Medicines safety: Methotrexate

Oral methotrexate is prescribed in the community setting for the treatment of people with autoimmune conditions, such as rheumatoid arthritis. In most cases, treatment is safe and effective with appropriate pre-treatment screening, ongoing monitoring and clear communication between prescribers, pharmacists and patients about how to take methotrexate correctly. However, serious adverse effects can occur with methotrexate, even at low doses, and incorrect use is associated with a significant risk of toxicity, which can be fatal.

KEY PRACTICE POINTS

- Methotrexate is a folate antagonist that has a range of therapeutic uses depending on the dose. At high doses, methotrexate is used for chemotherapy, whereas at low doses (i.e. ≤ 25 mg per week), it exerts immunomodulatory and anti-inflammatory effects and is used to treat some autoimmune conditions, e.g. rheumatoid arthritis, psoriasis.
- All patients should be co-prescribed folic acid supplementation to reduce methotrexate-related adverse effects and toxicity (unapproved indication). Methotrexate interferes with folate metabolism, leading to folate deficiency, e.g. gastrointestinal disturbance, mouth ulcers.
- Serious adverse effects, e.g. myelosuppression, hepatoxicity and pulmonary toxicity, can occur with methotrexate (including at low doses), and there is a significant risk of toxicity if accumulation occurs due to factors such as reduced renal clearance, dosing errors (e.g. daily instead of weekly dosing) or medicine interactions
- To increase safe prescribing of methotrexate, clinicians should be familiar with the risks associated with treatment and how to manage them. Methotrexate is often initiated in a specialist care setting; however, specialist involvement is not a requirement for funded treatment and clinicians who are confident about prescribing methotrexate can initiate it in primary care.
- Pre-treatment screening should include assessment for contraindications and cautions, risk factors for toxicity, medicine interactions and immunisation status. Baseline laboratory tests include full blood count, serum creatinine, liver function tests and a pregnancy test, where appropriate.
- The patient should be provided with comprehensive information about how to take methotrexate, the risks associated with treatment and strategies for reducing risk
  - Educate patients about symptoms and signs that indicate an urgent need for medical attention, e.g. dyspnoea, non-productive dry cough, fever, severe sore throat, unexplained bruising
- Regular monitoring is essential for identifying adverse effects and reducing the risk of toxicity. Initially, follow-up should occur more often, reducing in frequency over time. During follow-up, ask about and assess for any adverse effects and toxicity, and request relevant laboratory tests.

Methotrexate: Mechanisms and clinical applications

Methotrexate is a folate antagonist that was initially developed for use as a chemotherapy medicine.[1] It acts as a competitive inhibitor of the enzyme dihydrofolate reductase, reducing the formation of tetrahydrofolate (the active form of folate derived from folic acid), an essential molecule involved in DNA and RNA synthesis.[1] This mechanism targets rapidly dividing cells and prevents them from undergoing DNA replication, underlying the therapeutic application of methotrexate in oncology regimens.[2, 3] In addition to targeting malignant cells, methotrexate also affects other rapidly dividing non-malignant cells, such as those in the gastrointestinal mucosa and bone marrow; this leads to many of its adverse effects, which can be reduced with folic acid supplementation.[4, 5]

At low doses, methotrexate has anti-inflammatory and immunomodulatory effects and is used in the community setting for people with systemic autoimmune rheumatic diseases and inflammatory dermatological conditions.[6, 7] Methotrexate is approved and indicated for severe, recalcitrant rheumatoid arthritis and psoriasis that is non-responsive to other treatments.[3] It is also used off-label for the management of other dermatological conditions (e.g. atopic dermatitis, systemic sclerosis), and inflammatory bowel disease.[7, 8] The mechanisms underlying the clinical benefits of methotrexate in these conditions are not fully understood; adenosine signalling, inhibition of pro-inflammatory cell signalling pathways and modulation of immune cell activity are believed to be involved.[1, 5]

Prescribing low-dose methotrexate safely

Low-dose methotrexate is usually initiated in a secondary care setting, or in primary care with specialist guidance, as it can be associated with significant adverse effects and has close monitoring requirements. However, specialist involvement is not a requirement for funded treatment and clinicians who are confident about prescribing methotrexate can initiate it in primary care (see: "Changes to the funding restrictions for methotrexate"). The medicine data sheet specifies that methotrexate should only be prescribed by clinicians with expertise in its use and a full understanding of the risks associated with treatment.

