RC PSYCH
ROYAL COLLEGE OF PSYCHIATRISTS

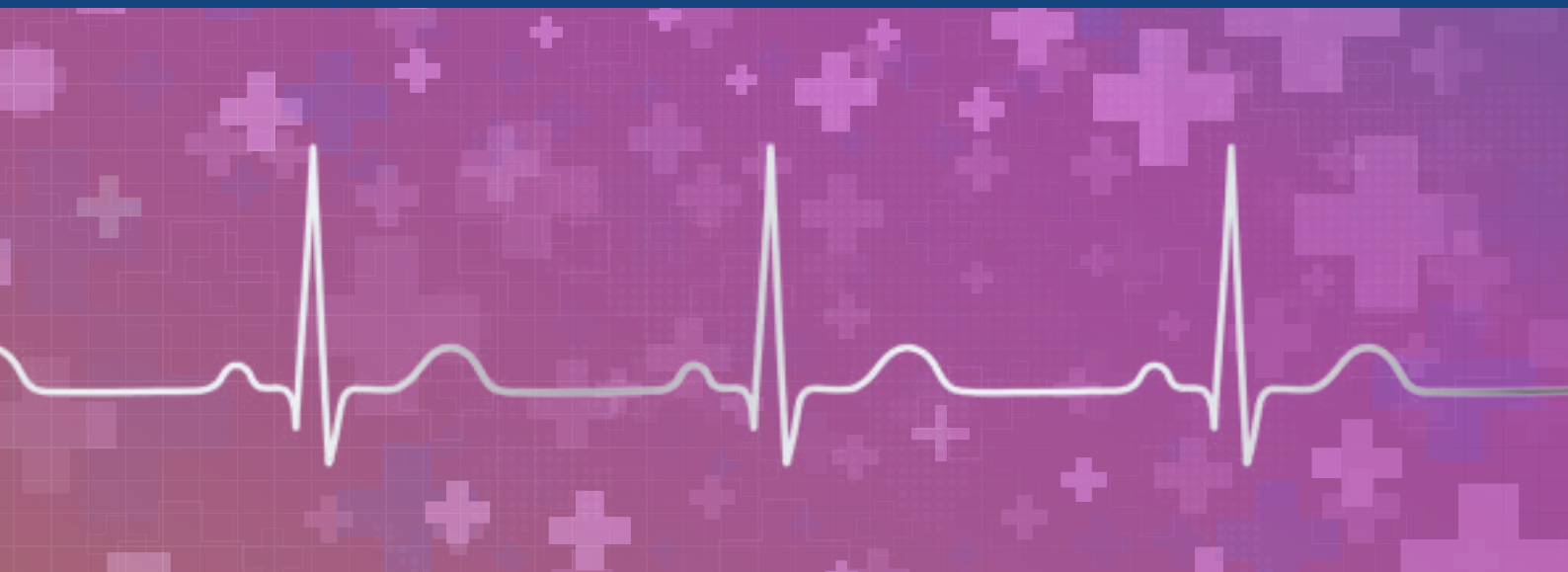
PRACTICAL GUIDE

Wim's Protocol

For the safe prescribing and monitoring of clozapine

June 2026

Version 1.1



Foreword: Wim's legacy

"Wim's Protocol is, at its heart, a legacy to my little brother, William Northcott (Wim).

Wim was a one off – once met, never forgotten. He was kind, intelligent, and deeply compassionate, with a remarkable sense of humour. Wim was deeply loved by his family and his carers. While his diagnoses of autism, schizophrenia, and OCD shaped the course of his life, they never defined him and the light, fun and love he emitted to those in his orbit.

Wim died suddenly on 13 June 2021 at the age of 39 at his care home. After ten years of treatment with clozapine, he developed myocarditis and associated toxicity that remained undetected due, in part, to a lack of clinical monitoring.

I was resolute that Wim's death would elicit meaningful change and after two years of research, I concluded that a new safety protocol for clozapine was needed. From the outset, it was essential that any protocol developed in his name should reflect the standard of care and monitoring that could have saved his life.

The incredible team led by Lade and Ed at the Royal College of Psychiatrists have achieved this. Wim's Protocol will strengthen clinical vigilance, improve early detection of adverse events and save lives.

Together we have ensured that Wim's death will not be in vain. Wim was a hidden treasure that never had the chance for the world to see him shine. I'm hopeful his legacy will be a shining light for patient safety. It feels like a dream to say, 'Wim's Protocol is finally here'."

— **Kate Northcott Spall**

Clinical foreword

"The death of William Northcott, known as Wim, was a tragedy.

At the time of his death, Wim was taking clozapine, an antipsychotic medication that can be life-changing for people with treatment-resistant schizophrenia.

Clozapine is one of the most effective treatments we have in psychiatry, and it is vital that people who may benefit from it are able to access it. However, its safe use depends on careful physical health monitoring, clinical vigilance and clear action when concerns arise. This is because clozapine can have very serious adverse effects or interactions, some of which can be fatal if they are not detected and acted upon early enough.

Wim's death brought this need for vigilance into sharp focus. This protocol, named in his memory, aims to strengthen clozapine care by providing evidence-based guidance for physical health monitoring at every stage of treatment, with recommendations that can be delivered across a range of settings.

Wim's sister, Kate Northcott Spall, and our Presidential Lead for Physical Health, Dr Ed Beveridge – supported by Dr Mao Fong Lim and Nichola Crawford, a carer expert by experience – have done a fantastic job leading the development of this work. This involved working with many others who brought lived experience, academic and clinical expertise to the process.

I'm delighted to see the protocol finally published after almost two years of careful consultation and analysis.

Speaking to the clinical community specifically, we must all become better at monitoring our patients who are on clozapine and we must never stop striving to improve. With this in mind, Wim's Protocol should be understood as an evolving guide built on existing understanding and that can be further built upon by others.

The College looks forward to encouraging clinicians and provider organisations to take up the protocol, as well as promoting the protocol more widely so that those who require clozapine can access it safely, be provided with the right support and live the long healthy lives they deserve."

— **Dr Lade Smith CBE**
President, Royal College of Psychiatrists

Authorship and recognition

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- **Mrs Kate Northcott Spall**
- **Dr Lade Smith,** President, RCPsych
- **Lorna Templeton,** Vice-Chair, Mental Health Pharmacy Strategy Group

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- Royal College of General Practitioners (RCGP)
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Introduction

What is Wim's Protocol?

Wim's Protocol is a practical guide to safer clozapine care.

It explains what physical health monitoring is needed before and during clozapine treatment, which warning signs may indicate serious side effects, and what action patients, carers, support workers and healthcare professionals should take if concerns arise.

Why clozapine matters

Clozapine is the only antipsychotic medication licensed for **treatment-resistant schizophrenia**. (This means schizophrenia for which symptoms have not adequately improved after treatment with at least two different antipsychotic medicines.)

For many people, clozapine can be life-changing. It can relieve or resolve symptoms, helping people return to education or employment and reconnect with friends, family and their communities. Across the wider population, clozapine is also associated with increased life expectancy for people with treatment-resistant schizophrenia.

Like all medicines, clozapine can cause adverse effects. Some of clozapine's adverse effects can be serious and, in rare cases, can be fatal if they are not prevented or detected early enough. Some of the serious adverse effects associated with clozapine include agranulocytosis, constipation and pneumonia, among others.

Concerns about these risks can make clinicians less willing to prescribe clozapine, even when it is indicated. As a result, some people who could benefit from clozapine may miss out. Wim's Protocol aims to solve this problem.

Why Wim's Protocol is needed

The purpose of Wim's Protocol is to strengthen the safety of clozapine treatment through clearer physical health monitoring, while supporting greater clinical confidence in prescribing so that people who may benefit from clozapine can access it in a timely way.

Wim's Protocol aims to reduce the risk of serious adverse effects by improving recognition of 'red flag' physical health symptoms and other contributory factors. This enables clinicians, patients, carers and other key people in a patient's life to notice potential warning signs and escalate concerns when they arise.

