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ISMP

Acute Care
ISMP Medication Safety Alert!®
Educating the Healthcare Community About Safe Medication Practices

QuarterWatch™ (2016 Annual Report)
Part I: Consumers at risk from drug withdrawal symptoms

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. In **Part I** of this newsletter feature, we examine the 2016 reporting totals and one critical topic in the 2016 annual report:

- Previously underestimated drug withdrawal symptoms reported by large populations of patients who have stopped taking opioids, antidepressants, and certain anticonvulsants/neuropathic pain medications, antianxiety drugs, sedative/hypnotic drugs, and various other medications

In **Part II**, which will appear in the July 27, 2017 newsletter, we will examine the other important clinical issue described in the 2016 annual report—unacceptably high risk of acute injuries linked to oral anticoagulants. The full annual report, which is now available at: www.ismp.org/sc?id=1702, also evaluates the quality and usefulness of the key drug monitoring system in the US, FAERS, and suggests a full-scale modernization of its reporting requirements to achieve better postmarketing drug surveillance in the modern age of digital information.

Adverse Drug Event Report Totals for 2016

In 2016, FDA received 1,165,073 reports of adverse events from the therapeutic use of prescription and over-the-counter (OTC) drugs, a 1.9% decline from the previous year. This marks the first annual decline in new reports since 2000, although when viewed from the perspective of a decade, there has been a large overall increase in the total number of reports submitted to FAERS (e.g., 273,100 in 2007 vs. 1.2 million in 2016). The 2016 total includes 311,790 domestic reports of injuries classified as serious, including 45,255 (14.5%) that were fatal and 110,179 (35.3%) requiring hospitalization. These injuries affected every body system and included severe damage to the kidneys and liver, fatal cardiac events, cancer, potentially life-threatening allergic reactions, as well as neuropsychiatric effects such as depression, suicidal thoughts, and aggressive and violent acts. For 8.1% of the 2016 cases, a medication error contributed to the reported injury.

Although the largely voluntary FAERS reports capture only a fraction of the severe events and injuries that might be occurring, the therapeutic use of drugs is extensive (4.5 billion outpatient prescriptions dispensed in the US in 2016), and injuries related to medication use are a major public health risk in the same order of magnitude as illicit drug use.

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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.

SAFETY briefs

HIGH-ALERT

Patient ingested cardboard "tablets" in demonstration pack! In our September 24, 2015 newsletter, we published a *Safety Brief* about the accidental dispensing of a demonstration starter pack of **XARELTO** (rivaroxaban) to a patient being discharged from the hospital. The demonstration pack is designed to look exactly like a Xarelto starter pack, but it only contains pictures of each tablet printed on a cardboard insert (**Figure 1**). This demonstration pack is supposed to be used to teach patients to take the 15 mg tablets twice a day for the first 21 days and then transition to the 20 mg tablets once daily starting on day 22. But, the demonstration pack looks very similar to

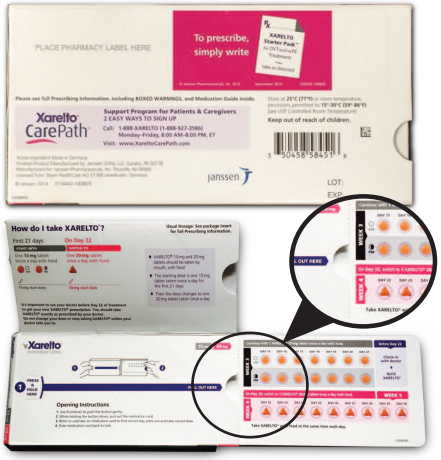

Figure 1. The demonstration starter pack of Xarelto contains pictures of the pills but no actual medication.

the starter pack, even listing the drug's national drug code and, upon opening the pack, instructions for the patient to find the correct day and press out and take the correct dose. The pack also has a tamper-proof locking mechanism where you would expect to find the drugs, and a place on the back of the package for a pharmacy label. The labeling does not identify that the product is for demonstration purposes.

