Management of clozapine-associated neutropenia

ARTICLE

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SUMMARY

Clozapine is the only evidence-based intervention for treatment-resistant schizophrenia. One of the drug's most well-known and potentially fatal adverse effects is agranulocytosis (severe neutropenia). Hence, regular blood tests are an essential component of clozapine treatment. This article presents a narrative review of the history, incidence, potential aetiology and management of clozapine-associated neutropenia. It gives an overview of clozapine monitoring requirements, including those for benign ethnic neutropenia. We point to the growing body of evidence that the risk of clozapine-induced agranulocytosis is mostly confined to the first year of treatment and that the risk of fatality is considerably lower than previously assumed. Given the absence of alternative evidence-based interventions for treatment-resistant schizophrenia, we suggest that rechallenging with clozapine should be considered in most patients with clozapine-associated mild to moderate neutropenia who do not respond to other treatments. A more careful risk–benefit analysis is needed in cases of severe neutropenia (agranulocytosis).

LEARNING OBJECTIVES

After reading this article you will be able to:

- demonstrate basic knowledge of the causes and clinical presentation of neutropenia
- understand the risk of clozapine-associated neutropenia and critically appraise the current haematological monitoring requirements
- manage clozapine-associated neutropenia and decide when to rechallenge with clozapine.

KEYWORDS

Clozapine; adverse effects; neutropenia; agranulocytosis; schizophrenia.

Clozapine is the most effective and only evidence-based treatment for treatment-resistant schizophrenia. Therefore, it is recommended by almost all national and international guidelines for the above indications (National Institute for Health and Care Excellence 2014; Barnes 2020; Correll 2022).

Clozapine has been shown to reduce all-cause mortality in schizophrenia, including suicide (Meyer 2020). However, its use is associated with a few severe, and potentially fatal, adverse effects. As a result, it is reserved for treatment-resistant schizophrenia and requires mandatory blood monitoring because of the risk of clozapine-associated neutropenia (CAN) and agranulocytosis (CAA). Unfortunately, this has led to clozapine acquiring a reputation as a 'toxic drug'. Consequently, clinicians and patients often prefer less effective antipsychotics at higher doses or in combination, to minimise adverse effects. A national audit of psychosis services in England and Wales revealed that in 2017 only 26% of patients with treatment-resistant schizophrenia (described in the report as patients who were not currently in remission) were receiving clozapine (Royal College of Psychiatrists 2018).

In light of the various potential causes of neutropenia (including autoimmune disorders, nutritional deficiencies, infections and medications – see Aetiology below), pinpointing a single specific causal factor can be challenging in individual patients. To attribute causality to a drug the following criteria should be met:

- the occurrence of neutropenia soon after initiation of the medication and normalisation of the neutrophil count within a month after its discontinuation
- other possible causative factors are absent (e.g. recent viral infection, chemotherapy, radiotherapy or history of congenital or immune-mediated neutropenia)
- recurrence of neutropenia on rechallenge, although such an approach cannot be taken to identify the causative factor, owing to the associated risk.

Globally, there are varied guidelines for the monitoring and management of CAN/CAA, influenced by past incidents of fatal adverse effects. Current guidelines on management (in the UK and many other countries) assume a causal link if a patient on clozapine develops neutropenia. Hence, throughout this article we have used the term clozapine-associated neutropenia/agranulocytosis (CAN/CAA) rather than clozapine-induced neutropenia/agranulocytosis (CIN/CIA). However, it is important to make a clinical judgement about a possible

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First received 9 Sep 2023
Final revision 30 Jun 2024
Accepted 7 Jul 2024

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https://doi.org/10.1192/bja.2024.51 Published online by Cambridge University Press

causal link, when considering rechallenging with clozapine.

Clozapine can lead to various blood disorders, including neutropenia, eosinophilia and thrombocytopenia. For this article, the focus will be on neutropenia.

Neutropenia

Neutrophils are the most abundant type of granulocyte in the human body, constituting 40–70% of total white blood cells. They play a crucial role in combating bacterial and fungal infections and their deficiency can cause severe, potentially fatal infections.

'Normal' neutrophil counts and BEN

In the UK, the normal neutrophil count range for White individuals is $1.5–8.0 \times 10^9$/L. It is important to note that there is diurnal variation, with counts 10–20% higher in the early afternoon. Neutrophil counts may also temporarily increase following exercise or cigarette smoking.

In certain ethnic groups neutrophil counts consistently below 1.8×10^9/L have been observed. This persistent neutropenia, referred to as benign ethnic neutropenia (BEN), has no discernible cause or increased risk of infection. It is a benign genetic condition commonly observed in Black individuals of African or African–Caribbean descent, and less frequently in individuals from Arab ethnic groups and Yemenite Jews. That these neutrophil counts seem to be low may also be attributed to the fact that the 'normal' neutrophil range has been established based on White populations. Approximately 25–50% of Black people have been reported to have BEN, which may explain why this population is less likely to be prescribed clozapine and has a higher frequency of reported CAN/CAA cases. A study by Oloyede et al (2021b) reviewed patients prescribed clozapine in two mental health trusts in London and found that only 17% of Black patients were registered as having BEN and were therefore being monitored. Most of these individuals (68%) were identified only when their neutrophil counts were subthreshold after the initiation of clozapine (during mandatory clozapine monitoring) or after rechallenge, rather than at the initiation of clozapine (Oloyede 2021a).

