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# Safer prescribing of high-risk medicines: tricks, tips and tales of caution


Pharmacological treatment is an integral part of the practice of medicine, and is one of the most significant factors in improving patient health. However, some medicines, when used outside of therapeutic indications or doses, or even when used appropriately, can become a “poison” rather than a “cure”.

Medicine-related adverse events can occur due to many reasons, including routine use of the medicine, an error in prescribing, acute illness and medicine interactions. Certain patients are more likely to be at risk of medicine adverse effects, e.g. elderly people, young children, people with multiple comorbidities, people taking multiple medicines and people who are immunocompromised. Certain medicines are also more commonly associated with adverse events, including those that are prescribed most often (e.g. paracetamol, NSAIDs, ACE inhibitors, statins) and those with a narrow therapeutic index (e.g. warfarin, lithium and digoxin).

In addition to medicines themselves which are associated with a higher risk of adverse effects, there are also situations in which the way medicines are prescribed can pose an increased risk. For example, prescribing medicines on discharge from hospital can result in adverse events if patients are uncertain about medicine doses or instructions, or new medicines are prescribed which are similar to, or interact with, medicines in the patient’s usual regimen. Stat dispensing (i.e. patients are given the full 90 day supply of their medicine) also has the potential to increase the risk of adverse events or pose a safety

risk, e.g. taking a medicine when it is no longer necessary, fewer visits to pharmacies and therefore less opportunity to discuss adverse effects and the potential risk of accidental poisoning or intentional overdose (although these risks can apply to any volume of some particular medicines).

One strategy for minimising the risk of harm of medicines is to have up to date knowledge, including recommended dosing, monitoring requirements and potential adverse effects to observe for. The following article on clozapine marks the beginning of a new series in Best Practice Journal, focused on medicines which have significant risks that can occur alongside their beneficial effects. The use of these medicines needs special care to reduce the likelihood of serious adverse outcomes; vigilance by both prescribers and patients is needed.

 Adverse drug reaction reporting is one of the most important sources of data for assessing the safety and quality of a medicine. If your patient has experienced an adverse effect related to a medicine, regardless of whether you feel it is serious or significant, this should be reported to the Centre for Adverse Reactions Monitoring (CARM). You can submit a report directly using the “Adverse Drug Reactions Reporting” module on your bestpractice decision support dashboard. Once opened, the tool automatically pre-populates the patient’s relevant details.



## Clozapine and its adverse effects: neutropenia, agranulocytosis and constipation

Clozapine is an atypical antipsychotic used in the treatment of patients with schizophrenia. It is the only antipsychotic shown to be effective for treatment-resistant schizophrenia, and at least one-third of patients show a moderate improvement after a 6 to 12 month trial of this medicine.<sup>1</sup> Despite there being clear benefits associated with clozapine, its use is very restricted because of significant safety concerns. Clozapine can only be initiated by a Psychiatrist for patients with schizophrenia after at least two other antipsychotics have been trialled. General Practitioners and Pharmacists have an important role in helping to recognise and manage adverse effects and medicine interactions with clozapine.

### Clozapine has significant adverse effects

Clozapine is associated with several significant adverse effects, including agranulocytosis, neutropenia, constipation (which can be severe), myocarditis and adverse metabolic effects. These adverse effects are not necessarily dose-related and may occur at any time during treatment. For this reason, patients taking clozapine require close monitoring for the development of any adverse effects, and should be regularly questioned about the onset of any symptoms.

### Clozapine can cause potentially fatal neutropenia and agranulocytosis

Clozapine has been reported to cause neutropenia in 2 – 3% of people taking this medicine and agranulocytosis in 1%.<sup>1</sup> These are rare adverse effects but can be fatal. Patients taking clozapine are monitored with regular leukocyte and differential blood counts, weekly during the first 18 weeks of treatment, followed by blood tests every four weeks for the duration of their treatment.<sup>2</sup> These blood tests are required as part of the

safety protocol for clozapine treatment. This protocol requires that patients are registered on the manufacturer's blood monitoring database and that they comply with regular blood tests in order for ongoing supply of clozapine to be made by the dispensing Pharmacist.

