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ISMP 25 YEARS ADVANCING MEDICATION SAFETY

Acute Care ISMP Medication Safety Alert!®

Educating the Healthcare Community About Safe Medication Practices

QuarterWatch™ (includes new data from Quarter 2, 2019)

Methotrexate errors, trends among addictive drugs, and underreporting of serious events

The latest issue of ISMP's QuarterWatch™ describes findings that focus on:

- Confusion about daily-vs-weekly doses of oral methotrexate that has led to patient harm and death
- Growth in adult use of prescribed amphetamine-like stimulants while exposure declines for use of therapeutic opioids
- Underreporting of serious adverse drug events to the US Food and Drug Administration (FDA)

The following is a summary of the full QuarterWatch™ report, which can be found with references at: www.ismp.org/node/482. A description of QuarterWatch™ is also provided.

Preventable Oral Methotrexate Errors

Methotrexate is a high-alert medication with a narrow therapeutic index and an exceptionally wide range of doses and duration of treatment. It has a Boxed Warning listing 11 different risks, all serious and many fatal. Examples include bone marrow suppression, renal impairment, hepatotoxicity, tumor lysis syndrome, opportunistic infections, and severe toxic reactions. It was first approved in 1953 to treat advanced cancers. However, oral use has grown rapidly, primarily as a treatment for rheumatoid arthritis and psoriasis. From 2013 to 2017, we estimate that the number of people exposed to methotrexate nearly doubled, from 561,000 to 1 million patients.

For non-oncologic uses, it is essential that methotrexate be taken only on a *weekly* basis rather than *daily*. The consequences of daily administration are dire. Even 1 week of daily administration can result in many painful and severe adverse effects, including death. There are few oral medication errors with more immediate and severe consequences.

We analyzed 14 reported cases of mistaken daily administration of methotrexate reported to FDA in the 18 months ending with June 30, 2019. All occurred in patients age 65 years or older. In 5 cases, the patients died; the other 9 patients required hospitalization. In some cases, death and injury were the result of daily administration for 1 week or less.

In 6 of these cases, the error was made by the patient. An older population is likely to take multiple *daily* medications and have trouble reading the instructions on medication labels; thus, it is not surprising some patients became confused. The risk of confusion is worsened if the "weekly" dose is ordered in 3 smaller divided doses taken 12 hours apart. Patients have also been confused by directions for escalating doses. For example, instructions on a methotrexate (2.5 mg) prescription vial to "Take 3 tablets by mouth 1 day a week for 2 weeks then increase to 4 tablets by mouth 1 day thereafter" led to taking 3 tablets daily. Within 5 days, the patient was hospitalized with septic shock, pancytopenia, and hypotension. Even the FDA-approved Patient Information section of the prescribing information fails to prominently highlight the detrimental consequences of daily oral methotrexate dosing for rheumatoid arthritis and psoriasis. Notably, the warning against daily administration is buried about halfway through the Patient Information in a general paragraph about dosing and thus fails to effectively communicate the potentially fatal consequences of non-adherence to weekly administration.

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SAFETY briefs

HIGH-ALERT

Tragic error involving fentaNYL nasal spray. The Drug Commission of the German Medical Association recently communicated through the International Medication Safety Network's (IMSN) member-only blog about a tragic error that happened with **INSTANYL**, a brand of fenta**NYL** nasal spray available in Europe. It is intended to be used in cancer patients with breakthrough pain. **LAZANDA** (fenta**NYL** nasal spray) is a similar product available in the US. Unfortunately, in Germany, a 28-year-old man accidentally took 2 sprays of his partner's fenta**NYL** nasal spray after confusing it as a nasal spray he was using for a cold. Both nasal spray bottles looked very similar. He experienced respiratory depression and loss of consciousness. Despite resuscitation attempts, he did not survive.

Figure 1. Instanyl bottle and storage case available in Germany and other countries.

The product in Germany is supplied in a childproof package, including a storage case, to prevent confusion and accidental usage by children or others (**Figure 1**). How-

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In the other 8 cases, the oral methotrexate was ordered, labeled, or dispensed incorrectly. In one case, a community pharmacy dispensed a 3-month supply of methotrexate with instructions to take six 2.5 mg tablets *daily* instead of *weekly*. The patient survived after a long hospitalization.

