# Potential impact of a relaxation of the criteria for entry to the UK Clozapine Central Non-Rechallenge Database: a retrospective cohort study using anonymised data from all three clozapine monitoring services in the UK

**Authors**

Ebenezer Oloyede\*1,2

Eromona Whiskey\*1,2,4,5

Cecilia Casetta2,4

Olubanke Dzahini1,3

Danielle Dunnett2

Fiona Gaughran2,4

Sukhi Shergill2

Philip McGuire2

James H MacCabe**†**2,4,5

David Taylor**†**1,3

\*Joint first authors, **†**Joint last authors

**Affiliations**

1Pharmacy Department, South London and Maudsley NHS Foundation Trust, London, UK

2Department of Psychosis Studies, Institute of Psychiatry, Psychology & Neuroscience, King’s College London, London, UK

3Institute of Pharmaceutical Science, King’s College, London 5th Floor, Franklin-Wilkins Building 150 Stamford Street, London SE1 9NH

4National Psychosis Service, South London and Maudsley NHS Foundation Trust, London, UK

5NIHR Biomedical Research Centre for Mental Health South London and Maudsley NHS, London, UK

**Corresponding author**

*Ebenezer Oloyede*

*Pharmacy Department, South London and Maudsley NHS Foundation Trust, London, UK*

*Tel: +44 (0)20 322886288*

*Email:* *Ebenezer.oloyede@slam.nhs.uk*

**Declaration of Interest Statement**

All authors declare no conflict of interest.

**Funding Statement**

The study did not receive direct funding. JHM, FG, PM are part-funded by the **National Institute for Health Research (NIHR) Maudsley Biomedical Research Centre at South London and Maudsley NHS Foundation Trust and King’s College London**. The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health and Social Care

**Acknowledgements**

We would like to thank Britannia Pharmaceuticals Limited, Leyden Delta B.V and Viatris Inc. for allowing access to anonymised data and their (non-financial) support for this study.

**Author Contributions**

## Abstract

Background: Clozapine is uniquely effective in treatment resistant psychosis. In the United Kingdom (UK), patients must discontinue clozapine indefinitely if placed on the Central Non-Rechallenge Database (CNRD) after their haematological parameters fall below certain thresholds. These patients often suffer severe and enduring deterioration in their mental health as a result of stopping clozapine treatment. In the United States (US) in 2015, the haematological monitoring guidelines were relaxed, allowing greater flexibility for clozapine maintenance and rechallenging after suspected neutropenia. Our objective was to investigate the implications of a similar policy change on clozapine utilisation in the UK.

Methods: This was an observational, retrospective analysis of patients registered on the CNRD in the UK. First, we determined the proportion of patients placed on the CNRD under the UK who would have had to discontinue clozapine treatment under the US Food and Drug Administration (FDA) criteria. Second, we compared the haematological characteristics of patients who did or did not meet FDA criteria for discontinuing clozapine, including the time to CNRD registration from clozapine initiation and the proportion of cases of agranulocytosis. Third, we investigated the success rates of clozapine rechallenge after being placed on the CNRD, again comparing the groups who met or did not meet FDA criteria.

Results:3371 patients were placed on CNRD, of whom only 566 (15%) met the equivalent criteria for clozapine discontinuation under the FDA guidelines. Data on 519 rechallenged CNRD patients were examined; 416 (80%) rechallenges were successful. Clozapine rechallenge success rates were broadly similar to those who did not meet and those who did meet the US CNRD registration criteria (81% vs 78%).

Conclusions:These findings suggest that implementing the revised FDA’s monitoring criteria in the UK would significantly reduce clozapine discontinuation for haematological reasons, which would greatly improve the mental health outcomes of these patients, without having a major impact on their physical health. The evidence suggests an urgent need to revise the UK clozapine monitoring guidelines in a way which more evenly balances mental and physical and health risks to improve outcomes in treatment-resistant schizophrenia.

Keywords:Clozapine, CNRD, Benign Ethnic Neutropenia, Agranulocytosis

Word count:

## Introduction

Agranulocytosis is defined as the absence of granulocytes (i.e. neutrophils, basophils, and eosinophils), but the term is often used clinically to refer to severe neutropenia (i.e., an absolute neutrophil count [ANC] of <0·5x109/L).1 Psychotropic-induced agranulocytosis has been reported in literature as early as the 1950’s, attributed to administering the ‘first-generation’ antipsychotic chlorpromazine.2 Despite such cases preceding clozapine’s development, clozapine is probably most often associated with rare cases of agranulocytosis or neutropenia.3 This stems from unfortunate circumstances in Finland during clozapine’s relatively rigorous pre-marketing development, where fatalities occurred that were ultimately linked to clozapine-induced blood dyscrasias.4 Such events prompted stringent pharmacovigilance monitoring in most countries when the drug was reintroduced in 1989.5 However, of perhaps greater significance is the impact these events have had on clozapine’s reputation as having a perceived higher risk of causing this adverse haematological event. This is especially compared to other antipsychotics, despite accumulating evidence to the contrary.6-10 To date, this has contributed significantly to clozapine’s underutilisation.11 More recently, literature has emerged highlighting that many cases of neutropenia on clozapine are unrelated to clozapine use. Clozapine use is associated solely with the much rarer life-threatening agranulocytosis (LTA), and monitoring schemes have been very successful in reducing the incidence of LTA to almost zero. However, this has come at the cost of a very large number of false positives, whereby patients with neutropenia that is not severe, or not related to clozapine, having to discontinue treatment, often with devastating and lifelong consequences to their mental health. We therefore sought to explore whether monitoring schemes could be revised such that true clozapine-induced LTA would still be identified, but with fewer false alarms.