### What can General Practitioners do?

- Patients who present with evidence of infection, such as flu-like symptoms, sore throat or fever must have a white blood cell and differential blood count requested immediately to rule out neutropenia or agranulocytosis. It should be indicated on the laboratory form that the patient is taking clozapine and that results are required on the same day. Depending on the result, urgent haematology referral or emergency hospital admission may be required.
- Where possible, avoid prescribing other medicines concurrently which may cause additive bone marrow suppression, e.g. co-trimoxazole, trimethoprim, nitrofurantoin, carbamazepine and antineoplastics.

### Constipation can be severe and fatal

Constipation is a frequent adverse effect of clozapine; up to 60% of patients may become constipated while taking it.<sup>3</sup> A common scenario is for patients to present with symptoms of constipation, after a prolonged period (i.e. greater than one week) without having a bowel motion. The mechanism by which clozapine slows the gut is unclear but has been postulated to be due to the anticholinergic and anti-serotonergic properties of clozapine.<sup>4</sup> This hypomotility can result in intestinal obstruction, bowel ischaemia, necrosis, perforation, toxic megacolon and related aspiration pneumonia.<sup>5</sup>

Risk factors for gastrointestinal hypomotility include recent initiation of clozapine treatment, higher clozapine doses, concomitant use of other anticholinergics (e.g. benztropine and tricyclic antidepressants) and concurrent illness – some case reports suggest that illness and fever can increase serum clozapine levels and lead to an increased risk of adverse effects.

Between 2007 and 2011, the Centre for Adverse Reactions Monitoring (CARM) received 14 reports of clozapine-related gastric hypomotility; of those, two cases were fatal and another two cases were life-threatening.<sup>5</sup>

#### What can General Practitioners do?

- Treat pre-existing constipation, advise patients about the high risk of constipation when taking clozapine and provide advice about diet, exercise and fluid intake
- Ask patients regularly about bowel function; the first four months of treatment appears to be the highest risk period for developing constipation<sup>3</sup>
- Have a low threshold for prescribing laxatives for constipation; a stimulant and softening laxative such as senna with docusate or a macrogol laxative\* are appropriate options.<sup>3</sup> Regularly review treatment. An alternative option is to prescribe preventative laxative maintenance treatment, e.g. a macrogol laxative\*, in all patients treated with clozapine.<sup>6</sup>
- Where possible, avoid prescribing other constipating medicines (e.g. opioids), particularly those with anticholinergic properties (e.g. tricyclic antidepressants), for patients taking clozapine

\* Macrogol laxatives are currently only subsidised with Special Authority approval; see New Zealand Formulary for details.

#### Myocarditis and later onset cardiomyopathy have been reported

Clozapine is associated with a small but significant risk of myocarditis and cardiomyopathy. Fatalities have been reported in New Zealand.<sup>7</sup> Although these adverse effects can occur at any time, there is an increased risk of myocarditis in the first one to two months of treatment with clozapine, while cases of cardiomyopathy have generally occurred later, approximately nine months after treatment initiation.<sup>8</sup>

#### What can General Practitioners do?

- Consider the possibility of myocarditis in patients taking clozapine who present with unexplained fatigue, dyspnoea, tachypnoea, fever, chest pain, tachycardia, palpitations or other signs and symptoms of heart failure,

particularly during the first two months of treatment<sup>8</sup>

- If myocarditis is suspected, it may be useful to arrange an immediate ECG, CRP, CK, full blood count (check eosinophils in particular) and troponin tests to assess the urgency of a cardiology assessment and to indicate if hospital admission is required<sup>8</sup>
- If myocarditis or cardiomyopathy is suspected, this should be reported to the patient's Psychiatrist immediately; it is likely that clozapine treatment will be ceased

