Clozapine - aide memoire for General Practitioners

Clozapine is an antipsychotic used in the treatment of schizophrenia when other antipsychotics have not worked. It may also be used for psychotic disorders occurring in Parkinson's disease when standard treatment has failed. Clozapine is classed as a RED drug which means it must only be prescribed by secondary care mental health services. Prescribing responsibility will not transfer to GPs under any circumstances. However GPs should record clozapine on the patient's medication record so that a complete list of medication is available.

Since clozapine can cause neutropenia and agranulocytosis regular blood tests are required. The monitoring schedule is

- Weekly for the first 18 weeks of treatment
- Fortnightly between weeks 18 and 52
- Four weekly after 1 year of treatment and ongoing

A traffic light system is used to direct action in response to white blood cell levels:

- Green – Blood test is within usual parameters and so clozapine can be continued.
- Amber- White cell count 3.0-3.5 x 10^9/L and neutrophils 1.5-2.0 x 10^9/L. Continue taking clozapine and monitor white cell count twice a week until it recovers to the normal range.
- Red- White cell count less than 3.0 x 10^9/L and neutrophils less than 1.5 x 10^9/L. Stop taking clozapine immediately, monitor white cell count daily and look for signs of infection.

Patients who develop signs of infection such as sore throat and raised temperature are advised to contact their GP or member of the mental health team. GPs should check FBC and notify the mental health team.

Brand
TEWV has standardised on Clozaril® as the brand of clozapine used across the Trust. Blood test monitoring is co-ordinated by 'Novartis' through their Clozaril Patient Monitoring Service (CPMS).

Side effects and monitoring
While outcomes of this treatment are good, side effects are common. Unfortunately it is associated with a range of troublesome side-effects some of which can have a profound effect on a patient's on-going physical health. The benefits of clozapine can take up to one year to be realised. During this period intensive support may be required to ensure treatment is optimised by titration to therapeutic doses, management of side effects, checking and resolving adherence issues.

Some side effects occur in the first few weeks of treatment and usually wear off. Others persist and can have on-going effects on physical health or indicate serious problems requiring urgent action.

GPs should be aware of clozapine side effects so that physical health problems can be appropriately managed, cardiovascular and metabolic risk factors reduced and patient safety improved.

Clozapine and smoking: In smokers, metabolism of clozapine is significantly increased and so plasma clozapine levels are reduced. On cessation of smoking, plasma clozapine levels can rise dramatically (up to 70%) and only achieve steady state approximately 7-10 days after smoking cessation. If patients change their smoking habit the mental health team must be advised so that plasma levels can be monitored and dose adjustments made. Dose adjustments are also required if patients replace smoking with nicotine replacement therapy.

Clozapine and constipation: All patients on clozapine must be monitored and treated for constipation. Clozapine-induced gastrointestinal hypomotility is probably less well recognised but can progress to severe and fatal bowel obstruction (see side effect table for more information).

