Clozapine Information Sheet		
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NHS
Nottinghamshire Area Prescribing Committee

Clozapine

Red

Information Sheet for Primary Care

Please consult the manufacturers Summary of Product Characteristics (SPC)[1] for further information

Clozapine is a RED drug, prescribed, monitored and supplied by Nottinghamshire Healthcare NHS Foundation Trust. However, familiarity with the contents of this document will serve to protect patients treated with clozapine from adverse events associated with its use.

IMPORTANT POINTS

Ensure that clozapine is added to the GP electronic patient's medication list

File this document prominently in the patient's GP notes
Add patient to the severe mental illness (SMI) register
Perform annual physical health check
Arrange urgent full blood count if signs of infection inc. sore throat & flu symptoms
Primary care do not re-titrate if there has been a break of >48hr between doses; alert the mental health team urgently.
Check drug interactions
Stopping smoking can increase clozapine levels, be alert to smoking status
Be alert to constipation, it can lead to clozapine toxicity and bowel perforation

IMPORTANT DRUG INTERACTIONS

Clozapine is contraindicated with other medicines with a substantial potential to depress bone marrow function (e.g. carbamazepine, oxcarbazepine, penicillamine, chloramphenicol (not topical), any chemotherapy regimen, depot antipsychotics).

Clozapine is cautioned with:

- other medicines with sedative effects, including alcohol
- other medicines with anticholinergic or respiratory depressant effects
- other medicines with hypotensive effects or those known to prolong the QTc interval
- rifampicin or phenytoin – *may decrease clozapine plasma levels*
- CP4501A2 inducers such as omeprazole, may lead to decreased clozapine levels
- CP4501A2 inhibitors such as fluvoxamine, ketoconazole, erythromycin, clarithromycin and ciprofloxacin, may lead to increased clozapine levels.
- CP4502D6 inhibitors such as fluoxetine, paroxetine and venlafaxine, may increase clozapine levels. Sertraline may do to a lesser extent.

This is not an exhaustive list. Please see BNF and SPC[1] for further information.

SMOKING AND CAFFEINE INTERACTIONS

Smoking cessation (tobacco and cannabis) can increase clozapine plasma levels by up to 72% (polycyclic aromatic hydrocarbons contained in the smoke induce the CYP450-1A2 system). Note that Nicotine Replacement Therapy and E-cigarettes will NOT affect clozapine levels.

If your patient wants to quit/cut down smoking, **inform the relevant mental health team before any changes to smoking status are made.** This will enable baseline and on-going review of clozapine blood levels, monitoring of side effect burden and possible dose reduction(s).

Plasma clozapine levels are increased by caffeine intake and decrease by 50% following a 5 day caffeine-free period. Advise patient to maintain a stable caffeine intake and inform the mental health team of any changes.

Licensed Indications[1]

Clozapine has been shown to be the drug treatment of choice in treatment-resistant schizophrenia[2]. Response rates are reported to be 30% at 6 weeks and 60% at one year. The average maintenance dose is around 400mg/day, though it is licensed up to 900mg/day. Some patients will experience adverse effects at doses much less than 400mg/day. In non-responders (despite therapeutic plasma levels), clozapine is sometimes augmented with a second antipsychotic e.g. sulpiride or amisulpride.

Approximately 1-2% of patients on clozapine may develop neutropenia leading to agranulocytosis. Regular full blood counts (FBC) are conducted for all patients taking clozapine, co-ordinated by a centralised monitoring service. The Zaponex® brand of clozapine is prescribed by Nottinghamshire Healthcare NHS Foundation Trust co-ordinated by the Zaponex Treatment Access System (ZTAS). Each patient will have their own unique ZTAS Patient Identification Number.

There are other brands of clozapine with similar patient monitoring systems (e.g. Clozaril, Clozaril Patient Monitoring Service (CPMS) and Denzapine, Denzapine Patient Monitoring Service (DPMS)). It is important to ensure patients do not inadvertently switch between different brands of clozapine to ensure patient safety.

Dose Initiation and Breaks in Treatment

Clozapine will always be initiated by a specialist under close supervision either as an in-patient or as an out-patient with close support from the Crisis/Home Treatment Team. Many of the adverse effects of clozapine are dose-dependent and associated with speed of titration. It is started at a low dose (12.5mg once a day) and increased slowly. Doses above 200mg/day are generally given in two divided doses with the larger portion at bedtime.

