

CLOZAPINE: reducing the risk of harm

SAFETY

Clozapine is a RED drug in the [Pan Mersey APC formulary](#).

Service users prescribed clozapine will have it prescribed, monitored, and dispensed via their local mental health trust. Where a service user is under the care of a third party, e.g., during an acute medical admission, this may lead to a break down in care. This guidance is aimed at highlighting these risks and providing solutions for the non-specialist.

Administrative action points for general practice

- DO NOT issue clozapine prescriptions.
- **Add clozapine to the GP prescribing system (hospital section)** – this will enable the interactions software to detect potential problems, and clozapine will appear on the Summary Care Record (SCR). The dose should not be specified and instead instruct to refer back to the specialist service for advice and confirmation of the current dose.
- Refer to the [Pan Mersey APC advice on SCR](#).

Clinical action points for all prescribers and other non-mental health hospitals

- Clozapine can cause neutropenia (3% of service users) and agranulocytosis (0.5%).
- Consider urgent FBC if there are signs and symptoms of infection, e.g., sore throat, fever, or flu like symptoms
- **Note** that the symptoms of COVID-19 and neutropenia can be indistinguishable.
 - Any patient taking clozapine presenting with suspected COVID-19 must also have neutropenia excluded with an urgent FBC.
- Urgently inform the psychiatrist, CMHT *, care-coordinator and/or other lead clinician if there is:
 - Clinical or haematological episodes of neutropenia or agranulocytosis.
 - Episodes of erratic or non-compliance with clozapine therapy.
 - A break in treatment of more than 48 hours: do not restart clozapine.
 - Abrupt discontinuation of clozapine: this can lead to an acute rebound psychosis.
 - Any change in smoking status.
 - Potential clozapine-induced constipation: can be life threatening, consider A&E referral.
- Contact your local CMHT and/or supplying pharmacy with any clozapine-related queries or for advice.
- Contact Psychiatry Liaison during all acute hospital in-patient user stays.
- Carefully consider the potential for drug interactions (see below).
- Always report appropriate clozapine side effects on a Yellow Card, e.g., neutropenia, severe constipation.

* CMHT (Community Mental Health Team) refers to the relevant, local mental health team providing care for your service user; this may include the Recovery Team, Early Intervention Team, Health & Wellbeing team, etc.

Action points for community pharmacists

- DO NOT dispense clozapine prescriptions (unless you are registered with the appropriate monitoring service).

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Clozapine: information for healthcare professionals

Background information

Clozapine is an atypical antipsychotic indicated for treatment resistant schizophrenia (TRS) or psychotic disorder in Parkinson's disease.

There are 3 brands of clozapine (see below for manufacturer contact details):

- **Clozaril** (Viatris) prescribed by Cheshire and Wirral Partnership NHS FT, Lancashire and South Cumbria NHS FT, Mersey Care NHS FT, North West Boroughs Healthcare NHS FT.
- **Denzapine** (Britannia Pharmaceuticals Ltd) prescribed by Mersey Care NHS FT; only oral suspension prescribed by Cheshire and Wirral Partnership NHS FT.
- **Zaponex** (Leyden Delta) not prescribed within Pan Mersey APC.

Patient registration

Every service user prescribed clozapine must be registered with one of the three manufacturers before they can be prescribed and dispensed clozapine; this is arranged by the secondary care psychiatric team.

The CMHT and/or supplying pharmacy will monitor the efficacy and tolerance of clozapine, manage the ongoing mandatory full blood count testing required, and prescribe and supply the clozapine.

Clozapine is usually dispensed only by appropriately registered pharmacies; this is usually the local mental health Trust's dispensary.

Side Effects

| Very common side effects include (≥10%) | | |
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| Constipation – can be life threatening (see below) * ‡ | | Tachycardia † |
| Drowsiness or sedation † | | Dizziness |
| Common side effects include (≥1% and <10%) | | |
| Urinary incontinence | Urinary retention | Weight gain † |
| ECG changes † | Postural hypotension | Syncope |
| Akathisia † | Extrapyramidal symptoms | Seizures, convulsions, or myoclonic jerks |
| Tremor † | Rigidity | Blurred vision |
| Headache | Fatigue | Anorexia |
| Hypersalivation † | Dry mouth | Nausea |
| Vomiting | Leucocytosis | Eosinophilia |
| Leucopenia | Agranulocytosis * | Elevated liver enzymes |
| Fever or benign hyperthermia (if associated with leucopenia or neutropenia or cardiac symptoms or temperature > 38 °C) * | | Disturbances in sweating or temperature regulation (if associated with cardiac symptoms) * |
| * These side-effects can lead to an acute life-threatening condition; consider urgent referral to A&E | | |
| † May persist and indicate development of myocarditis * or cardiomyopathy * | | |
| ‡ Management of these side effects would usually be led by the local mental health team | | |

Service users taking clozapine may present at your GP surgery with side-effects of clozapine. These can generally be managed symptomatically, however some will require referral back to the CMHT.

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Always inform the CMHT if a service user develops any suspected clozapine-related side-effects

Clinically significant side effects

Agranulocytosis

Clozapine can cause neutropenia AND agranulocytosis.

- Be cautious if any signs or symptoms of a low white cell count are present: consider taking urgent WBC or refer to A&E
- Other drugs that cause neutropenia are contraindicated, see **drug interactions** below
- **Always** report clozapine associated neutropenia on a [Yellow Card](#)

Constipation

Clozapine can cause constipation (commonly) and exacerbate drug induced constipation. This can (rarely) lead to intestinal obstruction, faecal impaction and paralytic ileus. This can be fatal.

