

Methotrexate Medication Incidents in the Community

A MULTI-INCIDENT ANALYSIS BY ISMP CANADA

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INTRODUCTION

Methotrexate is a folate antagonist used in oncologic and non-oncologic situations alike.^{1,9} Most commonly associated with its use as a chemotherapeutic agent, low-dose methotrexate may also be prescribed for conditions such as psoriasis, asthma and rheumatoid arthritis. The different indications in turn require varying dosing schedules, facilitating error in all steps of the medication-use process.⁹ As its mechanism of action is targeted towards the interference of DNA synthesis, replication and repair, the side effect profile of methotrexate is also significant. Toxicities may include immunosuppression, blood dyscrasias, renal dysfunction, and stomatitis.¹ Due to the heightened risk of errors associated with methotrexate, the agent is listed as a high-alert medication in the *ISMP List of High Alert Medications in Acute Care Settings*.⁴

It is essential for healthcare practitioners and patients to recognize the potential safety risks posed by the use of methotrexate. The rationale of this multi-incident analysis is to therefore examine medication incidents within the community as related to methotrexate use. Voluntarily reported through ISMP Canada's Community Pharmacy Incident Reporting (CPhIR) Program (<https://www.cphir.ca>), a multi-incident analysis was conducted to identify common themes and subthemes. An overview of the findings is provided, along with potential contributing factors and system-based solutions.

MULTI-INCIDENT ANALYSIS OF METHOTREXATE MEDICATION INCIDENTS

Reports of medication incidents involving "Methotrexate" or "MTX" or "Metoject" were extracted from the CPhIR program between April 2010 and August 2014. Of the 161 incidents retrieved, 137 met inclusion criteria and were included in the qualitative, multi-incident analysis. All medication incidents were independently reviewed by two ISMP Canada analysts.

The majority of incidents resulted in no error (i.e. near misses), with two resulting in mild harm (i.e. symptoms were mild, temporary and short-term, with no treatment or minor treatment required). As illustrated in Tables 1 to 4, the medication incidents were categorized into three themes, with each theme categorized into further sub-themes. Note that incident examples were limited by the descriptions provided by the reporters in the "Incident Description" field.

TABLE 1 – Themes and Subthemes of the Methotrexate Multi-Incident Analysis

THEMES	SUBTHEMES
Associated Medications	Drug Interactions
	Look-alike/Sound-alike Drug Names
	Concomitant Drugs
Dosing Complexities	Calculation Error
	Frequency Error
	Parenteral Route
	Multi-Medication Compliance Aids
Medication-Use Process	Prescribing
	Order Entry
	Preparation/Dispensing

TABLE 2 – Theme One – Associated Medications**SUBTHEME: Drug Interactions**

<i>Incident Examples</i>	<i>Potential Contributing Factors</i>	<i>Commentary</i>
<i>A patient, currently on methotrexate, was prescribed amoxicillin for an infection. The drug interaction was caught by the pharmacist, and the antibiotic was changed to cefprozil.</i>	<p>Lack of knowledge of clinically relevant drug interactions</p> <p>(Table 5 provides an overview of medications that may potentially increase methotrexate toxicity)</p>	<p>To prevent alert fatigue, pharmacies should utilize an updated drug interaction (DI) detection system, focusing on clinically significant interactions.</p> <p>Education of pharmacy staff of potential drug interactions should be implemented. This strategy does not necessarily require the memorization of all possible interactions, but to remind the team to be cognizant when dealing with the high-alert drug.</p>

SUBTHEME: Look-alike/Sound-alike Drug Names

<i>Incident Examples</i>	<i>Potential Contributing Factors</i>	<i>Commentary</i>
<i>A prescription for methotrexate was entered on the computer as methotrimoprazine. The error was found when the pharmacist called the doctor to clarify the dose.</i>	<p>Close proximity of storage</p> <p>Confirmation bias*</p> <p>*Definition: selective thinking, i.e. seeing what one wants to see, instead of what is actually there</p>	<p>Possible computerized solutions may include computerized alerts for look-alike/sound-alike drugs when entering prescriptions, as well as a bar-coding system when preparing prescriptions.</p> <p>Independent double checks (IDCs) may mitigate the risk of potential error. (Note: bar-coding systems are a computerized method of IDC.)</p>