Tolerance to the sedative and hypotensive effects is rapidly lost. If the patient has not taken clozapine for longer than 48 hours you should advise that the usual dose **must not** be resumed. The mental health team must be contacted urgently as the dose must be re-titrated, usually from 12.5mg/day. Please report any concerns regarding non-adherence with treatment to the mental health team.

Patients Running out of Medication

Clozapine prescriptions should not be made by primary care prescribers or NEMS. If a patient in the community runs out of their clozapine medication, they should be advised to contact their usual mental health team urgently. Out of hours, patients should contact the crisis team (24 hours) on 0808 196 3779.

When and How to Discontinue Treatment

Discontinuation will usually be managed by secondary care. Gradual discontinuation over at least 1-2 weeks is recommended to avoid the risk of acute withdrawal syndromes associated with abrupt discontinuation of clozapine. If the patient stops clozapine without medical advice please refer immediately to the relevant mental health team.

Monitoring

All patients receiving clozapine will have their white blood cells, neutrophils, platelets and eosinophils checked by the Mental Health Team each week, fortnight or month depending on how long they have been on clozapine and the specification of ZTAS. In some cases the GP practice may agree to take the routine blood tests if this is more acceptable for the patient and there has been prior discussion and agreement with the mental health team.

General Monitoring Requirements

Ask about compliance and side effects at every consultation.

All patients should be offered an annual physical health check by their GP (more often if clinically indicated). A copy should be sent to the mental health team and put in the secondary care notes.

Particular attention should be given to:

Lifestyle factors	Smoking, alcohol, substance misuse, diet, level of physical exercise, sexual health, contraceptive advice
Cardiovascular risk factors	Blood pressure and lipids
Endocrine disorders	Hyperglycaemia/diabetes
Response to treatment	Including changes in symptoms and behaviour
Other side-effects	Such as weight gain (monitor BMI, waist circumference), sexual dysfunction, lethargy, hypersalivation, constipation, urinary incontinence

Schedule for Physical Monitoring[2]

	Initial Baseline Health Check & During first year (Secondary Care)	**Annual Health Check By GP** *(frequency may increase if clinically indicated)*
Thyroid Function	√	√
Liver Function	√	√
Renal Function	√	√ (dependent upon age)
Full Blood Count	√ (check weekly / fortnightly / monthly)	√ (check weekly / fortnightly / monthly)
Constipation Screening	√ At each supply of clozapine	(if patient presents with GI issues)
E.C.G.	√ (if indicated)	(only if indicated) See Nottinghamshire APC Antipsychotic Prescribing Guidelines for more information
Fasting Blood Plasma Glucose and HbA1c	√ (repeat at 3 months and 12 months)	√
Weight / Height (B.M.I.) (plotted on chart)	√ (weekly for 6 weeks then at 3 months and 12 months)	√ (check if any visible weight changes)
Waist circumference (plotted on chart)	√	√
Lipid Profile	√ (repeat at 3 months and 12 months)	√
Pulse and Blood Pressure	√ (**repeat during titration and after each dose change)**	√
Prolactin level	√	*(only if indicated)*