The current UK guidelines mandate that if an individual taking clozapine has two consecutive neutrophil counts of < 1.5x109/L or WBC < 3.0x109/L, clozapine must be stopped indefinitely and the patient must be registered in the clozapine non rechallenge database (CNRD), a mandatory database that safeguards patients from being inadvertently re-exposed to clozapine treatment after a suspected haematological reaction.1 Notably, several other countries around the world mandate equivalent haematological thresholds for clozapine discontinuation.12 Many patients, on discontinuing clozapine, suffer a severe relapse of their psychotic disorder, which is not alleviated by other antipsychotics.13 In our view, the monitoring requirements should aim to balance the haematological risks of neutropenia against the mental health risks of discontinuing clozapine in treatment resistant psychosis. However it appears that the haematological monitoring requirements prioritise haematological risk, but have insufficient regard for psychiatric risk. 12There has been considerable interest amongst clinicians and national regulatory bodies in how to address this.14-16 In an important development, the United States (US) Food and Drug Administration (FDA) relaxed ANC cut-offs for clozapine cessation in 2015 compared to the UK and removed white cell count (WCC) monitoring requirements, allowing more patients to be maintained on this uniquely effective treatment.1

Our previous retrospective study, based in an Inner London mental health trust, suggested that implementing the updated United States (US) Food and Drug Administration (FDA) haematological monitoring criteria in the United Kingdom (UK) could reduce clozapine discontinuation and registration on the Central Non-Rechallenge Database (CNRD). In this study, we attempted to investigate this further at a national level, using data from the UK’s CNRD. While preliminary, this evidence suggests the need to review the UK’s clozapine monitoring guidelines to improve outcomes in Treatment Resistant Schizophrenia (TRS).

## Methods

To assess the potential impact that implementing the US FDA guidelines would have on clozapine continuation in the UK, we determined the proportion of patients placed on the CNRD under the UK who would have had to discontinue clozapine treatment under the US Food and Drug Administration (FDA) criteria. Second, we compared the haematological characteristics of patients who did or did not meet FDA criteria for discontinuing clozapine, including the time to CNRD registration from clozapine initiation and the proportion of cases of agranulocytosis. Third, we investigated the success rates of clozapine rechallenge after being placed on the CNRD, again comparing the groups who met or did not meet FDA criteria.

### Data Source and Ethical Approval

To accomplish these aims we analysed data from the UK CNRD. Non-identifiable data was provided by the three manufacturers of clozapine and associated haematological monitoring services in the UK; Clozaril® (Mylan) monitored by Clozaril Patient Monitoring Service (CPMS)17, Denzapine® (Britannia Pharmaceuticals Limited) monitored by Denzapine Monitoring System (DMS)18, and Zaponex® (Leyden Delta BV) monitored by Zaponex Treatment Access System (ZTAS).19 Data was provided from 1st January 2013 till 1st March 2021, to exclude patients who met previous CNRD criteria (i.e. a single red result).1

### Definition of Neutropenia, BEN and Clozapine Rechallenge

In the UK, clozapine monitoring is regulated by the MHRA using the criteria set out in Box 1, which includes lower haematological cut-off points for patients with the haematological phenotype benign ethnic neutropenia (BEN) since 2002.20 In this study, haematological events were defined according to the MHRA guidelines for absolute neutrophil counts (ANC) and white cell counts (WCC) values that required clozapine treatment interruption or discontinuation (Box 1). Under current recommendations, two consecutive red results are classified as a ‘confirmed’ red result. In this event, clozapine must be stopped and the relevant clozapine monitoring service submits the patient’s details to the CNRD. After this, the patient is classified as ‘non-rechallengeable’, meaning re-exposure to clozapine is not permitted except off-licence. There are rare cases where patients can be placed on the CNRD for other reasons, such as the absence of follow-up haematological monitoring after an initial red result, fully described elsewhere.1 However, such cases were not included in this study.

Clozapine manufacturers allow for clozapine re-exposure following CNRD registration under an off-licence agreement.1 The decision for clozapine rechallenge is undertaken individually and must be agreed upon by a multidisciplinary team, often in close liaison with a consultant haematologist. The final decision is driven by a comprehensive assessment, including extensive information gathered from various sources, such as haematological profiling, blood films, and haematinics.