#### Clozapine can be associated with weight gain, hyperglycaemia and dyslipidaemia

Metabolic disturbances, including weight gain, dyslipidaemia, hyperglycaemia and diabetes mellitus are associated with the use of all typical and atypical antipsychotics, to varying degrees, depending on the individual medicine.<sup>2</sup> Patients taking clozapine have an increased risk of all of these adverse effects, particularly type 2 diabetes mellitus.<sup>9</sup>

#### What can General Practitioners do?

- Give practical advice about diet and exercise and help patients to find activities that they are motivated to participate in
- Monitor lipid levels, HbA<sub>1c</sub> (fasting blood glucose may be more useful in the first three months of treatment due to rapid increases in glucose levels), blood pressure, weight, waist circumference and body mass index

#### Important medicine interactions

##### Clozapine levels are affected by cigarette smoking

People who smoke metabolise clozapine faster than those who do not smoke. This is due to the aromatic hydrocarbons in cigarette smoke (it is not due to nicotine). Therefore if a person taking clozapine stops smoking their clozapine levels can become elevated, leading to adverse effects, such as seizures.<sup>7</sup> Some evidence suggests that a 50% increase in clozapine levels may occur within two to four weeks of smoking cessation. Alternatively, if a patient begins smoking during treatment, clozapine levels may decrease and therapeutic effect may be compromised requiring an increase in the clozapine dose.<sup>10</sup>

#### What can General Practitioners do?

- Ensure the patient is aware that clozapine levels are affected by smoking and to report if their smoking status changes
- Smoking cessation should be planned with the clinical

team so that this effect can be monitored and managed; clozapine plasma levels may need to be monitored and the dose reduced<sup>7</sup>

- If clozapine plasma levels are monitored appropriately, nicotine replacement treatment is safe for patients taking clozapine who wish to give up smoking

### Clozapine is subject to CYP interactions

Clozapine is metabolised by the CYP450 isoenzymes, therefore clozapine levels may be affected by the concomitant use of medicines that inhibit or induce these enzymes. Inducers will decrease clozapine levels, e.g. carbamazepine, phenytoin, rifampicin and omeprazole. Inhibitors may significantly increase clozapine levels, e.g. erythromycin and SSRIs (paroxetine and fluoxetine).

#### What can General Practitioners do?

- Avoid, wherever possible, prescribing medicines that interact with clozapine to patients taking clozapine. If there is no alternative and interacting medicines are co-prescribed with clozapine, more frequent monitoring of clozapine levels and for adverse effects will be necessary.

**ACKNOWLEDGMENT:** Thank you to **Andrew McKean**, Senior Pharmacist, Hillmorton Hospital, Christchurch for expert review of this article.

### Pharmacists – be alert for adverse effects

Pharmacists also have an important role in ensuring the safe use of clozapine.

When interacting with a patient who is taking clozapine, Pharmacists can:

- Ask regularly about bowel function
- Consider the possibility of neutropenia or agranulocytosis (and the need for referral for a white blood cell and differential blood count) in patients who present with evidence of infection such as flu-like symptoms, sore throat or fever
- Consider the possibility of myocarditis in patients who present with unexplained fatigue, dyspnoea, tachypnoea, fever, chest pain, tachycardia, palpitations or other signs and symptoms of heart failure – particularly during the first two months of treatment

Pharmacists are also in the position of counselling patients on the safe and effective use of clozapine, including the importance of:

- Compliance with their treatment regimen
- Reporting the first sign of a cold, influenza, sore throat or other infection immediately
- Having the next blood test on the day it is due
- Safe storage of clozapine

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# Safer prescribing of high-risk medicines

## Colchicine – extremely toxic in overdose

Colchicine is a plant-based alkaloid, extracted from *Colchicum autumnale* (autumn crocus, meadow saffron) and *Gloriosa superba* (glory lily) used to treat gout and some other inflammatory conditions.<sup>1</sup> It is considered a high-risk medicine because it is associated with significant toxicity when not used correctly.