Diagnosing BEN involves observing persistently low levels of neutrophils over time, while excluding alternative causes of neutropenia, such as autoimmune disorders, infection or other medical conditions that can affect white blood cell count.

In the UK, a haematologist must confirm the diagnosis of BEN, whereas in the USA, a psychiatrist can make this judgement clinically (we return to this below, in 'Clozapine monitoring requirements'). Hence, if BEN is suspected then the patient should be referred to a haematologist. The specialist might perform a simple blood test for the presence of 'Duffy-null genotype' as may alleviate the need for unnecessary tests into alternative causes of neutropenia. A positive test for the Duffy-null genotype alongside a low neutrophil count can be used to confirm the diagnosis of BEN. However, a negative Duffy-null genotype test against a background of neutropenia may not rule out BEN, since it can have multiple causes, including but not limited to variations in genes beyond the Duffy-null gentype (Meyer 2020; Palmblad 2018).

Early identification and registration with BEN monitoring systems is paramount to prevent unnecessary discontinuation of clozapine treatment (Oloyede 2021a).

Classification

Neutropenia is categorised as mild, moderate or severe, with severe neutropenia regarded as agranulocytosis (Table 1). Infection risk rises significantly when neutrophil counts drop below 0.1×10^9/L, and a group of haematologists considers a count below 0.1×10^9/L with fever or signs of sepsis as true agranulocytosis (Rattay 2021).

Aetiology

Neutropenia can be classified as congenital, acquired or hereditary (Table 2). The most common cause of acquired neutropenia is pharmaceutical agents and it is more common in elderly patients and those managed with polypharmacy. Assessing the incidence and aetiological pathway of neutropenia is challenging owing to its rare occurrence as an adverse effect. Generally, if discontinuation of a drug leads to improvement in neutrophil counts and re-exposure leads to recurrence of neutropenia, it suggests that the drug may be a causative factor, as seen with clozapine. Viral infections are the most common cause of transient neutropenia.

Although cytotoxic drugs often cause dose-dependent neutropenia, clozapine, and other drugs such as carbimazole, valproate, carbamazepine, lamotrigine and mirtazapine, cause idiosyncratic

TABLE 1 Classification of neutropenia

	Neutrophil count
Mild	$1.0–1.499 \times 10^9$/L
Moderate	$0.5–0.999 \times 10^9$/L
Severe (agranulocytosis)	$<0.5 \times 10^9$/L

Sources: Myles et al (2017); Rattay & Benndorf (2021)

BJPsych Advances (2024), page 1 of 11 doi: 10.1192/bja.2024.51

https://doi.org/10.1192/bja.2024.51 Published online by Cambridge University Press

TABLE 2 Common causes of neutropenia

Congenital	Acquired	Hereditary
Kostmann syndrome Cyclic neutropenia	Drug-induced: cytotoxic chemotherapy, clozapine, chlorpromazine, quetiapine, valproate, carbamazepine, lamotrigine, mirtazapine, mianserin, carbimazole, acyclovir, ampicillin, amoxicillin/clavulanic acid, cefotaxime, ceftriaxone, cefuroxime Nutritional deficiency: vitamin B_{12}, folate Viral: Epstein–Barr virus, cytomegalovirus, hepatitis, HIV, influenza Malignant: leukaemia, lymphoma, myelodysplasia Hypersplenism	Benign ethnic neutropenia

dose-independent neutropenia thought to be immune-mediated (Rattay 2021).

Monitoring

Monitoring blood is crucial for managing drug-induced neutropenia, especially when incidence rate is high. Its aim is to detect and discontinue the offending agent promptly, to prevent neutropenia from progressing to agranulocytosis and associated complications. In cases of drug-induced agranulocytosis, the recovery of neutrophil counts can take an average of about 9 days after the withdrawal of the offending agent. During this period, appropriate preventive measures should be taken to avoid infection (Pick 2014).

Most cases of drug-induced neutropenia occur soon after the initiation of the medication. There is no unanimous agreement regarding the optimal duration for monitoring. Some recommendations propose setting the monitoring duration based on the median time of neutropenia onset (based on the available evidence), along with an additional safety margin, subjectively determined.

Clinical presentation

At the outset, individuals with neutropenia show no symptoms. However, later on, they may experience fever, sore throat, difficulty swallowing and inflammatory mucosal lesions due to opportunistic infections. Agranulocytosis is a medical emergency that can be fatal if not effectively managed. Previously, agranulocytosis had limited treatment options and high mortality rates. However, current monitoring practices enabling early identification and improved treatment options have reportedly significantly reduced the rate of fatality from 20 to 5% (Pick 2014); mortality increases with age and is also affected by associated comorbidities (Curtis 2017).

