Call to action: Longstanding strategies to prevent accidental daily methotrexate dosing must be implemented

Methotrexate is a folic acid antagonist that was originally approved to treat a variety of cancers. Used for oncologic indications, methotrexate is administered in cyclical frequencies and in variable doses based on body surface area and the type of cancer being treated. The labeled indications for methotrexate later expanded to include the treatment of nononcologic conditions, including psoriasis (approved in 1971) and rheumatoid arthritis (approved in 1988). Other nononcologic off-label uses include the treatment of Crohn's disease, multiple sclerosis, inflammatory myositis, reactive arthritis (Reiter's syndrome), graft-versus-host disease, Takayasu arteritis, uveitis, and ectopic pregnancy. For most nononcologic indications, a low dose of methotrexate is administered just once or twice weekly—for example, 7.5 mg per week when initiating treatment for rheumatoid arthritis.

Relatively few medications are dosed weekly; thus, accidental daily dosing of oral methotrexate has occurred all too frequently. This type of wrong frequency error has originated in all stages of the medication use process, from prescribing to self-administration. These errors have resulted in serious methotrexate overdoses that led to vomiting, mouth sores, stomatitis, serious skin lesions, liver failure, renal failure, myelosuppression, gastrointestinal bleeding, life-threatening pulmonary symptoms, and death.

Since 1996, errors with daily oral methotrexate for nononcologic use have been reported to ISMP and published in more than 60 of our ISMP Medication Safety Alert! newsletters. ISMP has designated oral methotrexate for nononcologic use as a high-alert medication since 2003. Although the risk of errors with oral methotrexate for nononcologic use has been known for a long time, harmful and fatal errors are still occurring.

Methotrexate Errors

Misunderstood instructions

A recent error involved a correctly filled outpatient prescription for weekly methotrexate with an escalating dose change 2 weeks later. An 8-week supply of 2.5 mg tablets (30 tablets) was dispensed with label instructions that said, “Take 3 tablets by mouth one day for 2 weeks then increase to 4 tablets by mouth 1 day per week thereafter.” Unfortunately, despite counseling, the patient was confused by the label instructions and took 3 tablets (7.5 mg) daily for 5 days before serious symptoms led his doctor to identify the error.

Overall complexity with titrated methotrexate doses or divided weekly doses have previously caused confusion. For example, in our April 2017 issue, we reported on a case involving a patient with rheumatoid arthritis who was hospitalized after mistakenly taking methotrexate 3 tablets twice a day for 4 days instead of 3 tablets in the morning and 3 tablets in the evening once a week. The prescription label said, “Take 6 tablets by mouth weekly. Take 3 tablets in AM and 3 tablets in PM.” In the labeling for methotrexate, single oral doses of 7.5 mg once weekly are recommended for initial treatment of rheumatoid arthritis. However, divided oral doses of 2.5 mg at 12 hour intervals for 3 doses, given as a course once weekly, are also recommended. It appears that the use of divided doses has added to patient confusion.

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Another recent event involved an error that was caught during hospitalization but continued upon discharge when an incorrect entry for daily methotrexate on a patient’s home medication list was not corrected. An elderly man with rheumatoid arthritis was admitted to a hospital with renal failure. At home, he had been taking oral methotrexate 2.5 mg twice weekly. The admitting nurse created a list of the patient’s home medications. The admitting physician noticed that methotrexate was missing from the home medication list in the patient’s electronic health record and added it. However, he mistakenly documented that the patient had been taking oral methotrexate 2.5 mg twice daily. He then made this an active order during the patient’s hospitalization.

Noticing the daily order for methotrexate, a pharmacist in the central pharmacy contacted the physician to let him know that he must prescribe daily methotrexate on a hospital-mandated chemotherapy order template. However, the pharmacist did not verify that the patient had an appropriate oncologic indication for the order. The physician simply complied with the pharmacist’s request and prescribed the daily methotrexate via a chemotherapy order template. Fortunately, an oncology pharmacist identified the error after talking to the patient and corrected the active order, changing the dose from twice daily to twice weekly. However, it never crossed his mind to correct the methotrexate entry on the patient’s home medication list.

