




Clozapine: A reminder about **safe** and **effective** use

CLOZAPINE IS THE DRUG OF CHOICE for treatment resistant schizophrenia. It is one of the few drugs in New Zealand that can not be prescribed by GPs but they still need to be aware of potential problems associated with its use.

Clozapine use is closely monitored including weekly blood tests (white blood cell count and absolute neutrophil count) for the first 18 weeks of treatment, then four weekly thereafter throughout treatment and for four weeks after discontinuation.

Guidance has previously been provided about significant adverse effects and interactions with clozapine. In this article, we re-emphasise the vital role that primary care has in recognising and managing these issues.

 **Best practice tip:** A Christchurch GP has set up a pop-up alert on the medical record of his one patient receiving clozapine. It states: “On clozapine, watch for constipation, neutropenia and myocarditis”. Erythromycin, co-trimoxazole, trimethoprim and nitrofurantoin are entered under medical warnings with a note saying “Avoid – interaction with clozapine”. **See Page 38 for a ten minute tutorial on setting up a pop-up alert for patients on clozapine.**

Significant adverse effects

Adverse effects associated with clozapine include constipation, blood dyscrasias, myocarditis and metabolic syndrome.

Constipation

Constipation is a common adverse effect of clozapine and is related to its anticholinergic effects. It can be potentially serious; four deaths resulting from complications of severe constipation have been reported in New Zealand.¹

What can GPs do?

- Recognise and treat constipation in patients receiving clozapine to prevent the development of more serious complications such as obstruction and paralytic ileus.
- Avoid concomitant anticholinergic drugs (e.g. amitriptyline) as constipation is more likely to occur.
- Encourage patients to adopt measures which may prevent constipation such as a high fibre diet (at least three serves of vegetables, two serves of fruit and some cereal, bread, rice or pasta every day or more than 30g of fibre per day), adequate fluid intake (1.5 – 2 litres of fluid per day) and physical activity.

Blood dyscrasias

Clozapine can cause potentially fatal neutropenia and agranulocytosis (number needed to harm = 59).²

What can GPs do?

- **Patients who present with evidence of infection such as flu-like symptoms, sore throat or fever must have a full blood count done immediately to rule out neutropenia or agranulocytosis. It must be indicated on the laboratory form that the patient is on clozapine and it must be ensured that results are provided on the same day. Depending on the result, urgent haematology referral or emergency hospital admission may be required.** Recently a patient died from agranulocytosis secondary to clozapine. The laboratory was not aware that the patient was on clozapine and the sample was also clotted. This led to a significant delay in diagnosing the agranulocytosis.
- Avoid concomitant use of antibiotics that increase the risk of neutropenia. This includes those that are known to have a substantial potential to depress bone marrow function for example, sulphonamides, trimethoprim, co-trimoxazole and nitrofurantoin, or those that increase the plasma concentration of clozapine such as erythromycin.

Myocarditis

Fatal myocarditis and cardiomyopathy have been reported rarely with clozapine use.

What can GPs do?³

- Check patients, who have persistent tachycardia at rest, for other symptoms of myocarditis or cardiomyopathy. These include palpitations, arrhythmias, symptoms mimicking myocardial infarction, chest pain or other symptoms of heart failure.
- If myocarditis or cardiomyopathy is suspected, refer to the prescribing psychiatrist who may stop the patient's clozapine treatment. The patient should also be evaluated by a cardiologist.

Metabolic syndrome

Weight gain, hyperglycaemia and dyslipidaemia are all associated with clozapine.

What can GPs do?

- Give advice about diet and exercise. It may also be appropriate to use pharmacological management.
- Monitor relevant parameters such as lipid profile, fasting glucose, blood pressure and BMI.


Important drug interactions

Smoking

People who smoke metabolise clozapine faster than those who do not smoke. When a person stops smoking, the resulting increase in plasma levels can cause or worsen adverse effects. Smoking cessation should always be planned with the clinical team so that this effect can be monitored and managed.

Other drug interactions

Drugs that may increase the plasma concentration of clozapine include SSRIs, cimetidine, caffeine, lamotrigine, risperidone and combined oral contraceptives (interactions may only be supported by isolated case reports). Drugs that may decrease clozapine levels include rifampicin and anticonvulsants such as carbamazepine and phenytoin.

 See BPJ 4, April 2007, "Clozapine: Safe and effective use".

References:

1. Medsafe Prescriber Update 2007; 28(1):7. Available from: <http://www.medsafe.govt.nz/profs/PUArticles/clozGI.htm>. (Accessed May 2008)
2. Medsafe Prescriber Update 2004; 24(2):18. Available from: <http://www.medsafe.govt.nz/profs/PUArticles/ClozInfection.htm>. (Accessed May 2008)
3. Medsafe Prescriber Update 2003; 24(1):13. Available from: <http://www.medsafe.govt.nz/profs/PUArticles/clozcardiac.htm>. (Accessed May 2008)