Clozapine-associated neutropenia and agranulocytosis

Clozapine is a leading cause of drug-induced neutropenia and agranulocytosis, resulting in varying degrees of mandatory monitoring across the world.

History

Clozapine was initially developed in 1959 by Wander AG as an antidepressant with antipsychotic properties. It faced challenges in 1975 in Finland (Crilly 2007), when 18 patients receiving the drug for psychosis developed blood disorders, with 16 confirmed agranulocytosis cases, resulting in 8 fatalities complicated by secondary infection. These adverse effects occurred within the first 3 months of clozapine initiation, leading to its withdrawal from the market and halting its development programme. The sudden cluster of agranulocytosis cases occurred in 6 out of 62 hospitals. Investigations into potential factors, including genetics or environmental influences such as irregular dosing patterns or drug impurities, failed to provide any explanation at the time. Many patients relapsed on clozapine cessation and did not improve on another antipsychotic. Therefore, clozapine continued to be available on a compassionate basis. Owing to its superior efficacy compared with other antipsychotics in people with treatment-resistant schizophrenia, recognising clozapine's potential, the Sandoz pharmaceutical company approached the US Food and Drug Administration (FDA) to conduct a clinical trial specifically targeting that population. The FDA required strict blood monitoring to address concerns regarding agranulocytosis risk (Crilly 2007).

Kane et al (1988) conducted a rigorous trial that proved clozapine's superiority over chlorpromazine in treating TRS, leading to its FDA approval in 1989. To address concerns regarding neutropenia, Sandoz implemented the Clozaril® Patient Monitoring System. This established strict blood monitoring and discontinuation rules, with a 'no blood, no drug' policy enforced in many regions, ensuring medication dispensing only if there were satisfactory blood results.

Data over the following years indicated that the risk of CAA was highest during the initial 18 weeks to a year, decreasing significantly thereafter. As a result, the USA FDA modified its monitoring requirements in 1997, shifting from weekly to fortnightly after 6 months. In 2005 it moved to

https://doi.org/10.1192/bja.2024.51 Published online by Cambridge University Press

monthly monitoring after 1 year. Further amendments were made in 2015, with the removal of the requirement to monitor the total leukocyte count, as in CIN and CIA only neutrophil counts are affected. In addition, the ANC threshold for clozapine discontinuation was reduced and a statement was included that in certain cases, clozapine can be continued if the risk–benefit analysis favours this despite neutropenia. Oloyede et al (2022) assessed the implications of the revised US FDA criteria for the UK. They reported that only a small proportion (15%) of patients on the UK's Clozapine Central Non-Rechallenge Database (CNRD) would have discontinued clozapine, and they therefore called for an urgent review of the criteria.

In the UK, the Medicines and Healthcare products Regulatory Agency (MHRA) also approved clozapine in 1989. Guidelines were updated in 2002 to account for benign ethnic neutropenia (BEN), and in 2013 the criterion for required clozapine cessation and registration on the Clozapine Central Non-Rechallenge Database was changed from a single 'red' result on the ANC to an ANC red result confirmed by two consecutive tests (see 'Clozapine monitoring requirements' below). Since then, monitoring requirements have remained unchanged.

We discuss the current UK and US blood monitoring and discontinuation rules more fully in the section 'Clozapine monitoring requirements'.

Risks of CAN/CAA

Myles et al (2017) reviewed 108 studies, involving 450 000 patients, from over 30 years of worldwide clozapine usage, reporting the incidences of CAN and CAA as 3.8 and 0.9% respectively. As mentioned above, neutropenia in clozapine-treated patients may not always be directly caused by clozapine itself. Transient viral infections or concurrent medications can also trigger neutropenia. Sodium valproate co-prescription doubles the risk of clozapine discontinuation due to neutropenia (Malik 2018). Proton pump inhibitor co-prescription has a similar effect (Gurrera 2022). CAN might be prone to overdiagnosis because of surveillance bias (Taylor 2022), stemming from the misguided and cautious belief that every non-specific or sporadic episode of neutropenia must be linked to the use of clozapine, with the result that current UK and US guidelines mandate discontinuation of clozapine in all cases of neutropenia. However, this is not the case in Australia and New Zealand, where clozapine can be continued in cases of CAN not thought to be causally related to clozapine (Northwood 2024). Therefore, it is important to clinically differentiate CAN/CAA from clozapine-induced neutropenia/agranulocytosis (CIN/CIA), based on temporal correlation, onset during the high-risk period and absence of any other likely explanations.

In China, where clozapine has been used more extensively, including for non-treatment-resistant schizophrenia, a study has reported a CAA incidence of 0.2%, which is lower than the global average (Tang 2008). When interpreting these variations, it is important to consider genetic differences and disparities in monitoring practices.