|  |  |  |
| --- | --- | --- |
| **Current UK MHRA Guidelines** |  | **Current US FDA Guidelines** |
| **Status**  | **General population****Criteria** | **BEN criteria** | **Action** |  | **Status**  | **General population criteria** | **BEN criteria** | **Action** |
| ***Green*** |  |  |  |  | ***Normal range*** |  |  |  |
| WCC ANC | ≥ 3·5x109/L≥ 2·0x109/L | ≥ 3·0x109/L≥ 1·5x109/L | Continue clozapine |  | WCC ANC | Not mandatory≥ 1·5x109/L | Not mandatory≥ 1·0x109/L | Continue clozapine |
| ***Amber*** |  |  |  |  | ***Mild Neutropenia*** |  |  |  |
| WCC ANC | ≥ 3·0 & <3·5x109/L≥1·5 and <2·0x109/L | ≥2·5 and < 3·0x109/L≥ 1·0 and < 1·5x109/L | Continue clozapine with increased monitoring frequency (twice a week) until green result is obtained.  |  | WCC ANC | Not mandatory≥ 1·0 and < 1·5x109/L | Not mandatory≥ 0·5 and < 1·0x109/L | General criteria: Continue clozapine with increased monitoring frequency (three times a week) until ANC returns to normal range. BEN: Continue clozapine  |
| ***Red*** |  |  |  |  | ***Moderate - Severe Neutropenia*** |  |  |  |
| WCC ANC | <3·0x109/L<1·5x109/L | <2·5x109/L< 1·0x109/L | Stop clozapine (interruption) and sample blood daily, monitoring for infection. Patient not re-exposed to clozapine until there have been two separate green results on 2 consecutive days. Two consecutive red results are classified as a ‘confirmed’ red result, where a patient is registered on the CNRD. |  | WCC ANC | Not mandatory< 1·0x109/L | Not mandatory< 0·5x109/L | Haematology consultation recommended, stop treatment (interruption) for suspected clozapine-induced neutropenia. Moderate Neutropenia: Sample blood daily. Resume treatment once ANC normalises to ≥1·0x109/L aSevere Neutropenia: Sample blood daily. Do not rechallenge unless prescriber determines` benefits outweigh risks.  |
| aThe prescriber must provide a "treatment rationale" in the national monitoring system REMS but there is no mandatory discontinuation or mandatory non-rechallenge category.ANC: Absolute Neutrophil Count BEN: Benign Ethnic Neutropenia UK: United Kingdom FDA: Food and Drug Administration MHRA: Medicines and Healthcare Products Regulatory Agency US: REMS: Clozapine Risk Evaluation and Mitigation Strategy United States WCC: White Cell Counts |

**Box** **1.** Comparison of UK Medicines and Healthcare Products Regulatory Agency (MHRA) guidelines for clozapine monitoring compared to US FDA guidelines

### Study Sample

The study sample included all patients on the 1st March 2021 registered on the CNRD under the current criteria. The initial and confirmatory ANC and WCC values that resulted in CNRD registration were provided by clozapine registries. Available demographic data, including ethnicity, were provided by clozapine registries. The number of patients who developed agranulocytosis was identified. Agranulocytosis was defined as ANC values <0·5x109/L while treated with clozapine.1 The flowchart in Fig.1 shows the sample selection.

**Figure 1.** Study flowchart

**Proportion of Patients that would have Discontinued Clozapine under US FDA Criteria**

The US FDA monitoring parameters (Box 1) were applied to patients ever registered on the CNRD. In cases where BEN had been diagnosed by a haematologist (N=72), the FDA BEN MHRA criteria were applied.

### Haematological Outcomes of Patients Placed on CNRD

The time to CNRD registration from clozapine initiation and the number of agranulocytosis cases in our cohort were identified. The time to CNRD was presented using a Kaplan–Meier plot.

### Haematological outcomes of Clozapine Rechallenge

CPMS provided a dataset of unique patients rechallenged on clozapine after CNRD registration. For patients with more than one rechallenge attempt, only the first event was included in the primary analysis. The number of patients who had a further neutropenia meeting CNRD criteria following rechallenge was also documented. FDA parameters were applied to the haematological results for these patients to determine if clozapine would have been discontinued under FDA guidelines. Successful rechallenge was defined as no recurrence of CNRD registration. Success rates between those who did not meet CNRD criteria under the US FDA monitoring criteria on first exposure and those who did were compared.

### Statistical analysis

Statistical analysis was carried out using Stata, version 15. The percentage of patients who would not have met CNRD criteria and clozapine interruption under the revised US guidelines were calculated. Kaplan-Meier survival curves were used to graphically present the time to CNRD registration from the clozapine start date.

## Results

3731 unique patients had been registered on the CNRD and were included in this study (Fig 1). Clinical and demographic characteristics of the study population are shown in Table 1.

|  |  |  |  |
| --- | --- | --- | --- |
| Characteristic | Rechallenged(n= 519) | Not Rechallenged(n= 3212) | Total(n= 3731) |
| Female gender (%) | 192 (37) | 1228 (38) | 1420 (38) |
| Age at CNRD registration (years ± SD) | 38 (13) | 48 (14) | 47 (15) |
| BEN diagnosis (%) | 2 (0.4) | 70 (2.2) | 72 (1.9) |
| Mean time to BEN diagnosis from first clozapine initiation (years ± SD)a | MD | 1.2 (1.8) | 1.2 (1.8) |
| Median time to BEN diagnosis from first clozapine initiation (years, IQR)a | MD | 0 (5) | 0 (2) |
| Diagnosis (%) |  |  |  |
| F20 Paranoid Schizophrenia | 519 (100) | 3026 (94) | 3545 (95) |
| F25 Schizoaffective disorder | 0 (0) | 23 (0.7) | 23 (0.6) |
| F31 Bipolar disorder | 0 (0) | 11 (0.3) | 11 (0.3) |
| Other | 0 (0) | 152 (5) | 152 (4.1) |
| Ethnicity (%) |  |  |  |
| White | 451 (86) | 2638 (82) | 3089 (83) |
| Black | 23 (4) | 337 (10) | 360 (10) |
| Asian | 33 (6) | 157 (5) | 190 (5) |
| Other | 12 (2) | 80 (2) | 92 (2) |
| Cases of agranulocytosis | 19 (4) | 322 (10) | 341 (9) |
| Mean time to CNRD registration from clozapine initiation (years ± SD) | 4.1 (4.2) | 3.0 (3.7) | 3.2 (3.8) |
| Median time to CNRD registration from clozapine initiation (years, IQR) | 2.6 (5.7) | 1.4 (4.5) | 1.6 (4.6) |
| MD; Missing Data |

