root, and vitamins. By its name and by the way it's advertised, Elavil OTC Sleep seems at first to be an over-the-counter (OTC) formulation of amitriptyline. In a report sent to us recently, a pharmacist expressed concern about this product being misinterpreted as an amitriptyline product.

This is potentially dangerous for many reasons, including if a patient is suspected of taking an Elavil overdose.

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and dopamine receptors. Clinical discontinuation studies of antidepressants with shorter half-lives showed 46%-78% of patients experienced two or more symptoms. We also saw signals for venlafaxine (**EFFEXOR**), desvenlafaxine (**PRISTIQ**), sertraline (**ZOLOFT**), and **PAR**oxetine (**PAXIL**).

**Gamma-aminobutyric acid (GABA).** In most settings, drugs that enhance the function of GABA receptors and increase the effects of this neurotransmitter have sedative, hypnotic, or anti-anxiety effects. The most widely used GABA-related drugs are benzodiazepine tranquilizers, notably **ALPRA**zolam (**XANAX**), clonazepam (**KLONOPIN**), and **LOR**azepam (**ATIVAN**). Another widely used sleep medication, zolpidem (**AMBIEN**), also targets GABA receptors, and had a signal. A third family of drugs provide a synthetic form of GABA and can affect perceptions of pain. Withdrawal symptom signals were also identified for two drugs in this group, pregabalin (**LYRICA**) and gabapentin (**NEURONTIN**).

**Opioid.** This class of drugs is the best known for withdrawal effects, and 13 different opioids were identified in the data. It included the most potent opioid, fentanyl, the most widely used opioid, acetaminophen-**HYDRO**codone, as well as drugs to treat opioid addiction and overdose—buprenorphine, methadone, and naltrexone.

**Dopamine.** Antipsychotic drugs block normal signaling from dopamine D<sub>2</sub> receptors, but affect other neuroreceptors as well. We identified signals for the two widely used antipsychotics, **QUE**tiapine (**SEROQUEL**) and **OLAN**zapine (**ZYPREXA**). A signal was also seen for methylphenidate (**RITALIN**), which has an indirect effect on dopamine neurotransmission.

### Conclusion

This annual **QuarterWatch**™ report outlines two major drug safety issues where better focus on drug risks can substantially reduce the extent of injury. Few outpatient drug treatments cause injuries to 6% or more of the patients treated for a year. However, those risk levels are seen for oral anticoagulant drugs, a class of high-alert medications, and a CDC study shows injuries have increased. The need is great to reduce the risks associated with this class of drugs. Drug withdrawal effects are well known for the opioids; however, both FDA-approved warnings for practitioners and information for consumers give little hint of the extent of withdrawal symptoms that many will experience when discontinuing antidepressants and some other drugs. Better guidance on how to safely discontinue many drugs is needed for both practitioners and consumers. Given that 84.3% of adults who take psychiatric drugs are long-time users, we have to wonder how many have tried to discontinue the drugs and may have misinterpreted withdrawal symptoms as a sign that their symptoms were recurring, thus perpetuating long-term use.

The full **QuarterWatch**™ report including methods, data tables, and recommendations can be found at: [www.ismp.org/sc?id=1702](http://www.ismp.org/sc?id=1702).

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Which Elavil? It could also cause confusion during medication reconciliation.

The US Food and Drug Administration (FDA) has already reacted to this product. In a June 8, 2017 letter to the manufacturer, Belmora, FDA said that marketing the product violates the US Federal Food, Drug, and Cosmetic Act and is misbranded ([www.ismp.org/sc?id=2977](http://www.ismp.org/sc?id=2977)).



**Figure 1.** This over-the-counter sleep aid does not contain amitriptyline.

**Checklist for vaccination clinics.** Flu season is quickly approaching. It is time to start preparing for your vaccination clinics. The Influenza Workgroup of the National Adults Influenza Immunization Summit has a number of resources for immunizers and vaccination clinics. One particular tool is a checklist that provides step-by-step guidance to help vaccination clinic personnel follow US Centers for Disease Control and Prevention (CDC) guidelines and best practices for vaccine handling, preparation, administration, and documentation. You can access the checklist as well as a pledge for organizations to affirm that they will adhere to the best practices at: [www.ismp.org/sc?id=2976](http://www.ismp.org/sc?id=2976).

