SAFER
SAFER USE OF HIGH RISK MEDICINES

CLOZAPINE SAFE PRESCRIBING – WE ARE COUNTING ON YOU

- **REGULARLY CHECK FOR SYMPTOMS OF NEUTROPENIA AND AGRANULOCYTOSIS**
- **MANAGE CONSTIPATION PROACTIVELY**
- **ASSESS FOR MYOCARDITIS AND CARDIOMYOPATHY**
- **BE AWARE OF OTHER ADVERSE REACTIONS AND INTERACTIONS – ESPECIALLY SMOKING**

Clozapine has drastically improved the lives of patients with treatment resistant schizophrenia, but it can cause serious adverse effects. Clozapine can only be initiated by a Psychiatrist, but symptoms of adverse effects may present first in Primary Care.

Clozapine is associated with neutropenia which may progress to a potentially fatal agranulocytosis. Severe constipation, myocarditis and adverse metabolic effects need to be assessed regularly; these are not always dose-dependent.

- **REGULARLY CHECK FOR SYMPTOMS OF NEUTROPENIA AND AGRANULOCYTOSIS**

Advise patients to be alert for symptoms of neutropenia (eg fever, sore throat or flu-like symptoms). Anyone taking clozapine and presenting with these symptoms needs an urgent full blood count, medical review, and their mental health team notified immediately.

If you have a patient who is taking clozapine, please consider putting an alert on their file to raise awareness that even minor symptoms could be serious.

Regular blood monitoring is necessary for pharmacists to supply clozapine. Patients are registered with the manufacturer's blood monitoring database; *ClopineConnect™* for Clopine®, or *CareLink Plus™* for Clozaril®. General Practitioners involved in prescribing need to use the blood monitoring database; they will be provided with training and access via a web portal.

A baseline full blood count is required 10 days prior to commencing clozapine, then **weekly** full blood counts during the first 18 weeks of treatment. 28 day ('monthly') monitoring is required thereafter and for 4 weeks after discontinuation. Despite this vigilance, deaths from agranulocytosis have occurred in New Zealand. Agranulocytosis tends to develop during the first 6 months of treatment and is not dose-related. Neutropenia can occur at any time.

Other medicines that increase the risk of neutropenia should not be used with clozapine. These include co-trimoxazole, trimethoprim, nitrofurantoin, carbamazepine, and antineoplastics associated with bone marrow suppression.

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- **MANAGE CONSTIPATION PROACTIVELY**

Clozapine causes constipation in at least 80% of patients and can occur at any time. Complications from constipation are the most common reason for clozapine-induced mortality and serious morbidity in New Zealand.
The risk is increased with concurrent anticholinergics (eg tricyclic antidepressants), opioids, iron supplements and calcium channel blockers, other illnesses and high doses. Provide access to stimulant laxatives, give dietary advice and address pre-existing constipation prior to initiating clozapine. Bulking laxatives may make existing constipation worse.
Symptoms of serious complications include abdominal pain or distension, vomiting, watery diarrhoea (overflow), reduced appetite and nausea. Advise patients and their families to report these symptoms immediately; treatment interruption and review is recommended. Patients with no bowel movement in five days should be admitted to hospital for treatment.

- **ASSESS FOR MYOCARDITIS AND CARDIOMYOPATHY**

Clozapine is associated with a small but significant risk of myocarditis and cardiomyopathy; fatalities have been reported in New Zealand. Symptoms of cardiomyopathy include signs of heart failure, flu-like illness, sinus tachycardia, hypotension and chest discomfort.
Symptoms of myocarditis are often non-specific and may include flu-like illnesses, gastrointestinal upset, unexplained fatigue, chest pain, dyspnoea, marked fluctuations in blood pressure, and electrocardiogram changes.
Patients presenting with any of these symptoms should be referred urgently for a cardiology review, and the patient's psychiatrist notified.

- **BE AWARE OF OTHER ADVERSE REACTIONS AND INTERACTIONS**

Adverse effects including sedation and postural hypotension are more pronounced if the dose is not gradually titrated or a 'normal' dose is given after a treatment interruption. Weight gain and glucose intolerance (leading to type 2 diabetes) can also occur. Metabolic changes may increase cardiovascular and cerebrovascular risk. Monitor weight, blood pressure, HbA_{1c} and lipid parameters closely and encourage dietary and lifestyle modifications such as exercise. If necessary, use risk-lowering medications such as statins and metformin.

Other problematic side effects include enuresis, hypersalivation, increased sweating and tachycardia. Clozapine has been associated with increased incidence of pneumonia, and pulmonary aspiration, and can lower the seizure threshold.

Interactions

Clozapine interacts with a range of medicines that may **decrease** the plasma levels of clozapine. These include carbamazepine, phenytoin, rifampicin and omeprazole.
Clozapine levels are affected by **cigarette smoking**, however it is the constituents of smoke, not nicotine itself, that increases the metabolism of clozapine. Clozapine levels

can double when patients stop smoking. If patients stop smoking, monitor plasma clozapine levels and contact their mental health service; a dose reduction may be required. It is important that patients are aware of this and report any changes in smoking status during treatment.

Other medicines including erythromycin, ciprofloxacin and selective serotonin re-uptake inhibitors (SSRIs) such as paroxetine and fluoxetine can increase the plasma levels of clozapine. A high caffeine intake (more than 400mg/day) can increase levels, and subsequently decrease them by nearly 50% after a 5 day caffeine-free period.
Note: Clozapine can also enhance the central effects of alcohol, CNS depressants, and benzodiazepines.

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KEY REFERENCES

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