Clozapine ~ an aide-memoire for General Practitioners

Clozapine is an antipsychotic used in the treatment of schizophrenia when other antipsychotics have not worked. It is normally initiated **only by psychiatrists** and on-going prescribing remains in secondary care. Since clozapine can cause neutropenia and agranulocytosis regular blood tests are required. We advise that Clozapine is added to the repeat list BUT it is clearly defined as "hospital prescribing only" to avoid it being inadvertently issued-this can be done in the box where dosage instructions are recorded. If it is included on the repeat list it will automatically appear on the SCR. In this way all prescribers should be aware that the patient is receiving the medication and also any newly prescribed drugs will be checked for interactions. *This guidance has been produced in response to a SI –a FP10 prescription was issued for Clozapine which could not be fulfilled*

Brands

There are three brands of clozapine currently available in the UK

1. Clozaril (Brand used by NEP)
2. Denzapine
3. Zaponex

Monitoring

Each brand of clozapine is associated with a mandatory monitoring service**, with results required BEFORE the prescription can be fulfilled**, to detect any drop in white blood cells. The monitoring schedule is weekly for the first 18 weeks of treatment fortnightly between weeks 18 and 52 and four weekly after 1 year of treatment.

The traffic light system is used to direct action required when the white blood cell levels fall.

1. Green – Blood test is within usual parameters and so clozapine can be taken.
2. Amber- White cell count 3-3.5 x *109/L* and neutrophils 1.5-2 x 109/L. Continue taking clozapine and monitor white cell count twice a week until it recovers.
3. Red- White cell count less than 3 x 109/L and neutrophils less than 1.5 x 109/L.**Stop taking clozapine**, monitor white cell count daily and look for signs of infection.

Patients who develop signs of infection such as sore throat and raised temperature should contact their doctor or member of the mental health team.

Treatment Breaks

If treatment is stopped for more than 48 hours it is important to restart gradually from 12.5mg once or twice on the first day. **Please contact your local specialist or clozapine clinic**.

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. Patients must be advised not to change their smoking habit without medical consultation.
See link below for further information:
http://www.sussexpartnership.nhs.uk/component/jdownloads/finish/2030/2673?Itemid=0

Side-effects:

The main side-effects associated with clozapine are:

- Neutropenia / agranulocytosis
- Pyrexia which is generally benign, but consider checking white cell count

- Seizures. The risk is dose dependent and an anticonvulsant such as sodium valproate is often added if doses of clozapine exceed 600mg per day
- Cardiovascular events such as cardiomyopathy and myocarditis are rare. However, symptoms such as chest pain and shortness of breath should be viewed with caution
- Hypotension and hypertension
- Constipation due to slowing of intestinal peristalsis can lead to life-threatening gastrointestinal obstruction. Laxatives should be used to prevent constipation
- Weight gain is common and often profound (5kg+) so dietary advice is essential
- Diabetes and impaired glucose tolerance. Blood glucose should be monitored annually by the clozapine clinic and results sent to general practitioner
- Drowsiness and sedation. The larger proportion of dose is best taken at night
- Urinary incontinence. May respond to an adjusted dose schedule
- Hypersalivation. Hyoscine 300mcg (Kwells) sucked at night can be effective

Drug Interactions with Clozapine

The following are the most common drug interactions.**Drug**	**Interaction**	**comments**
Bone marrow suppressants eg carbamazepine and long acting depot antipsychotics	Increase the risk and or severity of bone marrow suppression	Drugs known to have a substantial potential to depress bone marrow function should **not** be used concurrently with clozapine Depot antipsychotics should also **not** be used concurrently because they cannot easily be removed in cases of neutropenia.
CNS depressants such as opiates, antihistamines, benzodiazepines and alcohol	Concomitant use may enhance the sedative effect of clozapine	Patients should be monitored and consideration given to changing the other sedating medicines. Advise patients to avoid alcohol. Benzodiazepines and clozapine can rarely cause circulatory collapse so monitor carefully especially during dose titration
Antipsychotic drugs	Antipsychotics may increase the risk of sudden cardiac death by causing QTc interval prolongation	Sertindole and pimozide should be stopped before clozapine is started
Antihypertensive agents	Increased risk of hypotension	Use with caution in combination with clozapine.
SSRI antidepressants such as fluvoxamine, fluoxetine and paroxetine	Can affect the metabolism of clozapine via inhibition of CYP2D6 and thereby increase plasma clozapine levels	Fluoxetine and paroxetine may be co-prescribed. However, fluvoxamine also inhibits CYP1A2 and is best avoided as levels can be significantly increased
Antibiotics such as erythromycin and ciprofloxacin	Can elevate clozapine levels	Avoid combination if possible.
Phenytoin and rifampicin	Can decrease plasma clozapine levels by enzyme induction	Consider measuring serum clozapine to ensure therapeutic levels are maintained.
Lithium	May increase the likelihood of neuroleptic malignant syndrome developing	Clozapine + lithium combinations are sometimes used.