The patient received the correct dose—one 2.5 mg tablet—of methotrexate on Wednesday during his 5-day hospital stay before being transferred to a skilled nursing facility (SNF). Upon discharge, the physician reconciled the patient’s list of home medications for continuation upon discharge. In doing so, he pulled the erroneous methotrexate entry over to the list of medications to continue upon discharge, thus prescribing oral methotrexate 2.5 mg twice daily for the patient while at the SNF. The patient received twice daily methotrexate for more than a week before he was rehospitalized with a change in mental status, severe neutropenia, and mucositis. Sadly, he never recovered and died in the hospital about a week later.

**Look-alike, sound-alike issues**

Some reported errors have also involved accidentally selecting methotrexate instead of the intended diuretic metOLazone. Both drug names start with “m-e-t” and have overlapping tablet strengths of 2.5, 5, and 10 mg. In one case, a pharmacy technician who was entering a telephone prescription for oral metOLazone 2.5 mg daily accidentally selected methotrexate 2.5 mg daily. She had searched for metOLazone using the first three letters of the drug name and the strength and selected methotrexate 2.5 mg by mistake since it met both criteria. The computer system did not flag the methotrexate order to require verification of an appropriate oncologic indication since the dosing frequency was daily. The medication was dispensed without the pharmacist noticing the error. The patient’s husband picked up the medication and was asked if he had any questions. When he had no questions, counseling was not provided. The patient took methotrexate 2.5 mg daily as directed on the label and died less than a month later.

**Recommendations**

Ongoing errors with oral methotrexate for nononcologic use suggest that more needs to be done to reduce the risk of patient harm. Most of the wrong frequency and wrong drug errors with methotrexate could be prevented by implementing known risk-reduction strategies. We call on clinicians, technology vendors, and drug information vendors to implement the following strategies.

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- Default to a weekly dosing schedule in prescriber and pharmacy order entry systems
- Require verification and entry of an appropriate oncologic indication in order entry systems for daily orders
- Educate patients and provide them with verbal and written instructions that specify the weekly dosing schedule and emphasize the danger with taking daily or extra doses; ask patients to repeat back the instructions to validate understanding
- Verify the dose and frequency of all medication lists and patient instructions (including discharge and ambulatory care visit summaries)
- Limit the prescription quantity to a 30-day supply (e.g., dispensing just eight 2.5 mg tablets for a 5 mg weekly dose would reduce the risk of a serious overdose)

Other important risk-reduction strategies for clinicians, technology/drug information vendors, and the US Food and Drug Administration (FDA) are provided below.

Clinicians: Medication reconciliation

- Update and edit the patient’s home medication list as needed throughout the episode of care so it can accurately guide medication reconciliation.
- Ask patients about their use of specific prescription and over-the-counter medications that could increase the risk for methotrexate toxicity.

Clinicians: Prescribing

- Provide clear directions on oral methotrexate prescriptions. Avoid “take as directed” instructions, include the strength and dose in mg, and provide clear instructions for weekly dosing. Limit the number of tablets to a 4-week (30-day) supply.
- Consider specifying a day of the week in the directions to reduce the risk that the patient will receive instructions for daily use. If possible, avoid Monday as the day to take the weekly dose, since “Monday” may be misread as “morning.”
- Include a specific clinical purpose (e.g., rheumatoid arthritis, psoriasis) within the prescription.

Clinicians: Dispensing

- Create a forcing function (e.g., electronic stop in the sales register that requires intervention and acknowledgement by a pharmacist) to ensure that every oral methotrexate prescription is reviewed with the patient or a family member when a prescription is presented or refills are processed.
- Provide clear instructions on pharmacy labels for weekly dosing and specify the day of the week (written in full, not abbreviated) the medication should be taken. Affix an auxiliary warning label (preferably preprinted) to remind patients that the dose should be taken weekly.
- When available and covered by the patient’s insurance, dispense oral methotrexate for nononcologic use in a dose pack that helps guide patients to take the proper dose weekly. Dispensing loose tablets of methotrexate for nononcologic use in prescription vials is highly discouraged if methotrexate dose packs are available and covered by the patient’s insurance.

Clinicians: Patient education

- Provide all patients with a copy of the free ISMP high-alert medication consumer leaflet on oral methotrexate (found at: www.ismp.org/ext/68).
- When possible, provide the patient with a visual calendar to clarify the weekly dosing schedule.
- If folic acid is prescribed along with methotrexate, educate patients about the differences between the medications and their respective administration schedules.1

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generated label within 24 hours of dispensing the medication. This “double-check” is a manual redundancy to ensure prescription accuracy and prevent or minimize patient harm.