SIDE EFFECTS	ACTION
VERY COMMON (>1/10)	
CONSTIPATION	Advise on diet, fluid, exercise and offer laxatives if necessary. Constipation can lead to clozapine toxicity so must always be addressed and actively treated. See information below.
Hypersalivation	Inform mental health team. May be treated with hyoscine hydrobromide (e.g. Kwells®). NB. Off-label use.
Sedation, dizziness	Manipulation of dosage times may alleviate daytime sedation i.e. try the majority of the dose at night. Dose may be too high. Do not drive/operate machinery. Inform mental health team.
Tachycardia (but see myocarditis/ cardiomyopathy)	Dose may have been increased too quickly or dose is too high. Inform mental health team.
COMMON (>1/100, <1/10)	
Dry mouth	Advise symptomatic relief. May be a sign of dose being too high. Consider informing the mental health team.
Increased liver enzymes	Inform the mental health team if the elevation of the values is clinically relevant (more than 3 times the UNL) or if symptoms of jaundice occur
Blurred vision	May be a sign of the dose being too high. Consider informing the mental health team. Careful supervision is indicated in the presence of narrow-angle glaucoma. Do not drive/operate machinery.
Nausea and vomiting	Take after food or divide doses. If severe consider antiemetic
Urinary retention/incontinence	Consult mental health team and urologist. Nocturnal incontinence may respond to dose reduction or taking the night-time dose earlier in the evening. Acute retention may need emergency catheterisation/hospital admission.
Hypertension, postural hypotension, syncope,	Dose may have been increased too quickly or dose is too high. Inform mental health team.
Weight gain	Encourage a healthy balanced diet, regular exercise. Monitor and refer to dietician or mental health team if appropriate. See the Nottinghamshire APC Antipsychotic Prescribing Guidelines for more information on the management of antipsychotic induced weight gain,
Seizures/convulsions/ myoclonic jerks/extrapyramidal symptoms	More common with higher doses of clozapine. Inform mental health team immediately.
Leukopenia/ neutropenia	If patient reports symptoms of infection (e.g. flu-like symptoms, sore throat, high temperature) an urgent full blood count is indicated. Inform mental health team immediately. Clozapine to be discontinued if White Cell Count $<3.0x10^9$/L or Neutrophil Count $<1.5x10^9$/L.
Fever, benign hyperthermia, sweating	Check Full Blood Count. Reduce rate of dose titration. Not usually related to blood dyscrasias but beware myocarditis (see below).
Eosinophilia	If eosinophil count rises above $3.0x10^9$/L inform mental health team
Dysarthria	Dose may have been increased too quickly or dose is too high. Inform mental health team.
UNCOMMON (>1/1000, <1/100)	
Agranulocytosis	If patient report symptoms of infection (e.g, flu-like symptoms, sore throat, high temperature) an urgent full blood count is indicated. Inform mental health team immediately. Clozapine to be discontinued if WCC$<3.0x10^9$/L or Neutrophil Count $<1.5x10^9$/L.
Neuroleptic malignant syndrome (NMS)	Hyperthermia, muscle rigidity, autonomic instability, altered consciousness, raised CPK. Discontinue ALL antipsychotic(s). If suspected immediate referral to a hospital is required.

RARE/VERY RARE (<1/1000)	
Myocarditis/ cardiomyopathy	If suspected clozapine should be stopped and patient referred to cardiologist immediately. Suspect in patients who have persistent tachycardia at rest, palpitations, arrhythmias, chest pain, and other signs/symptoms of heart failure or symptoms that mimic Myocardial Infarction. Flu-like symptoms may also be present. Inform mental health team.
Dysphagia	Refer to mental health team.
Impaired glucose tolerance, diabetes mellitus	Monitor and manage according to local diabetes guidelines. Refer if appropriate.
Thrombocytopenia	If platelets fall to <50x10^9/L. Inform mental health team immediately for review of treatment.

Clozapine and Constipation[3,4]

As per the MHRA Drug Safety Update from October 2017[5], clozapine is associated with a potentially fatal risk of intestinal obstruction, faecal impaction, and paralytic ileus.

Clozapine-induced gastrointestinal hypomotility can occur at any point in treatment and can be potentially life threatening. All patients taking clozapine should be asked about their bowel habit at every contact.

All patients taking clozapine should be advised to:
- Increase the amount of fibre in their diet.
- Increase their fluid intake.
- Increase exercise (aim for 30 minutes five times per week).

If a patient taking clozapine reports constipation or symptoms such as:
- Not passing a stool in 3 days.
- Straining on defecation.
- Lumpy or hard stools (1-2 on the Bristol Stool Form Scale)
- Feeling that bowel movement has not been completed, or that anus is blocked.

an urgent abdominal examination should be carried out.

Patients experiencing:
- Medium to severe abdominal pain or discomfort lasting over one hour.
- Swollen or distended stomach.
- Overflow diarrhoea.
- Sickness or vomiting (particularly if it smells of stool).
- Absent bowel sounds.
- Symptoms of sepsis (high or low temperature, confusion, drowsiness).

should be advised to attend A&E for urgent assessment as there is a possibility of intestinal obstruction.

If intestinal obstruction is ruled out, consider:
- Senna 15mg ON plus docusate 100mg TDS. Review every 48 hours and increase doses if needed up to a maximum of 30mg/day senna and 500mg/day docusate.

If further laxative required:
- add macrogol 1-3 sachets daily.

Patients should be advised to attend A&E if any of the symptoms of gastrointestinal obstruction listed above occur.

Laxative treatment should be reviewed and reduced to the lowest effective dose once symptoms have resolved. However, most patients on clozapine will require a long-term stimulant laxative (such as senna) as a minimum.