Although the problem in the 2015 incident was resolved before the patient was dis-

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Drugs with Withdrawal Effects

Summary of analysis. 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 have been well studied, this safety issue extends to drugs used in even larger patient populations, most notably antidepressants, and certain anticonvulsants/neuropathic pain medications, antianxiety drugs, and sedative/hypnotics. For many of these drugs, the severity, duration, and likelihood of withdrawal effects appear to be underestimated in prescribing information and Medication Guides. In some cases, withdrawal effects have been too poorly studied to support adequate estimates of injury rates.

Methods

To identify drugs with withdrawal effects, we selected all of the 2016 reports with a Standardized MedDRA Query preferred term indicating some form of withdrawal syndrome. Then, to be included as a suspect drug, there had to be at least 10 reported cases of withdrawal effects, at least twice as many cases as expected given the total number of adverse event reports for the drug, and at least a 95% probability that the number of withdrawal effects could not have occurred by chance.

Results

Signal drugs. We identified 4,016 cases of drug withdrawal effects, with 42 drugs that met our requirements as a clear and credible signal of drug risk. The overall results are shown in **Table 1** (page 3). The proportional reporting ratio (PRR) reflects how unexpected the finding was. For example, a PRR of 4 means that the number of withdrawal syndrome reports was 4 times more than expected, given the total number of reports for that drug.

The drugs with a credible signal related to withdrawal effects include:

- 10 antidepressants that inhibit the reuptake of serotonin, including **DUL**oxetine, which had the largest number of withdrawal reports in 2016 (n = 888), **PAR**oxetine, venlafaxine, desvenlafaxine, and sertraline
- 10 drugs with effects on gamma-aminobutyric acid (GABA) neurotransmission that produce sedative, hypnotic, and antianxiety effects, including widely used benzodiazepines such as clonaze**PAM**, **ALPRAZ**olam, and **LOR**azepam; a common sleep medication, zolpidem; and two synthetic forms of GABA often used to reduce neuropathic pain, pregabalin and gabapentin
- 13 opioids, including one of the most potent opioids, fenta**NYL**; the most widely used opioid, **HYDRO**codone and acetaminophen; as well as drugs used to treat opioid addiction and overdose, buprenorphine, methadone, and naltrexone
- 2 drugs that block normal signaling from dopamine D_2 receptors, including widely used antipsychotics, **QUE**tiapine and **OLANZ**apine; as well as methylphenidate, which has an indirect effect on dopamine neurotransmission
- 6 other medications with various mechanisms of action, including a muscle relaxant (baclofen) and an antihistamine (cetirizine)

Withdrawal symptoms. The most frequently reported withdrawal symptoms in 2016 are shown in **Table 2** (page 4). Most individuals had more than one symptom and often several. The occurrence of discontinuation symptoms depended in part on how quickly the discontinued drug was eliminated from the body. For example, for antidepressants, symptoms usually appeared within a few days of stopping the medication. But withdrawal symptoms can begin within hours for short-acting opioids and may not manifest until 30 hours after discontinuation for long-acting opioids.

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charged, we suggested that the patient could have "eaten the cardboard tablets, believing the medicine was imbedded in the cardboard (stranger things have happened)." Well, according to a letter just published in the *American Journal of Health-System Pharmacy*, there's at least one documented case where this did happen (Nguyen TT, MacLasco A, Vitto MJ. Medication mismanagement using the rivaroxaban demonstration pack. *Am J Health Syst Pharm*. 2017;74[12]:872-3)! In this case, a 65-year-old woman with baseline bipolar disorder, schizophrenia, and mild dementia presented to an emergency department (ED) with severe shortness of breath. She had just been discharged from a hospital one week earlier after being diagnosed with a pulmonary embolus. She reported adherence to rivaroxaban, which had been prescribed upon hospital discharge, but repeatedly noted that the tablets "tasted like cardboard." When the patient's Xarelto pack was shown to the ED staff, it was clear that a demonstration starter pack had been dispensed in error, and that the patient had been cutting out and ingesting cardboard images of the tablets. A computed tomography (CT) scan showed progression of the previous embolus and a new, acute embolus in another lobe of the lung.