Colchicine has long been used to treat acute flares of gout, due to its anti-inflammatory properties. Although not an approved indication, colchicine is also used for prophylaxis of gout flares, particularly during the first few months of urate-lowering treatment (usually allopurinol). Colchicine inhibits neutrophil migration, chemotaxis, adhesion and phagocytosis in the area of inflammation. It reduces the inflammatory reaction to urate crystals, but has no effect on uric acid production or excretion.<sup>2</sup>

Non-steroidal anti-inflammatory drugs (NSAIDs), e.g. naproxen, and low-dose corticosteroids are also used for acute management of gout flares and prophylaxis of flares during the initiation of urate-lowering treatment. For many patients, NSAIDs are associated with less adverse effects and risk of toxicity than colchicine,<sup>3</sup> and may be the preferred treatment. However, colchicine is still an important treatment option as it is particularly useful for patients with co-morbidities, such as diabetes, renal impairment and peptic ulcer disease, in whom NSAIDs and prednisone may cause significant adverse effects.<sup>4</sup>

### Colchicine can cause significant toxicity and death

Colchicine has a narrow therapeutic index, which means that the range between therapeutic and toxic doses is small, and in some cases they overlap.<sup>1</sup> Acute overdose exceeding 0.5 mg/kg is usually fatal.<sup>1</sup> Fatalities have been associated with doses as low as 7 mg. In contrast, patients have survived doses up to 60 mg.<sup>5</sup> In a case series of nine patients presenting with colchicine overdose in the Auckland region over a 15 year period, eight died.<sup>5</sup> Four of the patients had taken an accidental overdose of colchicine (ranging from 18 – 24 mg) due to lack of knowledge about the medicine.<sup>6</sup> Colchicine is particularly toxic to children and even one or two tablets can cause serious toxicity.<sup>5</sup>

### Gastrointestinal disturbance is usually the first sign of toxicity

Abdominal pain, diarrhoea, nausea and vomiting are usually the first symptoms of colchicine toxicity. A burning sensation in the throat, abdomen or on the skin has also been reported. These symptoms, particularly diarrhoea, can also occur with doses within the therapeutic range. Later features of toxicity (24 hours to seven days after ingestion) include tachypnoea, electrolyte disorders (e.g. hypocalcaemia, hypophosphataemia), hypovolaemia, haematological effects (e.g. leukopaenia, thrombocytopenia), cardiac dysrhythmias, renal failure and liver damage.<sup>1,5,6</sup> The cause of death is usually progressive multiple organ failure and sepsis.<sup>1</sup>

## Adverse effects can occur even at “safe” doses

Prior to 2005, colchicine dose instructions included the advice to continue dosing until the pain settled or gastrointestinal adverse effects occurred. The standard dose instructions have now been changed to improve safety. Patients are advised to stop taking colchicine immediately if they experience abdominal pain, diarrhoea, nausea or vomiting, or a burning feeling in their throat, stomach or on their skin.<sup>5</sup>

Table 1 shows the current New Zealand dosing recommendations for colchicine used in patients with gout.<sup>7,8</sup> Internationally, specifically in Australia and the United States, even lower doses are recommended. A study comparing low-dose colchicine (1.2 mg followed by 0.6 mg in 1 hour; 1.8 mg total) with high-dose colchicine (1.2 mg followed by 0.6 mg every hour for 6 hours; 4.8 mg total) found that efficacy of the low-dose regimen was comparable to the high-dose regimen, however, there was a significant reduction in the rate of adverse effects with the low dose regimen.<sup>9</sup> The lower dosing regimen is now recommended in colchicine guidelines in Australia and the United States.