SUBTHEME: Concomitant Drugs

<i>Incident Examples</i>	<i>Potential Contributing Factors</i>	<i>Commentary</i>
<i>A patient was prescribed both folic acid and methotrexate tablets. When the pharmacist was checking the prepared prescriptions, it was realized that the labels were switched.</i>	<p>Concurrently prescribed drugs*</p> <p>*Note: Folic acid and methotrexate are commonly prescribed together to decrease the toxic effects of methotrexate. An example would be their concurrent use in rheumatoid arthritis.²</p> <p>*Note: Medications may be used in combination with methotrexate in certain conditions. An example would be the use of both hydroxychloroquine and methotrexate in moderate-severe cases of rheumatoid arthritis.²</p>	<p>In the scenario where multiple medications are being dispensed simultaneously, independent double checks may mitigate the risk of potential error of mixing up the prescription labels.</p>

TABLE 3 – Theme Two – Dosing Complexities**Subtheme: Calculation Error**

Incident Examples	Potential Contributing Factors	Commentary
<p>A patient received a prescription for methotrexate injection, with instructions to inject 25 mg weekly. The prepared prescription instructed the patient to inject 2 mL weekly, when the strength of the dispensed product was actually 25 mg/mL.</p> <p>A patient received a prescription for methotrexate 10 mg once weekly, dispensed as 2.5 mg strength tablets. The weekly dose calculated was ten of the 2.5 mg strength tablets, instead of four.</p>	<p>Multiple strengths and formulations available</p> <p>Uncommon dosage schedules*</p> <p>Reliance on mental calculations</p> <p>Confirmation bias</p> <p>*Note: Methotrexate may be indicated for a number of different conditions, each of them requiring different dosage schedules. The complexity increases with the availability of both injectable and oral options, each with varying strengths.^{3,9} All factors may increase the risk of error in calculating the desired dose and/or quantity.</p>	<p>Use of handwritten calculations should be actively practiced. Independent double checks may also mitigate the risk of error, such as with verifying initial calculations.</p> <p>Pharmacy staff should be educated and familiarized with the different strengths and formulations available (i.e. those commonly stocked in the pharmacy).</p>

Subtheme: Frequency Error

Incident Examples	Potential Contributing Factors	Commentary
<p>A patient received a new prescription for methotrexate, to be taken as a once weekly dose. Although the patient received written instructions from her doctor and counseling from the pharmacist, there was a gap in communication and the patient instead took her weekly dose spread out over the course of the week. The error was found when the patient asked the pharmacist for clarification.</p> <p>A prescription for methotrexate 2.5 mg tablets instructed the patient to take 5 tablets once weekly. The prescription was entered as 5 tablets once daily.</p>	<p>Lack of standardized prescribing templates</p> <p>Uncommon dosage schedules*</p> <p>Practitioner/patient miscommunication</p> <p>Confirmation bias</p> <p>*Note: The dosing frequency changes between indications. For example, oral methotrexate may be taken as a once weekly dose for rheumatoid arthritis, or as a daily dose for a pre-defined amount of time in certain cancers^{1,2}</p>	<p>Pre-defined order sets, where the indication for methotrexate is clearly defined, may standardize the prescribing process.⁵</p> <p>Independent double checks may also mitigate the risk of potential error.</p> <p>Patient education and follow-up is essential to confirm understanding and appropriate use of the medication.⁹</p>

Subtheme: Parenteral Route

Incident Examples	Potential Contributing Factors	Commentary
<p>A patient requested a refill of her methotrexate injection. The pharmacist noticed the refill was several days late, and it was realized that the patient was re-using vials intended for single-use.</p>	<p>Multiple strengths and formulations available</p> <p>Practitioner/patient miscommunication</p>	<p>To prevent potential dispensing errors, segregation of single- and multi-use vials may also be implemented.</p> <p>Patient education and follow-up is essential to confirm understanding and appropriate use of the medication.</p>