In 2015, ISMP contacted Janssen, the manufacturer, to ask the company to properly and prominently identify that the demonstration pack does not contain medication. The authors of the letter describing the more recent event also contacted the manufacturer about the medication error. These and other errors associated with "demonstration" products, including the administration of imitation intravenous (IV) solutions intended for simulation only, indicate the need for an industry-wide regulation requiring clear and prominent labeling of these products. For now, if you use any demonstration or simulation products, be sure to add an auxiliary label stating, "For Demonstration Only" or "For Simulation Only," and keep these products away from actual medications or solutions.

Name mix-up: rifAMPin and rifapentine. A patient was started on outpatient

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Discussion

Why withdrawal symptoms occur. The data in **Table 1** show that withdrawal effects are (with a few exceptions) linked to the major neurotransmitters or receptors that are the primary targets of psychoactive drugs. When drugs alter the functioning of these

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Table 1. Drugs with signals for withdrawal symptoms, 2016

Drug name	Class/Use	Cases	PRR*
Effects on serotonin			
DULoxetine	Antidepressant	888	135.6
PARoxetine	Antidepressant	275	55.3
venlafaxine	Antidepressant	119	15.4
desvenlafaxine	Antidepressant	59	19.5
sertraline	Antidepressant	55	5.0
mirtazapine	Antidepressant	37	10.8
citalopram	Antidepressant	34	5.3
bu**PROP**ion	Antidepressant	21	3.8
escitalopram	Antidepressant	15	3.7
FLUoxetine	Antidepressant	13	3.2
Effects on GABA			
pregabalin	Anticonvulsant (often used for neuropathic pain)	198	6.8
vigabatrin	Anticonvulsant	59	12.6
gabapentin	Anticonvulsant (often used for neuropathic pain)	45	2.9
clonaze**PAM**	Benzodiazepine	36	9.5
ALPRAZolam	Benzodiazepine	34	5.6
clo**BAZ**am	Benzodiazepine	34	17.2
zolpidem	Sedative/hypnotic	20	5.1
LORazepam	Benzodiazepine	18	7.2
dexmedetomidine	Sedative	18	26.8
diaze**PAM**	Benzodiazepine	16	4.5
Effects on opioid receptors			
buprenorphine/naloxone	Addiction treatment	195	38.7
oxy**CODONE**	Analgesic	159	18.2
fenta**NYL**	Analgesic	154	10.1
buprenorphine	Addiction treatment	130	13.7
naltrexone	Addiction treatment	84	16.3
naloxegol	Opioid constipation	54	28.5
morphine	Analgesic	47	6.5
tra**MAD**ol	Analgesic	33	6.3
HYDROcodone	Analgesic	19	5.8
HYDROcodone/acetaminophen	Analgesic	18	5.8
naloxone	Overdose treatment	17	38.7
morphine/naltrexone	Addiction treatment	14	19.5
methadone	Addiction treatment	13	8.3
Effects on dopamine			
QUEtiapine	Antipsychotic	26	3.1
OLANZapine	Antipsychotic	19	2.9
methylphenidate	ADHD	17	2.0
Other mechanisms			
baclofen	Muscle relaxant	315	37.7
cetirizine	Antihistamine	41	4.1
ziconotide	Analgesic	22	18.4
omeprazole	Proton pump inhibitor	17	2.0
pramipexole	Anti-Parkinson agent	13	12.2
clo**NID**ine	ADHD, hypertension	12	7.6

**PRR: Proportional Reporting Ratio*

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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). 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 rif**AMP**in 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 rif**AMP**in. He then contacted the patient's provider for clarification, but 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 rif**AMP**in 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 rif**AMP**in, 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 rif**AMP**in 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). 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. Rif**AMP**in has also been confused with rif**AXIM**in, a name pair

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neurotransmitter or receptor circuits, the central nervous system usually makes counter adjustments in signal transmission, reuptake, or receptor expression. Cellular receptor changes made in response to the intrusion of psychoactive drugs include receptor up-regulation (neurons express more receptors) or downregulation (receptors disappear), and sensitization (more easily triggered) or desensitization (become less responsive). The extent of this neural remodeling varies greatly with the individual patient, drug half-life, dose, and duration of treatment. When the drugs are withdrawn, especially abruptly, a wide array of symptoms may occur as these circuits seek to readjust. For some individuals, discontinuation is easy or accompanied by minor symptoms, and only a short taper period is needed. For others, the effects are more severe, more prolonged, and in a few cases, do not resolve.