**Table 1.** Socio-demographic and clinical characteristics of patients registered on the CNRD

### Comparison of Patients with Haematological Events during Clozapine Treatment under UK MHRA and US FDA Guidelines

Table 2 outlines and compares the distribution of patients who would have met the criteria for clozapine treatment interruption or discontinuation under current MHRA guidelines and their treatment status if FDA criteria were applied. Of the 3731 patients who had haematological events that qualified for CNRD registration and treatment discontinuation under current MHRA guidelines, 566 (15%) patients would have qualified for CNRD registration and clozapine discontinuation under FDA guidelines; 2096 (56%) patients would have required three times a week haematological monitoring; and 599 (16%) patients would have required clozapine interruption with daily haematological monitoring.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Guideline | Continue clozapine with routine monitoring  | Twice a week monitoring | Daily monitoring and clozapine interruption | Clozapine discontinuation |
| FDA (US) | 470 (13)a | 2096 (56) | 599 (16) | 566 (15) |
| a438 patients (12%) due to no WCC monitoring under US FDA criteria. US: United States FDA: Food and Drug Administration  |

**Table 2.** Clozapine monitoring requirements for patients on the CNRD under US FDA criteria.

### Time to CNRD Registration

Figure 2 shows the Kaplan-Meier curve to CNRD registration from clozapine initiation. The median time to CNRD registration from clozapine initiation was 1.6 (IQR 0.2-4.9) years.

 

**Figure 2.** Kaplan Meier for the time to CNRD registration from clozapine initiation.

### Outcomes of Patients Rechallenged on Clozapine

Of the 519 patients rechallenged on clozapine after CNRD registration, 100 (19%) were placed back on the CNRD following rechallenge. Only 28 (4%) of these patients would have had to discontinue clozapine under US FDA criteria. BEN was identified in 2 (0.4%) patients. Of these patients, one was black, and one was Caucasian.

|  |  |  |  |
| --- | --- | --- | --- |
| Characteristic | CNRD under FDA criteria(n=46) | Not CNRD under FDA criteria (n=473) | Total(n=519) |
| Female gender (%) | 18 (39) | 174 (37) | 192 (37) |
| Age at CNRD registration (years ± SD) | 39 (12) | 38 (13) | 38 (13) |
| BEN diagnosis (%) | 0 (0) | 2 (0.4) | 2 (0.4) |
| Diagnosis  |  |  |  |
| F20 Paranoid Schizophrenia | 46 (100) | 473 (100) | 519 (100) |
| F25 Schizoaffective disorder | 0 (0) | 0 (0) | 0 (0) |
| F31 Bipolar disorder | 0 (0) | 0 (0) | 0 (0) |
| Other | 0 (0) | 0 (0) | 0 (0) |
| Ethnicity |  |  |  |
| White | 36 (78) | 415 (88) | 451 (86) |
| Black | 2 (4) | 21 (4) | 23 (4) |
| Asian | 6 (13) | 27 (6) | 33 (6) |
| Other | 2 (4) | 9 (2) | 12 (2) |
| Cases of agranulocytosis | 17 (37) | 2 (0.4) | 19 (4) |
| Mean time to CNRD registration from clozapine initiation (years ± SD) | 5.1 (5) | 4.0 (4.1) | 4.1 (4.2) |
| Median time to CNRD registration from clozapine initiation (years, IQR) | 3.8 (7.6) | 2.6 (5.3) | 2.6 (5.7) |
| Mean rechallenge duration (years ± SD) | 3.9 (3.6) | 4.8 (4.7) | 3.8 (4.6) |
| Median rechallenge duration (years, IQR) | 3.3 (4.8) | 2.6 (6.6) | 1.8 (6.1) |
| Number of patients placed back on CNRD after rechallenge (%) | 10 (22) | 90 (19) | 100 (19) |
| Number of patients who would have been placed back on CNRD after rechallenge under FDA criteria (%) | 4 (9) | 24 (5) | 28 (4) |

**Table 3.** Socio-demographic and clinical characteristics of patients rechallenged on clozapine

**Discussion**

***Our findings***

To the best of our knowledge, this is the largest study evaluating the potential impact of changes to the clozapine monitoring guidelines of the UK MHRA on treatment access and maintenance. In this national sample of patients registered on the UK CNRD, we found that only 566 (15%) would have had to discontinue clozapine immediately under US FDA criteria. A further 16% would have been required to suspend clozapine treatment with increased monitoring, and resume treatment when their neutrophil count was above 1.0x109/L. 2096 (56%) patients would have been allowed to continue clozapine with increased monitoring under FDA criteria, and the remaining 470 (13%) would have been able to continue clozapine under standard monitoring. Among patients who were rechallenged on clozapine after being placed on the CNRD, only 100 (19%) suffered a further neutropenia and were placed back on the database.