- **Always** ask about constipation in anyone taking clozapine.
- **Always** consider lifestyle factors in managing clozapine associated constipation, e.g., improving fluid and fibre intake, and exercise.
- **Always** aggressively treat constipation in anyone taking clozapine to prevent it deteriorating.
- **Avoid** bulk forming laxatives.
- **Always** assess anyone taking clozapine for constipation if they are also taking anti-muscarinics, e.g., hyoscine or pirenzepine (an unlicensed anti-muscarinic for hypersalivation), etc. Review the prescribed laxatives. Ask the CMHT to review causative medication.
- If you are concerned about the risk of impaction or bowel infarction, immediately refer to A&E for (surgical) assessment.
- **Always** inform the CMHT of acute constipation and primary care actions.
- **Always** report clozapine associated constipation on a [Yellow Card](#).

Hypersalivation

- Clozapine can cause profound hypersalivation, severely impacting quality of life.
- An off-label antimuscarinic like hyoscine (Kwells) or atropine eye drops (sub-lingual) is often recommended.
- Unlicensed pirenzepine is sometimes recommended but will usually be prescribed by the mental health trust with the clozapine.
- **Always** consider the impact these additional anti-muscarinics will have on constipation.
- Refer to the [Pan Mersey advice on managing hypersalivation](#).
 - Glycopyrronium is rarely used for clozapine induced hypersalivation as it does not feature in mental health treatment algorithms.

Seizure

- Clozapine can rarely cause seizures, typically at doses above 500 mg daily.
- Antiepileptic drugs use for prophylaxis or treatment include valproate, topiramate or lamotrigine.
- **Always** report clozapine associated seizures on a [Yellow Card](#).

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Drug interactions

Commonly used antibiotics which are safer to co-prescribe, and antibiotics to avoid, are listed below. This is **not** an exhaustive list.

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| CARE: It is essential to ensure that an antibiotic is not prescribed for an indication caused by an underlying neutropenia; consider a routine FBC when prescribing antibiotics | | |
| Antibiotics SAFE to prescribe include | Antibiotics to AVOID because they can cause neutropenia include | Antibiotics to AVOID because they increase serum clozapine concentrations include |
| Azithromycin Clarithromycin (Caution: QT prolongation) Fusidic acid eye drops Penicillins Tetracyclines | Dapsone Isoniazid Metronidazole Nitrofurantoin Quinolones Rifampicin Sulphonamides Trimethoprim | Erythromycin Quinolones Rifampicin |

| | |
|--|--|
| Other drugs to use with CAUTION include | Other drugs to AVOID include |
| Mirtazapine due to neutropenia risk and weight gain Topical and ocular chloramphenicol due to neutropenia risk SSRIs including fluoxetine, paroxetine, fluvoxamine due to increased and toxic serum clozapine concentrations | Carbamazepine Chemotherapy and cytotoxic agents Carbimazole Chloramphenicol (non eye-drop formulations) Depot antipsychotics |

- If use of an interacting drug is unavoidable, **please inform the CMHT urgently.**
- Contact the CMHT urgently if your service user receives a diagnosis of cancer that will require chemotherapy; **the oncologist must** liaise urgently with the consultant psychiatrist and mental health pharmacist.

Non-Drug Interactions

Smoking: clinically significant

- Inhaled tobacco smoke (not nicotine or e-cigarettes) can affect clozapine plasma concentrations.
 - Smoke inhalation can significantly reduce clozapine plasma concentrations and can lead to loss of efficacy.
 - Stopping smoking can significantly increase clozapine plasma concentrations and can quickly lead to toxicity.
- Therefore, refer to the CMHT before the service user quits or cuts down smoking (including switching to e-cigarettes). The CMHT can then modify the clozapine dose and arrange for the appropriate monitoring.
 - This is especially important during acute in-patient stays where smoking is (temporarily) reduced or stopped.

Caffeine

- Caffeine may interact with clozapine and can increase plasma clozapine concentrations; a corresponding decrease in clozapine serum concentrations can occur after even a short caffeine-free period
- Advise service user to maintain a stable caffeine intake. Inform the CMHT of any changes
- Caffeine is found in coffee, tea, cola drinks, chocolate, energy drinks such as Red Bull, Monster Energy etc.

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Service user information about clozapine

www.choiceandmedication.org/nwbh

www.choiceandmedication.org/cheshire-and-wirral

www.choiceandmedication.org/merseycare

www.choiceandmedication.org/lancashirecaretrust

Prescribing information for clozapine

- Clozapine: <https://www.medicines.org.uk/emc/search?q=clozapine>
- Clozaril SPC: <https://www.medicines.org.uk/emc/product/4411>
- Denzapine SPC: <https://www.medicines.org.uk/emc/product/6087/smpc>
- Zaponex SPC: <https://www.medicines.org.uk/emc/product/7715/smpc>
- BNF: <https://bnf.nice.org.uk/drug/clozapine.html>

Contact details for clozapine manufacturers

- Clozaril Connect, Viatrix' portal, <https://www.clozaril.co.uk/> has professionals' and service user resources
Tel: 0845 - 769 8269
- Denzapine's portal: <https://www.denzapine.co.uk/> Tel: 0333 - 200 4141
- Zaponex portal: <https://www.zaponex.co.uk/> Tel: 0207 - 365 58 42

References

1. MHRA Drug Safety Update (October 2017): [Clozapine: reminder of potentially fatal risk of intestinal obstruction, faecal impaction, and paralytic ileus](#). [Accessed 3rd November 2020]