This protocol is intended to inform, not replace, existing local guidance, and to provide core standards for prescribers and other healthcare professionals involved in clozapine care across the UK.

Wim's Protocol: A shared guide for clozapine care

Safe and effective support for people with treatment-resistant schizophrenia is a collaborative effort. Decisions around which medication to use, and how to use it safely, are usually made by clinicians. However, patients and those who care for them should be supported to take an active role in decision making as they are able and if they so wish.

In reality, most day-to-day support for people taking clozapine is not from clinical staff, but from family, friends, support workers and other people within their community. We hear time and time again from carers that they want to be involved more and that with the right information, they can provide better support to their loved ones and work more effectively with clinical teams.

Wim's Protocol seeks to support and improve this collaboration and therefore is aimed at a wide audience. Some of the content is intended for healthcare professionals to use, specifically where we are describing the details of physical health monitoring or how to identify and treat potentially serious side effects. Other content is aimed primarily at patients, carers, support workers and others who see our patients day to day, to help them to understand more about the impact of clozapine on the people they look after.

Our vision is to enable patients and their network to take a more active part in their care, to know what questions to ask and what issues to raise. We have therefore deliberately kept everything in one document.

Where a particular section is more relevant to a particular group, this is indicated. Otherwise, the content is for everyone.

What the protocol covers

- ✓ **Physical health monitoring across the clozapine pathway:**
  Detailed, evidence-based guidance on physical health monitoring from the point at which clozapine is first considered through when it is being used for long-term maintenance treatment.
- ✓ **Minimum standards for investigations and interventions:**
  Clear expectations for the core investigations and interventions that all prescribers should undertake. This protocol is intended to inform, not replace, local policy and guidance. We recognise that provision and resources vary between organisations, and that many services will exceed these standards, including testing and implementing innovative technologies and models of care. This is welcomed and encouraged.
- ✓ **Identification of 'red flag' symptoms:**
  This document identifies 'red flag' symptoms for patients and their wider support network that may signal serious adverse effects, severe illness, or preventable harm. While not all such symptoms indicate an emergency, their recognition should prompt timely help-seeking.
- ✓ **Escalation guidance for patients and carers:**
  Clear and accessible escalation pathways for patients, carers, and others in their support network to follow when red flag symptoms arise.
- ✓ **Clinical guidance for healthcare professionals:**
  Detailed clinical information for medical and other healthcare professionals involved in the care of people taking clozapine, including escalation processes.

What the protocol does not cover

- × **Identifying patients suitable for clozapine:**
  This protocol does not provide detailed guidance on identifying candidates for clozapine. For this, clinicians should refer to existing established clinical sources, such as NICE or SIGN guidelines, as well as the RCPsych's 2026 position statement Clozapine for treatment-resistant schizophrenia: The case for timely and appropriate use.
- × **Continuation following adverse events:**
  Comprehensive guidance on when it may not be appropriate to continue clozapine following an adverse event is beyond the scope of this document. This includes decision-making around clozapine rechallenge (restarting clozapine after it has been stopped because of an adverse event) following neutropenia and agranulocytosis.
- × **Management of specific patient groups:**
  Detailed recommendations for specific patient groups (such as children and young people, older adults, people who are pregnant or individuals with intellectual disability) are not included in this document. Where available, relevant external resources are signposted. Future editions of this protocol will expand on these areas.
- × **Management of comorbid physical health conditions:**
  This protocol does not provide detailed guidance on the treatment of coexisting physical health conditions in individuals receiving clozapine.

What everyone should know about clozapine

This section is aimed primarily at patients, carers, support staff and others without a healthcare background who support people who take clozapine day to day.

Potentially serious adverse effects of clozapine

- **Myocarditis** (inflammation of the heart muscle): This is most likely to occur in the first 1–6 weeks of treatment. Warning signs include chest pain, fever and flu-like symptoms.

- **Constipation** (difficulty passing stools): Clozapine can slow the bowel, and this can sometimes lead to bowel obstruction. Not opening your bowels at all for 2–3 days, or constipation with abdominal pain, vomiting or diarrhoea, may be a warning sign of a serious problem. Severe dehydration can make constipation worse.

- **Infection:** Clozapine can increase the risk of serious infections, particularly chest infections such as pneumonia. Warning signs include chest pain, shortness of breath or fever. Infections can also affect the level of clozapine in the body, which increases the risk of clozapine toxicity – which is when the amount of clozapine in someone's system becomes too high and may cause harm.

- **Venous thromboembolism** (a blood clot in a vein, usually in the leg or pelvis, which can travel to the lungs): Warning signs include rapid onset of shortness of breath or chest pain, especially if there has been swelling of the calves. Severe dehydration can also increase the risk of this happening.

- **Cardiomyopathy** (disease of the heart muscle, which can make it harder for the heart to pump blood): This may develop over a longer period, possibly years. Warning signs include shortness of breath, ankle swelling and feeling more tired than usual over time.

- **Excessive drowsiness:** Drowsiness is a common side effect of clozapine, but it can become a concern if it is severe. It can also indicate that the level or dose of clozapine is too high. This may be especially risky for people who are taking other sedating drugs, whether prescribed or non-prescribed, or drinking alcohol.

- **Seizures/fits:** People who already have epilepsy may experience more fits than usual, and people who do not have epilepsy may experience a fit, or fits, for the first time. This is especially common when clozapine levels are high.

The 'red flag symptoms' information and table in Appendix 1 is designed to help patients and their support networks recognise possible warning signs of serious side effects, and to understand when to seek help.

Smoking

Why it's important to keep your prescriber updated on your smoking or vaping habits

Smoking tobacco, whether on its own in cigarettes or with other drugs such as cannabis, affects the amount of clozapine in your bloodstream which can affect the dose you need to take. If you smoke more, you may need a higher dose of clozapine to keep the symptoms of your illness under control.

If you smoke less, or stop smoking, the level of clozapine in your bloodstream may rise. This can increase your risk of experiencing side effects, so your dose may need to be reduced.

It is therefore very important to tell your prescriber or clozapine clinic if you:

- start smoking
- stop smoking
- increase or decrease the number of cigarettes you smoke
- switch from smoking to vapes or e-cigarettes
- switch from vapes or e-cigarettes to smoking.

We encourage you to discuss smoking at every appointment including what help you can be given to stop, as this is one of the best ways to improve your physical health.

Other medicines and substances

Some medicines and other substances can interact with clozapine and may make you more vulnerable to its side effects.

1 **Prescribed medication**
Clozapine has interactions with a significant number of prescribed medications. How these interactions affect patients varies from drug to drug and it may sometimes be necessary to change the dose of clozapine.

Always let your prescriber or clozapine clinic know if you have stopped one of your medicines or started a new medicine.

See clozapine interaction information from the BNF to learn more.

2 **Alcohol**
Both clozapine and alcohol can cause sedation, which may make it difficult to perform some skilled tasks and may cause serious side effects like reduced breathing, unconsciousness or coma.

It is best to limit your alcohol intake when you are on clozapine. You should always let your prescriber or clozapine clinic know if your alcohol use has increased. This also gives you the opportunity to get support to reduce or stop drinking, if you want it.

3 **Sedatives**
Alongside alcohol, other drugs which cause sedation should be used with great care or avoided if possible. These include benzodiazepines (such as diazepam), hypnotics or sleeping tablets (such as zopiclone), antihistamines (such as promethazine) and others. As well as obtaining them on prescription, some people buy them from pharmacies or online or obtain them from other sources. You should always let your prescriber or clozapine clinic know if you are taking any sedatives so that they can discuss any adjustments to your clozapine or other medicine doses.

4 **Caffeine**
Caffeine in coffee, energy drinks and cola amongst other products can have a small effect on the level of clozapine in your blood. People may use caffeine as a way of managing sedation from clozapine, but it can have adverse effects of its own including anxiety. If you are drinking a large amount of coffee or other caffeinated drinks it is helpful to let your prescriber or clozapine clinic know.