Other adverse events consistent with some form of an overdose (but without information about how the injury occurred) were among the 1,810 domestic reports of methotrexate injuries received by FDA in the 12 months ending on June 30, 2019. Most notable were suppression of bone marrow (n = 117), mucosal inflammation (n = 54), lung fibrosis and other damage (n = 130), and infections (n = 267).

A recently published FDA-sponsored study demonstrated the extent of daily rather than weekly administration of oral methotrexate (Herrinton LJ, Woodworth TS, Eworuke E, et al. Development of an algorithm to detect methotrexate wrong frequency error using computerized health care data. *Pharmacoepidemiol Drug Saf.* 2019;28[10]:1361-8). The investigation found 3 confirmed cases of dose frequency errors requiring treatment among just 722 patients receiving their initial methotrexate prescription, a rate of 4 per thousand. (No confirmed errors were found with refills.) This incidence rate suggests the number of methotrexate dose frequency errors could be far greater than the 14 cases we investigated that were reported to FDA over 18 months.

Conclusion. Given that this oral medication can cause potentially fatal errors affecting up to 1 million people, we should ensure that adequate safety precautions are in place to protect patients. Unfortunately, we estimate that the risk for error is growing rather than declining. Patient use has nearly doubled between 2013 and 2017, and as explained on page 4 (**Extent of Underreporting**), the adverse event reporting rates for many older drugs (like methotrexate) are likely less than 1%. This means that we not only have inadequate precautions in place, but we also have a post-market surveillance system that is unable to measure the extent of this risk or assess whether we are making progress or losing ground.

We believe FDA should require manufacturers of oral methotrexate used for non-oncologic indications to take the following steps to deal with wholly preventable but often fatal errors:

- Provide oral methotrexate tablets for non-oncologic use in calendar packaging (as with alendronate [**FOSAMAX**]) to discourage daily use, and include on the package a warning that emphasizes weekly use only (e.g., "For use ONLY one day per week," "For weekly use ONLY")
- Simplify dosing schedules to take methotrexate just once a week rather than in several divided doses 12 hours apart
- Improve the Patient Information section of the prescribing information to prominently state the importance of the weekly dose regimen for the appropriate indications and the consequences of non-adherence

For decades, ISMP has highlighted for healthcare providers harmful and fatal oral methotrexate errors and how to prevent them. In fact, the *ISMP Medication Safety Alert!* has warned healthcare providers about this risk on more than 60 occasions. For years, we have recommended defaulting to a weekly dosage regimen when entering electronic orders or prescriptions for all oral methotrexate, requiring an appropriate oncologic indication for all daily methotrexate orders, and provision of patient and family education. While these are included in our *Targeted Medication Safety Best Practices for Hospitals* (Best Practice #2, www.ismp.org/node/160), compliance has been voluntary and partial. These Best Practices should be considered mandatory

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ever, as happened in Germany, that does not mean the nasal spray bottle will always be placed back into the case after use, as it should. Lazanda, available in the US, is supplied in a glass bottle in a child-resistant container (**Figure 2**) and is only available through a restricted program called the Transmucosal Immediate Release Fenta**NYL** (TIRF) Risk Evaluation and Mitigation Strategy (REMS). Pharmacies, distributors, and healthcare professionals who prescribe to outpatients are required to enroll in the program. The purpose of the TIRF REMS access program is to mitigate the risk of misuse, abuse, addiction, overdose, and serious complications due to medication errors. However, this program cannot prevent inadvertent use of the product when confused as another nasal spray.

Figure 2. Lazanda nasal spray, available in the US, is supplied with a child-resistant container (not pictured).