## Interactions increase the risk of colchicine toxicity

The risk of colchicine toxicity is increased when inhibitors of cytochrome P450 3A4 (CYP3A4) or P-glycoprotein (P-gp) are taken concurrently, e.g. some azole antifungals (e.g. fluconazole), calcium channel blockers (e.g. diltiazem, verapamil) and macrolide antibiotics (e.g. erythromycin) (see New Zealand Formulary for full list).<sup>8</sup>

If these medicines are required at the same time as colchicine, the dose of colchicine should be reduced and the patient

monitored for symptoms and signs of colchicine toxicity. These combinations are contraindicated in patients with renal or hepatic impairment, as this increases the risk of toxicity.<sup>10</sup>

## Managing colchicine toxicity

All patients with known or suspected overdose of colchicine, or displaying symptoms of colchicine toxicity, should be immediately referred to hospital. There is no specific antidote for colchicine when taken in overdose and treatment options are limited. Haemodialysis and haemoperfusion are not effective because colchicine has a large volume of distribution, binds significantly to plasma proteins and has rapid distribution.<sup>6</sup> If a patient presents soon after ingestion, repeated doses of activated charcoal can be given to remove colchicine from the gastrointestinal tract. Although colchicine is rapidly absorbed from the gastrointestinal tract, removal of even a small amount can improve the patient's prognosis.<sup>6</sup> Patients who do not present soon after ingestion, and those with pre-existing renal or hepatic impairment, have a less favourable prognosis.<sup>6</sup> Patients with colchicine toxicity are managed with supportive care.

## Avoiding adverse effects


### Manage gout more effectively

Patients who frequently use colchicine for acute gout flares should be encouraged to take long-term urate-lowering treatment, e.g. allopurinol. Preventative treatment will reduce the frequency of flares, and therefore reduce the need for acute treatment with colchicine, and the risk of toxicity.<sup>11</sup> Urate-lowering treatment is indicated for patients with gout who: experience recurrent flares, e.g. two or more in one year, have tophi, concomitant renal impairment or changes characteristic

**Table 1:** Recommended colchicine dosing regimen<sup>7,8</sup>

Indication	Dose
Treatment of acute gout	1 mg, followed by 500 micrograms every six hours until relief of pain, up to 2.5 mg (five tablets of 500 micrograms) on the first day; maximum 1.5 mg (three tablets) on subsequent days; total maximum 6 mg (12 tablets) over four days; course not to be repeated within three days  NB: In elderly patients, patients with renal or hepatic impairment, or patients weighing < 50 kg, if it is necessary to use colchicine the initial dose should not exceed 1 mg (two tablets of 500 micrograms) in the first 24 hours; total maximum 3 mg (six tablets) over four days; course not to be repeated within three days
Prophylaxis during initiation of urate-lowering treatment	500 micrograms, once or twice daily, during the first three to six months treatment with a urate-lowering medicine, such as allopurinol

of gout on x-ray. Ideally, urate-lowering treatment should be initiated early before there has been any erosive damage to joints and before tophi have appeared.


 For further information, see: "An update on the management of gout", BPJ 51 (Mar, 2013).

### Provide patients with clear instructions

Patients are at risk of overdose if they have a poor understanding of how to take colchicine and its potential adverse effects. Appropriate patient education includes:

- Providing clear advice about how to take colchicine, especially the maximum dose
- Advising patients to stop taking colchicine and see their doctor if they develop nausea, vomiting or diarrhoea; unusual bleeding or bruising; muscle pain or weakness; or numbness or tingling in their fingers or toes
- Ensuring patients are aware that colchicine is not an analgesic for general use and should not be used to manage pain not due to gout
- Advise patients to tell a doctor or pharmacist about all the medicines they take and to check before taking new medicines

Advice should be tailored to the patient's level of health literacy. This is particularly important for patients for whom English is not their first language. Of the four accidental overdose cases reported in Auckland, three of those patients were of Pacific Island descent. It is possible that language barriers, cultural differences and health literacy may have been contributing factors to these accidental overdoses.<sup>6</sup>

 A patient information handout on colchicine is available from: [www.saferx.co.nz/colchicine-patient-guide.pdf](http://www.saferx.co.nz/colchicine-patient-guide.pdf)

### What can General Practitioners do?

- Provide patients with clear instructions on how to take colchicine, both verbal and written, and check for understanding. Advise patients about the dangers of overdose, overuse and the importance of safe storage.
- Limit prescriptions to 12 tablets for acute attacks of gout (6 tablets for older people)
- Prescribe monthly for prophylactic use and ensure colchicine is stopped after three to six months
- Be aware of significant medicine interactions with colchicine

**ACKNOWLEDGEMENT:** Thank you to **Associate Professor Matt Doogue**, Clinical Pharmacologist and Endocrinologist, University of Otago – Christchurch and Canterbury District Health Board for expert review of this article.