Low-dose methotrexate is prescribed as a **once-weekly** dose.[3] In general, methotrexate has a favourable benefit/risk profile and toxicity is rare with appropriate pre-treatment screening, monitoring and clear communication between prescribers, pharmacists and patients about how to take the medicine correctly.[1, 4] However, serious adverse effects can occur even at low doses (e.g. myelosuppression, hepatotoxicity and pulmonary toxicity), and there is a significant risk of toxicity if methotrexate is taken incorrectly, e.g. at higher doses or more frequently than prescribed, which can be fatal.[4]

Prescribers, pharmacists and patients must be familiar with the serious adverse effects that can be associated with methotrexate and strategies to reduce the risk of toxicity related to prescribing, dispensing and administration errors.

Many safety considerations with methotrexate are related to its pharmacokinetics

Methotrexate, as a folate antagonist, uses the same active transport mechanisms as folate for absorption in the gastrointestinal tract.[1, 2] These transporters become saturated at higher doses, limiting the amount that can be absorbed at one time (see: "Medicine errors are a significant cause of methotrexate toxicity").[1, 2] Following absorption, methotrexate undergoes intracellular metabolism to form methotrexate polyglutamates—active compounds of the medicine that accumulate within cells.[1, 5] This contributes to the prolonged clinical effects and risk of toxicity. Methotrexate is eliminated primarily via the kidneys through organic anion transporters; reduced renal function and interactions with medicines that compete for these transporters (e.g. NSAIDs, some antibiotics)

Changes to the funding restrictions for methotrexate

As of February, 2026, the Retail Pharmacy-specialist funding restriction that previously applied to some formulations and strengths of methotrexate, including the available oral tablets (2.5 mg and 10 mg), has been removed. This means that treatment in the community is now funded without requiring a prescription or recommendation from a specialist. The purpose of this change was to remove administrative burden and clarify the status of vocationally registered general practitioners as specialists. It is not expected to significantly alter clinical practice but rather provide greater flexibility for prescribers to initiate treatment in primary care, if they are experienced in the use of methotrexate for the condition they are prescribing it for, and it is safe and appropriate to do so.

can decrease clearance and increase the risk of toxicity (see: "Check for potential medicine interactions" and "Clinical risk factors for toxicity").[1, 4, 9]

Determine whether methotrexate is appropriate

Prior to initiating methotrexate, discuss the risks and benefits of treatment and ongoing monitoring requirements with the patient (see: "All patients prescribed methotrexate require regular laboratory monitoring").[7] Methotrexate should only be initiated if the patient understands and is able to adhere to the dosing regimen and monitoring requirements.[7]

Pre-treatment screening should include a relevant patient history to identify contraindications and cautions, risk factors for complications or toxicity, immunisation status and medicine interactions, and baseline laboratory tests. Seek advice from a relevant specialist prior to prescribing methotrexate if there is any uncertainty.

Assess for contraindications and cautions

Significant contraindications for methotrexate include serious or untreated infections (e.g. tuberculosis, hepatitis B), alcohol use disorder, pre-existing hepatic disorders (e.g. severe hepatic impairment), severe renal impairment, myelosuppression and pre-existing blood dyscrasias (e.g. anaemia).[3] Methotrexate is contraindicated during pregnancy and breast-feeding (see: "Reproductive toxicity of methotrexate").[3]

For a full list of contraindications and cautions, refer to the NZF

Identify patients at risk of complications and toxicity from methotrexate

Baseline laboratory tests. Baseline laboratory testing is recommended to identify pre-existing renal, hepatic or haematological abnormalities that may increase the patient's risk of adverse effects and toxicity with methotrexate, and to provide a reference point for future monitoring results.[3, 6] This should include a full blood count, serum creatinine and liver function tests, as well as a pregnancy test for all females of child-bearing potential (see: "Reproductive toxicity of methotrexate").[3] Additional tests may be required for some patients depending on the condition methotrexate is being prescribed for, e.g. some specialists recommend serum procollagen type III N-terminal peptide (P_3NP) testing for patients with psoriasis who may be at increased risk of hepatic fibrosis.[3]

