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Proposed changes to blood monitoring and prescribing requirements for clozapine

Evidence review

August 2025

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New Zealand Medicines and Medical Devices Safety Authority

Contents

Introduction

Clozapine is the only antipsychotic medicine approved for treatment-resistant schizophrenia (TRS).

Approximately one-third of people with schizophrenia meet the criteria for treatment-resistance and are eligible for clozapine treatment. A recent systematic review and meta-analysis showed a mean prevalence of treatment-resistance of 36.7%.[1]

Clozapine is an important treatment option as it has also been shown to reduce suicidal ideation and behaviour. In a multicentre international trial comparing the risk for suicidal behaviour in 956 people with schizophrenia or schizoaffective disorder at high suicide risk who were randomized to clozapine or olanzapine, suicidal behaviour was significantly lower in those treated with clozapine.[2]

Prevalence of schizophrenia in New Zealand

The prevalence of schizophrenia in New Zealand can be estimated using National Collections data. In the period 2022/2023, 18,603 people in NZ had a diagnosis of schizophrenia/psychotic disorders.[3] The estimated NZ population in June 2023 was 5,223,100, of which, 4,254,800 people were aged 15 years and older.[4] Therefore, approximately 0.44% of the population aged 15 years and older had a schizophrenia/psychotic disorder diagnosis.[3] This number aligns with a 2021 estimated age-standardised prevalence of individuals with schizophrenia of 0.4% in New Zealand, 0.3% in Finland and 0.2% in the UK.[5]

From this data, we estimate that approximately 5,500 to 6,700 people with a schizophrenia/psychotic disorder diagnosis in NZ may have TRS.

Clozapine use in New Zealand

In New Zealand, the number of people with schizophrenia/psychotic disorder diagnosis who take clozapine can be *approximated* from community pharmacy dispensing data (Table 1). Since there are around 4,200 people taking clozapine and an estimated 6,700 people with TRS, about two-thirds of those with TRS are being treated with clozapine.

Table 1: Clozapine use in New Zealand

Number of people with a schizophrenia/psychotic disorder diagnosis 2022/2023[a]			Number of people dispensed clozapine[b] 2022[a]	Percentage of people with a diagnosis taking clozapine
Female	Male	Total		
6,594	12,009	18,603	4,216	22.7%

Notes:

a. The diagnosis data is for the year 2022/2023, and the dispensing data is for 2022. We have assumed that the diagnosis data refers to the government financial year, with a duration of one year.

b. The Pharmaceutical Collection only includes community dispensed pharmaceuticals and does not include hospital dispensings, bulk and practitioner supply orders and prescriptions that were never dispensed. A person will be counted once in each category they appear. Aggregating across groups does not result in a distinct count of people.

Sources:

Diagnosis: Te Whatu Ora (Health New Zealand). 2024. *Mental Health and Addiction: Service Use web tool* 5 September 2024. URL: https://tewhatuora.shinyapps.io/mental-health-and-addiction-web-tool/ (accessed 19 November 2024).

Clozapine dispensing: Health New Zealand. 2024. *Pharmaceutical Data web tool* version 12 September 2024 (data extracted from the Pharmaceutical Collection on 23 July 2024). URL: https://tewhatuora.shinyapps.io/pharmaceutical-data-web-tool/ (accessed 19 November 2024).

Neutropenia

While clozapine treatment has significant benefits, there are also risks, including the potential to cause severe neutropenia (agranulocytosis). The risk of bacterial infection increases if the neutrophil count drops below $1.0x10^9$/L, and the risk is most significant when the count drops below $0.5x10^9$/L.[6]

However, there are individuals from certain ethnic populations who are otherwise healthy and not prone to repeated or severe infections who have neutrophil counts below $1.8x10^9$/L. This is called benign ethnic neutropenia (BEN) or benign familial neutropenia. BEN most frequently occurs in individuals of African descent, with an estimated prevalence rate ranging from 25% to 50%. Case reports suggest it also occurs in some Caucasian and Chinese populations.[7]