***Comparison with other studies***

A retrospective US cohort study reported that five (3%) of 246 patients with TRS would have qualified for treatment interruption during the first year of clozapine treatment under the previous US guidelines (equivalent to the current UK and European guidelines) but only one patient (0.7%) qualified under the revised FDA recommendations.21. To date, it remains unclear whether these changes have contributed to an increase in clozapine prescriptions in the US or, as important, compromised patient safety.14,22-24 Nevertheless, the current evidence underscores the potential impact revisions of clozapine haematological regulations can have on improving treatment access.25

***Neutropenia Timescale, Agranulocytosis Episodes and BEN***

In our study, CNRD registration was recorded at a median of 1.6 years of treatment. This situation contrasts with widely accepted reports of the risk of clozapine-induced agranulocytosis being highest between weeks 6 and 18 of the first six months of clozapine treatment.26,27 While there are rare cases of late-onset agranulocytosis reported in the literature, it is highly likely that many cases of CNRD registration in our cohort were unrelated to clozapine use.28-30 Such findings are consistent with our previous study where CNRD registration was recorded at a median of 2 years of treatment.1

From a clinical standpoint, identifying true LTA and differentiating this from cases of transient neutropenia, is imperative, since the risk of severe infection is elevated only in LTA.31 A recent case series showed that true clozapine-induced LTA, while rare, is characterised by an acute and precipitous drop in neutrophil counts that presents an immediate threat to life. However, the intensity of monitoring inevitably also identifies clinically insignificant, non-pathological episodes of neutropenia that occur coincidentally to the use of clozapine, and these often result in clozapine cessation.32 Consistent with this view, a study from Iceland, which then had no monitoring system, identified several patients who recorded ANC results that in other countries would have required clozapine cessation, but almost all continued with no sequelae.33 From our data, only 341 (9%) of patients on the CNRD had an episode of agranulocytosis during clozapine treatment. This occurred after a median of 3 months from clozapine initiation (results not shown) compared to 22 months for mild neutropenia, supporting the view that the two are clinically distinct.34

In our study, 438 patients (12%) were registered onto the CNRD solely because of low WCC, even when ANC values were above the threshold to continue treatment. Under revised FDA guidelines, these patients would not have discontinued because WCC is not assessed based on clinical and scientific knowledge of immunology.21 In our study, 3% of patients were placed on the CNRD after recording at least one baseline red result. By definition, a red result at baseline cannot have been caused by clozapine treatment. One possible cause is benign ethnic neutropenia (BEN).26 Our previous study exploring BEN shows that early identification of BEN is essential to prevent premature discontinuation of clozapine.20 Notwithstanding, this has proven challenging in clinical practice because of lack of formal guidance on its identification in those receiving clozapine treatment - better pathways should therefore be implemented to ensure all such patients are assessed for differentials such as BEN.

***Clozapine Rechallenge***

Clinicians undoubtedly face a difficult task when deciding patient suitability for clozapine rechallenge after a neutropenia, compounded by considerable discordance between success rates in the literature.35-42 In parallel to our previous study, we attempted to investigate whether a change in clozapine blood monitoring parameters would compromise patient safety by investigating those who were rechallenged. We identified 519 patients who were rechallenged on clozapine following CNRD registration. Notably, 473 patients (91%) did not meet the US FDA monitoring criteria. Of course, an unknown proportion of these patients may have gone on to meet FDA criteria, had they continued on clozapine. Of the 519 patients rechallenged, 100 patients (19%) had to stop clozapine treatment due to a recurrence of neutropenia, and success rates were broadly similar in patients who did not versus those who did meet the US FDA monitoring criteria (81% vs 78%). If we assume that patients with true clozapine-induced LTA will progress to more severe agranulocytosis and thus meet FDA criteria, then these results suggest that discontinuing clozapine treatment at an earlier stage (where only the CNRD criteria are met) would not have a significant impact on the success rates of rechallenge, but would have led to more patients discontinuing clozapine. The mean time on treatment was four years, which is comparable to data from population studies and is believed to be beyond the highest risk period for LTA.43

An important challenge ahead is characterising which patients would benefit most from clozapine rechallenge. While beyond the scope of this study, one may speculate that patient selection for clozapine rechallenge was somewhat influenced by clinical and demographic factors, as shown in table 1. Interestingly, in our cohort, patients who were rechallenged on clozapine were younger, less likely to be black and experienced CNRD registration later. Previous studies have demonstrated age and agranulocytosis as risk factors for clozapine-induced dyscrasia.35,36 In addition, successful rechallenge has been associated with a shorter duration of first exposure to clozapine – possibly due to intrinsically low neutrophils as opposed to clozapine-induced dyscrasia.35 Consistently, undiagnosed BEN and more stringent thresholds for clozapine discontinuation in those with BEN in the UK may contribute to fewer rechallenges in those of black ethnicity.20

***Clinical Implications and Future Research***

Recent literature has highlighted the weak evidence base and the rather arbitrary haematological cut-off points for clozapine cessation on an international scale.14 This is reflected by the substantial variability in international clozapine use and haematological monitoring regulations.44 For example, countries with less stringent monitoring requirements, such as Iceland and Finland, have demonstrated higher clozapine use than other countries with similar agranulocytosis prevalence rates.12 Furthermore, two recent meta-analyses have challenged the view that clozapine-exposed groups are at an increased risk of neutropenia and agranulocytosis compared with those who take other antipsychotics6,7. These studies also questioned the need for regular monitoring beyond one year of treatment.45

There is increasing evidence that stopping clozapine abruptly, as required when a patient enters the CNRD, often leads to severe psychotic relapse, reduced responsiveness and discontinuation symptoms.46-49 Relaxing the CNRD criteria in line with the US FDA monitoring criteria in the UK may reduce the proportion of patients who would have to suffer these outcomes. Collectively, this complements a growing body of evidence that suggests that the stringency of the monitoring for clozapine-induced blood dyscrasias, including agranulocytosis, may be disproportionate, and that an optimal balance between the risks and benefits may be achieved by relaxing the monitoring requirements.1,25,45 Moreover, while the UK and Ireland are the only countries in Europe required to have a CNRD and monitoring system by the marketing authorization holder, the haematological cut-off values for white blood cell and neutrophil counts requiring clozapine discontinuation are similar for many countries around the world. Therefore, our study may suggest that the urgent need to evaluate clozapine monitoring requirements may extend internationally and, more specifically, lower neutrophil cut-off points to improve access to this uniquely effective treatment. While the changes made by the US FDA are a positive step towards improving access to clozapine treatment, both threshold-based systems give way to a significant proportion of false positives for LTA. Thus, future work should seek to establish monitoring strategy and thresholds for treatment discontinuation, based on ANC patterns, in collaboration with haematologists. The time to decide whether the current haematological monitoring guidelines should be on public health agendas in the UK has passed. Now is the time for action.