Infection. The immunomodulatory effects of methotrexate can increase the risk of complications in people during active infections and reactivate latent or chronic infections, e.g. tuberculosis, hepatitis B.[6] Treat active infections before initiating methotrexate and consider prophylactic treatment for patients with latent tuberculosis or a history of hepatitis B in the event of reactivation.[3, 6]

Pulmonary risk. Methotrexate can be associated with pulmonary toxicity.[6] Assess the patient's history of respiratory disease and any relevant symptoms and conduct a respiratory examination (e.g. inspection, palpation, percussion, auscultation) to identify those who may be at increased risk of pulmonary complications.[6, 7] Arrange further investigations (e.g. respiratory function testing, chest X-ray) for patients with respiratory symptoms, pre-existing respiratory conditions or significant risk factors (e.g. smoking and aged ≥ 40 years); seek respiratory advice as needed.[7]

Toxicity. Assess for other factors that might increase the patient's risk of methotrexate toxicity (see: "Clinical risk factors for toxicity").[6] For example, alcohol increases the risk of hepatotoxicity with methotrexate;[7] advise patients to avoid alcohol or limit their intake to fewer than one to two standard drinks once or twice per week.[3]

Check immunisation status

Check patients are up to date with National Immunisation Schedule vaccinations, as well as influenza, COVID-19 and pneumococcus.[3, 6] Offer catch-up vaccinations prior to starting treatment. Consider vaccination against herpes zoster (Shingrix; funded for some people planning to take methotrexate) and varicella vaccination (Varilrix) in patients with no history of varicella infection or immunisation (funded for certain groups).[6, 7, 10] Immunisation with live vaccines is not generally recommended during treatment,[3, 6] unless the dose of methotrexate is ≤ 0.4 mg/kg per week.[10]

For further information on immunisation recommendations for people prescribed disease-modifying anti-rheumatic drugs (DMARDs), see: https://immune.org.nz/factsheets/immunisation-for-adults-with-immune-mediated-inflammatory-disease-imid-who-require-immunosuppressive-treatment

Check for potential medicine interactions

Consider potential interactions with the patient's pre-existing prescription medicines and ask about their use of any over-the-counter (OTC) or complementary medicines.[7]

Key medicine interactions to consider:

Trimethoprim alone or in combination with sulfamethoxazole can increase the risk of myelosuppression due to folate deficiency, by inhibiting dihydrofolate reductase.[7, 11] This risk can persist for weeks to months following methotrexate discontinuation.[6]

Other antibiotics, e.g. penicillins, tetracyclines, ciprofloxacin, can increase the plasma concentration of methotrexate by reducing renal clearance via organic anion transporters.[7, 9] In most cases, this interaction is not clinically significant with short courses of antibiotics and low-dose methotrexate, however, people with pre-existing renal impairment may be at increased risk of toxicity.[7] More frequent laboratory monitoring may be required for patients taking methotrexate who are prescribed longer courses of antibiotics, e.g. doxycycline for acne.[7]

Low-dose methotrexate can usually be continued alongside short courses of oral antibiotics prescribed for acute mild infections, e.g. uncomplicated urinary tract infections.[6] However, methotrexate should generally be withheld if a patient develops a severe infection, e.g. requiring IV antibiotics.[6]

NSAIDs, e.g. ibuprofen, naproxen, aspirin, can reduce renal clearance of methotrexate by competing with organic anion transporters in the kidney, increasing the risk of toxicity due to high plasma concentrations, particularly in patients prescribed higher doses of methotrexate and those with renal impairment.[3] NSAIDs can usually be continued with low-dose methotrexate if required (e.g. for rheumatoid arthritis) with close monitoring for toxicity and advice to avoid additional OTC NSAIDs.[3]

Additive toxicity can also occur if methotrexate is concurrently prescribed with other medicines that have similar pharmacological effects, such as those associated with:[9]