Cases of severe neutropenia were noted after clozapine was introduced as a treatment for schizophrenia. By the end of 1986, and before the introduction of monitoring, there had been 112 cases of severe neutropenia worldwide, with a fatality rate of 35 to 44%. The rate of severe neutropenia was estimated to be 2.6 cases per 100 patient years.[8] Since mandatory blood monitoring began, the rate of severe neutropenia has dropped to around 1%, with a fatality rate of between 0% and 6%. However, the rates of severe neutropenia in people taking clozapine are still higher than for other medicines. A study comparing clozapine with olanzapine estimated rates of neutropenia-associated hospitalisation of 2.2 (95% confidence interval [CI]: 1.3–3.9) per 1,000 person years for people taking clozapine and 0.2 (95% CI: 0.003–1.3) per 1,000 person years for people taking olanzapine.[9]

Information to support changes to clozapine blood monitoring

Opinions and proposals

European Clozapine Task Force (2025)[10]

In 2025 the European Clozapine Task Force proposed changes to clozapine monitoring (Figure 1) including:

- relaxing the blood monitoring schedule after 12 and 24 months
- only measuring absolute neutrophil count (ANC)
- changing the ANC threshold for clozapine initiation/continuation
- using an adjusted threshold for people with BEN
- only stopping clozapine treatment if the ANC falls below $1x10^9$/L (or below $0.5x10^9$/L in BEN).

Figure 1: European Clozapine Task Force proposals for clozapine blood monitoring

	Current SPC[1]	Proposals[2]
Mandatory routine blood monitoring schedule	**WBC[3] and ANC[4]** ○ baseline before initiation ○ weekly for 18 weeks after initiation ○ then monthly irrespective of treatment duration	**First 12 months** ANC ○ baseline before initiation ○ weekly for 18 weeks after initiation ○ then monthly for 34 weeks **After 12 months[5]** ○ ANC every 12 weeks if no history of leukopenia or neutropenia during the first year **After 24 months[5]** ○ yearly ANC if no history of leukopenia or neutropenia during two years
Standard thresholds for		
Initiation/continuation	○ ANC ≥ 2.0 x 10^9/L ○ WBC ≥ 3.5 x 10^9/L	○ ANC ≥ 1.5 × 10^9 per L[6]
Monitoring twice a week	○ ANC 1.5-2 x 10^9/L ○ WBC 3.0-3.5 x 109/L	○ ANC 1.0-1.5 x 10^9/L[6]
Discontinuation (red)	○ ANC <1.5x10^9/L ○ WBC <3.0x10^9/L	○ ANC < 1.0 × 10^9 per L[6]
BEN[7] adjusted thresholds for		
Initiation/continuation		○ ANC ≥ 1.0 × 10^9 per L[6]
Monitoring twice a week		○ ANC 0.5-1.0× 10^9 per L[6]
Discontinuation		○ ANC < 0.5 × 10^9 per L[6]
Monitoring schedule after clozapine interruption	interruption > 3 days and < 4 weeks ○ weekly for 6 weeks then monthly *interruption* > 4 weeks ○ weekly for 18 weeks then monthly	irrespective of the duration of interruption ○ no need to resume weekly schedule if no history of neutropenia during two cumulative years of monitoring

1. Summaries of Product Characteristics ; 2. Only Absolute Neutrophil Count criteria are given as the majority of authors (60%) are in favour of restricting mandatory monitoring to ANC based on Food and Drug Administration regulation revisions in 2015; however, no consensus could be reached among the members of the European Clozapine Task Force on this point ; 3. White Blood Cells count ; 4. Absolute Neutrophil Count ; 5. Even if the frequency of routine mandatory monitoring is reduced, ANC must be performed immediately in the event of possible symptoms of infection (e.g. fever, sore throat, mouth/throat ulcers). Additional ANC may be considered after addition of valproic acid to clozapine, especially during the initiation period. 6. Food and Drug Administration criteria; 7. Benign Ethnic Neutropenia (haematology consultation may be needed to confirm the diagnosis).