5 **Other substances**
Other substances such as cannabis, stimulants (such as cocaine or MDMA), opioids (such as heroin), ketamine, spice and others may have unpredictable interactions with clozapine which may be dangerous. It is important to avoid using other substances when taking clozapine if you can and to let your prescriber or clozapine clinic know what you are using especially if this has changed. This will also be a way to get help to reduce or stop using substances, if you want it.

Red flag symptoms

This section is aimed primarily at patients, carers, support staff and others without a healthcare background who support patients taking clozapine day to day.

The following **10 red flag symptoms** may indicate the onset of potentially serious side effects of clozapine.

1. Constipation (especially with nausea, vomiting and stomach pain)
2. Fever
3. Feeling like you have flu
4. Chest pain
5. Shortness of breath
6. Swelling of legs or ankles
7. Feeling dizzy or faint
8. Feeling more drowsy or sleepy than usual
9. Diarrhoea or vomiting
10. New or increased seizures or fits

We encourage people who take clozapine, and the people who support them, to become familiar with these potential side effects and to seek medical help if they arise.

More information

As part of this document, we have produced two separate resources in the appendices that give detailed information about what to do when red flag symptoms occur.

- **Monitoring, missed doses and clozapine red flag symptoms** (Appendix 1)

  This is designed for patients, carers, support staff and others without a healthcare background who support people taking clozapine day to day.

  The table shows when to raise a symptom at your next clozapine appointment, when to contact your prescriber or clozapine clinic before your next appointment, and when to get urgent medical advice or help.

  Clear text labels are used for these three levels of urgency: 'Not urgent', 'Seek medical advice soon (within 24–48 hours)', and 'Seek medical help now'. These levels are also colour coded as green, amber and red, respectively, which some people may find useful. This is similar to the colour coding approach used for full blood count results in some services.

- **Additional information for healthcare professionals** (Appendix 2)

  This is designed for psychiatrists, GPs, medical professionals from specialties other than psychiatry, non-medical prescribers and other healthcare professionals involved in supporting patients who are taking or about to take clozapine. It provides advice on what interventions may be needed when patients report a red flag symptom. The symptoms and escalation points are clearly labelled within a table that uses green, amber and red colour coding to indicate the levels of urgency, as in Appendix 1.

Monitoring guidance

This section is aimed primarily at psychiatrists, GPs and other medical specialists, non-medical prescribers and other healthcare professionals involved in supporting patients who are taking or about to take clozapine.

Prescribing and monitoring responsibilities

- Responsibility for prescribing, monitoring and ensuring engagement with monitoring lies with the initiating clinician or clinical service unless specific alternative arrangements are in place.

- GPs are not usually expected to prescribe clozapine or monitor side effects but should be aware that a patient is on clozapine and consider it as an important factor for escalation if a patient presents with symptoms of concern.

- We recognise that there may be instances where GPs or non-medical prescribers are involved in prescribing clozapine. If GP practices are expected to undertake any of this work, this would require appropriate training, funding, formal shared care agreements and clarity around responsibilities and liability, including around managing disengagement from clozapine monitoring.

Key terms in this guidance

Abbreviation/test	Explanation	Reference range
NT-proBNP	B-type Natriuretic Peptide (BNP) is a hormone produced by cardiomyocytes in response to increased cardiac wall tension or stretch. Here it is used as a marker for heart failure or cardiomyopathy. N-terminal pro-B-type natriuretic peptide (NT-proBNP) is preferred in community settings due to its stability (viable for testing up to 72 hours) and diagnostic sensitivity.	**<400 ng/L:** Heart failure unlikely **400–2,000 ng/L (raised):** Refer for specialist assessment and echocardiogram **within 6 weeks** **>2,000 ng/L (high):** Refer for specialist assessment and echocardiogram within **2 weeks**
hs-troponin I	High-sensitivity troponin I. Troponin I (a subtype found in cardiomyocytes) is released into the bloodstream following myocardial injury. Here it is used as a marker for myocarditis.	**(Male)< 34 ng/L** **(Female)< 16 ng/L**
HbA1c	HbA1c measures average blood glucose levels over the past 2–3 months by checking the percentage of glycated haemoglobin. It is a primary tool for diagnosing and monitoring diabetes.	**Normal:** <42 mmol/mol (6.0%) **Pre-diabetes:** 42–47 mmol/mol (6.0–6.4%) **Diabetes:** ≥48 mmol/mol (6.5%)
Lipids	Lipid profile for monitoring the risk of dyslipidaemia and metabolic syndrome. Includes total cholesterol, LDL and triglycerides.	**Total Cholesterol:** <5.0 mmol/L **LDL:** <3.0 mmol/L **Triglycerides:** <1.7 mmol/L
SpO2	Oxygen saturation	**Normal:** 95–100% **Target (COPD patients):** 88–92%
BMI	Body mass index	**Underweight:** <18.5 **Healthy weight:** 18.5–24.9 **Overweight:** 25.0–29.9 **Obese:** >30.0
GASS-C	Glasgow antipsychotic side effect scale for clozapine. Read the GASS-C scale	

Abbreviation/test	Explanation	Reference range
BP	**Blood pressure:** Monitored to detect postural hypotension or clozapine-induced hypertension	**Normal:** Approximately **120/80 mmHg** Clinical concern if: systolic **<90 mmHg** or **>140 mmHg**.
HR	**Heart rate**	**Normal resting heart rate:** 60–100 bpm **Tachycardia:** >100 bpm **Persistent tachycardia** >120 bpm requires urgent investigation
CRP	**CRP (C-Reactive Protein):** An inflammatory marker used during the titration phase to screen for myocarditis. Also a marker of infection.	**Normal:** <3 mg/L For specific myocarditis detection ranges, see Additional information for healthcare professionals (Appendix 2).
ECG	**Electrocardiogram:** To monitor the electrical activity of the heart, QTc prolongation or cardiac changes (e.g., myocarditis, cardiac hypertrophy).	**Normal QTc:** **Men:** <440 ms **Women:** <470 ms
U&Es	**Urea and electrolytes:** Includes urea, creatinine, eGFR, sodium and potassium.	**Creatinine:** **Men:** 59–104 µmol/L **Women:** 45–84 µmol/L **eGFR:** >90ml/min/1.73m2 **Urea:** 2.5 – 7.8 mmol/L **Sodium:** 135–146 mmol/L **Potassium:** 3.5–5.3 mmol/L
LFT	**Liver function tests:** Standard panel includes: Alanine Aminotransferase (ALT), Aspartate Aminotransferase (AST), Alkaline Phosphatase (ALP), Bilirubin, and Albumin.	**ALT** 3-40 IU/L **AST** 3-30 IU/L **ALP** 30-100 IU/L **Bilirubin** 3-17 µmol/L **Albumin** 35-50 g/L
FBC	**Full blood count:** Mandatory monitoring for agranulocytosis using a traffic light system.	See CPMS for thresholds (including adjusted range for patients with BEN)
QRISK3	QRISK3 is a risk calculator that estimates a person's risk of developing cardiovascular disease, including a heart attack or stroke, over the next 10 years. Read the QRISK3 scale	

Preparation

Preparation involves assessing suitability and safety, engaging the patient and support network, coordinating with relevant professionals, and putting practical arrangements in place to support timely clozapine initiation and monitoring. Before initiating clozapine, teams should complete the following actions to confirm suitability, address safety considerations, coordinate care and support the patient to engage with treatment and monitoring.