- Hepatotoxicity, e.g. azathioprine, sulfasalazine
- Myelosuppression, e.g. allopurinol, ciclosporin
- Pulmonary toxicity, e.g. leflunomide

Medicine interactions can be checked using the NZF interactions checker

Initiating low-dose oral methotrexate

Oral methotrexate is initiated at a low dose and up-titrated according to the patient's response and tolerability.[3] Doses usually range from 7.5 mg to 25 mg, once weekly, depending on the indication; see the NZF for further information. Once the patient has achieved optimal treatment response, gradually reduce the dose to the lowest effective dose.[3]

Co-prescribe folic acid

All patients taking low-dose methotrexate should also be prescribed folic acid supplementation.[6] Co-administration of folic acid can reduce the risk of gastrointestinal, hepatic and bone marrow adverse effects associated with methotrexate.[4, 6] Folic acid increases tolerability of methotrexate treatment and is associated with fewer treatment discontinuations.[6]

The recommended dose of folic acid for the prevention of methotrexate-induced toxicity (unapproved indication) is 5 mg, once weekly, to be taken on a different day to methotrexate.[3] A useful mnemonic to help patients remember when to take each medicine is "*methotrexate on Monday, folic acid on Friday*".[17]

Reproductive toxicity of methotrexate

Females. Exposure to methotrexate during pregnancy, particularly in the first trimester, is associated with an increased risk of fetal complications and miscarriage.[12] Discuss with females of child-bearing potential about the risks associated with unplanned pregnancy while taking methotrexate and the importance of using effective contraception during treatment.[3] It is generally recommended that contraception is used for three to six months following methotrexate discontinuation and that treatment is withdrawn approximately three months in advance of planned conception.[3, 13]

For further information on contraception options, see: https://bpac.org.nz/2021/contraception/options.aspx

Males. The manufacturer of methotrexate recommends that males should use reliable contraception while they are taking this medicine, and for at least three months after it is discontinued; this advice is also given in the NZF.[3, 14] However, this is an evolving area of research. The findings of a 2025 systematic review suggest that low doses of methotrexate (i.e. ≤ 25 mg/week) are not associated with negative effects on male fertility, including sperm quality and reproductive hormones, or an increased risk of adverse fetal outcomes.[15] Guidelines from the British Society for Rheumatology (2023) and European Alliance of Associations for Rheumatology (2025) state that low-dose methotrexate can be continued in males planning to conceive.[12, 16]

Adverse effects can occur at therapeutic doses

Adverse effects are the primary reason for treatment discontinuation in patients prescribed low-dose methotrexate.[17] Gastrointestinal symptoms, e.g. nausea, vomiting, diarrhoea, mucositis and mucosal ulceration, are the most common adverse effects associated with methotrexate-induced folate deficiency.[4] Other adverse effects include fatigue, dizziness, headache, cough, alopecia and cutaneous eruptions.[4]

For a complete list of adverse effects associated with methotrexate, refer to the NZF

Serious adverse effects associated with methotrexate

More serious adverse effects that can occur in people taking low-dose methotrexate include myelosuppression, hepatotoxicity and pulmonary toxicity.[3]

Myelosuppression is a significant cause of methotrexate-related fatalities.[4] Risk factors include older age, renal impairment and concurrent use of other anti-folate medicines, e.g. trimethoprim.[3] Onset can be abrupt, often occurring without abnormalities in routine laboratory monitoring results, and may be idiosyncratic or related to intercurrent illness.[6] Symptoms can include a severe sore throat, new mouth or throat ulcers (sometimes associated with mucositis), fever and unexplained bruising.[6, 7]

Hepatotoxicity. Minor elevations in liver transaminases occur frequently following initiation of methotrexate and, in most cases, are asymptomatic and transient.[4, 6] However, methotrexate can be associated with a risk of progression to hepatic fibrosis and cirrhosis.[4] The risk of hepatotoxicity is highest in people with underlying metabolic or hepatic conditions, e.g. chronic hepatic disease, obesity, dyslipidaemia, type 2 diabetes.[3, 17] People with psoriasis may be at increased risk due to the higher baseline prevalence of liver diseases, e.g. metabolic dysfunction-associated steatotic liver disease (MASLD), non-alcoholic steatohepatitis (NASH), in this population.[17] Symptoms that may indicate hepatotoxicity include nausea, vomiting, abdominal discomfort and dark urine.[3]