Most patients who develop CAA do so within a month of starting clozapine, and approximately 89% of those who develop it do so within the first year. After 1 year, the risk of CAA diminishes to a negligible level, on a par with other antipsychotics (Myles 2018). Isolated cases of late-onset events have been reported years after clozapine initiation. Such occurrences have led to the suggestion that clozapine may not be the direct cause in these cases. Consequently, over the past decade, there have been increasing debates about the issue of mandatory long-term monthly monitoring (Myles 2018; Nielssen 2020).

At present there are limited data indicating how many patients with CAN would progress to CAA, as in most countries clozapine is withdrawn at the onset of CAN. Based on incidence data, Myles et al (2018) estimated that 75% of patients with mild CAN would not progress to CAA. In Iceland, where clozapine monitoring is less stringent compared with the UK, Ingimarsson et al (2016) retrospectively followed up 10 patients with mild neutropenia: 1 developed CAA, 3 discontinued clozapine, and 6 continued clozapine for at least a year, without progression to CAA. Currently, there are no predictors of the progression from CAN to CAA. Therefore, CAN should not be assumed to be an initial phase of CAA. Hence, concerns have been raised in the UK regarding the premature discontinuation of clozapine because of red results.

Aetiology of CAN/CAA

The aetiology of CAN and CAA remains elusive, despite efforts to understand the pathophysiological processes and identify high-risk patients. Several sound studies have reported potential associations with specific human leukocyte antigens (HLA-B38, DR4, DQw3, DQB1), indicating increased susceptibility to CAA/CAN. Such haplotypes were expected to help identify high-risk patients and adjust monitoring frequencies accordingly. However, current evidence lacks the robustness required to support such changes and therefore more research is required (Mijovic 2020).

BJPsych Advances (2024), page 1 of 11 doi: 10.1192/bja.2024.51

https://doi.org/10.1192/bja.2024.51 Published online by Cambridge University Press

Clozapine affects both myeloid precursor cells and mature neutrophils. Evidence indicates that CAN and CAA are primarily caused by the activation of clozapine into a chemically reactive nitrenium ion or its metabolite (*N*-dimethyl clozapine). These can induce neutropenia through direct toxicity or by triggering an immune reaction, or possibly both. The immune mechanism is supported by the association with specific HLA haplotypes and the observation that some patients experience a more rapid onset of CAA on rechallenge (Mijovic 2020).

The observation that, in most cases, CAN will not progress to CAA implies that CAN may not be an initial stage in the pathological process leading to CAA. This creates a potential for CAN and CAA to be understood as separate pathologies. CAN primarily affects peripheral neutrophils, while CAA affects both peripheral neutrophils and their precursors (Gurrera 2022). Furthermore, not all people with CAA experience serious or life-threatening consequences: a proportion see spontaneous normalisation of neutrophil counts without significant clinical sequelae (Taylor 2022).

Taylor et al (2022) reviewed the pattern of neutropenia in cases of life-threatening CAA with a rapid decline to zero/near zero neutrophils. These were associated with signs of infection, hospital admission and/or treatment with antibiotics or granulocyte colony-stimulating factor (G-CSF). Time for neutrophils to fall from an absolute neutrophil count (ANC) $>2 \times 10^9$/L to $<0.5 \times 10^9$/L averaged 8.4 days (range 2–15 days), with prolonged nadir and delayed recovery. This pattern differed from non-life-threatening CAA, where neutropenia episodes were brief and benign. These findings may help in identifying patients requiring immediate care escalation because of a high risk of decline.

Clozapine monitoring requirements

Blood monitoring for patients prescribed clozapine serves a secondary prevention purpose. It helps identify neutropenia early, allowing prompt discontinuation of treatment.

Current UK and US clozapine monitoring requirements are outlined in Table 3. In both countries, test results are evaluated using a traffic-lights system of green, amber and red, although the specific threshold counts are different for the countries and, as mentioned above, the USA does not require monitoring of the total white blood cell count.

Three brands of clozapine are sold in the UK (Clozaril®, Denzapine® and Zaponex®) and the three marketing authorisation holders of these brands are responsible for blood monitoring via their respective systems (the Clozaril Patient Monitoring Service, Denzapine Monitoring System and Zaponex Treatment Access System). Current requirements mandate blood monitoring by the monitoring service specific to the clozapine brand prescribed. If a patient develops a red result (ANC $<1.5 \times 10^9$/L) confirmed by two consecutive tests, clozapine must be discontinued. These patients should not be retried on clozapine and are registered on the UK's CNRD, which is shared by the marketing authorisation holders. Between May 2002 and March 2022, 3731 patients were registered on the database (Oloyede 2022).