- Explore whether the patient would benefit from clozapine.
- Discuss the plan with the patient, family and others in the network if the patient consents.
- Assess past medical history and review medical records (including via NHS Summary Care Record if available), looking in particular for cardiac history/cardiology referrals or reviews and abdominal surgery/gastroenterology referrals or reviews. Check for existing swallowing problems, which may be exacerbated on clozapine.
- Review current medication, prescribed and over the counter, identify potential interactions/contraindications and any allergies.
- In patients potentially at risk (African, Caribbean and Middle Eastern heritage and low baseline neutrophil count), establish benign ethnic neutropenia (BEN*) status by reviewing records, consulting haematology or with genetic testing where available.
- Consult with primary and secondary care specialists as necessary (e.g. cardiology or haematology) if there are questions about suitability, safety, contraindications and pre-emptive measures.
- Explore expedited referral pathways/rapid access clinics for medical specialist reviews if available to avoid delays in clozapine initiation.
- Liaise with health and care professionals involved in patient's care (e.g. GP, secondary care specialists, community mental health teams, other community health teams, social care providers). Provide them with 'red flag' symptom guidance and address any other concerns.
- Identify whether community or inpatient initiation is preferable.
- Register with the relevant clozapine monitoring service once baseline full blood count (FBC) is completed (see below).
- Provide information and resources about clozapine including risks, smoking and other substances and red flag symptoms to patient, carers and other key members of their support network. Offer smoking cessation support.
- Offer substance use support including referral to specialist services.
- Ensure preventative health measures are in place (e.g. flu and pneumonia vaccination, participation in cancer screening).
- Explore practical and personal barriers to engaging with monitoring and identify solutions (e.g. visiting arrangements, remote monitoring).

* This is also known as Duffy-null associated neutrophil count (DANC).
For more information, see ACKR1/DARC-associated neutropenia – Knowledge Hub

Baseline measurements

What to check before starting clozapine	Additional information
Bloods: FBC, U&Es, LFT, HbA1c, lipids, CRP, troponin I, NT-proBNP	Baseline CRP, Troponin I and NT-proBNP (or BNP) recommended to guide cardiac monitoring during titration.
ECG. (Echocardiogram **and** cardiology advice in the presence of pre-existing cardiac disease, strong family history of sudden death or raised BNP beyond normal limits.)	
Physical observations: HR, lying/standing BP, SpO2, temp	
Physical examination where possible to establish a baseline to identify side effects such as weight gain. Include cardiovascular and respiratory systems, abdominal examination and examination of lower limb oedema.	
GASS-C	Establish baseline of symptoms described in GASS-C even in the absence of taking clozapine.
Frequency of opening bowels and type (as per Bristol Stool Chart)	
Discuss red flag symptoms, smoking, alcohol and other substances.	
Cardiometabolic baseline Weight, BMI, diet, physical activity, fluid intake Consider risk prediction (e.g., QRISK3)	

Titration phase (weeks 1–4)

Reminder: Ensure clozapine is included in primary care medication record. See Additional information for healthcare professionals (Appendix 2) for advice around escalating any symptoms of concern.

Caution:
These **serious side effects** may occur during this phase of treatment

VERY RARE: Neuroleptic malignant syndrome (weeks 1–2)
RARE: Myocarditis (weeks 1–6)

Frequency	Monitoring requirements	Additional information
Daily	Physical observations (HR, lying/standing BP, SpO2, temp) 3–4 hours after each dose (except nighttime). Daily observation may not be possible for community titration.	
Weekly	FBC	
	Discuss red flags, smoking, alcohol and other substances.	
	Myocarditis detection ECG (Weeks 1–4) CRP, troponin I, NT-proBNP where available. (Weeks 1–4)	• Enhanced monitoring informed by Wagner et al. (2025); see full citation in References. • If CRP, troponin I or BNP are raised, refer to: Additional information for healthcare professionals (Appendix 2)
	Weight, BMI (Weeks 1–4)	For management of weight gain: • Refer to: – Lester Tool 2023 – The 2025 Lancet Psychiatry Physical Health Commission report – The Weight Management & Mental Health framework for Wales (WMMH) • Consider adjunctive metformin (off-licence use).
	GASS-C (Weeks 1–4)	

Target doses for the titration phase

Female non-smokers: 250mg/day	**Female smokers:** 450mg/day
Male non-smokers: 350mg/day	**Male smokers:** 550mg/day

Note: Target doses need to be adjusted for those with **Asian ancestry** and for **older patients**.

Titrate using clinical judgement, balancing treatment response against side effects.

Monitoring clozapine levels during the titration phase can be helpful, e.g.,

- to identify slow metabolisers, particularly if side effects seem disproportionate to the dose
- to review dosing if there is significant clinical improvement before the planned target dose is reached.

Stabilisation phase (weeks 5–8)

Reminder: Ensure clozapine is included in primary care medication record.

See Additional information for healthcare professionals (Appendix 2) for advice around escalating any symptoms of concern.

Caution:
This **serious side effect** may occur during this phase of treatment

RARE: Myocarditis (weeks 1–6)

Frequency	Monitoring requirements	Additional information
Weekly	Physical observations: HR, lying/standing BP, SpO2, temp.	
	FBC	
	Discuss red flags, smoking, alcohol and other substances.	
	Myocarditis detection: CRP, hs-troponin I (weeks 5–8) ECG (week 8)	• Enhanced monitoring informed by Wagner et al. (2025); see full citation in References. • If CRP, hs-troponin I or BNP are raised, refer to Additional information for healthcare professionals (Appendix 2)
	Weight, BMI (weeks 5–6)	For management of weight gain: • Refer to: – Lester Tool 2023 – The 2025 Lancet Psychiatry Physical Health Commission report – The Weight Management & Mental Health framework for Wales (WMMH) • Consider adjunctive metformin (off-licence use).
	GASS-C (weeks 5–6)	

Target doses for the stabilisation phase

Female non-smokers: 250mg/day	**Male non-smokers:** 350mg/day
Female smokers: 450mg/day	**Male smokers:** 550mg/day

Note: Target doses need to be adjusted for those with **Asian ancestry** and for **older patients**.

Titrate using clinical judgement, balancing treatment response against side effects.

Monitoring clozapine levels during the titration phase can be helpful, e.g.,

- to identify slow metabolisers, particularly if side effects seem disproportionate to the dose
- to review dosing if there is significant clinical improvement before the planned target dose is reached.

Early maintenance (weeks 9–18)

Reminder: Ensure clozapine is included in primary care medication record.

See Additional information for healthcare professionals (Appendix 2) for advice around escalating any symptoms of concern.

Frequency/Time point	Monitoring requirements	Additional information
Weekly	Discuss red flags, smoking, alcohol and other substances.	
	FBC	
Every 4 weeks	Physical observations: HR, lying/standing BP, SpO2, temp	
At Week 12	GASS-C	
	Week 12 Cardiometabolic checkpoint: ECG, HbA1c,* weight, BMI, lipids, diet and physical activity assessment **Fasting glucose may also be considered where feasible to obtain*	**For management of weight gain:** • Refer to: – Lester Tool 2023 – The 2025 Lancet Psychiatry Physical Health Commission report – The Weight Management & Mental Health frame-work for Wales (WMMH) • Consider adjunctive metformin (off-licence use).

Clozapine plasma level:
Check after titration when the target dose or clinical response is achieved; repeat after any further dose changes where clinically indicated

Maintenance (weeks 18–52)

Reminder: Ensure clozapine is included in primary care medication record.

See Additional information for healthcare professionals (Appendix 2) for advice around escalating any symptoms of concern.

Frequency/Time point	Monitoring requirements	Additional information
2-Weekly	Discuss red flags, smoking, alcohol and other substances	
	FBC	
4-Weekly	Physical observations: HR, lying/standing BP, SpO2, temp	
At 6 Months	U&Es	
	GASS-C	
	Cardiometabolic checkpoint: ECG, HbA1c,* weight, BMI, lipids, diet and physical activity assessment **Fasting glucose may also be considered where feasible to obtain*	**For management of weight gain:** • Refer to: – Lester Tool 2023 – The 2025 Lancet Psychiatry Physical Health Commission report – The Weight Management & Mental Health framework for Wales (WMMH) • Consider adjunctive metformin (off-licence use).
At 9 months	Cardiometabolic checkpoint: ECG, HbA1c,* weight, BMI, lipids, diet and physical activity assessment **Fasting glucose may also be considered where feasible to obtain*	

At the end of 12 months on clozapine

Reminder: Ensure clozapine is included in primary care medication record.

See Additional information for healthcare professionals (Appendix 2) for advice around escalating any symptoms of concern.