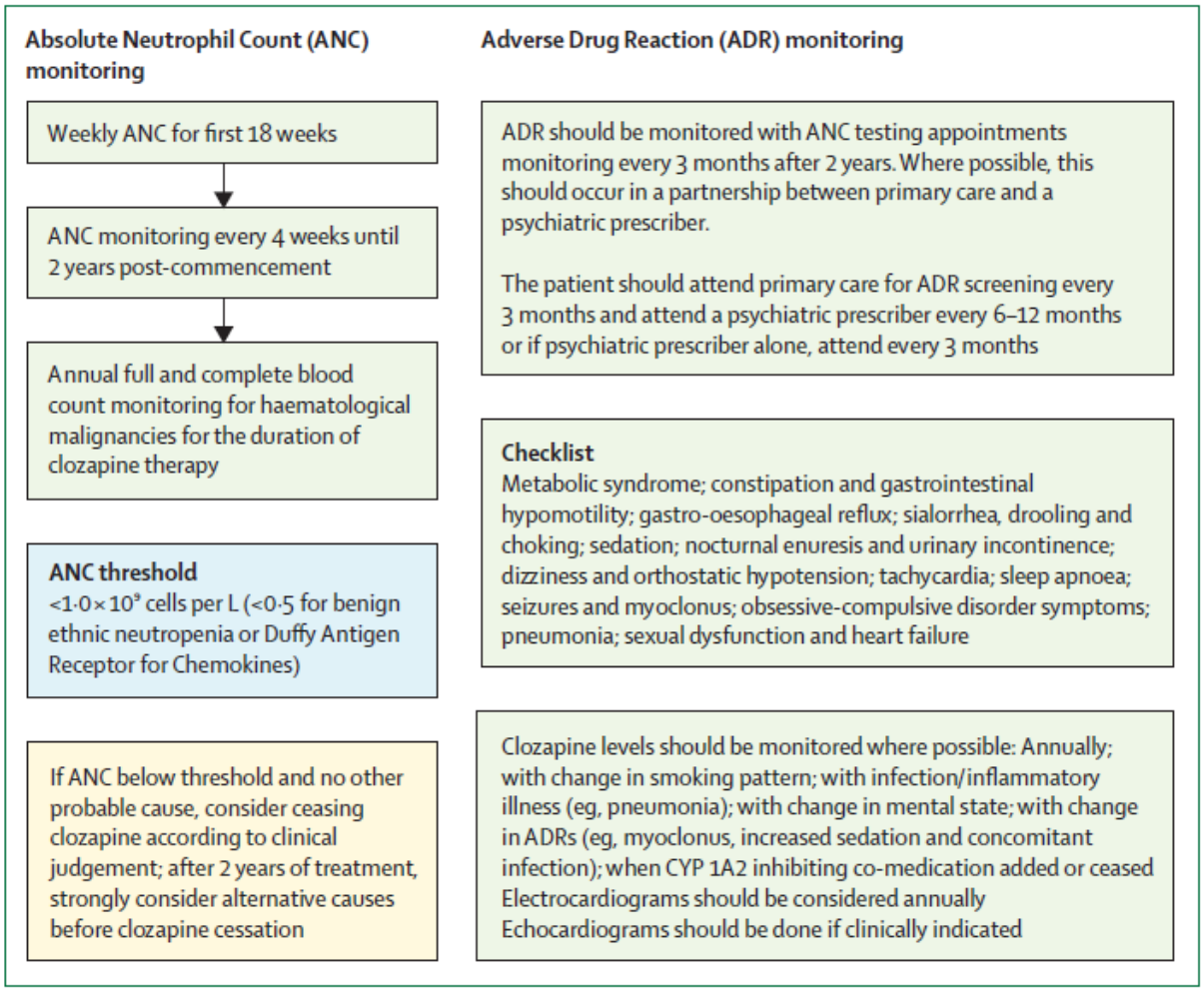
Siskind et al (2025)[11]

An international Delphi panel, with members drawn from the Treatment Response and Resistance in Psychosis working group, the International Guidelines for the Algorithmic Treatment of schizophrenia working group, and clinical academics, published consensus guidelines on clozapine monitoring. The recommendations state that:

- The ANC cessation threshold should be $1x10^9$/L (or $0.5x10^9$/L in BEN).
- ANC should be measured weekly for the first 18 weeks of treatment and then every 4 weeks up to 2 years of treatment.
- Full blood count should be measured annually thereafter for the duration of treatment.
- If ANC falls below the threshold, consider ceasing clozapine according to clinical judgement.