Side effect	Management
Agranulocytosis This is a potentially life-threatening situation and should be closely watched for. It occurs most frequently in the first 18 weeks of treatment.	The possibility of neutropenia should be considered in patients who present with symptoms such as fever, chills, sore mouth, sore throat or infection. Check FBC. If the white cells are all normal or raised, treat with an anti-pyretic and antibiotics (see interactions) if indicated. If any of the white cells are LOWERED or if there is ANY concern, contact the Consultant Psychiatrist or on-call doctor if out of hours.
Increased Heart Rate and Other Cardiac Symptoms Tachycardia very common in early stages of treatment, but usually benign. Sudden deaths associated with myocarditis have occurred in some patients; non-specific cardiac symptoms in a patient on clozapine should be thoroughly investigated.	Tachycardia, if persistent at rest and associated with fever, hypotension or chest pain, may indicate myocarditis. Referral to cardiologist advised. Benign sinus tachycardia can be treated with atenolol.
Constipation Very important to recognise and treat, as if left untreated can progress to intestinal obstruction or faecal impaction. This can be a chronic and serious problem, even life threatening http://www.wales.nhs.uk/sites3/Documents/428/RW%20-%20CPhO%20Letter%20clozapine.pdf	Enquire about bowel function routinely and advise patient regarding exercise, fluids and high fibre diet. Symptoms of constipation should be treated with regular laxatives, bulk forming laxative (Fybogel) and if necessary a stimulant laxative (senna) are advised. Inform the mental health team if constipation persists. Avoid adding drugs that may cause constipation as a side effect e.g. antimuscarinic medicine.
Hypersalivation This usually occurs in the initial stages of treatment especially at night, but tolerance can develop.	Prop pillows up at night, towel on pillow and chew sugar-free gum. If troublesome patient may be prescribed hyoscine hydrobromide 300mcg (Kwells) usually at night, but can be given up to a maximum of three times daily. Encourage adequate fluid intake. For extreme hypersalivation refer back to psychiatrist.
Seizures Clozapine is associated with seizures and this can be dose related. At doses above 600mg daily there is a greatly increased incidence of developing seizures.	Refer **urgently** to Consultant Psychiatrist. Carbamazepine should not be prescribed.
Weight gain Usually during the first year of treatment. It is common and often profound (>10 kg)	Dietary counselling and lifestyle advice is essential.

Interactions with Clozapine

The following are the most common drug interactions (Taken and abridged from SPC for Clozaril 25/07/2013)

Drug	Interactions	Comments
Bone marrow suppressants (e.g. carbamazapine, chloramphenicol), sulphonamides (e.g. co-trimoxazole), pyrazolone analgesics (e.g. phenylbutazone), penicillamine, cytotoxic agents and long-acting depot injections of antipsychotics	Interact to increase the risk and/or severity of bone marrow suppression.	Clozapine must not be used concomitantly with other agents having a well known potential to suppress bone marrow function.
Benzodiazepines	Concomitant use may increase risk of circulatory collapse, which may lead to cardiac and/or respiratory arrest.	Caution advised if using together. Respiratory depression and collapse more likely to occur at start of this combination or when clozapine is added to an established benzodiazepine regimen.
Anticholinergics	Clozapine potentiates action of these agents through additive anticholinergic activity.	Observe patients for anticholinergic side-effects, e.g. constipation, especially when using to help control hypersalivation.
Antihypertensive agents	Clozapine can potentiate hypotensive effects of these agents due to sympathomimetic antagonistic effects.	Caution is advised. Patients should be advised of the risk of hypotension, especially during the period of initial dose titration.
Alcohol, MAOIs, CNS depressants, including narcotics and benzodiazepines	Enhanced central effects. Additive CNS depression and cognitive and motor performance interference when used in combination with these substances.	Caution is advised if clozapine is used concomitantly with other CNS active agents. Advise patients of the possible additive sedative effects and caution them not to drive or operate machinery.
Highly protein bound substances (e.g. warfarin and digoxin)	Clozapine may cause increase in plasma concentration of these substances due to displacement from plasma proteins.	Patients should be monitored for the occurrence of side effects associated with these substances, and doses of the protein bound substance adjusted, if necessary.
Antibiotics such as erythromycin and ciprofloxacin	Can elevate clozapine levels	Avoid combination if possible. Consider closer monitoring involving FBCs
Phenytoin	Addition of phenytoin to clozapine regimen may cause a decrease in the clozapine plasma concentrations.	If phenytoin must be used, the patient should be monitored closely for a worsening or recurrence of psychotic symptoms. Consider measuring serum clozapine to ensure therapeutic levels are maintained.
Lithium	Concomitant use can increase the risk of development of neuroleptic malignant syndrome (NMS).	Observe for signs and symptoms of NMS.
CYP1A2 inhibiting substances (e.g. fluvoxamine, caffeine, ciprofloxacin)	Concomitant use may increase clozapine levels	Potential for increase in adverse effects. Care is also required upon cessation of concomitant CYP1A2 inhibiting medications as there will be a decrease in clozapine levels.
CYP1A2 inducing substances (e.g. omeprazole)	Concomitant use may decrease clozapine levels	Potential for reduced efficacy of clozapine should be considered.