12-month clozapine review and monitoring checklist

- ✓ Bloods: FBC, U&Es, LFT, NT-proBNP
- ✓ Clozapine plasma levels
- ✓ ECG
- ✓ Physical observations: HR, lying/standing BP, SpO2, temp
- ✓ Physical examination
- ✓ Review of systems. Should include cardiovascular, respiratory, abdominal and examination of pedal oedema.
- ✓ GASS-C
- ✓ Discuss red flags, smoking, alcohol and other substances.
- ✓ Cardiometabolic checkpoint: ECG, HbA1c*, weight, BMI, lipids, diet and physical activity assessment

Beyond 1 year on clozapine

Reminder: Ensure clozapine is included in primary care medication record.

See Additional information for healthcare professionals (Appendix 2) for advice around escalating any symptoms of concern.

Frequency/ Time point	Monitoring requirements
Monthly	Discuss red flags, smoking, alcohol and other substances.
	FBC (if still on monthly monitoring)
3-Monthly	FBC (if opted-in and suitable)
6-Monthly	Cardiometabolic checkpoint: ECG, HbA1c*, weight, BMI, lipids, diet and physical activity assessment **Fasting glucose may also be considered where feasible to obtain.*
Every year	GASS-C
	Bloods: U&Es, LFT, BNP, clozapine levels
	Physical examination: Review of systems. Should include cardiovascular, respiratory, abdominal and examination of pedal oedema.

Additional considerations:
Dosage, specific patient groups and physical illness

Missed doses

For retitration after missed doses, please refer to local guidelines

Specific patient group considerations

- Please adapt monitoring for communication needs as required (e.g. in intellectual disability).
- Consider checking levels and reviewing dose during menopause/perimenopause or following changes in hormone replacement therapy/hormonal contraception.
- For children and young people, see the 2025 Lester Tool adolescent supplement.

Physical illness

In the event of acute physical illness, see:

- Additional information for healthcare professionals (Appendix 2):
  including specifically the Table of clinical symptoms: common, concerning and emergency presentations

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Appendices

Appendix 1: Monitoring, missed doses and clozapine red flag symptoms

This section is aimed primarily at patients, carers, support staff and others without a healthcare background who support patients taking clozapine day to day.

Monitoring

People taking clozapine are supported by a clozapine monitoring service, often called a 'clozapine clinic'. This clinical team monitors blood test results and helps make sure the patient has the correct supply of clozapine medication. (You can ask your clozapine clinic questions about your physical health, medication, side effects, missed doses and anything else covered in this document.)

Clozapine clinics may not be available 24 hours a day, 7 days a week. However, some medical problems may need urgent attention and should not wait until the clinic is available. This guide is designed to help people taking clozapine, and those who support them, to know what to do if a symptom or concern arises.

What to do about missed doses

It is very important that clozapine is taken as prescribed.
If you or the person you care for misses a dose, please follow the advice below.

Length of time since last dose	What to do
Less than 48 hours	Take your next dose as soon as possible
More than 48 hours	Inform your clozapine clinic. Do not take your usual dose of clozapine
Remember: If in doubt, ask your prescriber or clozapine clinic.	

Red flag symptoms

The table on the next page lists symptoms and concerns that may arise in people taking clozapine. Some are common or lower-concern symptoms that do not usually need urgent attention. Others may need medical advice soon or urgent medical help now.

The table is designed to help you decide how quickly advice or help is needed.
It is organised into three levels: not urgent, seek medical advice soon, and seek medical help now. For each symptom or concern, the table explains what to do depending on how severe it is and whether any other symptoms are present.

If the table says 'seek medical help now'

If the symptoms or concerns you notice are described in the 'seek medical help now' section of the table, get urgent medical advice. Do not wait for your next clozapine clinic appointment.

- **Call 999 if you think it is an emergency**
  This includes when the person taking clozapine has collapsed, is unconscious, is struggling to breathe, has severe chest pain, has become very unwell, or you are seriously worried.
- **Get urgent medical advice if it is not an emergency**
  You should still seek urgent medical advice even if it is not an emergency.
  Contact the urgent medical advice service where you are.
  - **England:** call 111 or go to 111.nhs.uk
  - **Wales:** call 111 or go to 111.wales.nhs.uk
  - **Scotland**: call NHS 24 on 111 or go to nhs24.scot
  - **Northern Ireland:** contact GP out-of-hours or, where available, your local urgent care or Phone First service.

  If you are not sure whether it is an emergency, these services can advise you what to do next, including whether you need emergency help.

Important:
When seeking help, always clearly tell the service that you, or the person you are concerned about, is taking clozapine.

Table of red flag symptoms for people taking clozapine

Symptom or concern	**Not urgent** Raise this with your clozapine clinic team or mental health team at your next appointment and ask for advice. Follow the additional advice below.	**Seek medical advice soon (within the next 24–48 hours)** Inform your clozapine clinic or mental health team. If your next appointment is more than 48 hours away, call the clinic as soon as you can. Follow the additional advice below.	**Seek medical help now** Get urgent medical advice or, if you think it is an emergency, call 999. Do not wait for your next clozapine clinic appointment. **When seeking help, always make sure you inform the service that you, or the person you are supporting, is taking clozapine.**
Constipation (Not being able to open your bowels as usual or you are struggling when you do so)	If you have not opened your bowels for 48 hours, take laxatives regularly. If you are not already taking laxatives, please inform your clozapine clinic, who may be able to supply you with laxatives or advise you on how to get them quickly. The laxative usually recommended is called senna, 7.5–15 mg once daily, available over the counter in most pharmacies. Severe dehydration will worsen constipation, so ensure you drink enough, especially in hot weather. Increase both your fluid and fibre intake. Aim for around 2 litres of fluid and 25–30g of fibre a day. Increasing your fibre intake without also increasing your fluid intake can make constipation worse, so remember to drink more water. Avoid bulk-forming laxatives such as ispaghula husk: Ask your local pharmacy to check what is safe to take.	If you are approaching 72 hours without opening your bowels despite being on regular laxatives, you may need additional laxatives. Speak with your clozapine clinic as soon as possible to help arrange this and/or book an appointment with your GP. If this cannot be arranged quickly then please speak with 111 to ensure you have the necessary laxatives. Any other symptoms like persistent stomach pain, diarrhoea or nausea are concerning. Please see the 'Seek medical help now' section to the right for more information.	Seek urgent advice for any of the following: • You have not opened your bowels for **over** 72 hours. • You have abdominal pain that is moderate to severe, lasting more than an hour. • You have abdominal pain with diarrhoea, vomiting or bloating.

Symptom or concern	**Not urgent** Raise this with your clozapine clinic team or mental health team at your next appointment and ask for advice. Follow the additional advice below.	**Seek medical advice soon (within the next 24–48 hours)** Inform your clozapine clinic or mental health team. If your next appointment is more than 48 hours away, call the clinic as soon as you can. Follow the additional advice below.	**Seek medical help now** Get urgent medical advice or, if you think it is an emergency, call 999. Do not wait for your next clozapine clinic appointment. **When seeking help, always make sure you inform the service that you, or the person you are supporting, is taking clozapine.**
Fever (Increased body temperature – you may feel hot, sweaty, tired, or shivery)		Fever can be common when starting clozapine. If you have fever, but no other symptoms, paracetamol can help if it is safe for you to take it. **But if you feel very unwell and the fever lasts longer than 48 hours, seek urgent medical advice.**	If you have a fever with any other symptoms (e.g., cough, chest pain, shortness of breath, feeling like your heart is racing or irregular, flu-like symptoms, stiffness in your muscles, abdominal pain or feeling generally unwell), get urgent medical advice. If you are admitted to hospital, tell the medical team you are taking clozapine so they can seek specialist advice. If you are not admitted to hospital, speak with your clozapine clinic team urgently for advice.
Feeling like you have the flu (Tired, achy, and unwell—like your body is fighting something off)		If your flu-like symptoms have lasted less than 3 days and you have no other symptoms, such as chest pain or shortness of breath, ensure you stay well hydrated and take paracetamol if it is safe for you to do so.	Get urgent advice for any of the following: • You have flu-like symptoms with chest pain or shortness of breath • You are feeling very unwell • Your symptoms have lasted more than 72 hours
Chest pain			If you have any type of chest pain, get urgent medical advice. Call 999 if symptoms are severe or you feel very unwell.