Outpatient prescribers of TIRF medicines are required to complete a Patient-Prescriber Form with their patients to inform them about the risks, the need to properly store the drug at all times, and how to properly dispose of unneeded medicine. Possible mix-ups with other nasal spray products should be reviewed as a warning, and patients should be reminded of the dangerous adverse effects if fenta**NYL** nasal spray is used by those for whom the medication has not been prescribed. Detailed educational material for physicians and patients is available for Instanyl, which explicitly refers to risks when used by other persons. Although not stated in the US product labeling for Lazanda, prescribing and dispensing an adequate supply of naloxone is highly recommended for patients receiving opioids at home.

HIGH-ALERT

Only one bortezomib product can be used subcutaneously. Of the three bortezomib products available on the market, only **VELCADE** is approved for subcutaneous administration. The others are labeled

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guidelines for all healthcare providers. Additionally, no more than a 30-day supply should be dispensed by community pharmacies.

Prescription Opioid Exposure Declines

The opioid crisis has triggered one of the largest and most intense public health campaigns in recent years. Among the many federal initiatives have been stricter prescribing guidelines and documentation requirements, abuse-deterrent formulations, and outreach programs for disposal of unused opioids. Nevertheless, between 2013 and 2017, reported overdose deaths associated with therapeutic or illicit use of prescription opioids have increased by 18%. However, hidden in the reports of opioid overdose deaths is a mostly favorable trend in exposure to prescription opioids: Since 2013, the therapeutic use of prescription opioids has declined steadily, and a large majority of use has been short-term (30 days or less). Changes between 2013 and 2017 (measured in reported outpatient opioid prescriptions) include the following:

- **The trend.** Overall, reported use of prescription opioids declined by 25%, from 49 million persons in 2013 to 37 million persons in 2017. Nevertheless, more than 1 in 10 Americans reported taking opioids in 2017.
- **FentaNYL**. Reported use of prescription fenta**NYL** products declined by 55%; however, the death toll from overdoses of illicit fenta**NYL** is increasing.
- **HYDROcodone and acetaminophen** (e.g., **LORCET, NORCO, VICODIN**).The most widely used opioid for many decades, this combination product declined in use by 40% between 2013 and 2017, a reduction of 8 million persons. However, a new abuse-deterrent formulation of **HYDRO**codone, **HYSINGLA ER**, acquired 2.6 million users in 2017.
- **Lower-potency opioids.** Tra**MAD**ol use declined by 19%, and codeine products by 40%. (FDA published warnings to restrict the use of codeine and tra**MAD**ol in children [www.ismp.org/ext/325], which may have contributed to the overall decline.)
- **OxyCODONE.** This opioid, frequently implicated in illicit use and overdose deaths, was an exception to the downward trend in use. Overall, 4.2 million persons reported using oxy**CODONE** products in 2017, largely unchanged from 2013.

Conclusion. The 25% reduction in prescription opioid utilization demonstrates the result of multiple public health campaigns aimed at reducing deaths from opioid overdoses. A steady stream of media publicity also has likely reduced public willingness to take opioids even for short-term pain relief. However, the reported death rates from prescription opioids have continued to increase slowly, and illicit opioid overdose deaths have grown rapidly. This suggests the need for more research into the pathways that lead to dependence and addiction to identify the most effective point for intervention. For example, short-term dispensing limited to a few days' supply might provide needed pain relief without substantial risks.

Prescribed Amphetamine and Methylphenidate Use Expands

While therapeutic opioid use declined between 2013 and 2017, we observed a substantial increase in prescriptions for amphetamine and methylphenidate products, the other major Schedule II drugs. These potent stimulants of the central nervous system (CNS) increase the release of multiple neurotransmitters, including dopamine and norepinephrine. Despite well documented risks of dependence and addiction, an estimated 7.8 million persons, about 2.4% of the US population, reported taking amphetamine products in 2017.

Overall, reported use of amphetamine and methylphenidate products increased by 37% from 2013 to 2017, with the most rapid growth among adults (66% increase) rather than children (14% increase). The changes in exposure are shown in **Table 1** (page 4).

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for intravenous (IV) administration only. Velcade can be administered IV as a bolus injection at a concentration of 1 mg/mL, or subcutaneously at 2.5 mg/mL. The other FDA-approved bortezomib products, which are available from Dr. Reddy's and Fresenius Kabi, are not labeled for subcutaneous use. Recently a hospital reported that a pharmacist dispensed the Fresenius Kabi product for subcutaneous use.