We recently learned of an error that was caught by a pharmacist as part of a post-fill audit program. During order entry of a new prescription for amitriptyline 10 mg, the pharmacist selected amitriptyline 100 mg by mistake. He happened to be the only pharmacist on staff that day and he both entered and verified the prescription. (Note: Whenever possible, one person should enter the prescription in the pharmacy computer system and a pharmacist [or second pharmacist if originally entered by a pharmacist] should conduct an independent verification of the order entry.) The patient picked up the prescription the following day. Later in the evening another pharmacist was conducting the post-fill audit and caught the error. The patient was called immediately. Thankfully she had not taken any of the medication as she was not scheduled to take a dose until bedtime. If you have not already done so, we recommend you institute a post-fill audit program. If a program is already in place, consider expanding the post-fill audit program to include random checks of the will call bins to compare the label to actual product/contents dispensed.

Help your patients prepare for the new school year. Just like any other location where medications are administered, errors can and do happen at schools. As children are returning to school, prescribers and pharmacists can take steps to help parents, school staff, and school nurses safely navigate the use of medications at school. Prescribers should include complete instructions that parents as well as school staff and nurses can use for the prescription and over-the-counter medications ordered for a child. The instructions should include: name of the child; date of the order; name, purpose, and dose of the medication; explicit instructions on how of—continued on page 4—Call to action >
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- Educate patients about the key symptoms of methotrexate toxicity and to whom to report the symptoms.

**Clinicians: Patient monitoring**
- If a methotrexate dosing error is discovered, ensure the patient receives immediate medical attention.²³

**Technology/drug information vendors**
- Build computer order entry systems to ensure clinicians have access to the functionality needed to prevent methotrexate errors (e.g., default to weekly dosing, hard stop for verification of indication).
- In integrated ambulatory prescribing and pharmacy systems as well as long-term care systems and electronic medication administration records (eMARS), link methotrexate order entry and verification to laboratory results (e.g., CBC, serum creatinine, liver enzymes) to prompt review of renal function and other monitoring parameters by pharmacists, nurses, and prescribers.
- Include a robust drug–drug and drug–disease interaction module for methotrexate, with links to laboratory results where possible, so prescribers and pharmacists can effectively evaluate the potential for toxic effects.

**FDA** (which is currently evaluating the need for regulatory action)
- Change and limit the approved dosing regimen to once weekly as a single dose (not divided doses 12 hours apart or twice weekly), if appropriate. Work with drug information vendors and professional societies to disseminate any changes.
- Encourage manufacturers to package oral methotrexate for nononcologic use in patient dose packs that direct consumers to the correct weekly dosing.
- Require prominent warnings about weekly administration on the packaging of oral methotrexate for nononcologic use, as is done in other countries (Figure 1).

Figure 1. In Spain, blister packs of oral methotrexate limit the quantity of tablets available to patients. The outer carton and blister packs include the nononcologic indications and a warning that the dose is once a week for these approved indications (red text).

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> ten to administer the medication, how long the medication is to be given (e.g., during the school year, for 1 week), and by which route it should be administered; any special instructions or precautions; possible side effects; and whether or not the child may self-administer the medication. When dispensing medications, pharmacists should ensure the pharmacy label’s instructions include explicit guidance, as appropriate, on the time of administration and how long the medication should be given (e.g., during the school year, for 1 week). Pharmacists also should offer to divide, if possible, the child’s medication into 2 bottles, each with its own label, so one can be provided to the school and one can be kept at home.

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**Special Announcements**

Accepting Cheers Awards nominations
Nominations for this year’s Cheers Awards will be accepted through September 7, 2018. The awards spotlight efforts to improve medication safety from all healthcare disciplines. To submit a nomination, visit: www.ismp.org/node/1036.

Free webinar: Global medication safety
Join ISMP on September 26 for a FREE webinar, Working Together to Address Global Drug Safety Issues with Packaging and Labeling. Speakers will discuss drug product issues that contribute to medication errors around the world, and successful changes countries have made to reduce the risk of errors. Practitioners outside the US are encouraged to attend. For details, visit: www.ismp.org/node/1113.

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References