What we know about antidepressant withdrawal. While the withdrawal effects of opioids are well studied,[1] only a few controlled studies have examined the likelihood of withdrawal symptoms after abrupt discontinuation of antidepressants. An analysis of 6 trials of **DUL**oxetine (ranked #1 in our analysis) showed that 44.4% of patients experienced at least one withdrawal symptom.[2] Another comparison showed that 66% of **PAR**oxetine patients and 60% of sertraline patients experienced withdrawal symptoms.[3] In a study of venlafaxine, 78% of patients reported withdrawal symptoms.[4] Glenmullen, and Breggin et al., describe antidepressant withdrawal symptoms and provide practical advice on discontinuation in their two books,[5,6] concluding that the symptoms are most frequent and severe for drugs with a half-life of 12 hours or less, and the least frequent for drugs that remain in circulation for days, notably **FLU**oxetine. **Table 1** (page 3) confirms the weaker signal for some antidepressants with longer half-lives. The authors also note that initial withdrawal symptoms often mimic the original problem (e.g., depression, insomnia), misleading patients into believing their problems are recurring after discontinuation of an antidepressant.

Table 2. Most frequent withdrawal symptoms, 2016*

Rank	Preferred Term	Number**	Percent
1	Nausea	955	2.8
2	Dizziness	939	2.8
3	Paresthesia***	935	2.8
4	Insomnia	831	2.5
5	Anxiety	812	2.4
6	Suicidal ideation	719	2.1
7	Headache	713	2.1
8	Agitation	694	2.0
9	Fatigue	686	2.0
10	Irritability	682	2.0
11	Hyperhidrosis	651	1.9
12	Vertigo	547	1.6
13	Confusional state	483	1.4
14	Tremor	470	1.4
15	Vomiting	448	1.3
16	Nightmare	414	1.2
17	Mood swings	408	1.2
18	Diarrhea	406	1.2
19	Sleep disorder	379	1.1
20	Pain	337	1.0

** Identified in 1% or more of cases*
*** One case could mention multiple symptoms*
****Mostly electric shock-like sensations*

Where data are lacking. Little clinical study information about withdrawal effects could be found for two groups of drugs, the synthetic GABA agents and antipsychotic drugs. The only discussion in the prescribing information for pregabalin and gabapentin was a brief mention that anti-epileptic drugs should not be discontinued abruptly due to an increased risk of seizures. No discussion of discontinuation could be identified in the package inserts for **OLANZ**apine and **QUE**tiapine. Further complicating the analysis is the fact that the synthetic GABA agents and antipsychotics are frequently combined with other psychoactive agents, notably antidepressants and benzodiazepines.

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that is included on *ISMP's List of Confused Drug Names* (www.ismp.org/sc?id=492).

Elavil OTC Sleep—not a drug! A supplement known as **ELAVIL OTC SLEEP** (**Figure 1**) 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. Which Elavil? How should the overdose be treated? It could also cause confusion during medication reconciliation regarding what the patient is really taking. The US Food and Drug Administration (FDA)

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

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. The drug's website made multiple claims that this product is a drug because it is intended for use in the cure, mitigation, treatment, or prevention of disease. The drug's website, which we first accessed on June 16, was no longer functional when we tried to access it again on June 26.

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Warnings and controls. Widespread adult exposure to drugs with withdrawal symptoms is compounded by another problem: standard information for physicians and patients is inadequate or misleading for some drugs. For some drug classes, elaborate controls, stark warnings, and other measures are in effect to manage the risks of long-term use and problems that may occur when stopping the drug. In modestly varying degrees, these measures apply to opioids, benzodiazepines, and many other sedatives. On the other hand, warnings and consumer information for some drugs are inadequate.