Symptom or concern	Not urgent Raise this with your clozapine clinic team or mental health team at your next appointment and ask for advice. Follow the additional advice below.	Seek medical advice soon (within the next 24–48 hours) Inform your clozapine clinic or mental health team. If your next appointment is more than 48 hours away, call the clinic as soon as you can. Follow the additional advice below.	Seek medical help now Get urgent medical advice or, if you think it is an emergency, call 999. Do not wait for your next clozapine clinic appointment. **When seeking help, always make sure you inform the service that you, or the person you are supporting, is taking clozapine.**
Shortness of breath			If you have any new shortness of breath, seek urgent medical advice. Call 999 if symptoms are severe or you feel very unwell.
Swelling of legs and/or ankles		If you do not have other symptoms, please book a GP appointment as soon as possible.	Seek urgent advice if either of the following applies: • you also feel short of breath, faint and are more tired than usual. • you notice that one leg is more swollen than the other.
Feeling dizzy or faint	If this is infrequent and you have no other symptoms, this is not concerning. If this happens when you are getting out of bed or standing up from a seated position, take some time to sit up, or hold on to something for support. Ensure you are well hydrated, especially during hot weather. Consider booking a GP appointment to discuss the issue further.		If this is interfering with your daily life or is happening every day (or almost every day) and has resulted in you falling or nearly falling, arrange an urgent appointment with your GP or call your urgent medical advice service (e.g., 111), where available. Seek urgent advice now if either of the following applies: • You have fainted or fallen because of dizziness. • You have swollen legs or ankles and are short of breath in addition to feeling dizzy or faint.

Symptom or concern	**Not urgent** Raise this with your clozapine clinic team or mental health team at your next appointment and ask for advice. Follow the additional advice below.	**Seek medical advice soon (within the next 24–48 hours)** Inform your clozapine clinic or mental health team. If your next appointment is more than 48 hours away, call the clinic as soon as you can. Follow the additional advice below.	**Seek medical help now** Get urgent medical advice or, if you think it is an emergency, call 999. Do not wait for your next clozapine clinic appointment. **When seeking help, always make sure you inform the service that you, or the person you are supporting, is taking clozapine.**
Feeling more drowsy or sleepy than usual	If this is occasional and does not interfere with your daily life, it is not concerning. Consider reducing your alcohol intake if you drink. If you wish to stop drinking or taking recreational/non-prescribed drugs, please inform your mental health team. Some prescribed medication can make you feel sleepy, so speak with your doctor, GP or mental health team about this if you are concerned.	If this is significant and interferes with your daily life, especially if you are unsteady on your feet, or have choked on saliva or food, this may be concerning, and you should inform your clozapine clinic. It's important to inform your team if you have taken any drugs that may make you sleepy.	Carers should seek urgent advice or call 999 if someone has passed out, is unconscious or is breathing differently from usual. If admitted to hospital: Seek urgent advice from the doctors about whether to continue taking clozapine. If not admitted to hospital: Speak with your clozapine team as soon as possible for advice.
Diarrhoea or vomiting (Loose stools or being sick)	If this lasts less than 48 hours and there are no other symptoms, this is not concerning. Try to stay hydrated and eat if you can.	If this is significant and interferes with your daily life, seek medical advice. If you are unable to eat, but can still drink, then remain well hydrated and seek medical advice if this lasts more than 48 hours.	Seek urgent advice if any of the following apply: • You are vomiting and unable to keep your clozapine down. • You have diarrhoea or vomiting during or after a long period of constipation (going more than 72 hours without opening your bowels) • You have severe abdominal pain in addition to diarrhoea or vomiting. • You are unable to eat or drink anything.

Symptom or concern	**Not urgent** Raise this with your clozapine clinic team or mental health team at your next appointment and ask for advice. Follow the additional advice below.	**Seek medical advice soon (within the next 24–48 hours)** Inform your clozapine clinic or mental health team. If your next appointment is more than 48 hours away, call the clinic as soon as you can. Follow the additional advice below.	**Seek medical help now** Get urgent medical advice or, if you think it is an emergency, call 999. Do not wait for your next clozapine clinic appointment. **When seeking help, always make sure you inform the service that you, or the person you are supporting, is taking clozapine.**
Fits/seizures in people who are not known to have epilepsy (These can look like shaking, stiffening, staring blankly or losing awareness of what is happening.)			If you, or the person you care for, has a seizure and has no known diagnosis of epilepsy, seek urgent medical advice. Call 999 if the person is injured, has trouble breathing, has another seizure or remains very confused, very drowsy or is difficult to wake up afterwards.
Fits/seizures in people with known epilepsy		If you or the person you care for already has epilepsy and they have a seizure that presents as typical for them, make sure they have recovered as they normally would and then inform the clozapine clinic that you/they have had a seizure. If the frequency of seizures has increased, inform the clozapine clinic or seek urgent help if you are concerned. If you or the person you are caring for is on medication for epilepsy, please ensure that you/they are taking this. Follow the advice of your epilepsy or neurology team and inform them if your seizures have changed or if you are otherwise concerned.	Seek urgent medical advice or call 999 if you or the person you care for has any of the following: • a seizure after recently starting a new medication, changing clozapine dose, changing how much they are smoking, taking drugs, or drinking more/less alcohol than usual. • a seizure that causes, or nearly causes, an injury or harm to themselves • a history of seizures, and this seizure lasts longer than 5 minutes or is different from usual, or if multiple seizures are experienced.

Remember: If in doubt, seek urgent medical advice.

Always inform the medical team that you are taking clozapine as they may not be aware.

Additional points to remember:	
Smoking	Changing the number of cigarettes you smoke (either cutting down or increasing smoking) can affect the amount of clozapine in your blood. This can cause problems with your mental or physical health. It is very important that your prescriber or clozapine clinic team are made aware of any change in your smoking habits. They should also be told if you swap some/all your cigarettes for vaping or using nicotine replacement medication. If you or your relative becomes unwell then you should inform the medical team about recent changes in smoking habits.
Alcohol, caffeine, substances or non-prescribed drugs	Alcohol, caffeine, substances or non-prescribed drugs with clozapine can interact with clozapine in ways that may be hard to predict and may worsen side effects. Please inform your prescriber or clozapine clinic if you are drinking alcohol or caffeine more, less, or differently than usual. Please also inform your prescriber or clozapine clinic if you are using substances or non-prescribed drugs, or if your pattern of use has changed recently. If you need support with alcohol or substance use, your clozapine team can help you access support.

Appendix 2:
Additional information for healthcare professionals

This section is aimed primarily at psychiatrists, GPs, medical professionals from specialties other than psychiatry, and non-medical prescribers and other healthcare professionals involved in supporting patients who are taking or about to take clozapine.

1 Clozapine is an antipsychotic medication mainly used for treatment resistant schizophrenia.

2 Frequent Full Blood Count (FBC) testing is required to monitor for agranulocytosis. Based on satisfactory FBC results, clozapine is dispensed by the patient's clozapine clinic.

3 Clozapine may not be visible on the patient's list of GP prescribed medication. If a patient reports/is reported to be on clozapine, it is important to get more information. Seek advice from the psychiatric liaison team or the local mental health service if possible.

4 When a patient arrives at an acute hospital it is vital to undertake medicines reconciliation and ensure there is a supply of clozapine – do this in conjunction with pharmacy colleagues. Gaps in treatment may cause a high-risk deterioration in a patient's mental health.

5 If a patient is off clozapine for more than 48 hours, their treatment will have to be re-titrated gradually to their usual dose, with the support of a psychiatric team. Do not directly resume the previous dose.

6 If a patient on clozapine is seen in an acute hospital, notify and seek advice from liaison psychiatry, especially when deciding to stop or restart clozapine. Seek advice if the patient is experiencing any factors affecting clozapine levels listed under point 9 below where a dose adjustment may be required.

