

CLOZAPINE - SAFE PRESCRIBING - WE ARE COUNTING ON YOU

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- ▶ CLOZAPINE CAN CAUSE LIFE-THREATENING NEUTROPENIA/AGRANULOCYTOSIS
- ▶ RECOGNISING SIDE EFFECTS EARLY IN PRIMARY CARE MAY BE LIFE-SAVING
- ▶ PATIENTS REQUIRE RIGOROUS BLOOD MONITORING ON A REGULAR BASIS
- ▶ MYOCARDITIS/CARDIOMYOPATHY ARE RARE BUT POTENTIALLY SERIOUS REACTIONS
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CLOZAPINE CAN CAUSE LIFE-THREATENING NEUTROPENIA AND AGRANULOCYTOSIS

Clozapine (Clopine®, Clozaril®) has drastically improved the lives of many patients with resistant schizophrenia, but it can cause many serious side effects which may present first in primary care. **It is considered a 'high-risk' medicine because it is associated with neutropenia and agranulocytosis** (a reported incidence of 3% and 0.7% respectively)¹ as well as other very serious adverse events.²

Please advise patients to be alert for neutropenic symptoms (e.g. fever, sore throat or flu-like symptoms). Anyone on clozapine presenting with these needs an urgent full blood count, medical review, and their mental health team notified immediately^{2,3,4}. If you have a patient who is taking clozapine, please consider putting an alert on their file to raise awareness that minor-sounding symptoms could be serious.

PATIENTS REQUIRE RIGOROUS BLOOD MONITORING ON A REGULAR BASIS

Everyone taking clozapine must undergo rigorous blood monitoring on a regular basis. Patients are registered with the manufacturer's blood monitoring database, i.e. *ClopineConnect*[™] for Clopine® brand, or *CareLink Plus*[™] for Clozaril® brand. In New Zealand, clozapine can be only initiated by a psychiatrist^{2,3}.

Patients treated with clozapine must have weekly full blood counts for the first 18 weeks of treatment, then monthly monitoring throughout treatment and for four weeks after discontinuation^{2,3}. However, despite this vigilance a death

from agranulocytosis has occurred in New Zealand⁴.

Be aware there are many medicines that may increase the risk of neutropenia when used concurrently with clozapine, e.g. some **antibiotics** (e.g. **co-trimoxazole** and **erythromycin**), **carbamazepine**, and **antineoplastics** associated with bone marrow suppression^{2,3}.

Clozapine cannot be prescribed for patients with bone marrow suppression or those with a history of clozapine-induced blood dyscrasias^{2,3}.

MYOCARDITIS AND CARDIOMYOPATHY ARE RARE BUT POTENTIALLY SERIOUS REACTIONS

Clozapine is associated with a small but significant risk of myocarditis and cardiomyopathy and fatalities have been reported in New Zealand. They may occur at any time but there is a greater risk of myocarditis within one month of initiating clozapine; in comparison, cardiomyopathy usually has a latent onset at approximately nine months after starting clozapine. Compared to the general population, clozapine-treated patients have a 17 to 322 times greater rate of myocarditis, and a 14 to 161 times greater rate of fatal myocarditis^{5,6}.

Symptoms are often non-specific and include (but are not limited to) flu-like illness, chest pain, dyspnoea, marked fluctuations in blood pressure, and electrocardiogram changes^{2,3}.

Patients presenting acutely should be referred urgently for a cardiology review^{2,3,4}.

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SEVERE CONSTIPATION HAS CAUSED FATALITIES

Clozapine causes constipation in a significant proportion of patients⁷ and there have been four deaths associated with bowel obstruction in New Zealand⁴.

The risk of severe constipation is increased when clozapine is used with other medicines that are constipating, i.e.

anticholinergics (e.g. **tricyclic antidepressants**), **opiates**, and **calcium channel blockers**^{2,3}.

PLEASE MANAGE CONSTIPATION PROACTIVELY

The use of **laxatives**, monitoring of bowel habit, and avoiding drug combinations that exacerbate constipation is recommended^{2,3,4}.

CLOZAPINE IS ASSOCIATED WITH MANY OTHER ADVERSE REACTIONS

Clozapine shares many adverse effects that are common to other antipsychotic medicines, e.g. sedation and postural hypotension, although the risk of these can be reduced with slow dose titration⁸.

Weight gain and glucose intolerance (leading to type 2 diabetes) may occur^{9,10}. Diabetic coma has occurred in patients who were previously non-diabetic. Monitor weight, glucose and lipid parameters closely and encourage dietary and lifestyle modifications, e.g. exercise. If necessary, use risk-lowering medications when appropriate, e.g. **statins** for elevated lipids⁴.

Other problematic side effects that require ongoing monitoring and management include enuresis¹¹, hypersalivation¹², and tachycardia⁸.

Clozapine can raise liver enzymes and monitoring is recommended¹³.

Clozapine also lowers the seizure threshold which can be troublesome at higher doses¹⁴.

CLOZAPINE IS ASSOCIATED WITH A NUMBER OF DRUG INTERACTIONS

Clozapine interacts with a range of medicines because it is a substrate for CYP450 isoenzymes. Care is needed when prescribing inducers or inhibitors of these enzymes^{2,3}.

INDUCERS – MAY DECREASE CLOZAPINE EFFECT

Concomitant administration of substances known to **induce** CYP450 enzymes may **decrease** the plasma levels of clozapine, e.g. **carbamazepine**, **phenytoin**, **rifampicin** and **omeprazole**^{2,3}.

Clozapine levels are affected by **cigarette smoking**. But remember, it's the constituents of smoke (and not **nicotine** itself) that induce liver enzymes and increase the metabolism of clozapine. As a consequence, **elevated clozapine levels may occur when patients stop smoking** – there have been reports of seizures. For patients on high dose clozapine who cease smoking, it may be advisable to monitor plasma clozapine levels and/or consider a dose reduction^{4,15}.

INHIBITORS – MAY INCREASE CLOZAPINE EFFECT

Administration of drugs known to **inhibit** the activity of CYP450 isoenzymes may **increase** the plasma levels of clozapine, e.g. **erythromycin** and **selective serotonin re-uptake inhibitors** (SSRIs) such as **paroxetine**^{2,3}.

The plasma concentration of clozapine can also be increased by a **high caffeine intake** (more than 400mg/day). However, clozapine levels can decrease by nearly 50% after a 5 day caffeine-free period^{2,3}.

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For further information on other high-risk medicines visit our website at: www.saferx.co.nz

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