For example, we surveyed the FDA-approved prescribing information for the three antidepressants with the strongest signals in 2016 and found that none came close to revealing the 44.4% to 78% incidence rate of withdrawal symptoms seen in discontinuation studies.[2-4] **DUL**oxetine prescribing information lists 11 withdrawal symptoms (included in **Table 2**, page 4) but notes that each occurred at a "1% or greater" rate. But the first listed symptom, dizziness, was reported to occur in 19% of patients after long-term use.[2] While it is true that dizziness occurs in more than 1% of patients, this statement is misleading. The same is true for nausea (9.9%) and anxiety (9.8%).[2] While prescribing information recommends monitoring patients for symptoms when discontinuing treatment, no specific details are provided about how long or how slowly antidepressants may need to be tapered. While the Medication Guide warns consumers to never stop an antidepressant without first talking to a healthcare provider, it vaguely suggests that sudden discontinuation "can cause other symptoms." The prescribing information and Medication Guides for **PAR**oxetine and venlafaxine provide some additional details about withdrawal effects and taper regimens, and the Medication Guides list a few withdrawal symptoms.

Limitations

Neither our list of common withdrawal symptoms nor table of suspect drugs is comprehensive. For example, other information sources or warnings associate abrupt withdrawal of benzodiazepines with seizures and beta-blockers with rebound exacerbation of coronary artery disease. Also, other drugs with actions similar to those identified may share withdrawal effects but didn't have enough reports in 2016 to meet our study criteria.

Conclusions

Both FDA-approved warnings for physicians and information for consumers give little hint of the extent of withdrawal symptoms that many will experience when discontinuing antidepressants and some other drugs. Withdrawal effects for psychoactive drugs are not systematically studied at the time of approval, and disclosure of withdrawal studies that are conducted has been limited. And a Medication Guide just instructing consumers not to stop a medication without consulting a healthcare provider is not an adequate warning, even if some withdrawal symptoms are succinctly mentioned. Furthermore, given that 84.3% of adults who take psychiatric drugs are long-time users,[7] 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 can be found at: www.ismp.org/sc?id=1702.

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Special Announcements

ISMP webinars

ISMP webinars are a convenient way to stay ahead of new trends in medication safety and gain knowledge in key areas. To register, visit: www.ismp.org/sc?id=349.

July 27: *2017 Update on The Joint Commission Medication-Related Standards*

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2017 MSI dates
September 14-15: Hackensack, NJ
December 1-2: Orlando, FL

Cheers Awards nominations

Nominations for this year's Cheers Awards will be accepted through **September 9**. Outside and self-nominations are accepted. The prestigious awards spotlight efforts to improve medication safety from all healthcare disciplines. To submit a nomination, visit: www.ismp.org/sc?id=1777.

To subscribe: www.ismp.org/sc?id=382

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ISMP Quarterly Action Agenda

ISMP One of the most important ways to prevent medication errors is to learn about problems that have occurred in other organizations and to use that information to prevent similar problems at your practice site. To promote such a process, the following selected items from the April–June 2017 issues of the *ISMP Medication Safety Alert!* have been prepared for leadership to use with an interdisciplinary committee or with frontline staff to stimulate discussion and action to reduce the risk of medication errors. Each item includes a brief description of the medication safety problem, a few recommendations to reduce the risk of errors, and the issue number to locate additional information. Look for our high-alert medication icon under the issue number if the agenda item involves one or more medications on the *ISMP List of High-Alert Medications* (www.ismp.org/sc?id=479). The Action Agenda is also available for download in a Microsoft Word format (www.ismp.org/sc?id=2965) that allows expansion of the columns in the table designated for organizational documentation of an assessment, actions required, and assignments for each agenda item. Continuing education credit is available for nurses at: www.ismp.org/sc?id=480.

