

Clozapine

Information for primary care



Berkshire Healthcare
NHS Foundation Trust

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 and **prescribing responsibility will not transfer to GPs under any circumstances**.

Please add clozapine to the GP practice medical record as a Hospital Only Medication to prevent inadvertent prescribing of interacting medicines, missed adverse effects and omitted medication on admission to acute services. Annotate with "contact BHFT Pharmacy for current dose" or similar rather than specific doses.

While outcomes of clozapine treatment are good, **side effects are common and can have a profound effect on a patient's on-going physical health**. Some side effects occur in the first few weeks of treatment and usually wear off. Others persist and can affect physical health or indicate serious problems requiring urgent action. Whilst these are routinely monitored by BHFT, the patient may present at other times or with symptoms that appear unrelated.

Adverse effects

Prevent and look for	Action if suspected
Constipation and Clozapine Induced Gastric Hypomotility (CIGH)	
<ul style="list-style-type: none">▪ Avoid prescribing constipating medicines including anticholinergics and opioids.▪ Advise patient on exercise, fluids and high fibre diet.▪ Enquire about bowel habit (ask if patient have a bowel movement today or yesterday and which type).▪ Look for other signs of constipation including overflow diarrhoea, abdominal pain, repeated UTIs, bloating, loss of appetite, nausea, straining, rectal bleeding or pain, bowel incontinence and behavioural changes▪ Often presents without impaction in rectum but higher obstruction in sigmoid colon.▪ Constipation can affect 60% of patients.▪ Many patients will not recognise they are constipated or not report.▪ High incidence of mortality▪ Check patient has access to laxatives either BHFT or GP on repeat medication.	<ul style="list-style-type: none">▪ Inform MH service if chronic constipation suspected or constipation persists.▪ Treat actively with stimulant and softening laxative (e.g. senna and docusate) add PEG osmotic e.g. Movicol/Laxido if needed. Check compliance, exclude obstruction.▪ Refer <i>urgently</i> to acute care if: Moderate or severe abdominal pain lasting more than 1 hour Abdominal distension Vomiting Overflow diarrhoea or bloody diarrhoea Absent or high pitched bowel sounds Metabolic acidosis Haemodynamic instability Leukocytosis Signs of sepsis▪ Have low threshold for referral to acute care, death can occur within hours.▪ Drug Safety Update 2017
Neutropenia and agranulocytosis	
<ul style="list-style-type: none">▪ Signs of infection including sore throat and raised temperature.▪ Most common in first 18 weeks of therapy.	<ul style="list-style-type: none">▪ Check FBC and notify the MH service.▪ White cells are all normal or raised, treat with an anti-pyretic and antibiotics (see interactions) if indicated.▪ Severe pneumonia or other serious infection notify the MH team urgently. Plasma levels may be required.▪ If white cells are LOWERED or if there is ANY concern, contact the Consultant Psychiatrist or on-call doctor if out of hours.▪ Drug Safety Update 2020

Nocturnal Enuresis	
<ul style="list-style-type: none"> May occur at any time Affects 20% 	<ul style="list-style-type: none"> Contact the MH service, clozapine regimen change may be required to avoid deep sedation. Desmopressin nasal spray may be used if severe.
Smoking	
<ul style="list-style-type: none"> If a patient stops or starts smoking including switching to NRT. Stopping can increase plasma levels by 70% within 7-10 days 	<ul style="list-style-type: none"> Inform Clozapine Service urgently as plasma level needed with dose alteration. Drug Safety Update 2020
Increased Heart Rate and Other Cardiac Symptoms	
<ul style="list-style-type: none"> Tachycardia is very common in early stages but usually benign. Sudden deaths associated with myocarditis have occurred most commonly in first 8 weeks, monitor for hypotension, tachycardia, fever, flu like symptoms, fatigue, dyspnoea with increased respiratory rate and chest pain. Hypotension usually limited to first 4 weeks Long term weight gain may lead to hypertension. 	<ul style="list-style-type: none"> Seek advice from cardiologist if tachycardia occurs in presence of chest pain, heart failure or overt signs of myocarditis. Clozapine should be stopped and Psychiatrist contacted for advice. Non specific cardiac symptoms in a patient on clozapine should be thoroughly investigated. Benign tachycardia may be treated with bisoprolol or atenolol.
Hypersalivation	
<ul style="list-style-type: none"> Occurs in initial stages and tolerance can develop. 	<ul style="list-style-type: none"> Prop pillows up at night, towel on pillow and chew sugar-free gum. Encourage adequate fluid intake. For extreme hypersalivation refer back to psychiatrist where hyoscine may be prescribed.
Seizures	
<ul style="list-style-type: none"> Greater incidence over 600mg and can occur at anytime. Myoclonus may precede a full tonic clonic seizure and more prevalent in initiation and when plasma level increases. 	<ul style="list-style-type: none"> Clozapine should be withheld and refer urgently to Consultant Psychiatrist. Carbamazepine should not be prescribed. In some cases prophylaxis may be required.
Weight gain	
<ul style="list-style-type: none"> Usually in first year and can be profound >10Kg. 	<ul style="list-style-type: none"> Dietary counselling and lifestyle advice. If lifestyle unsuccessful, contact MH team for advice as metformin or aripiprazole may be required.
Sedation	
<ul style="list-style-type: none"> Usually in first few months and wears off. 	<ul style="list-style-type: none"> Contact MH service, regimen may need adjusting.
Nausea	
<ul style="list-style-type: none"> Usually in first 6 weeks and wears off. 	<ul style="list-style-type: none"> Seek advice from MH. Cyclizine may be used or ondansetron, however ondansetron worsens constipation. Avoid metoclopramide and prochlorperazine (history of EPSE) and domperidone (history of cardiac disease or QTc prolongation).

Interactions

Drug	Interactions	Comments
Bone marrow suppressants (e.g. carbamazepine, chloramphenicol, sulphonamides, pyrazolone analgesic (i.e. phenazone) 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.
Opioids	Concomitant use may increase risk of additive CNS effects and constipation.	Use with caution and enquire about over sedation and bowel activity, prescribe peg osmotic laxatives and stimulants if necessary.

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 opioids 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. Plasma clozapine levels may be required, notify MH service.
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, hormonal contraceptives)	Concomitant use may increase clozapine levels	Potential for increase in adverse effects. Plasma levels may be required. Notify MH service. 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.

How to contact the relevant service

Clozapine clinic clozapine.clinic@berkshire.nhs.uk Tel: 0118 960 5296 Monday 2-4pm Thursday 9am-1pm & 2-4pm	Community Mental Health Teams / Psychiatrist Contact Psychiatrist using details as per clinic letter or contact reception in locality and ask for Duty
	Reading – Prospect Park House Reception 0118 960 5612
Medicines Information medicines.information@berkshire.nhs.uk Tel: 0118 960 5075 Monday – Friday 9-1pm	Wokingham – The Old Forge Reception 0118 890 707
	Newbury – Hillcroft House Reception 01635 292 020
Common Point of Entry /The Gateway gateway@berkshire.nhs.uk If referral is urgent, telephone 0300 365 2000 which is monitored Monday – Friday 8am-8pm (excluding bank holidays) or CRHTT on 0300 695 9999 (Option 1 West, Option 2 East)	Slough – New Horizons Reception 01753 690 950
	Windsor, Ascot and Maidenhead – Nicholson House Reception 01628 640 200
	Bracknell – Church Hill house Reception 01344 823 333

References - Prescribing Guidelines in Psychiatry 14th Edition. The Maudsley. 2021

Prepared by Janet Sear. Medication Safety Officer August 2021. Approved by Medication Safety Committee.