Monitoring requirements vary significantly globally, ranging from strict monitoring with 18 weeks of in-patient admission in Japan to no mandatory monitoring recommendations in many other countries (Bachmann 2017; Oloyede 2023a). However, most guidelines suggest discontinuing clozapine at an ANC between 0.5×10^9/L and 1.5×10^9/L (Nielsen 2016). Countries without mandatory blood tests have not reported any clusters of CAA-associated fatalities. Additionally, during UK COVID-19 restrictions, monitoring requirements were relaxed, from monthly to 3-monthly blood tests, for long-term clozapine patients without increased observed risks of CAN/CAA (Oloyede 2023b). Similarly, The Netherlands Clozapine Collaborative Group allows blood monitoring to be stopped or done at 3-month intervals after 6 months of initiating clozapine (off-label), and they have not reported any increased CAA risks (Schulte 2020).

Girardin et al (2014) examined the cost-effectiveness of monitoring in the UK, Europe and USA, revealing that these requirements improved quality-adjusted survival by just 1 day. In addition, over 5000 patients need to be monitored to prevent a single death, at an incremental cost-effectiveness ratio of at least $970 000 per quality-adjusted life-year gained. These findings highlight the substantial cost associated with current monitoring guidelines.

Nevertheless, mandatory monitoring guidelines have substantially reduced the mortality rate associated with CAA, which has decreased from 0.3 to 0.01% worldwide owing to rigorous blood monitoring and prompt discontinuation in cases of neutropenia (Electronic Medicines Compendium 2023). Thus, the absolute risk of a fatal outcome is very low. A systematic review and meta-analysis calculated that the risk of death from CAA is approximately 0.013% – or 1 in 7700 patients (Myles 2018). Until 2021, the UK had reported eight fatalities due to CAA (Oloyede 2021a).

The other drugs known to cause agranulocytosis, such as antithyroid medications (carbimazole, propylthiouracil) and antibiotics (sulphonamides, penicillin, cephalosporins), are not subjected to strict monitoring. The risk of agranulocytosis associated

https://doi.org/10.1192/bja.2024.51 Published online by Cambridge University Press

TABLE 3 Clozapine monitoring requirements and guidance in UK and USA

	Green result	Amber result	Red result	Comments
UK				
				BEN must be diagnosed by a haematologist.
Total WBC	>3.5 × 10^9/L Adjusted for BEN: >3.0 × 10^9/L	3.5–3.0 × 10^9/L Adjusted for BEN: 3.0–2.5 × 10^9/L	<3.0 × 10^9/L Adjusted for BEN: <2.5 × 10^9/L	
Neutrophil count (ANC)	>2.0 × 10^9/L Adjusted for BEN: >1.5 × 10^9/L	2.0–1.5 × 10^9/L Adjusted for BEN: 1.5–1.0 × 10^9/L	<1.5 × 10^9/L Adjusted for BEN: <1.0 × 10^9/L	
Frequency of monitoring	Weekly up to 18 weeks. Fortnightly up to 52 weeks (1 year). Monthly thereafter.	Increase to biweekly monitoring.	Increase to daily monitoring.	
Recommended action	Continue clozapine.	Continue clozapine. Return to normal monitoring frequency once green result is obtained.	Stop clozapine. Patient must have daily blood sampling and may only commence clozapine once two green results have been obtained on two consecutive days. Two consecutive red results (severe neutropenia/agranulocytosis): do not rechallenge, register patient on the CNRD.	
USA				
				BEN can be diagnosed by a psychiatrist or haematologist. Total WBC not required.
Neutrophil count (ANC)	>1.5 × 10^9/L Adjusted for BEN: >1.0 × 10^9/L	1.5–1.0 × 10^9/L Adjusted for BEN: 1.0–0.5 × 10^9/L	<1.0 × 10^9/L Adjusted for BEN: <0.5 × 10^9/L	
Frequency of monitoring	Weekly up to 26 weeks. Fortnightly up to 52 weeks (1 year). Monthly thereafter.	Increase monitoring to 3 times per week.	Increase to daily monitoring.	
Recommended action	Continue clozapine.	Continue clozapine. Return to normal monitoring frequency once ANC is within the normal range.	Stop clozapine. Consult haematology for suspected CAN. Moderate neutropenia: daily blood sampling, commence clozapine once ANC normalises. Severe neutropenia (agranulocytosis): daily blood sampling, do not rechallenge unless prescriber determines appropriate with a risk–benefit analysis.	

ANC, absolute neutrophil count; BEN, benign ethnic neutropenia; CAN, clozapine-associated neutropenia; CNRD, Clozapine Central Non-Rechallenge Database; WBC, white blood count.
Sources: Electronic Medicines Compendium (2024); US Food and Drug Administration Drug Approvals and Databases (n.d.).

with clozapine is not as high as once assumed and fatality is low. Moreover, as CAA onset is fairly rapid, the reliability of monthly blood tests to pick up CAA in an early stage is questionable (Taylor 2022). The need for regular blood tests and concerns about agranulocytosis are frequently cited reasons for the underutilisation of clozapine (Bogers 2016). Therefore, there is growing recognition that the current monitoring requirements in the UK are overly rigid and warrant review by the MHRA. Oloyede et al (2023a) compared monitoring guidelines across different countries and found that stringent requirements were associated with decreased clozapine utilisation and increased healthcare costs for managing schizophrenia. Concerns have also been raised about a narrow focus on the risk of neutropenia, neglecting other significant and potentially fatal adverse effects, such as constipation and pneumonia-induced toxicity, which may be causing more harm to patients.