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# Safer prescribing of high-risk medicines

## Methotrexate: potentially fatal in overdose

Low-dose methotrexate is commonly used in the treatment of patients with rheumatoid arthritis and other rheumatologic diseases, as well as severe psoriasis. It is prescribed as a weekly dose and is a preferred option due to its effectiveness, predictable adverse effect profile and low cost. However, it can also be highly toxic and even fatal. Although toxicity is more likely to occur in patients taking high doses, any dosing regimen may induce toxicity.<sup>1</sup>

While methotrexate is usually initiated in secondary care, many patients taking methotrexate will be monitored by their general practitioner, and receive repeat prescriptions in primary care. In 2013, 23.3 prescriptions for methotrexate were dispensed per 1000 patients registered in general practice in New Zealand.<sup>2</sup> General practitioners therefore need to be aware of strategies for safe prescribing of this potentially toxic medicine and be familiar with the symptoms and signs of methotrexate toxicity.

The mechanisms behind the anti-inflammatory effect of methotrexate in rheumatoid arthritis are not certain, but are thought to include suppressing DNA synthesis in inflammatory cells, reducing auto-antibody levels, anti-inflammatory effects of adenosine release, and reducing cytokine levels in synovial fluid to bring about a reduction in inflammatory disease activity and joint damage.<sup>3,4</sup> Methotrexate acts as an inhibitor of the enzyme dihydrofolate reductase, which interferes with folic acid metabolism. As the adverse effects (but not the anti-inflammatory effects) of methotrexate are mediated via the metabolism of folates, it is given with folic acid supplementation.

### Adverse and toxic effects of methotrexate

Adverse effects of methotrexate can occur at therapeutic levels and include headache, malaise, mouth ulcers and hairfall.<sup>5</sup> In overdose, vomiting, diarrhoea and gastrointestinal bleeding may occur, as well as severe bone marrow suppression and disturbance of liver function. Long-term liver injury, normally accompanied by elevations of ALT and AST, can result in hepatic fibrosis. Liver toxicity is more likely in patients with pre-existing risk factors for liver disease, and in patients taking methotrexate for the treatment of psoriasis than those taking it for the treatment of rheumatoid arthritis.<sup>6</sup>

Methotrexate can induce acute pneumonitis, which can be fatal. Patients may present with acute shortness of breath and a dry, persistent cough, possibly with fever.<sup>7</sup> A chest x-ray prior to initiating methotrexate is recommended to facilitate the diagnosis of potential lung disease at a later date.

Co-administration of folic acid, typically given as 5 mg weekly, a few days after each weekly methotrexate dose, has been shown to reduce the risk of adverse effects such as abdominal pain and nausea, abnormal serum transaminase levels, and increases adherence with a methotrexate regimen.<sup>8</sup>

### Methotrexate can be fatal

There have been documented cases of death attributable to methotrexate use in New Zealand and around the world. These have often involved patients taking methotrexate as a daily, rather than weekly dose due to patient, clinician and/

or pharmacy error. In New Zealand, fatal cases have occurred most recently in 2012 and 2006.<sup>9, 10</sup> In the United Kingdom, the National Patient Safety Authority released a report in 2004 on methotrexate prescribing after 25 deaths and 26 incidents of serious harm in the preceding decade.<sup>11</sup> In some of these cases, even once the error was identified, patients died due to ongoing deterioration after methotrexate withdrawal.

The usual cause of methotrexate-related mortality is pneumonitis, which can occur idiosyncratically (i.e. it is not dose related), even after one dose. Bone marrow suppression is another cause of mortality, with multiple organ failure and gastrointestinal bleeding occurring secondary to this.