Monitoring of Clozapine Blood Levels

As per the MHRA Drug Safety Update from August 2020[5], the monitoring of clozapine blood levels is advised in certain clinical situations. Clozapine blood levels are different from the routine Full Blood Count (FBC) that is mandatory for all patients on clozapine.

Across Nottinghamshire, some people have the routine FBC taken at their GP practice under local arrangements. If a clozapine blood level is required in addition to the routine FBC, this must always be on the request of the Mental Health Team looking after that person. If you do receive a request to undertake a clozapine blood level, be aware of the following:

1. Clozapine blood levels are trough levels and must be taken approximately 12 hours post dose. If the person takes a morning dose of clozapine, this dose should be delayed until after the blood test.
2. The blood sample type for clozapine levels is 1mL EDTA[6] – this should be separate to a FBC sample.
3. Clozapine blood levels can take up to 4 weeks to be reported and therefore aren't useful in emergency situations where clozapine toxicity is suspected.
4. Interpretation and response to the clozapine blood level is the responsibility of the Mental Health Team who requested the level.

If toxicity related to antipsychotic medication is suspected, immediate action should be taken in response to the symptoms displayed. Clinical signs of clozapine toxicity include: drowsiness, lethargy, areflexia, coma, confusion, hallucinations, agitation, delirium, extrapyramidal symptoms, hyperreflexia, convulsions; hypersalivation, mydriasis, blurred vision, thermolability; hypotension, collapse, tachycardia, cardiac arrhythmias; aspiration pneumonia, dyspnoea, respiratory depression or failure.

Precautions

- Clozapine has been associated with varying degrees of impairment of intestinal peristalsis, thought to be due to the anticholinergic properties of clozapine[5].Treat constipation seriously.
- Pregnancy and breast-feeding – refer to consultant
- Hyperglycaemia – Appropriate clinical monitoring is advisable in diabetic patients and in patients with risk factors for developing diabetes mellitus.
- Epilepsy – As with other antipsychotics caution is recommended when treating patients with a history of seizures as convulsive threshold may be lowered.
- Prostatic enlargement / narrow-angle glaucoma - due to anticholinergic properties of clozapine careful supervision is required in these conditions
- Patients with known cardiovascular disease or family history of **QT prolongation**.
- Patients with risk factors for stroke
- Patients with hepatic impairment - regular monitoring required
- Antipsychotic use maybe associated with an increased risk of venous thromboembolic events (VTE). All possible risk factors for VTE should be identified before and during antipsychotic treatment and preventative measures undertaken[6]

Patient information leaflets for clozapine and other antipsychotic medications can be found at:

- https://www.rcpsych.ac.uk/mental-health/treatments-and-wellbeing/antipsychotics
- https://www.mind.org.uk/information-support/drugs-and-treatments/antipsychotics-a-z/clozapine/
- For specific information please refer to the Notts HCT Pharmacist Mental Health Medicines Advice Line. Tel: **0300 303 5808**

References

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5. MHRA. (2017). Clozapine: reminder of potentially fatal risk of intestinal obstruction, faecal impaction and paralytic ileus. Available from: https://www.gov.uk/drug-safety-update/clozapine-reminder-of-potentially-fatal-risk-of-intestinal-obstruction-faecal-impaction-and-paralytic-ileus
6. MHRA. (2020). Clozapine and other antipsychotics: monitoring blood concentrations for toxicity. Available from: https://www.gov.uk/drug-safety-update/clozapine-and-other-antipsychotics-monitoring-blood-concentrations-for-toxicity
7. Nottingham University Hospitals. 2024. Clinical Pathology Service Directory. Available from: https://www.nuh.nhs.uk/download.cfm?doc=docm93jijm4n8153
8. MHRA. (2009). Antipsychotics: risk of venous thromboembolic events. Available from: https://www.gov.uk/drug-safety-update/antipsychotics-risk-of-venous-thromboembolic-events

Useful Contacts

Nottinghamshire Healthcare NHS Foundation Trust		Zaponex Treatment Access System (ZTAS)
Wells Road Centre Pharmacy	0115 9555 356	020 7365 5842
Blossomwood Pharmacy Office	0115 969 1300 (extension 14124)	http://www.ztas.co.uk/
Pharmacy advice line	0300 303 5808	
Crisis team (24 hours)	0808 196 3779	