Subtheme: Parenteral Route

Incident Examples	Potential Contributing Factors	Commentary
<p>A set of blister packages were prepared for a patient. The methotrexate tablets, intended as a once weekly dose, were dispensed as once daily dosing. The error was found after the patient had taken two extra doses.</p> <p>A prescription for methotrexate was written as 3 tablets once weekly every Sunday. In the blister packages, 1 tablet each was instead placed in the supper slot of Monday, Wednesday and Friday. Novasen and Vitamin B12 were also to be placed in those slots, causing confusion.</p>	<p>Lack of cross-referencing between packages</p> <p>Multiple medications within bubbles</p> <p>Uncommon dosage schedules</p> <p>Confirmation bias</p> <p>*Note: Multi-medication compliance aids present with additional complexities independent of the handling of methotrexate.¹⁰</p>	<p>A separate area of the pharmacy should be dedicated to preparing packages, where environmental distractions are minimal.</p> <p>Highlighting high-alert drugs (i.e. methotrexate) on compliance labels may aid in alerting both the practitioner and patient.</p> <p>Independent double checks may also mitigate the risk of potential error.¹⁰</p>

TABLE 4 – Theme Three – Medication-Use Process**Subtheme: Prescribing**

Incident Examples	Potential Contributing Factors	Commentary
<p>An MD erroneously wrote a prescription for methotrexate 25 mg weekly, when the patient usually takes methotrexate 10 mg weekly.</p>	<p>Reliance on hand-written prescriptions</p> <p>Lack of safeguards following therapy alterations</p>	<p>A systematic method of cross-referencing and documenting patient information may reduce the risk of over-dosing or under-dosing. Computerized examples include e-prescribing and automatic alerts following therapy alterations.</p> <p>Patient communication is essential to confirm acknowledgement and understanding of dose changes.</p>

Subtheme: Order Entry

Incident Examples	Potential Contributing Factors	Commentary
<p>A patient was prescribed an increase of their usual methotrexate dose. The change was not made when the previous prescription was copied.</p>	<p>Multiple strengths and formulations available</p> <p>Misreading/confusion between numbers</p> <p>Copying prescriptions</p> <p>Confirmation bias</p>	<p>The copy functionality is available in all pharmacy software systems to enhance pharmacy workflow. In order to prevent confirmation bias, policies may be considered within the pharmacy to limit the process of copying from previous prescriptions (where applicable). The inputted prescription information should be verified against the original prescriber-generated prescription order.⁷</p> <p>Educate pharmacy staff regarding the different strengths and formulations available (i.e. those commonly stocked in the pharmacy).</p>

Subtheme: Preparation/Dispensing

Incident Examples	Potential Contributing Factors	Commentary
A methotrexate prescription was dispensed to a patient who had the same last name as the intended patient. The error was found when the patient went to take their dose, and did not recognize the pill as their own.	Multiple prescriptions per patient Lack of patient verification Confirmation bias	Independent double checks may mitigate the risk of potential error. One example would be patient communication to confirm patient identity and understanding.

TABLE 5 – Medications That May Increase Methotrexate Toxicity⁸

NSAIDs	Antibiotics	Other
Salicylates	Trimethoprim/Sulfamethoxazole	Barbiturates
Naproxen	Sulfonamides	Colchicine
Ibuprofen	Penicillins	Dipyridamole
Indomethacin	Minocycline	Ethanol
Phenylbutazone	Ciprofloxacin	Phenytoin
		Sulfonylureas
		Furosemide
		Thiazide-diuretics


CONCLUSION

While methotrexate is an effective drug for a number of conditions, the potential repercussions to patient safety are significant should an error occur. This risk is further compounded by the agent's unique characteristics that may increase the probability of error occurrence. These include the complexity of methotrexate dosing, as well as the prescribing of potentially associated medications. As a high-alert drug, caution must therefore be exercised when dealing with the agent in all stages of the medication-use process.^{4,9}

System-based strategies may aid in reducing the risk of potential patient harm, and should be actively implemented in the workplace. This multi-incident analysis has demonstrated the key areas to which improvements can be made possible. These include the standardization of prescribing practices (i.e. pre-defined order sets), the implementation of safeguards in the community pharmacy (i.e. independent double checks) and a culture of patient-centered care (i.e. patient education and follow-up).

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