### Recommendations for managing risk

A number of common sense steps can be taken by clinicians, including pharmacists, to minimise the risk of methotrexate toxicity and potential accidental overdose. Given the number of documented fatalities which have arisen from simple errors in medicine dosing frequency, the most important lesson is to emphasise that **methotrexate should be taken as a weekly dose** and to put in place procedures, safeguards and reminders to ensure this dosage is followed by doctors, pharmacists and patients.

Steps during patient consultation to ensure weekly administration:

- Avoid writing “as directed” on prescriptions – give the specific dose and state this in mg.
- Write the day the medicine is to be taken in full on the prescription (one case of fatality occurred when a patient interpreted “Mon” as morning, resulting in a daily as opposed to weekly dose).<sup>12</sup>
- Highlight differences in the appearance of 2.5 mg and 10 mg tablets, especially when a patient is transferred from one tablet size to another. Prescribe only one strength of tablet at a time in order to avoid accidental ingestion of 10 mg tablets in place of 2.5 mg tablets.<sup>12</sup>
- Emphasise to the patient the differences between methotrexate and folic acid – cases have occurred where the two dosing regimens were inadvertently swapped by the patient.<sup>11</sup> A simple mnemonic tool is “Methotrexate for Monday”, “Folic acid for Friday” as a means of ensuring once weekly dosing for each on different days.
- Maintain contact with the secondary care team and patient contact with rheumatology and practice nurses. Research conducted in New Zealand found significantly

higher levels of patient awareness of signs and symptoms of methotrexate toxicity and awareness of weekly dosing in patients who had seen a rheumatology nurse.<sup>13</sup>

- If the patient has a carer, ask that they be present at consultations or that the need for accurate intake of medicines is discussed with them (with patient consent).
- In follow-up appointments specifically question patients on their medicine intake – How many tablets of methotrexate do you take? When do you take them?

Be vigilant for adverse effects, and ensure patients understand what these could be:

- Patients should be advised of key symptoms of methotrexate toxicity such as a sore throat, mouth ulcers, fever, dry persistent cough, vomiting or diarrhoea, and to report if any of these occur.
- Ensure that patient reports of adverse effects while taking methotrexate are relayed by practice staff to the patient’s usual clinician.<sup>9</sup>

Practice steps to ensure weekly administration:

- Check that prescribing software automatically defaults to weekly prescriptions for methotrexate.<sup>9</sup>
- Flag the patient’s notes to alert other practice staff to report any potential features of methotrexate toxicity.<sup>9</sup>
- Consider a short education session for practice staff on methotrexate risks and symptom awareness, and put processes in place so that methotrexate adverse effects can be reported to the treating clinician.
- Be aware of failures to report for appointments by patients taking methotrexate, and double check the reasons why.

Laboratory monitoring is essential (also see Table 1, over page):

- A full blood count, liver and renal function tests should be carried out before starting methotrexate, and repeated every two to four weeks initially, then every month to three months if results have been normal and the dose is stable.
- Ensure tests have been done within the last six weeks prior to writing repeat prescriptions.<sup>12</sup>
- Results showing decreased white blood cell counts or increased transaminase levels may indicate methotrexate toxicity. Discuss any abnormal results with the rheumatologist/dermatologist. See Table 1 for further details.

- Procollagen 3 (type III procollagen amino terminal propeptide, or PIIINP) may be used to monitor liver safety in patients with psoriasis. This is available as a Tier two test in the National Laboratory Test Schedule and will be arranged by a specialist. Liver biopsies may also be performed.


