



# Medicines Safety Update

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## Misadventures in oral methotrexate dosing

Inadvertent overdose of oral methotrexate – usually from accidental daily administration of a weekly dose – can lead to serious and potentially fatal toxicity.

Methotrexate is indicated for antineoplastic chemotherapy, as well as treatment of rheumatoid arthritis and psoriasis for severe, recalcitrant, disabling disease that is not adequately responsive to other forms of therapy. In Australia, methotrexate tablets are marketed as Methoblastin.

When used for the treatment of rheumatoid arthritis and psoriasis, methotrexate is typically prescribed in a once weekly dosage regimen. Taken correctly, methotrexate is usually a safe and effective medicine, but it has the potential for serious toxicity.

Dosing errors are a known and avoidable risk associated with methotrexate tablets, but a TGA investigation has found that the factors leading to such errors are complex.

Evidence from published literature and spontaneous adverse reaction reporting has identified factors along the entire medication management cycle that contribute to dosing errors, including prescribing, dispensing and patient factors.

### Adverse events

A search of our adverse event database, up to March 2018, identified 28 cases involving a weekly dose of oral methotrexate being taken incorrectly. Most cases identified incorrect daily dosing (dose range 2.5-30 mg). In some cases the dose was taken more frequently than weekly, but less frequently than daily. The most frequent duration of the erroneous dosing, when reported, was for one week or longer. Analysis of spontaneous case reports did not identify any trends in reporting.

The most frequently reported adverse effects were haematological (pancytopenia, thrombocytopenia, neutropenia), stomatitis, mucosal inflammation or ulceration, and gastrointestinal effects.

An assessment of the relationship between dosing and the severity of adverse reactions/outcomes was precluded by the limitations of spontaneous reporting (such as missing information and underreporting). However, the lowest fatal dose recorded was 2.5 mg daily, which was taken for at least one week.

The causes of error, where specified, identified from our adverse event reports included:

- patient confusion with another medicine – the most common medicine that patients confused methotrexate with was folic acid (which is commonly co-prescribed) including one fatal case
- non-English speaking background
- pharmacist dispensing practices were found to have contributed in five non-fatal cases and two fatal cases
- health professional administration or instructions.

These causes are consistent with those published in medical literature, both Australian and international.<sup>1-5</sup>

Despite the large quantity of literature available (case reports, retrospective studies and safety alert guidance), serious toxicity associated with low-dose methotrexate still occurs.

To address this risk, we have worked with the sponsor of Methoblastin to undertake the following regulatory actions:

- the carton and container label artwork have been updated to include a new warning – ‘Caution: Usual dose is once weekly. Check dose and frequency with your doctor or pharmacist.’

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- the [Product Information](#) has been updated to more prominently warn of the risk of accidental dosing errors, highlight that for rheumatoid arthritis and psoriasis methotrexate is most often prescribed as a once weekly dose.

### Information for health professionals

If you are treating patients with methotrexate tablets, we recommend reiterating the once weekly dosing regimen and specifying which day of the week the dose is to be taken.

You are also encouraged to educate those patients about the signs and symptoms of toxicity and advise them of the circumstances in which they should seek medical advice.

If you're a pharmacist dispensing methotrexate tablets, highlight to patients the importance of only taking the dose once weekly and reinforce the day of the week to be taken. Good dispensing practices can also help to avoid dosing errors, including:

- labelling the medicine container and not just the external packaging

- ensuring that the label specifies the number of tablets to be taken and the specific day of the week they should be taken.

### REFERENCES

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## Medicines associated with a risk of neuropsychiatric adverse events

Health professionals are reminded of the importance of effectively communicating to patients and caregivers the potential risks and benefits of treatment with medicines associated with a risk of neuropsychiatric adverse events before prescribing.

Neuropsychiatric adverse events can range from mild to severe, and encompass a broad range of symptoms including tremor, agitation, aggressive behaviour or hostility, anxiousness, depression, dream abnormalities, hallucinations, insomnia, irritability, restlessness, somnambulism [sleep-walking], suicidal thinking and behaviour.

Neuropsychiatric adverse events occurring in association with medicines, particularly suicidal thinking and behaviour, are a source of serious concern for consumers, and periodically generate complaints to the TGA.

Neuropsychiatric adverse events are a known risk associated with a number of medicines, including:

- antidepressants, particularly selective serotonin reuptake inhibitors (SSRIs)
- certain smoking cessation medications, including

varenicline and bupropion (marketed as Champix and Zyban respectively)

- certain antiepileptics, including sodium valproate, carbamazepine, levetiracetam, phenytoin, lamotrigine, topiramate, pregabalin and gabapentin
- isotretinoin (marketed as Roaccutane)
- atomoxetine (marketed as Strattera and generic brands)
- montelukast (marketed as Singulair and generic brands).

For all of the medicines listed above, the observed association with neuropsychiatric adverse events may be confounded by indication, because the medical conditions being treated are themselves known to be associated with an increased risk of altered mood, which may lead to suicidal thinking or behaviour. For this reason, it is often difficult to establish a definite causal relationship between a medicine and a severe neuropsychiatric adverse event.