Pulmonary toxicity, e.g. interstitial pneumonitis, pulmonary alveolar haemorrhage, is a rare but potentially life-threatening adverse effect that can develop at any time during treatment with methotrexate and progress rapidly.[3, 7] People taking methotrexate for systemic autoimmune rheumatic diseases (e.g. rheumatoid arthritis) are at increased risk as respiratory disease may be associated with the underlying disease pathology; other risk factors include pre-existing lung disease (e.g. sarcoidosis) and smoking.[6, 7] The symptoms of pulmonary toxicity can be non-specific and may include dry cough, dyspnoea and fever.[3, 7] Methotrexate-associated interstitial pneumonitis can be associated with eosinophilia (see: "All patients prescribed methotrexate require regular laboratory monitoring").[6]

Toxicity can also occur with incorrect use of methotrexate

Methotrexate has a narrow therapeutic index.[6] The risk of toxicity is greatest with high doses, although serious toxicity has been reported in people taking low-dose methotrexate.[4] In most cases, toxicity occurs due to the accumulation of methotrexate as a result of reduced renal clearance, medicine interactions or dosing errors.[4]

Clinical risk factors for toxicity

Methotrexate is primarily excreted via the kidneys, therefore, people with reduced renal clearance are at higher risk of toxicity due to increased plasma half-life.[4] The most established risk factor for methotrexate toxicity is chronic renal impairment, i.e. chronic kidney disease (CKD) ≥ G3.[6] Other factors that can increase the risk of methotrexate toxicity include concomitant use of medicines that decrease renal clearance of methotrexate, increasing age, obesity, alcohol consumption, pre-existing liver disease, significant co-morbidities, history of toxicity with other conventional synthetic DMARDs (e.g. leflunomide, sulfasalazine) and cytopenia or liver transaminase elevations within the preceding six months.[4, 6] Combination treatment with methotrexate and another DMARD is also associated with a higher risk of toxicity.[3]

Medicine errors are a significant cause of methotrexate toxicity

The once-weekly dosing regimen of methotrexate increases the risk of dosing errors.[6] Accidental overdose can occur if a patient mistakenly takes higher doses than prescribed, e.g. taking doses daily instead of weekly or confusing 2.5 mg and 10 mg tablets.[7]

Acute toxicity following a single high dose of oral methotrexate is rare, as the maximum amount that can be absorbed at one time is limited to approximately 25 mg in an average adult (i.e. maximum bioavailable dose is low).[2] However, lower doses taken repeatedly are more completely absorbed (i.e. have a higher overall bioavailability), therefore, medicine errors resulting in successive overdose or more frequent dosing are more likely to lead to accumulation and severe toxicity.[2] A methotrexate dose of 5 – 15 mg taken for three consecutive days can be sufficient to cause toxicity, with severity dependent on the duration of exposure.[2] Chronic oral methotrexate poisoning due to repeated dosing errors can be fatal, with a mortality rate of 5 – 30%.[2]

Monitoring for adverse effects and toxicity

At each follow-up appointment, monitor the patient for adverse effects and toxicity that can be associated with methotrexate; evaluate/manage as indicated (Table 1). Also perform periodic skin examinations, especially for patients at increased risk of skin cancer; methotrexate is associated with a small increased risk of skin cancer.[3, 8]

Recognising methotrexate overdose

Symptoms that can indicate methotrexate overdose include mucositis, mouth ulcers, fever, diarrhoea, erythema and, in rare cases, cutaneous necrolysis (skin necrosis with blistering and peeling).[7] Assess adherence; ask the patient about the number of tablets they take and how often they have been taking them (including folic acid).