The consensus guidance also included recommendations for monitoring other adverse reactions to clozapine (Figure 2).

Figure 2: Clozapine monitoring algorithm



Schulte et al (2024) [12]

The authors stated that mandatory monitoring programs are unnecessary, the responsibility is on the prescribers, and that absolute compliance to the haematological regulations must be weighed against patient access issues for clozapine.

Fernandez-Egea et al (2024) [13]

The authors noted that evidence linking decreased blood monitoring requirements with increased access to clozapine has not yet been established. The reduction in blood monitoring with clozapine is based on the premise that symptoms or signs of agranulocytosis will be identified by the user and communicated to the health service. Patients with TRS may have greater cognitive impairment that may affect insight and judgement, meaning they do not recognise the signs and symptoms of infection. The risk of clozapine-induced agranulocytosis reduces significantly after 2–3 years and that current monitoring thresholds are overly stringent both in terms of ANC cut-offs and duration of monitoring. However, changes to the monitoring requirements might have an impact on the delicate and often precarious support network for those with the most severe form of schizophrenia.

Information on stopping blood monitoring

Northwood et al (2024)[14]

This retrospective cohort study reviewed data for all people enrolled in the Viatris Clozaril Patient Monitoring System across Australia and NZ between 6 June 1990 and 25 October 2022. The study included 6,086 NZ patients and 20,544 Australian patients, with 2,635,075 unique blood test results. Of the 26,630 people taking clozapine, 1,146 (4.3%) had minor neutropenia, 313 (1.2%) had serious neutropenia leading to cessation, and 223 (0.8%) had serious neutropenia unrelated to clozapine without cessation. When adjusted for patient-years of exposure, the minor neutropenia event rate was 0.90 per 100 person years. The event rate for serious neutropenia resulting in clozapine treatment cessation was 0.18 per 100 person-years of exposure.

The mean time to minor neutropenia was 46.1 weeks (interquartile range [IQR]: 10.9–191.1). The mean time to serious neutropenia due to clozapine was 17.0 weeks (IQR: 9–102.5). The mean time to serious neutropenia unrelated to clozapine was 184.9 weeks (IQR: 28.1–360.7).

Competing risks analysis showed that cumulative rates of serious neutropenia leading to cessation slowed markedly after 18 weeks, with a cumulative incidence of 0.9% at 18 weeks and 1.4% at 104 weeks. In contrast, isolated minor neutropenic events continued to occur steadily throughout the follow-up period, with a cumulative incidence of 1.7% at 18 weeks and 3.5% at 104 weeks. The weekly incidence rate for serious neutropenia leading to cessation peaked at 9 weeks (0.128%) and reduced to a rolling average weekly incidence of 0.001% at 104 weeks.

Rates of serious neutropenia leading to clozapine cessation were found to be highest in the first 18 weeks and become negligible after 2 years of clozapine exposure.

Atkin et al (1996)[15]

This was a review of 6,316 patients registered in the Clozaril Patient Monitoring Service in the UK and Ireland between 7 January 1990 and 3 July 1994. Amongst these patients, there were 182 cases of neutropenia and 48 cases of severe neutropenia. Severe neutropenia was generally experienced in the first 18 weeks (43 of the 48 cases). The earliest time-to-onset of severe neutropenia was 5 weeks, and the longest was 16 months. Two people with severe neutropenia died, both within the first 12 weeks of treatment. Therefore, the period of greatest risk for developing neutropenia, including severe neutropenia, in this review was between 6 and 18 weeks after initiating clozapine treatment.