It is easy to think these products are equivalent to Velcade, but they are not. The formulation of the Fresenius Kabi product is different than that of Velcade. Dr. Reddy's was unable to verify whether its product formulation is also different than Velcade. There are no bioavailability studies to support subcutaneous administration.

The package inserts and the container labels for the Fresenius Kabi and Dr. Reddy's products mention, "For Intravenous Use Only," and there is no mention that these products should NOT be administered subcutaneously. The US Food and Drug Administration (FDA) should work with the manufacturers to help with further clarification of the proper routes of administration in product labeling. For now, "For Intravenous Use Only" should be further emphasized on the labels of the Fresenius Kabi and Dr. Reddy's products by using red type and a larger font.

Shiny foil causes reading and scanning difficulty. The product name on the label of granisetron 1 mg oral tablet unit dose packaging from Breckenridge Pharmaceutical is difficult to read. Also, we recently learned from one hospital pharmacy that the barcode would not scan in the pharmacy prior to dispensing (**Figure 1**). Either issue can lead to errors. No doubt the product would also

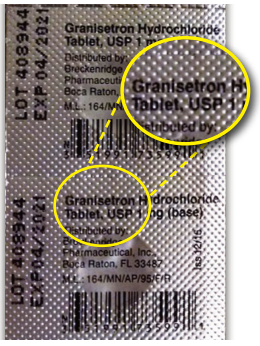

Figure 1. Shiny dimpled foil label on granisetron tablet unit dose packaging (Breckenridge) makes it difficult to read the text and scan the barcode.

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Table 1. US population exposure to amphetamine and methylphenidate products, 2013-2017

Drug Names	Frequent Brand Name	2013	2017	Percent Change
		Patients (in thousands)		
dextroamphetamine and amphetamine	**ADDERALL XR**	2,169	3,308	53%
lisdexamfetamine	**VYVANSE**	1,017	1,438	41%
methylphenidate	**CONCERTA**	1,944	2,513	29%
dexmethylphenidate	**FOCALIN XR**	530	503	-5%
Total		5,660	7,762	37%

Source: Medical Expenditure Panel Survey

The factors driving this rapid increase have not been studied; however, likely contributing factors include pharmaceutical promotion of some of the brand name drugs for adult indications (attention-deficit hyperactivity disorder [ADHD] and binge eating), off-label use by persons seeking increased alertness, continued use in adults who were initially prescribed amphetamines as children, and use in combination therapy with other psychoactive drugs.

Conclusion. The substantial growth of amphetamine and methylphenidate stimulants has gone largely unnoticed and reverses safety efforts of earlier decades to control the number of persons exposed to these drugs. While the risk of overdose with amphetamines is somewhat lower than with opioids, amphetamine and methylphenidate products have a long history of misuse. The FDA and public health community need to monitor and evaluate the rapidly increasing use in the adult population and investigate the extent to which the increase is due to promotion by manufacturers granted approved indications for adult use.

Extent of Underreporting to FDA

In the past year, more than 400,000 domestic reports of serious injury and death involving the therapeutic use of drugs were submitted to the FDA Adverse Event Reporting System (FAERS). But since this surveillance system is voluntary for consumers and health professionals, we wondered how many adverse drug events might go unreported.

To dig deeper into this question, we conducted 5 in-depth studies of specific drugs with higher rates of adverse effects and higher-quality scientific evidence about incidence—meloxicam, celecoxib, risperi**DONE**, apixaban, and adalimumab. We were limited to these case studies in part because of severe limitations in the underlying research about most adverse drug events. The examples selected have well documented but mostly high incidence rates over 1 full year of exposure: The FDA estimates that at least 2% of those treated with meloxicam or celecoxib will experience severe gastrointestinal (GI) events; studies show 9% of those treated with risperi**DONE** will develop movement disorders and 18% of those treated with apixaban will develop bleeds. Tuberculosis in patients taking adalimumab occurred much more rarely, in 2 per thousand patients. We focused on data from 2017 because it is the most recent survey available on overall patient exposure to therapeutic drugs. See the full QuarterWatch™ report for the specific methodology used to estimate the actual number of adverse events and reporting rate. Key results are shown in **Table 2** (page 5).