In summary, current monitoring guidelines in the UK are outdated and may be hindering the optimal use of clozapine. There is a need for simpler and more proportionate monitoring guidelines that reflect clinical significance and risks. Nevertheless, it remains essential to adhere to the existing guidelines until new recommendations are established.

BJPsych Advances (2024), page 1 of 11 doi: 10.1192/bja.2024.51

https://doi.org/10.1192/bja.2024.51 Published online by Cambridge University Press

Management of patients with CAN and CAA

Patients and their families considering clozapine should receive comprehensive information regarding the risks of CAN and CAA, along with country-specific guidance on discontinuation. This information should be periodically reiterated, particularly as clozapine is often prescribed during periods of acute illness.

In the UK and USA, if blood monitoring returns a red result (Table 3), the blood test should be promptly repeated, preferably in the afternoon, to avoid the morning nadir in the neutrophil count (Gurrera 2022). If confirmed, clozapine discontinuation is mandatory. A thorough assessment of the risks and benefits specific to the patient should be documented, considering other aforementioned potential causes of neutropenia, and ruling out BEN. Daily blood monitoring should continue until neutrophil counts normalise, and consultation with a haematologist is recommended for cases of CAA.

Discontinuing clozapine carries a high risk of cholinergic rebound and relapse of schizophrenia, necessitating informed patient and family involvement in risk management planning.

Early discontinuation of clozapine leads to rapid normalisation of neutrophil counts in most cases of CAN/CAA. However, patients with CAA are at an increased risk of infection, warranting precautions to minimise infective exposure. Depending on the severity and duration of neutropenia, hospital admission (psychiatric or acute setting) should be considered in consultation with a haematologist.

In specific cases where another causative agent is reasonably suspected, such as recent viral infection or ongoing chemotherapy, a lower threshold for clozapine discontinuation can be agreed in consultation with the marketing authorisation holder, although this would be regarded an off-label prescription.

The management of agranulocytosis encompasses preventive measures to reduce infection risk, prompt and intensive treatment of bacterial infections using antibiotics, and the potential utilisation of lithium and/or granulocyte colony-stimulating factor (G-CSF) to boost neutrophil counts.

Unfortunately, evidence-based treatment options for people with TRS who have discontinued clozapine remain limited. The choice of antipsychotic treatments should be guided by a thorough assessment of previously used antipsychotic medications, considering both their efficacy and any adverse effects. Limited evidence suggests a potential role for olanzapine, owing to structural similarities with clozapine, but a potentially more effective option is clozapine reintroduction (Luykx 2020; Gannon 2023). Therefore, if a patient fails to respond adequately to other antipsychotic drugs within a reasonable time frame, consideration should be given to clozapine rechallenge.

Clozapine rechallenge following a neutropenic episode

Currently, neutropenia is considered a contraindication for clozapine prescribing, making rechallenging with clozapine an 'off-label' prescription in the UK (Joint Formulary Committee 2023). Prescribers must obtain permission from the marketing authorisation holder and follow local governance processes. This includes discussing the risks and benefits with patients, their families and other health professionals involved in care. Owing to the risk of adverse effects resurfacing, rechallenges should take place in an in-patient setting with close blood monitoring, such as twice weekly for the initial 10 weeks (Dunk 2006). Consultation with a haematologist is advisable (Silva 2021). As CIN or CIA are probably immune-mediated adverse effects, starting with a lower clozapine dosage and slowly titrating it up is prudent.

Most evidence for rechallenges comes from case reports and case series rather than formal clinical trials, limiting the reliability of conclusions, especially after CAA episodes. Consequently, rechallenges are met with uncertainty and limited guidelines. However, as previously stated, CAN may not indicate a persistent pathological process, and patients may not progress to CAA even if they continue clozapine. Therefore, the risk of developing CAA is relatively low, and clozapine can be discontinued if neutropenia reappears. On the other hand, the risk of recurrence is significantly high in cases of CAA (especially if clozapine was the likely explanation for the initial episode of agranulocytosis). Therefore, rechallenge following CAA is generally not recommended (Manu 2012; Meyer 2020). The decision to pursue rechallenge, following an episode of CAA, should always be based on careful risk–benefit analysis and patients should be subjected to strict follow-up conditions (Corbeil 2023).