The incidence of severe neutropenia decreased by a factor of 10 from the first year of treatment to the second year (from 0.7% to 0.07%), which was significant ($p = <0.05$). Similarly, the incidence of neutropenia significantly decreased from 2.3% in the first year of treatment to between 0.5% and 0.7% in the second and fourth years of treatment ($p = <0.005$).

Munro et al (1999)[16]

Another review of the Clozaril Patient Monitoring Service in UK and Ireland included data from 12,760 patients from January 1990 to April 1997. The cumulative incidence of neutropenia was 2.7%. The cumulative incidence of severe neutropenia was 0.73% (93 patients). The peak risk of experiencing severe neutropenia was 6 to 18 weeks after starting clozapine treatment, with an incidence of 1.27%. The earliest time-to-onset of severe neutropenia was 4 weeks.

The risk of neutropenia was 77% higher in African-Caribbean subjects than in Caucasians (hazard ratio [HR]: 1.77; 95% confidence interval [CI]: 1.208–2.583; p=0.0033). Compared with Caucasians, Asian subjects had a 2.4 times higher risk of developing severe neutropenia (HR: 2.388; 95% CI: 1.098–5.194; p=0.03).

Lahdelma et al (2012)[17]

A review of Finnish cases of clozapine-induced severe neutropenia included reports to the Finnish National Agency for Medicines from 17 December 1982 to 31 December 2007. There were 163 cases of severe neutropenia, with a mean duration of clozapine treatment to neutropenia onset of 332 days/47 weeks (median 59 days/8 weeks). Of the 163 cases, 123 occurred within 5 months of starting clozapine and 130 cases within 12 months. It was reported that 60 of the 163 patients had received medicines reported to be associated with neutropenia during the week prior to neutropenia occurring.

Information on the presence or absence of infection was available for a total of 111/119 patients who experienced severe neutropenia within 18 weeks of starting clozapine treatment. Of these 111 people, 80.2% had a concomitant infection, indicating that the neutropenia had resulted in clinical effects. Five patients died, all of whom had concurrent infections and 4 of the 5 patients were taking other medicines that can also cause severe neutropenia.

Rubio et al (2024) [18]

This review used the Finnish Care Register for Health Care and the Prescription Register to identify 61,769 people diagnosed with schizophrenia or schizoaffective disorder between 1972 and 2014, and developed a Kaplan–Meier model of time to diagnosis of agranulocytosis during clozapine versus non-clozapine treatment over a 22-year observation period (1996 to 2017). There were 14,037 people taking clozapine and 47,732 people taking non-clozapine antipsychotics. The median duration of uninterrupted antipsychotic treatment episodes was 398 days (IQR: 95–1,193) for clozapine and 579 days (IQR: 151-1,607) for non-clozapine antipsychotics. Across the 22 years of follow-up, 398 cases of severe neutropenia were registered. The 398 cases consisted of 231 people taking clozapine treatment and 167 taking non-clozapine antipsychotics. The incidence of severe neutropenia was 17.33 events per 10,000 person years of clozapine treatment and 2.10 events per 10,000 person years of non-clozapine treatment.

From the 398 people experiencing severe neutropenia, 7 (2%) died within 30 days of diagnosis (4 people taking clozapine and 3 people taking non-clozapine antipsychotics). The fatality rate was 2.81 per 10,000 individuals exposed to clozapine and 0.63 per 10,000 individuals exposed to non-clozapine antipsychotics.

There was an elevated risk of severe neutropenia within the initial 6 months of clozapine treatment. The risk decreased over time for those taking clozapine but remained persistently elevated throughout follow-up (adjusted odds ratio [aOR]: 5.22; 95% CI: 1.78–15.25 for treatment duration of ≥54 months). For people taking non-clozapine antipsychotics, the risk of neutropenia became non-significant (aOR: 0.68; 95% CI: 0.21–2.18) after 6 months.