Overall, we found that only about 1% of the serious adverse events with our 5 primary suspect drugs had been reported to FAERS. However, variability in the reporting rate was large, ranging from less than 1 in 1,000 for severe GI harm from meloxicam, to 7.6% of cases of tuberculosis linked to the newer drug adalimumab. These cases showed that brand name drugs had much higher reporting rates than older generics. While

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prove difficult for nurses to visually identify due to glare under fluorescent light, or to scan the product at the bedside. The problem is likely due to the shiny dimpled foil label, which, as we pointed out in a December 4, 2014 *Safety Brief*, should not be used by drug manufacturers for unit dose packaging. Avoid purchasing any other products that have this type of packaging, as label readability and barcode scanning may prove difficult. Unit dose granisetron tablets are available from other manufacturers. ISMP has contacted Breckenridge about this packaging and the risk for error it imposes.

Double trouble: Similar drug names and labels. We have received several complaints about look-alike labels on Camber Pharmaceuticals products, including tablets and liquids. For example, Camber produces citalopram and escitalopram liquids in amber 240 mL bottles with highly stylized labels that contribute to their look-alike appearance (**Figure 1**). The company name, rather than the drug names, is placed at the top of the labels and is larger and more prominent than the drug names. Also, vertical stripes on the left of the label and common red color patterns make the bottles look quite similar. As a result, a hospital reported its concern about the potential for mix-ups.

Figure 1. Look-alike bottles of citalopram and escitalopram from Camber Pharmaceuticals.

What makes an actual mix-up even more likely is that the two drug names also look alike. In fact, ISMP has received several reports of mix-ups between these drugs names. For example, in the pharmacy, citalopram has been selected when processing orders for escitalopram. Citalopram is a selective serotonin reuptake inhibitor (SSRI)

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Table 2. Estimated annual adverse events and FAERS reports in 2017

Adverse Event	Primary Suspect Drug	Frequent Brand Name	Estimated Events	FAERS Reports	Reporting Rate
Severe GI harm	meloxicam	**MOBIC**	45,336	31	0.07%
Severe GI harm	celecoxib	**CELEBREX**	19,027	65	0.34%
Movement disorder	risperi**DONE**	**RISPERDAL**	33,269	265	0.80%
Bleeds	apixaban	**ELIQUIS**[1]	177,815	2,142	1.20%
Tuberculosis	adalimumab	**HUMIRA**[1]	615	47	7.64%
Total			276,062	2,550	0.92%

[1]*No generic available in 2017*

reporting is voluntary for consumers and health professionals, FDA requires drug manufacturers to report all cases they learn about in the ordinary course of business. In promoting their brand name drugs, drug manufacturers are much more likely to learn about adverse events through interactions with consumers and health professionals. Also, a rare and mostly unexpected event such as tuberculosis is more likely to be reported than more common medical problems with many possible causes.

Conclusion. We estimate that approximately 1% or fewer of serious adverse drug events that are likely occurring are subsequently reported to FAERS. In addition, the large variation in reporting rates means the number of cases reported to FAERS is not a uniform and reliable indication of how many events may be occurring in treated patients. Note that only 31 cases of severe GI disorders associated with meloxicam were reported to FAERS, even though we estimate more than 45,000 cases likely occurred in 2017. These 5 case studies do not provide enough data to support an estimate of the overall number of persons who experience serious drug-induced injuries in 1 years' time. But with more than 400,000 serious and fatal adverse events in the US reported to FAERS annually, it is clear that the extent of injury and death from the therapeutic use of drugs must be measured in the millions.