***Limitations***

The findings in this report are subject to at least five limitations. First, from the data derived from this study, it is unknown what would have happened to the 2096 patients (56%) who had to discontinue clozapine under UK guidelines but would have registered with an amber result under the US FDA thresholds had they continued to take clozapine. An amber result in the US does not warrant treatment discontinuation, but it does dictate repeated haematological monitoring (three times a week) until resolved. As clozapine was discontinued in our patients under the monitoring criteria in the UK, it is unknown what proportion of them would have developed more LTA with continued clozapine use. However, clinical studies have shown that most cases of mild neutropenia do not portend a serious haematological reaction to clozapine (i.e., agranulocytosis). There are suggestions that neutropenia versus agranulocytosis in clozapine treated patients may have different aetiologies.24,33,34. This statement is further supported by a recent case series suggesting that clozapine's erroneous association with neutropenia opposed to solely LTA may inadvertently impede efforts towards establishing genetic determinants for this adverse reaction. Second, due to limited data, whether clozapine-induced agranulocytosis caused any fatalities in our cohort is unknown. But recent meta-analytic data has emphasised previous findings that death associated with clozapine-induced agranulocytosis remains a rare event, even without strict monitoring regulations.50 The third limitation relates to the cohort of patients who were rechallenged on clozapine. Patients are typically only rechallenged after a comprehensive risk-benefit assessment in close liaison with a haematologist in an inpatient setting, where any potential deterioration in physical health can be promptly detected.35 This could limit the generalisability of our rechallenge results because patients are thoroughly investigated with haematology input before rechallenge. Thus, patients deemed at high risk of developing neutropenia and potential agranulocytosis are not rechallenged. However, in contrast to our previous study, where rechallenge attempts were performed in a single specialist service, our study includes a broader range of patients across the UK, suggesting greater generalisability. Fourth, it was not possible to distinguish between discontinuation and switching to a different brand and hence clozapine monitoring service, although this is an unusual event.51,52 Finally, in clinical practice, the accurate recognition and diagnosis of clozapine-induced agranulocytosis may be complicated by other causative factors for neutropenia such as concomitant medication or notably viral infections.53 Due to the lack of detail in our population-level data, it is unknown whether patients had pre-existing conditions increasing neutropenia likelihood, including patients who were rechallenged.54 Our data did not include information on the concomitant medication used during rechallenge, so the effects of concomitant treatments cannot be determined. However, along with previous literature, our smaller study highlighted the importance of concomitant medication as a differential for suspected clozapine-induced blood dyscrasias.51,55 Although the knowledge of interventions for clozapine rechallenge has improved over time, a comprehensive assessment of how this has affected success rates is still lacking.

**Conclusion**

The current regulations surrounding the clozapine non-rechallenge database have severe unintended consequences on mental health through the discontinuation of clozapine in patients whose treatment could safely be continued. Clozapine-associated blood toxicity is vastly over-diagnosed by threshold-based identification systems. It is our view that the regulations should take a more balanced approach in which mental, as well as physical health outcomes are considered. The results suggest that implementing the US FDA’s clozapine monitoring guidelines in the UK could be achieved with little or no change in the risk of agranulocytosis. This evidence suggests the urgent need to revise the UK’s clozapine monitoring guidelines to improve clinical outcomes in TRS. It also highlights a need for greater awareness and earlier diagnosis of BEN. Future efforts should focus on establishing pattern-based identification of clozapine-induced agranulocytosis opposed to threshold-based identification systems.

## References

1. Oloyede E, Casetta C, Dzahini O, et al. There Is Life After the UK Clozapine Central Non-Rechallenge Database. *Schizophr Bull*. Feb 2021;doi:10.1093/schbul/sbab006

2. Lomas J. Chlorpromazine and Agranulocytosis. *Br Med J*. 1954;2(4883):358-359.

3. Nazer LH, Shankar G, Ali BA-H, Al-Najjar T. Fatal agranulocytosis associated with psychotropic medication use. *American journal of health-system pharmacy : AJHP : official journal of the American Society of Health-System Pharmacists*. 2012;69(10):863-867. doi:10.2146/ajhp110195

4. Crilly J. The history of clozapine and its emergence in the US market:a review and analysis. *History of Psychiatry*. 2007;18(1):39-60. doi:10.1177/0957154x07070335

5. Hippius H. A historical perspective of clozapine. *J Clin Psychiatry*. 1999;60 Suppl 12:22-3.

6. Myles N, Myles H, Xia S, et al. A meta-analysis of controlled studies comparing the association between clozapine and other antipsychotic medications and the development of neutropenia. *Australian & New Zealand Journal of Psychiatry*. 2019;53(5):403-412.

7. Myles N, Myles H, Xia S, et al. Meta‐analysis examining the epidemiology of clozapine‐associated neutropenia. *Acta Psychiatrica Scandinavica*. 2018;138(2):101-109.