This study showed that after 3 years, the risk of severe neutropenia for people taking clozapine is comparable to the risk associated with taking non-clozapine antipsychotics in the initial 6 months of treatment.

Thai et al (2024)[19]

This retrospective chart review of patients at the Royal Ottawa Mental Health Centre investigated the impact of reduced blood monitoring frequency during the COVID-19 pandemic. The authors concluded that for a patient on clozapine for over 1 year with no history of an ANC <2.0x10^9/L, blood monitoring can be less frequent than the standard monthly protocol without increasing the risk of severe neutropenia.

Li et al (2020)[20]

This meta-analysis of 36 studies (260,948 patients) conducted between 1984 and 2018 examined the prevalence of severe neutropenia in people taking clozapine. The prevalence of severe neutropenia ranged from 0.1% to 2.7% in the 36 studies, with a pooled prevalence of 0.4% (95% CI: 0.3–0.6%).

In the studies that reported on deaths caused by clozapine-associated severe neutropenia, 33 fatalities were noted, and the pooled prevalence of death was 0.05% (95% CI: 0.03–0.09%). Among people with severe neutropenia, the pooled prevalence of death was 10.0% (95% CI 6.1–15.8%). The mean time to onset of severe neutropenia was 9.8 weeks in the studies which reported this information. There were 4 studies which reported that 53.7–87.5% of patients experienced agranulocytosis in the first 18 weeks of clozapine treatment.

While there are limitations to the information reviewed above, Medsafe considers that the evidence is sufficient to warrant stopping blood monitoring for people taking clozapine after a period of time. However, the evidence reviewed suggests different time periods at which the risk of severe neutropenia for people taking clozapine decreases to levels comparable to other medicines. Therefore, we are consulting on when monitoring can stop and who should be eligible to stop monitoring.

Information on monitoring thresholds

Oloyede et al (2022)[21]

The UK runs a database to help prevent inappropriate rechallenge with clozapine, called the UK Central Non-Rechallenge Database (CNRD). Patients on clozapine are placed on this database if their haematological parameters fall below particular thresholds, meaning they must discontinue clozapine indefinitely. Under exceptional circumstances, patients can be rechallenged on clozapine under an off-licence agreement. In 2015, the United States Food and Drug Administration (FDA) changed the monitoring thresholds for treatment interruption. The absolute neutrophil count (ANC) leading to treatment interruption was lowered from less than 1.5 x 10^9/L to less than 1.0 x 10^9/L, and platelet and white blood cell (WBC) count monitoring were ceased.

The study authors used the CNRD to investigate a similar policy change on clozapine use in the UK. The study also looked at patients who had been rechallenged with clozapine after CNRD registration, including the number of patients who had a further neutropenia. Between 2 May 2002 and 1 March 2021, there were 3,731 patients registered on the CNRD and included in the study.

The median WBC at CNRD registration was 2.9x10^9/L (IQR 2.5–3.6) and absolute neutrophil count (ANC) was 1.4x10^9/L (IQR 1.1–1.5). A total of 341 people (9%) on the CNRD had an episode of severe neutropenia at registration.

Applying the FDA thresholds, only 566 (15%) of 3,731 people in the database would have qualified for clozapine discontinuation. A total of 470 people (13%) would have been able to continue clozapine with routine monitoring, 2,096 people (56%) would have been able to continue clozapine but would have required haematological monitoring 3 times a week and 599 people (16%) would have required clozapine interruption with daily haematological monitoring.

There were 438 people on the CRND solely because they had low WBC, even though their ANC values were above the threshold to continue treatment. These 438 patients would have been able to continue clozapine treatment if only ANC thresholds were used.

While this information does not prove that the FDA thresholds provide adequate protection against severe neutropenia, it does highlight that a significant number of people have their treatment stopped, probably unnecessarily. Medsafe is consulting on using only ANC monitoring and adopting the FDA thresholds.