Dunk et al (2006) reviewed patients in the UK and Ireland registered with the Clozaril Patient Monitoring Service from 1998 to 2003. Approximately 53% were rechallenged following blood disorders, with a 62% success rate. Where neutropenia recurred, it was more rapid and severe than the sentinel event, occurring mostly within 10 weeks of clozapine reintroduction. However, all patients who discontinued clozapine and recovered

https://doi.org/10.1192/bja.2024.51 Published online by Cambridge University Press

within 20 days of the neutropenic episode avoided fatality. As one can expect, rechallenge was found to be more successful in those where an alternative cause of neutropenia could be identified. Oloyede et al (2022) reported even higher success rates based on finding from the UK's CNRD between 2002 to 2021, where 519 (16%) patients were rechallenged, with a success rate of 81% (419 patients). Higher success rates have been reported following a period of CAN than following CAA (Manu 2012).

Box 1 lists some general factors to be taken into consideration when deciding whether to rechallenge. Rechallenge options include clozapine alone or in combination with lithium and/or G-CSF, in an attempt to boost the ANC. Since there is limited literature and no comparative studies, decisions regarding these options should be tailored to each patient.

Rechallenge with clozapine alone

Following a neutropenic episode, patients who have a comparatively lower risk of developing CIA, such as those with a history of CAN, the presence of other potential causative factors (e.g. viral infection, other medications) or late-onset CAN, may be considered for clozapine monotherapy. However, predicting the risk of an individual case is challenging, necessitating close monitoring of the ANC for all. If the ANC declines, the addition of G-CSF or lithium can be considered.

Rechallenge with the support of G-CSF

G-CSF treatment rapidly corrects and sustains the ANC, within 4–24 h. This is through the shortening of the transit time of developing granulocytes through the bone marrow compartment, accelerating the release of neutrophils that have undergone recent cell division. The various types of G-CSF now available have revolutionised the management of carcinomas, by mitigating cytotoxic drug-induced neutropenia.

Two strategies are employed for preventing or managing CIN/CIAusing G-CSF: prophylactic (regular administration regardless of ANC) or as required (administered when ANC declines). Myles et al (2017) conducted a systematic review of 17 reports on clozapine rechallenge with G-CSF support (either alone or co-prescribed with lithium), involving 30 patients with CAN. The overall success rate was 76%, although patients co-prescribed lithium had a slightly lower success rate compared with those taking G-CSF without lithium (60 *v.* 81%). Most patients were followed up for over a year; however, no significant predictors of a successful rechallenge were identified. Overall, the authors favoured the prophylactic strategy, owing to improved patient adherence and the avoidance of delayed intervention for neutropenia. Recently Corbeil et al (2023) conducted another systematic review and reported 76% success rate of clozapine rechallenge supported by G-CSF in cases of CAN. They did not find any significant difference between the two administration strategies. They found that five out of six patients with CAA were also successfully rechallenged with concurrent G-CSF administration.

Filgrastim, a commonly used G-CSF, is ideally prescribed under the specialist care of a haematologist. It has a favourable adverse effects profile (commonly encountered adverse effects are transient bone pain, discomfort at the injection site and exacerbation of pre-existing inflammatory conditions). Hypersensitivity to G-CSF is the only contraindication to use. In the prophylactic strategy, it is typically administered one to three times weekly at a dose of approximately 5 μg/kg, with the dosing frequency adjusted to maintain the ANC within the normal range ($1.5–8.0 \times 10^9$/L). After a year of stable ANCs and no neutropenic episodes, consideration can be given to discontinuing G-CSF. If neutropenia recurs, G-CSF can be restarted. There are no significant long-term adverse effects associated with its use.

BOX 1 Factors to consider in deciding whether to rechallenge with clozapine following an episode of clozapine-associated neutropenia/agranulocytosis

- Severity of schizophrenia and associated risks
- History of response to clozapine and other antipsychotic drugs
- Response to alternative treatment, after the discontinuation of clozapine
- Severity of neutropenia and associated complications
- Possible link with clozapine – temporal relationship, onset within the high-risk periods and likelihood of other explanations

Rechallenge with the support of lithium

Lithium is known to induce leucocytosis, hence its place in the correction of a low ANC and prevention of discontinuation of clozapine secondary to neutropenia. Unlike G-CSF, lithium is frequently prescribed by psychiatrists, who are familiar with its adverse effects and monitoring protocol, and so feel more comfortable prescribing it.

The precise mechanism behind lithium-induced leucocytosis remains unclear but may involve the stimulation of granulocyte–macrophage colony-

BJPsych Advances (2024), page 1 of 11 doi: 10.1192/bja.2024.51

https://doi.org/10.1192/bja.2024.51 Published online by Cambridge University Press

stimulating factor (GM-CSF) or other cytokines (Mattai 2009). On average, lithium can increase the ANC by 88% of the baseline value (Focosi 2009). However, the hematopoietic effects may take 2–3 weeks to manifest, and therefore its use is reserved for prophylactic treatment only.

Boazak et al (2018) examined 27 articles involving 94 patients taking lithium to support clozapine rechallenge. The reported success rate was 87.2% (82 out of 94 patients). Two patients who discontinued lithium after a successful rechallenge experienced neutropenia. This suggests that lithium may mask the occurrence of CIN/CIA, emphasising the need for careful ANC monitoring on lithium discontinuation. If CIN/CIA develops, lithium can be reintroduced or neutrophil levels can be managed with G-CSF.