8. Tasker JR. Fatal agranulocytosis during treatment with chlorpromazine. *Br Med J*. 1955;1(4919):950-951. doi:10.1136/bmj.1.4919.950

9. Mena CI, Nachar RA, Crossley NA, González-Valderrama AA. Clozapine-associated neutropenia in Latin America: incidence report of 5380 Chilean users. *International clinical psychopharmacology*. 2019;34(5):257-263.

10. Rettenbacher MA, Hofer A, Kemmler G, Fleischhacker WW. Neutropenia induced by second generation antipsychotics: a prospective investigation. *Pharmacopsychiatry*. Mar 2010;43(2):41-4. doi:10.1055/s-0030-1249071

11. Farooq S, Choudry A, Cohen D, Naeem F, Ayub M. Barriers to using clozapine in treatment-resistant schizophrenia: systematic review. *BJPsych bulletin*. 2019;43(1):8-16. doi:10.1192/bjb.2018.67

12. Bachmann CJ, Aagaard L, Bernardo M, et al. International trends in clozapine use: a study in 17 countries. *Acta Psychiatr Scand*. Jul 2017;136(1):37-51. doi:10.1111/acps.12742

13. Baker M, White T. Life after clozapine. *Med Sci Law*. Jul 2004;44(3):217-21. doi:10.1258/rsmmsl.44.3.217

14. Whiskey E, Dzahini O, Ramsay R, et al. Need to bleed? Clozapine haematological monitoring approaches a time for change. *International clinical psychopharmacology*. 2019;34(5):264-268.

15. Kelly DL, Freudenreich O, Sayer MA, Love RC. Addressing barriers to clozapine underutilization: a national effort. Am Psychiatric Assoc; 2018.

16. Whiskey E, Barnard A, Oloyede E, Dzahini O, Taylor D, Shergill SS. An evaluation of the variation and underuse of clozapine in the United Kingdom. *Acta Psychiatr Scand*. Jan 2021;doi:10.1111/acps.13280

17. Mylan. Clozaril 25mg tablets. Accessed 14th July, 2020. <https://www.medicines.org.uk/emc/product/4411/smpc>

18. Limited BP. Denzapine 50mg/ml Oral Suspension. Accessed 17 July, 2020. <https://www.medicines.org.uk/emc/product/6121/smpc>

19. BV LD. Zaponex 100 mg Tablets. Accessed 17 July, 2020. <https://www.medicines.org.uk/emc/product/7715/smpc>

20. Oloyede E, Dzahini O, Barnes N, et al. Benign ethnic neutropenia: an analysis of prevalence, timing and identification accuracy in two large inner-city NHS hospitals. *BMC Psychiatry*. 2021/10/13 2021;21(1):502. doi:10.1186/s12888-021-03514-6

21. Sultan RS, Olfson M, Correll CU, Duncan EJ. Evaluating the effect of the changes in FDA guidelines for clozapine monitoring. *The Journal of clinical psychiatry*. 2017;78(8):0-0.

22. Curry B, Palmer E, Mounce C, Smith G, Shah V. Assessing prescribing practices of clozapine before and after the implementation of an updated risk evaluation and mitigation strategy. *Mental Health Clinician*. 2018;8(2):63-67.

23. Borrelli EP, Lee EY, Caffrey AR. Clozapine and hematologic adverse reactions: Impact of the Risk Evaluation and Mitigation Strategy program. *Mental Health Clinician*. 2020;10(3):70-75.

24. Bastiampillai T, Gupta A, Chan SK, Allison S. Changes for clozapine monitoring in the United States. *Mol Psychiatry*. Jul 2016;21(7):858-60. doi:10.1038/mp.2016.66

25. Schulte PFJ, Bogers J, Bond-Veerman SRT, Cohen D. Moving forward with clozapine. *Acta Psychiatr Scand*. Aug 2020;142(2):75-77. doi:10.1111/acps.13224

26. Atkin K, Kendall F, Gould D, Freeman H, Liberman J, O'Sullivan D. Neutropenia and agranulocytosis in patients receiving clozapine in the UK and Ireland. *Br J Psychiatry*. Oct 1996;169(4):483-8. doi:10.1192/bjp.169.4.483

27. Munro J, O'Sullivan D, Andrews C, Arana A, Mortimer A, Kerwin R. Active monitoring of 12760 clozapine recipients in the UK and Ireland. *The British Journal of Psychiatry*. 1999;175(6):576-580.

28. Lahdelma L, Appelberg B. Clozapine-induced agranulocytosis in Finland, 1982–2007: long-term monitoring of patients is still warranted. *The Journal of clinical psychiatry*. 2012;73(6):837-842.

29. Velayudhan R, Kakkan S. Late onset clozapine induced agranulocytosis. *Indian journal of psychological medicine*. 2014;36(4):425-427.

30. Patel NC, Dorson PG, Bettinger TL. Sudden late onset of clozapine-induced agranulocytosis. *Annals of Pharmacotherapy*. 2002;36(6):1012-1015.

31. Newburger PE, Dale DC. Evaluation and management of patients with isolated neutropenia. *Semin Hematol*. Jul 2013;50(3):198-206. doi:10.1053/j.seminhematol.2013.06.010

32. Matsui K, Ishibashi M, Kawano M, et al. Clozapine-induced agranulocytosis in Japan: Changes in leukocyte/neutrophil counts before and after discontinuation of clozapine. *Hum Psychopharmacol*. Jul 2020;35(4):e2739. doi:10.1002/hup.2739

33. Ingimarsson O, MacCabe JH, Haraldsson M, Jónsdóttir H, Sigurdsson E. Clozapine treatment and discontinuation in Iceland: A national longitudinal study using electronic patient records. *Nord J Psychiatry*. Aug 2016;70(6):450-5. doi:10.3109/08039488.2016.1155234

34. Rajagopal S. Clozapine, agranulocytosis, and benign ethnic neutropenia. The Fellowship of Postgraduate Medicine; 2005.