7 Clozapine can have some specific adverse effects which may be linked to preventable death. We have outlined these below and there is a separate 'red flag symptoms' table for patients and their support networks in Wim's Protocol.

8 Despite its potential side effects clozapine is associated with reduced all-cause mortality in patients with schizophrenia. It is important to ensure treatment can be continued where possible.

9 Clozapine levels: Plasma clozapine levels are important both to identify the correct dose for the patient and to diagnose clozapine toxicity if it is suspected.

Key adverse effects of clozapine

- Interpretation of clozapine plasma levels is complex and highly dependent on individual factors. Consult local guidelines or product literature (for example, the Zaponex factsheet on metabolism and clozapine plasma level interpretation).

- Clozapine plasma levels can be measured usually as trough levels 10–12 hours post dose. The results can take time to be returned (sometimes a week or more) unless point of care testing is available locally. Ideally bloods for clozapine levels should be taken when the level is at steady state which is usually when the same dose has been maintained for at least 3–5 days.

- The therapeutic range of clozapine is 350–600 ng/mL. Some patients may have good clinical response at lower levels of clozapine.

- A rapid or significant increase in levels from a patient's stable baseline – even if the new level remains within the therapeutic range – is potentially significant. It is a more sensitive indicator of potential toxicity or altered metabolism than any single absolute value and must be considered alongside the patient's clinical state.

- Excessively high clozapine levels can significantly increase risk of serious side effects, especially seizures, constipation and sedation.

- Some factors that can increase clozapine levels include acute infections, reducing or stopping tobacco smoking or switching to vapes/nicotine replacement therapy (NRT), significantly increased caffeine intake and drug interactions (e.g. ciprofloxacin, fluvoxamine – see BNF for further details).

Escalation:

Escalation advice for specific adverse effects is provided in the table that begins on the following page.

Clinical symptoms: Common, concerning and emergency presentations

Symptom	Common or lower-concern symptoms	Concerning symptoms	Urgent or emergency symptoms
Constipation Clozapine-induced gastrointestinal hypomotility is common. This can progress to paralytic ileus, bowel obstruction and can progress to fatal bowel perforation	People taking clozapine commonly become constipated. Patients are encouraged to flag to medical teams any worsening constipation relative to their baseline bowel habits. Ask the patient AND gain collateral about change in bowel habits. Perform a thorough physical examination, including abdominal examination and observations. **Non-pharmacological advice:** 1 Increase water intake (2L/day) 2 Increase fibre intake (25-30g/day) 3 Increase physical activity. **Explore concordance with laxative use and consider prescribing if indicated (adapted from Porirua protocol – senna and macrogol):** 1 Start regular senna 15mg tabs nocte (max 30mg nocte), review and increase every 48 hours until no longer constipated 2 If still constipated, see the concerning symptoms section. **Avoid bulk-forming laxatives such as ispaghula husk.** Reassuring signs: patient is physically well, observations normal, passing flatus, eating and drinking normally. **Safety net:** Ensure that the patient contacts their clozapine clinic/mental health worker and to seek urgent medical attention if pain, nausea/vomiting persists or worsens.	No bowel movements for >72 hours OR significant change from baseline bowel movement frequency are concerning, especially if abdominal pain, reduced eating and drinking, nausea, diarrhoea are present. **To treat constipation that persists despite max dose of laxatives given in 'common or lower-concern symptoms' column:** 1 Rectal examination to exclude impaction. If impacted, stop senna, and consider glycerol suppository, phosphate enema, or manual disimpaction. If ineffective, add macrogol one sachet BD. 2 If not impacted, continue senna and add macrogol 1 sachet BD 3 Review in 48 hours. If constipation persists, consult appropriate medical and surgical specialty to guide higher dose of macrogol or enema frequency. **If diarrhoea develops:** 1 Exclude overflow diarrhoea due to bowel obstruction 2 If not, gradually reverse steps, reduce and stop macrogol, and then senna. Think about contributing factors, such as dehydration, new medication interactions and change in smoking status. • Consider abdominal imaging alongside physical examination. • Consult liaison psychiatry for advice about continuing or stopping clozapine.	Any symptoms and signs suggestive of an acute abdomen/bowel obstruction/perforation. Moderate to severe abdominal pain lasting over an hour **OR** any abdominal pain/discomfort lasting over an hour **AND** one or more of the following: • Abdominal distension. • Diarrhoea (especially bloody) Vomiting • Absent or high-pitched bowel sounds Metabolic acidosis • Haemodynamic instability • Leucocytosis or other signs of sepsis Request urgent abdominal imaging (usually CT scan), bloods and surgical review for suspected bowel obstruction related to clozapine. If there are significant surgical concerns, **STOP** clozapine and inform liaison psychiatry immediately.

Symptom	Common or lower-concern symptoms	Concerning symptoms	Urgent or emergency symptoms
Fever Fever is common in people taking clozapine, but warrants further investigation, especially if associated with signs of sepsis. Consider: • Sepsis, especially pneumonia (see relevant section lower down in this table). This can include neutropenic sepsis/ agranulocytosis. • Myocarditis (see relevant section lower down in this table).	High temperature <38C is common, especially during the initiation of clozapine. Assess history, undertake physical examination and order bloods including FBC, CRP, hs-troponin I. Isolated mild pyrexia <38 degrees, with normal bloods/other investigations can be treated with paracetamol and oral fluids. Provide safety net advice to seek urgent medical advice if the fever is persistent or becomes worse, or new symptoms arise (e.g., chest pain, shortness of breath, cough).	High temperature >38 C. Undertake sepsis screen and investigate for any source of infection. Start appropriate treatment for presumed/confirmed infection. Bear in mind that the patient may have a low/normal WBC even if they have an infection due to bone marrow suppression from clozapine. • **Pneumonia – see relevant section lower down in this table** • **Myocarditis – see relevant section lower down in this table**	**Agranulocytosis/neutropenia:** **STOP** clozapine, referral to haematology and discuss with liaison psychiatry immediately regarding plan for antipsychotics. **If myocarditis is suspected:** **STOP** clozapine. Urgent referral to cardiology and liaison psychiatry immediately. Investigations include: FBC, CRP, hs-troponin I, echocardiography, ECG, NT-proBNP, U+Es. If CRP >100 or hs-troponin I >twice the upper limit of normal, stop clozapine, repeat echocardiography. If fever + tachycardia with raised CRP(<100) OR hs-troponin I < twice of upper limit, repeat CRP and hs-troponin I daily. **Neuroleptic malignant syndrome (NMS):** This is rare and can occur when starting or abruptly stopping clozapine. It is most common in the first 2 weeks of initiation. Symptoms include tachycardia, fever, autonomic instability, rigidity. Blood tests may show raised WBC and CK: **STOP** clozapine, provide supportive treatment (IV fluids), consider benzodiazepines, discuss with liaison psychiatry.