When commencing lithium therapy, it is recommended to begin with lower dosages (300–400 mg/day), adjusting the dose as required to achieve a serum level of at least 0.4 mmol/L (Blier 1998). Adjustment should be based on observed response to the therapy within 3 weeks following each change in dose, up to a serum level of 1.0 mmol/L (Meyer 2020). The precise relationship between serum lithium levels and leucocytosis remains undetermined and therefore the optimum dose needs to be determined on a case-by-case basis.

Rechallenge with the support of both G-CSF and lithium

The evidence supporting this approach is very limited. Therefore, it should be reserved for patients for whom other strategies have proven unsuccessful. In their systematic review Manu et al (2012) reported a success rate of 94%, although as mentioned above, in a later review Myles et al (2017) reported less impressive results (a 60% success rate), concluding that the combination may be less effective than G-CSF alone. However, these findings are based on a limited number of case reports/series, rendering it difficult to draw firm conclusions.

Conclusions

There is no doubt that neutropenia and agranulocytosis are significant adverse effects of clozapine that require close monitoring and management. However, an excessive focus on these and a failure to adjust the monitoring requirements proportionately based on the available evidence may be causing more harm than benefit to patients. Current monitoring guidelines are overly strict and often lead to premature and unnecessary discontinuation of clozapine, the most effective antipsychotic for treatment-resistant schizophrenia, in a significant number of patients. Since alternative evidence-based treatment options for treatment-resistant schizophrenia are limited, clozapine rechallenge should be a consideration (especially in cases of mild to moderate neutropenia), as it has reported success rates of up to 80%. Unfortunately, only a small proportion of patients in the UK are currently rechallenged with clozapine following neutropenia, leaving many on medications that result in uncontrolled or only partially controlled schizophrenia. Nevertheless, there remains a lack of comprehensive evidence and guidance to support rechallenges. Prospective studies are needed to determine effective patient selection criteria and evaluate the comparative effectiveness of available management options and rechallenge protocols.

MCQ answers
1 d 2 a 3 c 4 a 5 a

Key learning points

- ‘Red’ results on blood tests might not indicate a serious pathological process.
- Most patients with a red test result would not develop agranulocytosis.
- The risk of newly emergent agranulocytosis after the first year of clozapine treatment is minimal and probably equivalent to other antipsychotic drugs.
- Late-onset neutropenia might not be related to clozapine.
- Most patients who develop clozapine-associated neutropenia can be successfully rechallenged on clozapine, with or without the support of lithium and G-CSF.
- Rechallenge with the support of lithium and G-CSF can also be considered, after careful risk–benefit analysis, following clozapine-associated agranulocytosis.

Data availability

Data availability is not applicable to this article as no new data were created or analysed in this study.

Authors contributions

S.G. and A.B. reviewed the literature and wrote the initial draft of this article. S.N. and B.S. contributed to the revision of the initial draft. All authors approved the published version.

Funding

None

Declaration of interest

S.G. has received honoraria for lectures from Viatris (a manufacturer of clozapine).

https://doi.org/10.1192/bja.2024.51 Published online by Cambridge University Press

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https://doi.org/10.1192/bja.2024.51 Published online by Cambridge University Press

MCQs

Select the single best option for each question stem

1 Agranulocytosis refers to when an absolute neutrophil count is:
a $<1.5 \times 10^9$/L
b $<2.0 \times 10^9$/L
c $<3.0 \times 10^9$/L
d $<0.5 \times 10^9$/L
e $<1.0 \times 10^9$/L.

2 According to UK clozapine monitoring requirements, 'red' results refer to a total white blood count (WBC) or absolute neutrophil count (ANC) of:
a WBC $< 3.0 \times 10^9$/L or ANC $< 1.5 \times 10^9$/L
b WBC $< 2.0 \times 10^9$/L or ANC $< 1.0 \times 10^9$/L
c WBC $< 3.5 \times 10^9$/L or ANC $< 2.0 \times 10^9$/L
d WBC $< 3.0 \times 10^9$/L or ANC $< 1.0 \times 10^9$/L
e WBC $< 2.5 \times 10^9$/L or ANC $< 1.0 \times 10^9$/L.

3 The estimated risk of agranulocytosis on clozapine is:
a 2%
b 1.5%
c 0.9%
d 0.2%
e 0.1%.

4 Rechallenge of clozapine after a neutropenic episode:
a is contraindicated but can be tried off-label
b is absolutely contraindicated and should not be attempted
c can only be tried by haematologists
d can be tried on an out-patient basis
e is reserved for tertiary care centres.

5 The risk of clozapine-associated agranulocytosis:
a is highest during the first month of clozapine initiation
b remains static throughout the treatment duration
c is not affected by co-prescription of valproate
d is high in people with benign ethnic neutropenia
e increases with the treatment duration.

https://doi.org/10.1192/bja.2024.51 Published online by Cambridge University Press