**ISMP survey on texting medical orders.** The debate regarding whether healthcare providers should be allowed to send orders via text messages continued on page 4—**SAFETY** briefs >



### Not all "Mira-" products are the same: MiraLAX vs. MiraFIBER

You may be familiar with the osmotic laxative **MIRALAX** (polyethylene glycol 3350) that was formerly a prescription drug but is now available as an over-the-counter (OTC) drug product. MiraLAX is used to relieve occasional constipation and generally produces a bowel movement in 1 to 3 days.

Another "Mira-" product is **MIRAFIBER** (methylcellulose), an OTC fiber supplement marketed to support regular bowel movements. Directly above the product

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name MiraFIBER on the container label is the statement “From the makers of MiraLAX” (**Figure 1**).

The US Food and Drug Administration (FDA) recently received a report where an elderly consumer used MiraFIBER for 3 weeks believing it was the same as MiraLAX. The consumer reportedly experienced an intestinal obstruction. We think the statement “From the makers of MiraLAX” and the similarity in the “Mira-” product names may have contributed to the mix-up between the two products.



**Figure 1.** MiraFIBER (left) is labeled “From the Makers of MiraLAX” but it does not contain MiraLAX (polyethylene glycol 3350) (right).

Keep in mind the possibility of confusion and mix-ups if you have these products in your pharmacy. Consumers and pharmacists need to be aware of the differences between these products. If you encounter any errors with these products, please report them to ISMP at: [www.ismp.org/merp](http://www.ismp.org/merp).

*ISMP thanks Grace P. Jones, PharmD, BCPS, and LCDR Chi-Ming (Alice) Tu, PharmD, FISMP, BCPS, at the FDA Division of Medication Error Prevention and Analysis, for providing this article.*

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continues in healthcare. Technology-savvy healthcare professionals have embraced the convenience and usefulness of this 21st century form of communication, while opponents feel it is too informal to properly document patient care and worry about data security and the potential impact on patient safety. However, ISMP has received very few reports of medication errors associated with texted orders, so we know little about the potential safety issues and their scope. Thus, we **encourage all newsletter readers to participate in a 15-minute survey** ([www.ismp.org/sc?id=2942](http://www.ismp.org/sc?id=2942)) before **August 31** so we can learn more about these issues from those who are most affected by them. We really need your input to help guide our work on this topic, and we are sincerely interested in your opinions!

➔ **Special Announcement**

**Last ISMP MSI workshops**

Join us for one of the last two **ISMP Medication Safety Intensive (MSI)** workshops in 2017. For more information, go to: [www.ismp.org/sc?id=637](http://www.ismp.org/sc?id=637).

**MSI dates**

September 14-15: Hackensack, NJ  
December 1-2: Orlando, FL

**2017-2018 ISMP Fellows**

ISMP welcomes **Viktoriya Ingram, PharmD**, the **2017-2018 ISMP Safe Medication Management Fellow**, sponsored by Baxter International Inc. Viktoriya joins ISMP from Consonus Healthcare in California where she worked as a Consultant Pharmacist. Viktoriya provided medication regimen reviews and medication handling audits for long-term care facilities and worked with interdisciplinary teams to improve medication effectiveness and safety. She also served on a number of interdisciplinary committees. Viktoriya received her Doctor of Pharmacy in 2011 from Albany College of Pharmacy and Health Science in NY.

Viktoriya is joined by **David Valentine, PharmD**, also a **2017-2018 ISMP Safe Medication Management Fellow**, supported by the United States Air Force (USAF). David is an active duty USAF officer who holds the rank of Major. While working in both community and inpatient pharmacy settings, he initiated collaborative practice agreements; helped treat patients diagnosed with hyperlipidemia, hypertension, and diabetes; and managed a tobacco cessation clinic. David received his Doctor of Pharmacy from Midwestern College of Pharmacy in Glendale, AZ in 2011.

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Call 1-800-FAILSAF(E), or visit [www.ismp.org/MERP](http://www.ismp.org/MERP) or [www.ismp.org/VERP](http://www.ismp.org/VERP). ISMP guarantees the confidentiality of information received and respects the reporters' wishes regarding the level of detail included in publications.

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# Medication Safety Certificate Program

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