Symptom	Common or lower-concern symptoms	Concerning symptoms	Urgent or emergency symptoms
Respiratory symptoms Especially dyspnoea +/-chest pain/clinical signs of heart failure Pneumonia is common and more severe in patients taking clozapine, especially those with increased sedation and hypersalivation (aspiration pneumonia). Consider: • Cardiomyopathy if there are signs of heart failure (see relevant section lower down in this table) • Venus thromboembolism/pulmonary embolus (VTE/PE). (Clozapine increases risk of thromboembolic events.)	Assess symptoms in the context of the patient's baseline, as reported by the patient themselves or carers. Explore the degree of hypersalivation and sedation, both of which are common side effects. Hypersalivation can be treated with hyoscine hydrobromide 300mcg tds. This can usually be provided by the patient's prescriber or clozapine clinic provided they are made aware. Check if a patient has had respiratory vaccinations and explore barriers and/or remind patients to have vaccinations. Flag up to GP where applicable. Provide specific safety net advice around what signs of deterioration to look for. If providing outpatient treatment (e.g., oral antibiotics or anticoagulation), explore history of medication concordance and involve carers/support network.	**Pneumonia:** Be aware that patients on clozapine may have increased risk of atypical pneumonia due to physical comorbidities and other risk factors including higher rates of smoking. Patients may also have a low/normal WBC due to bone marrow suppression from clozapine. **VTE/PE:** Clozapine increases risk of VTE, including PE, so clinical staff should have a lower threshold of suspicion of patients on clozapine. Consider that patients may have decreased levels of mobility or activity. Also consider contributing factors, such as dehydration during periods of hot weather. **Cardiomyopathy – see relevant section lower down in this table** **Discuss with liaison psychiatry before stopping clozapine.**	In severely unwell patients, **consider reducing or stopping clozapine and refer to liaison psychiatry urgently.** While there is currently no high-level consensus evidence mandating routine clozapine dose reductions for all infections, clinicians should maintain a high index of suspicion for clozapine toxicity. In the presence of pronounced dose-related side effects or severe systemic illness (e.g., pneumonia, high fever, elevated CRP), a dose reduction should be considered, guided primarily by clinical presentation and, where available, urgently taken clozapine levels. **Heart failure – see relevant section lower down in this table**

Symptom	Common or lower-concern symptoms	Concerning symptoms	Urgent or emergency symptoms
Cardiovascular symptoms: **Myocarditis:** Most likely in first 1-6 weeks of starting clozapine treatment. It can occur later, but this is very rare. Myocarditis can occur without a fever. See monitoring guidance for myocarditis-specific investigations. **Cardiomyopathy:** This can occur at any time, including after long periods of maintenance treatment. It may persist after clozapine has been discontinued. Symptoms for both conditions above can include tachycardia, chest pain, signs of heart failure, syncopal symptoms, significant hypotension, arrhythmias.	Tachycardia (100-120bpm) is common, especially during initiation of clozapine, but it warrants further investigation. Tachycardia with normal ECG, hs-troponin I, CRP and no chest pain can usually be discharged with safety net advice. If in doubt, seek cardiology advice. Please provide specific safety net advice, e.g., to look out for worsening symptoms, new fatigue, ankle swelling, chest pain, depending on the clinical situation. If there is tachycardia with raised CRP or hs-troponin I, then it may be necessary to undertake daily monitoring of observations, CRP and hs-troponin I. If in doubt, seek cardiology advice.	If history is suggestive of heart failure sudden/progressive reduced exercise tolerance, please check NT-pro-BNP, refer to cardiology for further assessment. Pause titration of clozapine and increase to daily monitoring of CRP, hs-troponin I and physical observations if there are any of the following: • Symptomatic with fever, chest pain or shortness of breath. • Mildly raised CRP (below x3 upper limit of normal (ULN)) or troponin I (below x2 ULN) + fever • New ECG changes without symptoms If in doubt, seek cardiology advice.	**If a patient is in acute decompensated heart failure:** **STOP** clozapine and urgently refer to cardiology and liaison psychiatry immediately. Consider echocardiogram if there are any of the following: • hs-troponin I > x2 ULN • CRP > 100 • CRP > x10 normal limit with symptoms (fever, chest pain or shortness of breath) • ECG changes (ST elevation/T waves) with symptoms (fever, chest pain or shortness of breath) If in doubt, seek cardiology advice.

Symptom	Common or lower-concern symptoms	Concerning symptoms	Urgent or emergency symptoms
Seizures or myoclonic jerks • This could be related to a high clozapine level (clozapine is pro-convulsant) and may indicate toxicity. • Myoclonus could precede a seizure.		For new seizures, undertake baseline blood tests including clozapine level (see relevant section of table lower down) and investigate possible underlying causes such as infection or overdose. Consider CT head as per local policy, especially if there is focal neurology or after senior discussion. Assess for contributing factors that may lead to a raised clozapine level, such as dehydration, reduction in smoking, medication interactions and physical illness. Clozapine levels may take time to return, so ensure discussion with the psychiatric liaison team for appropriate follow-up of the result. They can then advise the inpatient or community team. Consider the level of social support and care in the community when thinking about discharge. Consider holding clozapine post-seizure for 24 hours, and restart at 50% dose if seizures have improved.	If a person's seizure has resulted in, or nearly resulted in, an injury or harm to themselves, if the seizure lasts longer than 5 minutes, if there is a change from usual seizure, or if there are multiple seizures: • Consider alcohol withdrawal or overdose • Follow local guidance for prolonged seizures or status epilepticus • Seek urgent neurology advice • If the decision is to stop clozapine urgently, refer to liaison psychiatry immediately.
Increased seizure frequency or severity (with pre-existing epilepsy) **Or a change in type of seizures** (with pre-existing epilepsy)	In patients with a history of epilepsy, please explore concordance with antiepileptic medication, whether they are presenting with increased seizures of a change in seizure pattern. Consider the level of social support and care in the community when thinking about discharge. Consider holding clozapine post-seizure for 24 hours, and restart at 50% dose if seizures have improved.	As above	As above

Symptom	Common or lower-concern symptoms	Concerning symptoms	Urgent or emergency symptoms
Sedation Especially where this is new or increased, and/or accompanied by an altered mental state While sedation is rarer, it can be an easily missed contributor to sudden death for patients on clozapine. Consider**:** • Raised levels of clozapine • Encephalopathy, head injury, hypo-active delirium.	• Assess sedation in context of base-line as reported by patient or carer. • Consider consequences of seda-tion, such as falls, increased risk of aspiration. • Explore any new medication, concordance with clozapine, changes in alcohol intake, con-current substance use (using urine drug screening if possible), reduced hepatic or renal clearance, dehydration. • Consider other causes of seda-tion based on clinical history and assessment. • Assess for contributing factors that may lead to a raised clozapine level – dehydration, reduction in smoking, medication interactions, physical illness. • Be wary of diagnostic overshad-owing, especially if the patient's mental state is noted not to be at baseline (e.g., different/more severe psychotic symptoms from usual). • Encourage patient to inform the clozapine clinic/care coordinator about what has happened.	• New sedation accompanied with altered mental state is con-cerning and should be assessed thoroughly. • If sedation is severe, consider over-dose of medication, among other causes of reduced GCS. • Refer to liaison psychiatry urgently and in parallel with medical assess-ment. Liaison psychiatry can help clarify the patient's baseline mental state and current mental state. • Consider reducing or withholding clozapine and/or other sedating medication. • Clozapine levels can be ordered, but results can take up to a week. Do not wait for the results to consider reducing dose/stopping clozapine if toxicity or serious illness is suspected, but do seek urgent advice on this from liaison psychiatry.	• In cases of respiratory depression, observe closely and protect the airway. Consider anaesthetics /ITU involvement. • Discuss reducing or stopping clozapine with liaison psychiatry if it is deemed to be a significant contributor to severe sedation fol-lowing assessment. • Consider neurology referral to investigate other causes.

Other key considerations	
Smoking	• Smoking cigarettes reduces clozapine levels. • Reducing/stopping smoking or switching to vaping increases clozapine levels. Has the patient recently stopped/cut down/started or changed to other forms of nicotine (vape, patch, gum)?
Alcohol	Has the patient started/stopped/changed the amount of alcohol consumed recently? Consider the cumulative sedative effect of alcohol and clozapine: Might they be in alcohol withdrawal?
Caffeine	Caffeine increases clozapine levels. Is the patient taking more/less caffeine than usual? Consider various caffeine sources, such as coffee, energy drinks etc.
Drugs	Is the patient using substances and has the pattern of use changed recently? Consider the cumulative sedative effect of drugs and clozapine.
New medication	Has the patient been started on new medication or had dose amendments that may change clozapine levels or contribute cumulatively to side effects (anticholinergic burden, sedative medications)?

Consent or capacity

Where there are concerns about consent or capacity, treatment should be considered in line with the relevant legal framework and local policy for the nation in which the person is being treated:

- **England and Wales:** Mental Capacity Act 2005
- **Scotland:** Adults with Incapacity (Scotland) Act 2000
- **Northern Ireland:** Relevant mental capacity and mental health legislation, including the Mental Capacity Act (Northern Ireland) 2016, where commenced/applicable