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**Patients who are taking clozapine require ongoing monitoring because of the risk of serious blood dyscrasias. What should pharmacists be checking before they dispense the medicine?**

# How clozapine patients can be monitored safely and effectively

By **Michael Dixon**, MRPharmS, and **Caroline Dada**

Clozapine is an atypical antipsychotic that is used for treatment-resistant schizophrenia. The drug is subject to strict monitoring requirements because it is associated with serious side effects, such as neutropenia, agranulocytosis, seizures, myocarditis and cardiomyopathy. The incidence of neutropenia among clozapine-treated patients is 2% and agranulocytosis 0.8%.

Some 30–60% of patients with treatment-resistant schizophrenia will respond to clozapine.[1,2] The decision to prescribe clozapine is usually made for patients who have been treated unsuccessfully with at least two other antipsychotic medicines (one of which is another atypical antipsychotic). A recent Cochrane review showed that clozapine had a number needed to treat of 21 versus typical antipsychotics for preventing relapse.[3] About 80% of patients with schizophrenia will relapse without antipsychotic treatment.

## What action to take

Pharmacists who encounter a prescription for clozapine should establish:

- What brand of clozapine the patient is taking
- The frequency of full blood count (FBC) tests and when the last one was taken
- The current dose of clozapine
- The patient's adherence to clozapine treatment — specifically, whether he or she has missed a dose more than 48 hours beforehand
- Who currently supplies the patient's clozapine

If the patient has been admitted to hospital, you should establish whether he or she has brought any clozapine with them.

## OBJECTIVES

Studying this article will help you to:

- Understand the frequency of blood monitoring for patients taking clozapine
- Understand restrictions on how much clozapine can be dispensed
- Ensure seamless transfer of care between NHS organisations for people taking clozapine

## DISCUSSION

- How do you deal with medicines that require strict monitoring but which you encounter rarely in your practice?
- How do you carry out the medicines reconciliation process for specialist medicines?
- What is your team's approach to recording decisions about clozapine monitoring and dispensing?

## Brand of clozapine

Each clozapine manufacturer has its own mandatory monitoring system. The prescribing consultant, patient and supplying pharmacy each have to be registered with the clozapine manufacturer. There are three brands of clozapine currently available in the UK, namely:

- Clozaril (Novartis) — monitoring website www.clozaril.co.uk
- Denzapine (Genus) — monitoring website www.denzapine.co.uk
- Zaponex (Teva UK) — monitoring website www.ztas.co.uk

The different brands are bioequivalent. The blood results need to be communicated to the relevant monitoring service to ensure you can safely dispense further supplies of clozapine.

## Timing of blood tests

Patients' risk of agranulocytosis reduces the longer they take the medicine (see Box 1) and the monitoring requirements reflect this. Patients newly started on clozapine must have an FBC taken weekly for the first 18 weeks of treatment then fortnightly for the next 34 weeks. After that they receive monthly monitoring for as long as they are taking clozapine.

The amount of clozapine that can be supplied varies depending on a patient's stage of monitoring. Specifically:

- Weekly FBC tests — maximum of 10 days' supply of clozapine (from the date of the most recent blood test)
- Fortnightly FBC tests — maximum of 21 days' supply of clozapine (from the date of the most recent blood test)
- Monthly FBC tests — maximum of 42 days' supply of clozapine (from the date of the most recent blood test)

The clozapine manufacturers use a traffic light system (green, amber, red) for guiding dispensing on the basis of FBC results, as described in Box 2 (p132).

## Side effect monitoring

Every patient receives an electrocardiogram before they are initiated on clozapine. Although there is no routine monitoring for myocarditis or cardiomyopathy during treatment, patients showing signs of heart failure should have their therapy stopped until the condition is investigated. Because the presentation of cardiomyopathy varies, investigations should be carried out for patients taking clozapine who develop palpitations, sweating and breathing difficulties.[4]

## Box 1: Agranulocytosis

| CLOZAPINE TREATMENT PERIOD | INCIDENCE OF AGRANULOCYTOSIS PER 100,000 PERSON-WEEKS OF OBSERVATION |
|---|---|
| Weeks 0–18 | 32.0 |
| Weeks 19–52 | 2.3 |
| Weeks 53 and longer | 1.8 |

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## Box 2: Traffic light system for dispensing clozapine

| | WHITE BLOOD CELL COUNT ($\times 10^9$/L) | NEUTROPHIL COUNT ($\times 10^9$/L) |
|---|---|---|
| GREEN<br>Clozapine can be dispensed | >3.5 | >2.0 |
| AMBER<br>Clozapine can be dispensed, but monitor full blood count twice a week | 3–3.5 | 1.5–2.0 |
| RED<br>Stop clozapine. Monitor full blood count daily until results return to normal* | <3 | <1.5 |

**Clozapine should also be stopped if the platelet count falls below 50×10⁹/L or the eosinophil count measures above 3×10⁹/L*

## Adherence to clozapine

Patients who have missed clozapine doses for more than 48 hours will need to have the medicine retitrated. They cannot continue taking their usual maintenance dose. If they miss more than three days of clozapine their blood testing frequency may need to change. The relevant clozapine manufacturer or mental health pharmacy should be contacted for further advice.