#### Check concurrent medicine and alcohol use:

- Impaired renal function can reduce the excretion of methotrexate and patients should report any use of medicines such as NSAIDs which reduce methotrexate excretion.<sup>5</sup>
- Alcohol intake should ideally be no more than one to two standard drinks twice per week,<sup>5</sup> although many patients admit to higher amounts without developing evidence of liver problems.
- Co-trimoxazole and trimethoprim should be avoided in patients taking methotrexate due to a theoretical increase in risk of bone marrow suppression.<sup>5,14</sup>

#### Pharmacy steps to avoid weekly dosing errors:<sup>9</sup>

- Ensure that methotrexate labels state that dosing is weekly and give the day of the week, written in full, that the medicine is to be taken.
- Ensure software alerts are given appropriate attention.
- Contact the prescribing clinician with queries or to check that dosing is appropriate when there is doubt.

- Place prepared scripts for medicines with alerts in a different area to general, non-high risk, medicines so that alerts can be appropriately checked and addressed before handing medicines to patients.
- Where prescriptions are manually entered into a pharmacy computer system, double check that entry is correct. When filling repeats, refer back to original script rather than computer system to ensure any errors which may occur when entering prescription details into computer software are not perpetuated.
- Be wary of needing to order stock to fill a script for high risk medicines; as this may indicate that a prescribing error has occurred.
- Have a system for recording “near miss” events, as these can identify sources of error.

 A Methotrexate Patient Guide is available from: [www.saferx.co.nz/methotrexate-patient-guide.pdf](http://www.saferx.co.nz/methotrexate-patient-guide.pdf)

**ACKNOWLEDGEMENT:** Thank you to **Associate Professor Andrew Harrison**, Rheumatologist, Clinical Head of Department, Wellington Regional Rheumatology Unit and Wellington School of Medicine, University of Otago, Wellington and **Dr Peter Jones**, Rheumatologist and Chief Advisor, Sector Capability

## Methotrexate is contraindicated in women who are pregnant or breast feeding

Care must be taken to avoid the use of methotrexate in women who are pregnant as it is an abortifacient and can exert teratogenic effects on the developing foetus.<sup>15</sup> If female patients of reproductive age are prescribed methotrexate, discuss appropriate contraception and delaying pregnancy plans. International treatment guidelines also recommend the use of contraception for male patients taking methotrexate,<sup>14</sup> although recent evidence suggests that paternal use of methotrexate does not increase the risk of miscarriage or birth defects.<sup>16</sup>



**Table 1:** Recommended monitoring for patients taking methotrexate, adapted from Chakravarty et al, 2008<sup>14</sup>

Laboratory monitoring	Frequency	What to look for	What to do
Full blood count (FBC)	Baseline	WBC $<3.5 \times 10^9/L$	Discuss with specialist team immediately.
	Every two to four weeks initially, then every month to three months if results have been normal on a stable dose.	Neutrophils $<2.0 \times 10^9/L$ Platelets $<150 \times 10^9/L$	
		MCV $> 105$ fL	Check vitamin B12, folate and TSH. If abnormal, treat any underlying abnormality.
Liver function tests (LFTs)	Baseline	AST, ALT $>$ twice the upper limit of reference range.	Withhold until discussed with specialist team. Other factors to consider: <ul style="list-style-type: none"> <li>• Check alcohol intake.</li> <li>• Review medicines which may cause liver dysfunction, e.g. NSAIDs</li> </ul>
	Every two to four weeks initially, then every month to three months if results have been normal on a stable dose.		
Serum creatinine	Baseline	Significant deterioration in renal function	Reduce dose
	Often performed at same time as LFT and FBC monitoring during dosing changes. Every three months for patients on stable treatment.		
Chest X-ray	Baseline		Repeat if respiratory symptoms occur (see below)
Symptoms	What to do		
Rash or oral ulceration	Withhold methotrexate until discussed with specialist team. Folic acid mouth wash may help with mucositis.		
Nausea and vomiting, diarrhoea	Giving methotrexate by subcutaneous injection is often a good way of avoiding nausea		
New or increasing dyspnoea or dry cough (pneumonitis)	Withhold and discuss URGENTLY with specialist team. Arrange chest x-ray and respiratory function tests		
Severe sore throat, abnormal bruising	Request immediate FBC and withhold until results available. Discuss any unusual results with specialist team		



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and Implementation, Ministry of Health for expert review of this article.

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