Key: ⚠ — ISMP high-alert medication

Issue No.	Problem	Recommendation	Organization Assessment	Action Required/Assignment	Date Completed
Wholesaler totes may be a source of fungal contamination					
(8, 9) ⚠	Two hospitals reported aerosolized fungal contamination in cleanrooms believed to be caused by contaminated wholesaler totes. In one hospital, *Penicillium* was discovered in both the anteroom and a laminar flow hood. Soon after, practitioners noticed the tote covers from the drug wholesaler had visible mold growing on them. *Cladosporium*, *Aspergillus*, and *Penicillium* species were cultured from the totes. Bringing grossly contaminated totes into a pharmacy increases the risk of contamination in the cleanroom.	Regularly inspect arriving totes and other packaging, and take immediate action if needed, including follow-up with the wholesaler or supplier to resolve the issue. Follow best practices developed by CriticalPoint (www.ismp.org/sc?id=2903) that call for the use of a sporicidal agent when unpacking supplies from corrugated cardboard boxes before bringing them into a cleanroom. (Sterile isopropyl alcohol is ineffective in eradicating these types of microorganisms.)			
Missed heparin-induced thrombocytopenia (HIT) diagnosis from heparin-coated device					
(9) ⚠	During a procedure, a wire and catheter had been dipped several times in a solution containing heparin before insertion to prevent clotting. The patient developed thrombocytopenia 6 days later. A lab test for HIT was positive but ignored because the primary care physician did not know about the undocumented source of heparin. Once home, the patient suffered a thrombosis in his arm, requiring amputation. Hidden and undocumented sources of heparin exposure make a diagnosis of HIT difficult.	Compile a list of drug-eluting stents and commercially available and/or user-applied medication-coated catheters/devices used in the facility. Establish a system to document in the patient's record any exposure to medication-containing devices. Look for hidden sources of medications if symptoms arise in patients suggesting possible HIT, an allergic reaction, or other drug reaction. Discontinue all sources of heparin (including heparin-coated catheters and heparin flushes), and initiate treatment if HIT is suspected or diagnosed.			

Issue No.	Problem	Recommendation	Organization Assessment	Action Required/Assignment	Date Completed
Unsafe practice: Reuse of a saline flush syringes					
(7)	A nurse was reusing prefilled saline flush syringes for multiple patients for 6 months before the unsafe practice was discovered. She believed it was cost-effective and safe if no fluids were withdrawn into the syringe. Follow-up with the 392 affected patients identified one documented case of hepatitis C transmission caused by reusing the flush syringes.	Educate nurses about injection and infusion safety, including recognition that any form of syringe and/or needle reuse is dangerous. Review related policies and procedures to ensure that the *ISMP Safe Practice Guidelines for Adult IV Push Medications* have been incorporated (www.ismp.org/sc?id=563). Monitor adherence with proper injection and infusion techniques.			
Unsafe practice: Administration of a product with a precipitate					
(7) ⚠	Six cases have been reported involving dispensing and IV administration of products despite a visible precipitate. In one case, a nurse administered a cloudy calcium gluconate and potassium phosphate infusion, which led to fatal pulmonary emboli. In another case, a baby received 10-fold overdoses of etoposide infusions with visible precipitates for 5 days. In a third case, a compounding error with **PROVAYBLUE** (methylene blue) led to precipitation of the drug, which was administered despite visible particulates.	Educate nurses, physicians, pharmacists, and pharmacy technicians to always observe medications and solutions for precipitates, and to avoid dispensing or administering the product if precipitates are visible or a solution that should be clear is cloudy. The use of an in-line filter for solutions that are prone to precipitation can help prevent particulates from entering the body; however, precipitates can still form in the tubing below the filter, and filters may become blocked, signaling a need to investigate.			
VinCRIStine extravasation unlikely with minibags					
(10) ⚠	Accidental mix-ups between intrathecal medications and IV vin**CRIS**tine have been uniformly fatal. One barrier to standardizing vin**CRIS**tine administration in minibags to prevent this error is that some nurses believe the risk of extravasation is higher than when administering the drug manually via IV push.	Twelve months of data collected at The Johns Hopkins Hospital found zero cases of extravasation among 1,300 minibag administrations of IV vin**CRIS**tine after changing from administration via syringe (www.ismp.org/sc?id=2921). *ISMP Targeted Medication Safety Best Practice* #1 calls for dilution of IV vin**CRIS**tine in a minibag to reduce the risk of mix-ups with intrathecal drugs (www.ismp.org/sc?id=417).			