## Continuity of care

In the vast majority of cases clozapine will be prescribed by a consultant psychiatrist and dispensed by a hospital pharmacy. A community pharmacy may be supplying clozapine under a service level agreement for patients receiving monthly blood tests. Contact the supplying pharmacy to find out the patient's current dose of clozapine, when he or she last collected supplies, the brand of clozapine and the directions prescribed. Clozapine often does not appear on GP records when a list of current medicines is obtained from a surgery. Ask patients whether they are receiving any other medicines apart from through the GP, especially if they have a diagnosis of schizophrenia and do not appear to be prescribed an antipsychotic.

For patients who have been admitted to hospital, it is important to contact the pharmacy that supplies their clozapine. This ensures the pharmacy team is aware of the admission, can advise on dosing and blood tests and can pass on the information to the mental health team. This also provides an opportunity to discuss ongoing supplies of clozapine for the patient during their inpatient stay and at the time of discharge.

During admission, contact the relevant clozapine monitoring service with relevant FBC results as required and confirm the FBC is acceptable before dispensing more clozapine. You will need the patient's name and date of birth to do this.

Check that none of the new medicines prescribed interacts with clozapine (eg, erythromycin and ciprofloxacin can increase clozapine levels, rifampicin can greatly reduce clozapine levels). Patients who stop smoking while an inpatient will need to have their doses reduced because smoking induces clozapine metabolism.

On discharge, contact the patient's clozapine pharmacy for directions on how much clozapine to dispense. Arrangements can also be made for the patient to be booked into the appropriate clozapine clinic for their next FBC and for further clozapine supplies.

## Specialist input

Specialist mental health pharmacists can advise on clozapine monitoring and dose titration in certain clinical scenarios, for example, patients who are:

- Physically unwell
- Receiving surgery
- Undergoing intensive care
- Nil-by-mouth

Some hospitals have a liaison psychiatry team that can advise and monitor mental health patients and their psychiatric conditions during acute admissions.

It is crucial that all staff involved with the prescribing, dispensing and administration of this medicine are trained appropriately. They need to know what processes to follow and when to seek specialist help — getting it wrong can be catastrophic.

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Answers

1 d; 2 b; 3 b; 4 b; 5 d

### References

1 National Institute for Health and Care Excellence. Core interventions in the management of schizophrenia in primary and secondary care. March 2009. www.nice.org.uk/cg82 (accessed 20 May 2014).

2 Barnes T and the Schizophrenia Consensus Group of the British Association for Psychopharmacology. Evidence-based guidelines for the pharmacological treatment of schizophrenia: recommendations from the British Association for Psychopharmacology. Journal of Psychopharmacology 2011;25:567–620.

3 Essali A, Al-Haj Haasan N, Li C, et al. Clozapine versus typical neuroleptic medication for schizophrenia (review). Cochrane Database of Systematic Reviews 2009, Issue 1.

4 Taylor D, Paton C, Kapur S. The Maudsley Prescribing Guidelines in Psychiatry. 11th edition. London: Wiley Blackwell; 2012.

## TEST YOURSELF

1 Which of the following brands of clozapine are available in the UK?

a) Clozaril
b) Denzapine
c) Zaponex
d) All of the above

2 What is the incidence of neutropenia with clozapine?

a) 0.8%
b) 2%
c) 5%
d) 8%

3 For patients taking clozapine who are receiving weekly blood tests, what is the maximum number of days' supply of clozapine that can be dispensed?

a) Seven days
b) 10 days
c) 21 days
d) 42 days

4 How many days can a patient go without a dose of clozapine before it has to be retitrated?

a) One
b) Two
c) Three
d) Four

5 What does having an "amber" blood test mean for patients taking clozapine?

a) Their white blood cell count (WBC) is less than 3×10⁹/L or their neutrophils are less than 1.5×10⁹/L
b) Their platelets are less than 50×10⁹/L
c) Their WBC is 3.5–4.0×10⁹/L or their neutrophils are 2.0–2.5×10⁹/L
d) Their WBC is 3.0–3.5×10⁹/L or their neutrophils are 1.5–2.0×10⁹/L

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