Including BEN criteria

Wu et al (2024)[22]

This was retrospective chart review of 41 patients treated under a modified haematological guideline for BEN at a single centre in Canada. The authors examined the number of haematological alerts before and after implementation of BEN guidelines. Prior to BEN identification, there were 1,041 haematological results reported as yellow and 323 reported as red. Following implementation of the guidelines, 9 yellow and 7 red results were reported.

Oloyede et al (2021)[23]

This was an observational, retrospective analysis of people taking clozapine in 2 large mental health trusts in the UK that investigated BEN prevalence and identification. The study included 2,020 patients, of which, 574 were black. BEN criteria were applied to 100 black patients and 11 non-black patients. The UK Central Non-Rechallenge Database (CNRD) was screened for black patients who had not been monitored under BEN criteria prior to CNRD registration. Potential BEN patients were identified by haematologists. For those who were then classified as BEN, the BEN monitoring parameters were applied to previous haematological results to determine whether CNRD registration would have occurred, had they been certified as BEN initially. A total of 18/26 black patients had available haematological data for retrospective BEN classification, of which, 8 cases were identified as BEN and 1 case was undetermined. For the 8 cases that were classified as BEN, none would have met the CNRD criteria if monitored under BEN criteria at clozapine initiation.

While this information does not prove that the BEN thresholds provide adequate protection against severe neutropenia, it does highlight that a significant number of people have their treatment stopped, probably unnecessarily. Medsafe is consulting on including BEN thresholds.

Managing 'Red' blood test results and clozapine rechallenge/restart

Not all cases of severe neutropenia occurring in patients taking clozapine are due to clozapine. Currently, clozapine must be stopped and the patient not re-exposed after a red result. However, there are risks to sudden discontinuation of clozapine and there is still a need for ongoing treatment. Reviews of CPMS data (and its international equivalents) show that clozapine treatment was not responsible for all of the reported neutropenias.

Oloyede et al, (2022)[21]

This review of patients included in the UK Central Non-Rechallenge Database (CNRD) found that, of the 519 patients who were rechallenged on clozapine after CNRD registration, 100 (19%) had neutropenia again and 419 (81%) were successfully rechallenged. These findings indicate that the majority of people may successfully retry clozapine after a 'red' result.

Northwood et al, (2024)[14]

This retrospective cohort study of people enrolled in the Viatris CPMS across Australia and NZ also looked at rechallenge with clozapine.[13] Competing risks regression for events according to previous clozapine exposure showed that for patients re-trialling clozapine who had not previously had a serious neutropenic event, the incidence of any neutropenic event was much lower than in patients with no previous clozapine exposure, particularly for serious neutropenic events with cessation (HR: 0.53; 95% CI: 0.22–0.68, $p<0.0001$). Therefore, for patients retrialling clozapine after treatment interruption, haematological monitoring might not need to recommence if there has been a cumulative 2 years of unremarkable monitoring.

Rubio et al (2024)[18]

This analysis of Finnish data identified 231 people who developed severe neutropenia whilst taking clozapine, including 76 (33%) who were rechallenged with a second trial of clozapine. Of the 76 rechallenged people, 11 (14%) developed another agranulocytosis event.

The available information supports a review to determine the cause of severe neutropenia, as clozapine may not need to be stopped. Therefore, Medsafe is consulting on managing red results and on restarting clozapine treatment.

Point-of-Care testing

The utility of a point-of-care finger prick method for blood monitoring in people taking clozapine patients has been investigated.

Atkins et al (2023)[24]

In this study, 226 people taking clozapine, who were having venous blood samples for haematological monitoring, also provided a finger prick capillary blood sample. The PixCell HemoScreen POCT analyser was used to test both the capillary and venous samples, and the venous sample was also tested using a standard laboratory method. The study found strong correlations between the result from the standard venous methods and the PCOT capillary and venous assays for WBC and neutrophils and eosinophils.

Point-of-Care test devices are not regulated in New Zealand making it difficult for Medsafe to recommend their use. However, some brands have been accepted in other countries and we are therefore consulting on whether they could be used here and, if so, whether this should be limited to particular brands.

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