Issue No.	Problem	Recommendation	Organization Assessment	Action Required/Assignment	Date Completed
Problems associated with the use of new BD U-500 insulin syringes					
(9) ⚠	Prescriber confusion led to the inappropriate prescribing of U-500 insulin syringes for outpatients taking U-100 insulin. In another organization, U-500 syringes were repeatedly prescribed in error via electronic systems because the "U-500" designation was to the far right of the entry and overlooked. Other issues include its lack of a needle guard to protect against needlesticks, and a capacity to measure only up to 250 units when patients may require higher doses.	Move the "U-500" designation to the left of the insulin syringe entry in prescribing systems. If U-500 syringes are not stocked, consider using the U-500 insulin pen to prevent dosing errors rather than using a tuberculin or U-100 syringe for U-500 insulin. During medication reconciliation, confirm the type of insulin syringe or pen patients are using to administer U-500 insulin. Refer to *ISMP's Guidelines for Optimizing Safe Subcutaneous Insulin Use in Adults* (www.ismp.org/sc?id=2966).			
Don't leave "Meds to Beds" prescription bags at bedside					
(8)	"Meds to Beds" programs bring prescription drugs to the patient's bedside prior to discharge and provide pharmacists with an opportunity to educate patients about their medications. We recently learned of an event in which a nurse gave a patient his medications, and then the patient opened the bag of discharge medications left at the bedside and nearly took the same medications.	Affix an auxiliary label to the bag of discharge prescriptions to remind patients that the medications are not for use while in the hospital. Do not leave the medications unsecured at the bedside. A plan should be established regarding where to secure these medications until discharge, after a pharmacist has reviewed them with the patient, and what to do if the patient is not in the room at the time of delivery.			
Safeguard oral chloral hydrate liquid if used for pediatric procedural sedation					
(10) ⚠	An ISMP survey indicates that oral chloral hydrate liquid is being compounded in some pharmacies for pediatric procedural sedation. About 1 in 5 reported patients spitting out the dose or vomiting, sedation failures, and prolonged sedation. Although most do not believe chloral hydrate has a role in pediatric sedation, 18% recommend its use in certain settings (e.g., radiology, neuroimaging, emergency department, dental procedures in a hospital).	If the drug is used in your facility, it should be prescribed in mg, not volumetric doses alone. Compound the drug using barcode technology (or an independent check), and dispense it in the exact prescribed amount. Only trained healthcare workers should administer the drug in a facility with immediate access to emergency equipment/medication, and the child should be monitored by a practitioner once the drug has been administered.			

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Death due to a pharmacy compounding error					
(12)	A lethal dose of baclofen suspension was administered to a child instead of tryptophan suspension due to a selection error during the compounding process. The ingredients were not independently verified prior to compounding the oral solution. The tryptophan and baclofen (used for topical preparations) were both supplied by the same manufacturer, with similarly designed labels, a white powder, and stored right next to each other.	Use ready-made products whenever possible. If compounding is necessary, ensure compliance with accepted standards (USP <795>) and conduct an independent double check of all ingredients prior to mixing, using barcode technology to augment the process. Label chemicals used for compounding with unique item numbers and barcodes. Segregate compounding ingredients intended for a single route of administration.			
Despite technology, verbal orders persist, read back is not widespread, and errors continue					
(10)	An ISMP survey on verbal orders suggests they are still used frequently despite electronic prescribing. Nearly half read back verbal orders less than 50% of the time, and 9% never read back the orders. The potential to mishear or mistranscribe verbal orders is high given different accents, dialects, pronunciations, sound-alike drug names, and background noise. About 14% of respondents were aware of an error caused by verbal orders in the past year.	Limit verbal orders to emergencies or when the prescriber is physically unable to electronically transmit, write, or fax orders. Except in emergencies, do not allow verbal orders for entire order sets when admitting or discharging patients. Transcribe verbal orders directly into the medical record, and read back the order. Assess how prevalent reading back orders is, and take any necessary steps to help practitioners fulfill this safety check, which is the single most important strategy to reduce errors with verbal orders.			
Divided methotrexate doses may lead to overdoses					
(7) ⚠	A patient with arthritis was hospitalized after taking daily methotrexate, misunderstanding the directions on the prescription vial to "Take 6 tablets by mouth weekly. Take 3 tablets in AM and 3 tablets in PM." The use of divided oral doses at 12 hour intervals, given as a course dose once weekly, has contributed to accidental daily methotrexate administration.	If possible, program computers to default to a weekly dose, avoid confusing instructions on a patient's prescription label if divided dosage regimens are used, and verify patient understanding of the directions for use. When possible, prescribe the drug as a once weekly single dose, and dispense the drug in 4-week dose packs when used for non-oncologic indications.			