Chronic low-dose oral methotrexate overdose can be fatal.[2] Urgent secondary care referral is indicated for patients if overdose is suspected, as treatment for methotrexate toxicity, e.g. folinic acid and supportive care, may be required.[2]

All patients prescribed methotrexate require regular laboratory monitoring

Regular laboratory monitoring is recommended for all patients prescribed methotrexate to proactively identify adverse effects and potential indicators of toxicity (Table 2).[6] Initially, monitoring should occur more often, e.g. every two to four weeks, reducing in frequency over time, e.g. three monthly. Additional monitoring may be required if laboratory parameters become abnormal during treatment.[3] Other risk factors for toxicity, e.g. alcohol intake, should be assessed at least annually, with monitoring frequency adjusted accordingly (see: "Clinical risk factors for toxicity").[6]

Mild abnormalities in laboratory test results that occur in people taking methotrexate are often unrelated to treatment, e.g. may reflect an acute illness or underlying disease activity, and resolve spontaneously.[6] For this reason, trends in results over time should be considered alongside absolute values, as well as alternative causes of abnormalities.[6] Significant changes in laboratory parameters from previous results, persistent abnormal results or deterioration may indicate toxicity and a need for further investigation.[6]

Table 1. Managing adverse effects associated with methotrexate.[3, 7] N.B. This list is not exhaustive.

Adverse effect	Recommended action
Mouth ulcers	Reduce the dose or withhold methotrexate if ulcers are severe. Request full blood count; seek specialist advice as needed. Folinic acid (calcium folinate) mouth wash may be recommended (formulated from tablets; funded on prescription or recommendation from a Specialist). Depending on the clinical situation, consider increasing the frequency of folic acid supplementation to twice per week or more (can be up to six times per week).
Nausea and vomiting	Advise the patient to take methotrexate with food or before bed. Consider prescribing ondansetron for severe nausea (unapproved indication); prescribe 8 mg, to be taken two hours before methotrexate dose (repeated 12 and 24 hours later, if required). Subcutaneous administration (weekly) of methotrexate may be considered if nausea limits tolerability.
Infection	Manage as indicated; ideally avoid anti-folate antibiotics, e.g. trimethoprim, sulfamethoxazole. If infection is severe (e.g. requiring IV antibiotics), withhold methotrexate and seek advice from a specialist.
Severe sore throat, abnormal bruising	Withold methotrexate and request an urgent full blood count; seek haematology advice regarding any abnormalities
New or increasing dyspnoea or dry, non-productive cough	Withold methotrexate or decrease dose and seek specialist advice; referral for a chest X-ray and/or pulmonary function testing may be indicated

Table 2. Laboratory monitoring recommendations for patients taking methotrexate. N.B. Additional laboratory tests may also be required depending on the condition methotrexate is prescribed for, and management considerations for individual patients may differ; use clinical judgement and seek specialist advice, as required.

Laboratory test	Frequency	Intervention threshold	Recommended action
Full blood count*	■ At baseline[3, 6] ■ Every two to four weeks, initially, then monthly for three months.[3, 6] If the dose is stable and laboratory test results are normal, frequency can be reduced to every three to six months.[3, 6] ■ Two weeks following a dose increase.[6] If laboratory test results are normal, return to usual monitoring schedule. N.B. More frequent monitoring is recommended for patients with risk factors for toxicity[6]. Click here for details.	Platelets < 150×10^9/L[6,18] Neutrophils < 1.6×10^9/L[6] Lymphocytes < 1.0×10^9/L[6,18] Eosinophils > 0.5×10^9/L[6, 18]	May indicate toxicity; seek specialist advice and consider withholding methotrexate.[3, 6]
Liver function tests		ALT/AST over twice the upper limit of normal[6] Progressive reduction in serum albumin or a result below the lower limit of normal in the absence of an alternative cause, e.g. active inflammation[6]	
Serum creatinine		Significant deterioration in renal function or renal impairment[3, 6]	Investigate the cause of renal function decline and reduce methotrexate dose or consider withholding treatment until renal function improves.[3, 6] Methotrexate is contraindicated in patients with severe renal impairment.[3]

* Elevated mean corpuscular volume (MCV) is no longer considered a reliable predictor of methotrexate toxicity or an indication to discontinue treatment[6]

Identifying and addressing barriers to monitoring

A retrospective cohort study that used electronic health record data from patients enrolled in general practices in England to examine the impact of the COVID-19 pandemic on DMARD safety monitoring identified substantial differences in adherence between patient groups.[19] Across the study period, the rate of overdue monitoring was consistently higher for younger patients and those from minority ethnic groups, living in more socioeconomically deprived areas or living with a serious mental illness or learning disability.[19] As regular laboratory monitoring is essential for reducing the risk of methotrexate toxicity, these findings highlight the importance of identifying patients who may have difficulty adhering to the monitoring requirements for targeted interventions to promote equitable patient outcomes.