The TGA has published articles reminding health professionals of the risk of suicidality and/or other psychiatric adverse events associated with antidepressants (October-December 2016), isotretinoin (August 2016), varenicline (February

2016 and August 2010), anticonvulsant pregabalin (December 2014), atomoxetine (October 2013) and montelukast (April 2013) in [previous issues of Medicines Safety Update](#).

### Risks and benefits

A decision to prescribe any of the above medications, as with any prescription medicine, should be based on an assessment of the risks and benefits for each individual patient, as well as consideration of any other treatment options available. Prescribers can refer to the relevant Product Information for specific information about the medication being considered.

In addition, prescribers should effectively communicate to patients – and when appropriate their families or carers – the expected risks and benefits of a proposed new medicine to enable them to make an informed decision about their treatment options.

With regard to patients being treated with antidepressants, several studies have shown that patients with mental illness and their carers feel that they have not received enough information about their medicines.<sup>1</sup>

One survey found that just over half of the inpatients and one third of community-based patients reported that they did not receive any medicines information. Carers were even less likely to report receiving medicines information or to be included in discussions or decisions regarding medicine use.<sup>1</sup>

With this in mind, you are strongly encouraged to provide patients with the relevant Consumer Medicine

Information, which is available through medical and pharmacy software, as well as from the [TGA website](#) and the [TGA's medSEARCH app](#), for any new medications from the above list they are prescribed.

### Additional education and regular monitoring

You are also encouraged to consider providing additional education to patients who are taking the above medications and to undertake regular monitoring for changes in mood or behaviour. In particular, patients and their carers should be advised to seek medical advice if they notice any changes in the patient's behaviour.

There are additional resources available for health professionals and consumers to help them make informed decisions about the use of antidepressants and to better educate patients and carers about their treatment, including information on the [NPS MedicineWise website](#).

### Discontinuation symptoms

Another important topic to discuss with patients when appropriate is discontinuation and potential discontinuation symptoms. It is important for patients and carers to be educated about the importance of not suddenly stopping treatment, especially when taking antidepressants and antiepileptics.

### REFERENCE

1. Tran N, Castle D. [Outcomes from a regular medication information programme for consumers with a mental illness](#). *Australasian Psychiatry*. 2010;49(2):150-7

Product  
Information  
on the go with  
**med**  
**SEARCH**

[www.tga.gov.au/medsearch-app](http://www.tga.gov.au/medsearch-app)

## Clozapine and gastrointestinal effects

Health professionals are reminded that clozapine has been associated with varying degrees of impairment of intestinal peristalsis. With this in mind, you should closely monitor bowel function and constipation in patients being treated with this drug.

Clozapine is an atypical antipsychotic agent indicated only in people with treatment-resistant schizophrenia. The [Product Information](#) for clozapine has been updated with information about the potentially fatal risk of intestinal obstruction, faecal impaction and paralytic ileus.

Clozapine-induced gastrointestinal hypomotility (also known as 'slow gut')/impaired intestinal peristalsis can lead to severe constipation and potentially fatal outcomes from faecal impaction, intestinal obstruction, paralytic ileus, megacolon and intestinal ischaemia or infarction.

A 2017 review of cases reported to the TGA and the New Zealand Pharmacovigilance Centre between 1992 and 2013 found 160 cases of serious gastrointestinal hypomotility from 43,132 people who commenced

clozapine over the study period (37/10,000 clozapine users). The case fatality rate was 18%, with 29 patients having died (7/10,000 clozapine users).<sup>1</sup>

We recommend close monitoring of bowel function and constipation in patients on clozapine, particularly in patients aged over 60 years and those at higher risk of constipation, such as patients:

- who are taking medications known to cause constipation (anticholinergics)
- with a history of bowel disease
- who have had bowel surgery.

Please note that clozapine is also contraindicated in patients with paralytic ileus.

The TGA previously published information about [clozapine and severe constipation in the February 2011 issue of Medicines Safety Update](#).

### REFERENCE

1. Every-Palmer S, Ellis PM. [Clozapine-induced gastrointestinal hypomotility: A 22-year bi-national pharmacovigilance study of serious or fatal 'slow gut' reactions, and comparison with international drug safety advice](#). CNS Drugs 2017 Aug; 31 (8): 699-709.

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### What to report? You don't need to be certain, just suspicious!

The TGA encourages the reporting of all **suspected** adverse reactions to medicines, including vaccines, over-the-counter medicines, and herbal, traditional or alternative remedies. We particularly request reports of:

- all suspected reactions to new medicines (see [Black Triangle Scheme](#))
- all suspected medicines interactions
- suspected reactions causing death, admission to hospital or prolongation of hospitalisation, increased investigations or treatment, or birth defects.

Reports may be submitted:

- **online** at [www.tga.gov.au](http://www.tga.gov.au)
- **by email** to [ADR.Reports@tga.gov.au](mailto:ADR.Reports@tga.gov.au)
- **by fax** to 02 6232 8392
- **using the 'blue card'** available from the TGA website

For more information about reporting, visit [www.tga.gov.au](http://www.tga.gov.au) or contact the TGA's Pharmacovigilance and Special Access Branch at [ADR.Reports@tga.gov.au](mailto:ADR.Reports@tga.gov.au)

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