35. Meyer N, Gee S, Whiskey E, et al. Optimizing outcomes in clozapine rechallenge following neutropenia: a cohort analysis. *J Clin Psychiatry*. Nov 2015;76(11):e1410-6. doi:10.4088/JCP.14m09326

36. Manu P, Sarpal D, Muir O, Kane JM, Correll CU. When can patients with potentially life-threatening adverse effects be rechallenged with clozapine? A systematic review of the published literature. *Schizophr Res*. Feb 2012;134(2-3):180-6. doi:10.1016/j.schres.2011.10.014

37. Silva E, Higgins M, Hammer B, Stephenson P. Clozapine rechallenge and initiation despite neutropenia- a practical, step-by-step guide. *BMC Psychiatry*. Jun 5 2020;20(1):279. doi:10.1186/s12888-020-02592-2

38. Lally J, Malik S, Krivoy A, et al. The Use of Granulocyte Colony-Stimulating Factor in Clozapine Rechallenge: A Systematic Review. *J Clin Psychopharmacol*. Oct 2017;37(5):600-604. doi:10.1097/jcp.0000000000000767

39. Simon L, Cazard F. [Clozapine rechallenge after neutropenia in resistant schizophrenia: A review]. *Encephale*. Aug 2016;42(4):346-53. Réintroduction de la clozapine après neutropénie dans la schizophrénie résistante : revue des données de la littérature. doi:10.1016/j.encep.2016.03.005

40. Béchard L, Corbeil O, Plante M, et al. Clozapine rechallenge following neutropenia using granulocyte colony-stimulating factor: A Quebec case series. *J Psychopharmacol*. Jul 6 2021:2698811211029737. doi:10.1177/02698811211029737

41. Boazak M, Goldsmith DR, Cotes RO. Mask Off? Lithium Augmentation for Clozapine Rechallenge After Neutropenia or Agranulocytosis: Discontinuation Might Be Risky. *Prim Care Companion CNS Disord*. Nov 29 2018;20(6)doi:10.4088/PCC.18l02282

42. Safferman AZ, Lieberman JA, Alvir JM, Howard A. Rechallenge in clozapine-induced agranulocytosis. *Lancet*. May 23 1992;339(8804):1296-7. doi:10.1016/0140-6736(92)91625-i

43. Masuda T, Misawa F, Takase M, Kane JM, Correll CU. Association With Hospitalization and All-Cause Discontinuation Among Patients With Schizophrenia on Clozapine vs Other Oral Second-Generation Antipsychotics: A Systematic Review and Meta-analysis of Cohort Studies. *JAMA Psychiatry*. Jul 31 2019;doi:10.1001/jamapsychiatry.2019.1702

44. Nielsen J, Young C, Ifteni P, et al. Worldwide Differences in Regulations of Clozapine Use. *CNS Drugs*. Feb 2016;30(2):149-61. doi:10.1007/s40263-016-0311-1

45. Cohen D, Monden M. White blood cell monitoring during long-term clozapine treatment. *Am J Psychiatry*. Apr 2013;170(4):366-9. doi:10.1176/appi.ajp.2012.12081036

46. Blackman G, Oloyede E. Clozapine discontinuation withdrawal symptoms in schizophrenia. *Therapeutic Advances in Psychopharmacology*. 2021;11:20451253211032053. doi:10.1177/20451253211032053

47. Blackman G, Oloyede E, Horowitz M, et al. Reducing the Risk of Withdrawal Symptoms and Relapse Following Clozapine Discontinuation—Is It Feasible to Develop Evidence-Based Guidelines? *Schizophrenia Bulletin*. 2021;doi:10.1093/schbul/sbab103

48. Grassi B, Ferrari R, Epifani M, Dragoni C, Cohen S, Scarone S. Clozapine lacks previous clinical efficacy when restarted after a period of discontinuation: A case series. Elsevier; 1999.

49. Miodownik C, Lerner V, Kibari A, Toder D, Cohen H. The effect of sudden clozapine discontinuation on management of schizophrenic patients: A retrospective controlled study. *The Journal of clinical psychiatry*. 2006;67(8):5908.

50. Xiao-Hong L, Xiao-Mei Z, Lu L, et al. The prevalence of agranulocytosis and related death in clozapine-treated patients: a comprehensive meta-analysis of observational studies. *Psychological medicine*. 2020;50(4):583-594.

51. Oloyede E, Dzahini O, Whiskey E, Taylor D. Clozapine and Norclozapine Plasma Levels in Patients Switched Between Different Liquid Formulations. *Ther Drug Monit*. Jun 2020;42(3):491-496. doi:10.1097/FTD.0000000000000711

52. Legge SE, Hamshere M, Hayes RD, et al. Reasons for discontinuing clozapine: A cohort study of patients commencing treatment. *Schizophr Res*. 07 2016;174(1-3):113-119. doi:10.1016/j.schres.2016.05.002

53. Meyer J, Stahl S. *The clozapine handbook: Stahl’s handbooks.* Cambridge University Press; 2019.

54. Boxer LA. How to approach neutropenia. *Hematology 2010, the American Society of Hematology Education Program Book*. 2012;2012(1):174-182.

55. Demler TL, Trigoboff E. Are clozapine blood dyscrasias associated with concomitant medications? *Innov Clin Neurosci*. Apr 2011;8(4):35-41.