Have a pragmatic discussion with patients prior to initiating methotrexate, explaining why regular laboratory monitoring is required and the importance of adherence. Discuss potential barriers to adherence and, where possible, offer solutions, e.g. use of digital reminders, scheduling laboratory test appointments in advance, involving the patient's family/whānau for support.

Best Practice Tip: Consider placing a recall in the Practice Management System (PMS) to periodically check that patients are undergoing routine laboratory testing; a text reminder may help with patient adherence.

Methotrexate toxicity in practice

There are multiple published reports of low-dose methotrexate toxicity.[4] One case involved a male patient aged 83 years with rheumatoid arthritis who had been taking methotrexate as prescribed (10 mg, once weekly) with folic acid supplementation for 16 months before presenting to the emergency department with symptoms of toxicity, including oral sores, dysphagia and a bilateral arm rash.[11] The patient was diagnosed with pancytopenia secondary to low-dose methotrexate toxicity, which was attributed to an increase in intracellular methotrexate levels due to renal impairment. The patient had been under the care of rheumatology; prior laboratory monitoring results showed a history of gradual eGFR deterioration and mild creatinine elevation, consistent with previously undiagnosed CKD G3a. Acute kidney injury associated with a suspected orofacial infection is also thought to have contributed to the onset of toxicity. The patient was hospitalised for ten days and required treatment for methotrexate toxicity.[11]

This case highlights the value of regular laboratory monitoring for identifying opportunities for intervention to prevent methotrexate toxicity. It also emphasises the importance of interpreting results in the context of long-term trends and regularly assessing patients for factors that may increase their risk of toxicity, which can change over time.

Strategies for reducing methotrexate toxicity

A number of common-sense steps can be taken by prescribers to minimise the risk of methotrexate toxicity. Key strategies include identifying patients who may be at increased risk at the time treatment is initiated and implementing appropriate monitoring to ensure that toxicity is detected early, if it occurs.[6] Given the significant role of medicine errors in serious toxicity,[6] it is imperative to implement procedures, safeguards and reminders to ensure that the once-weekly dosing regimen is adhered to by the patient, their carer(s) and other members of the primary care team, e.g. pharmacists.[20]

Provide patient education verbally and in writing

When initiating methotrexate, provide information to patients (and their carer, if relevant) about how to take the medicine, risks associated with treatment and strategies for reducing risk, ideally both verbally and in writing.[7]

A bpac^{nz} patient information sheet about methotrexate is available from: https://bpac.org.nz/2026/methotrexate-advice.aspx. Patient information is also available from Healthify: https://healthify.nz/medicines-a-z/m/methotrexate.

Key information to convey to patients:[3, 7]

- **Methotrexate is taken once per week**; this is different to most other medicines. Organisational aids are useful for ensuring correct once-weekly dosing, e.g. phone reminders, use of pill containers, documenting doses in a record book.
- **Treatment takes some time to work**, usually 3 – 12 weeks. Taking a higher dose or the correct dose more frequently is dangerous and will **not** make the medicine work more quickly or effectively.
- **Taking folic acid consistently is important** and reduces the risk of adverse effects. Folic acid is also taken once per week, on a different day to methotrexate.
- **Regular laboratory tests are essential for safety** and adherence is a requirement for treatment
- **Avoid or limit alcohol intake** to a maximum of one to two standard drinks, once or twice per week, as consumption increases the risk of toxicity
- **Effective contraception is required during and following treatment.** Females should use effective contraception for three to six months following treatment discontinuation, and males for three months.
- **Seek urgent medical attention if adverse effects develop**, as they may indicate toxicity. Key adverse effects include:
  - Sore throat, fever, unexplained bruising, mouth ulcers – may indicate a blood disorder
  - Nausea, vomiting, abdominal pain or dark urine – may indicate liver toxicity
  - Shortness of breath, cough – may indicate respiratory effects
- **Report use of any new medicines (including OTC and complementary medicines) and avoid anti-inflammatories that have not been prescribed,** e.g. ibuprofen, diclofenac, aspirin
- **Store methotrexate in a cool, dry place that is out of sight and reach of children** to prevent accidental poisoning, e.g. a high or locked cupboard[21]
  - Patient information about the safe storage of medicines is available from: https://healthify.nz/medicines-a-z/s/storing-medicines

