SAFER PRESCRIBING

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 co-morbidities, 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.[1] 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%.[1] 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.[2] 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.[3] 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.[4] This hypomotility can result in intestinal obstruction, bowel ischaemia, necrosis, perforation, toxic megacolon and related aspiration pneumonia.[5]

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.[5]

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[3]
- 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.[3] Regularly review treatment. An alternative option is to prescribe preventative laxative maintenance treatment, e.g. a macrogol laxative*, in all patients treated with clozapine.[6]
- 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.[7] 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.[8]

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[8]
- 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[8]
- 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.[2] Patients taking clozapine have an increased risk of all of these adverse effects, particularly type 2 diabetes mellitus.[9]

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_{1c} (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.[7] 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.[10]

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[7]

- 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.

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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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