New FDA/ISMP Fellow

ISMP welcomes the **2019-2020 FDA/ISMP Safe Medication Management Fellow**: Neha Kumar, PharmD. Neha will spend 6 months at ISMP and 6 months at the US Food and Drug Administration (FDA). Prior to the Fellowship, Neha completed a PGY-1 Pharmacy Practice Residency at Monmouth Medical Center in Long Branch, NJ. She received her Bachelor of Science degree in biological sciences from the University of Maryland in Baltimore County, MD, and her PharmD from the University of Maryland School of Pharmacy in Baltimore, MD.

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antidepressant, and escitalopram, the S-enantiomer of citalopram, is also an SSRI antidepressant. The dosing for escitalopram is about half of that of citalopram, so a mix-up could lead to an incorrect dose. The branded form of escitalopram, **LEXAPRO** oral solution, is still available, but the branded form of citalopram, **CELEXA** oral solution, is not. Barcode scanning will help prevent mix-ups, but we would also recommend purchasing one of these drugs from a different manufacturer so the bottles look different.

Figure 2. The expiration date and lot number are not so easy to decipher on this Camber label for methocarbamol 500 mg tablets.

Another issue with Camber products is the way the expiration date and lot number appear. As seen with the bottle of Camber methocarbamol tablets in **Figure 2**, the expiration date and lot number are not clearly marked as such, making it difficult to recognize either. Camber has been notified about the confusion and the need for label improvements.

Special Announcement

Attend ISMP symposia in December

ISMP will offer two midday symposia at the **ASHP Midyear Clinical Meeting** in Las Vegas:

- Tuesday, December 10: **Justifying Your Return on Investment with Integrated Medication Use Technology**
- Wednesday, December 11: **Transforming Smart Infusion Pump Safety: Paving the Way with the New ISMP Guidelines**

Come learn how to identify gaps in practice, overcome challenges, and implement ISMP recommendations. Space is limited; sign up now to save your seat! For information and to register, please visit: www.ismp.org/node/23.

ISMP Safe Medication Management Fellowships

ISMP is now accepting applications for three unique **Fellowship** programs commencing in **2020**

ISMP Safe Medication Management Fellowship

Location and Term: This 12-month Fellowship commences July 2020 at the Horsham, Pennsylvania (near Philadelphia) office of ISMP. Relocation to the Horsham/Philadelphia area is required.

Description: Now in its 28th year, this Fellowship offers a **nurse, pharmacist, or physician with at least 1 year of postgraduate clinical experience** an unparalleled opportunity to work collaboratively with the nation's experts in medication safety to assess and develop interdisciplinary medication error-prevention strategies. This Fellowship is open to US citizens (or applicants with a valid US visa).

FDA/ISMP Safe Medication Management Fellowship

Location and Term: This 12-month Fellowship commences August/September 2020. The Fellow will spend 6 months at the Horsham, Pennsylvania (near Philadelphia) office of ISMP and 6 months at the Silver Spring, Maryland (near Washington, DC) office of the US Food and Drug Administration (FDA). Relocation to the Horsham/Philadelphia and Silver Spring/Washington, DC, area is required.

Description: This Fellowship, open to a **healthcare professional with at least 1 year of postgraduate clinical experience**, is a joint effort between ISMP and FDA's Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis. The Fellowship allows the candidate to benefit from ISMP's years of medication safety experience along with FDA's valuable regulatory experience focused on medication error prevention.

ISMP International Medication Safety Management Fellowship

Location and Term: This 1-year Fellowship commences July 2020 at the Horsham, Pennsylvania (near Philadelphia) office of ISMP. Relocation to the Horsham/Philadelphia area is required.

Description: This Fellowship, open to a **healthcare professional with an advanced degree and at least 1 year of experience in an acute care setting**, will help train a medication safety leader seeking a long-term career at an international level. The Fellow will be involved in global medication safety initiatives, address worldwide safety issues, and help increase global reporting of medication errors. All applicants must be **fluent in written and spoken English and be a US citizen or gain official documentation** to remain in the US for the duration of the Fellowship and to travel internationally.

A competitive stipend is provided with all Fellowship programs.

How to Apply

Information and an application can be found at: www.ismp.org/profdevelopment/.
An application can also be requested by calling 215-947-7797.

The application deadline for all Fellowship Programs is March 31, 2020.