Be specific when prescribing methotrexate

Avoid ambiguity when prescribing methotrexate and include all relevant information about how to take the medicine correctly. To reduce the risk of dosing errors when prescribing:

- Avoid including the words "as directed" on prescriptions[22]
- Clearly specify the strength of methotrexate and write this out in full to avoid confusion about decimal point placement, e.g. "TWO AND A HALF MILLIGRAMS (2.5 mg)"[7]
- Agree on different days of the week the patient will take methotrexate and folic acid, and specify these on the prescription, avoiding abbreviations.[16] Consider using the phrase "each week" in place of "weekly", e.g. "Take one tablet on Monday each week".[22]
  - A simple mnemonic that can be used to ensure once-weekly dosing for each medicine is "*methotrexate on Monday, folic acid on Friday*"[17]
- Ideally prescribe only one strength of methotrexate tablets at a time to prevent patients mistaking 2.5 mg and 10 mg tablets[7]
- Consider limiting the quantity of methotrexate tablets to be dispensed at once, e.g. four-week supply[20]

Best Practice Tip: Check that your prescribing software defaults to once-weekly dosing for methotrexate prescriptions.

Safer dispensing of methotrexate in community pharmacy

Pharmacists should also be aware of the risks associated with methotrexate, as dispensing errors are associated with a significant risk of toxicity, e.g. incorrect medicine labelling instructing daily dosing instead of weekly, dose compliance aid packaging errors and accidental dispensing of methotrexate instead of another medicine with a similar name.

Pharmacy steps to avoid dispensing errors:[20, 22]

- Double check methotrexate prescriptions to ensure they specify the correct dose and frequency. If prescriptions are entered into the computer system manually, ensure this information is transferred correctly; consider setting weekly (instead of daily) dosing as a default for oral methotrexate.
  - Be wary of needing to order stock to dispense a prescription for oral methotrexate; this may indicate that a prescribing error has occurred
- Ensure software alerts are given appropriate attention and resolve concerns about dosing or medicine interactions with the prescriber before dispensing
- If folic acid has **not** been prescribed, contact the prescriber to check if this is needed
- Double check printed medicine labels are correct, i.e. specify once-weekly dosing and include the day of the week for each dose, written out in full
- Take extra care when dispensing methotrexate; consider implementing a specific checking system to confirm the tablet strength and quantity is correct, i.e. weekly dosing
- If methotrexate is being added to a blister pack or other compliance aid, add it last to ensure that it only appears once per week in the pack and on the right day
- Label packaging for pick up clearly so staff know that a pharmacist should review the prescription with the patient when they collect each repeat:
  - Confirm the indication
  - Reiterate the once-weekly dosing regimen
  - Explain that taking a higher dose than prescribed is dangerous
  - If 2.5 mg and 10 mg strengths are prescribed together, highlight differences in tablet appearance
  - If the strength the patient is prescribed has changed, encourage them to return any tablets of the previous strength to the pharmacy
  - Emphasise the differences in appearance between methotrexate and folic acid tablets to avoid confusion as both medicines are yellow
  - Ideally provide both verbal and written instructions and ask the patient to repeat back instructions to ensure understanding
- If medicine supply issues necessitate changes from the patient's usual regimen, e.g. differences in tablet appearance or the number of tablets required to make up their dose, ensure these are highlighted to the patient and clearly explained

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