Clozapine rechallenge after neutropenia: a retrospective cohort study in the UK

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Summary

Background Clozapine is contraindicated in patients with a history of neutropenia suspected to be clozapine-induced agranulocytosis. Under exceptional circumstances, patients may be rechallenged with clozapine under an off-licence agreement. The evidence regarding clozapine rechallenge after suspected clozapine-induced neutropenia remains sparse and conflicting. In this observational study, we aimed to review the outcomes of patients rechallenged with clozapine using data from the two largest clozapine manufacturers in the UK.

Methods We analysed data of patients in the UK and Ireland rechallenged on clozapine after they registered on the Central Non-Rechallenge Database (CNRD), provided by the Clozaril Patient Monitoring Service and Zaponex Treatment Access System, between Jan 1, 2013, and Dec 12, 2025. Unsuccessful rechallenge was defined as re-registration on the CNRD within 6 months. We calculated incidence proportion and incidence rates of severe neutropenia (agranulocytosis) using both threshold-based and pattern-based criteria. Demographic characteristics, details of each clozapine trial, and factors associated with unsuccessful rechallenge were examined. People with lived experience were not involved in the research or writing of this study.

Findings Of the 4719 patients registered on the CNRD, 1296 (27%) were rechallenged on clozapine, of whom 435 (34%) patients met the revised CNRD criteria. The cohort was predominantly male (278 [64%] male patients *vs* 157 [36%] female patients), with a median age of 34 years (IQR 25–46) at clozapine initiation, and was ethnically diverse: 321 (74%) White patients, 70 (16%) Black patients, 30 (7%) Asian patients, and 14 (3%) patients of other ethnicities. Median duration of follow-up was 2·2 years (IQR 0·5–4·9) or 1336 person-years. Within 6 months of rechallenge, 29 (7%) patients were re-registered on the CNRD having had a further neutropenic episode, and 87 (20%) patients had less than 6 months of rechallenge follow-up. Unsuccessful rechallenge within 6 months was associated with higher baseline absolute neutrophil count (hazard ratio [HR] 1·38 per 1×10^9/L [95% CI 1·09–1·61]), male sex (HR 2·16 [95% CI 1·11–4·02]), and increasing age (HR 1·06 per year [95% CI 1·01–1·11]).

Interpretation Clozapine rechallenge can be successful in a select group of patients after mandated clozapine cessation for suspected clozapine-induced neutropenia.

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Introduction

The reintroduction of clozapine in the 1980s marked a pivotal moment in the management of treatment-resistant schizophrenia, following Kane and colleagues' landmark demonstration of its superior efficacy over other antipsychotics.[1] This advance, however, came with an important caveat from regulatory bodies: mandatory haematological monitoring to mitigate the risk of clozapine-induced agranulocytosis, a rare but potentially fatal adverse effect.[2] Although monitoring protocols vary slightly by country, indefinite monitoring remains a global requirement.[2] A recent development is the European Medicines Agency (EMA) revisions, which permit annual monitoring after 2 consecutive years without neutropenia.[3] Nevertheless, the core design of haematological monitoring to detect early declines in neutrophil counts and mitigate against progression to clozapine-induced agranulocytosis remains unchanged. In the UK, patients prescribed clozapine typically undergo weekly white cell count (WCC) and absolute neutrophil count (ANC) monitoring for the first 18 weeks, followed by fortnightly tests for up to 1 year and monthly monitoring thereafter.[4] Patients who record consecutive WCC or ANC values below defined thresholds are registered on the Central Non-Rechallenge Database (CNRD), a national system shared by all UK clozapine manufacturers to prevent inadvertent re-exposure.

Although these monitoring safeguards have reduced the incidence of agranulocytosis, they have also introduced unintended consequences. The stringent criteria, combined with little consideration of benign haematological phenotypes and other modifiable factors, can lead to unnecessary treatment discontinuation and exclusion from clozapine treatment.[4] Consequently,

Research in context

Evidence before this study

For people with a diagnosis of schizophrenia who respond poorly to standard treatment with antipsychotic medication, clozapine is the treatment of choice. However, clozapine is underused in many parts of the world, due in part to its serious side-effect profile—including the risk of causing blood dyscrasias and, more specifically, potentially fatal severe neutropenia (agranulocytosis)—which has led to mandatory routine blood monitoring in many countries around the world. In the UK and other countries worldwide, patients receiving clozapine whose haematological parameters fall below certain thresholds are placed on the Central Non-Rechallenge Database, meaning that they are not allowed to be routinely prescribed clozapine again. However, recent studies suggest that some episodes of suspected clozapine-induced neutropenia might be transient, multifactorial, or unrelated to clozapine itself. We searched MEDLINE, PsycINFO, and Scopus databases for peer-reviewed articles and reviews published from database inception to Dec 1, 2025, with no language restrictions. Our search terms included clozapine-related terms ("clozapine", "clozapin*", "denzapine", "clozaril", "zaponex", and "loxapin*") and rechallenge-related terms ("rechallenge", "re-challenge", "initiation", "reinitiation", "re-initiation", "restart", "re-exposure", and "reexposure"). We identified two small cohort studies and several small case series and case reports, but little comprehensive investigation of clinical characteristics among people who undergo clozapine rechallenge after neutropenia. Such information would be valuable to guide clinical decision making and improve the safe use of clozapine in treatment-resistant schizophrenia.

Added value of this study

To our knowledge, this is the largest observational study to date examining outcomes following clozapine rechallenge after registration on a national non-rechallenge database. By using routinely collected data from the two largest clozapine monitoring systems in the UK, we were able to characterise demographic and clinical features of rechallenged patients, estimate the incidence proportion of recurrent mild to severe neutropenia at 7%, and identified male sex, increasing age, and higher baseline neutrophil counts as possible factors associated with unsuccessful rechallenge.

Implications of all the available evidence

Taken together with previous smaller studies, our results suggest that clozapine rechallenge can be done safely in carefully selected patients following suspected neutropenia. These findings support a more individualised, risk-based approach to rechallenge decisions, rather than automatic permanent discontinuation. Future policy discussions and guideline revisions should consider emerging evidence from large observational cohorts alongside clinical judgement, while recognising ongoing uncertainty around risk factors. Improving access to clozapine for people with treatment-resistant schizophrenia must balance haematological safety with the substantial mental and physical health risks associated with untreated illness.

clozapine licensing has faced sustained scrutiny, with repeated calls for regulatory changes to improve utilisation and clinical outcomes.[5–8] For clinicians, adherence to licensing requirements is generally appropriate; however, there are circumstances where strict compliance can conflict with the patient's best interests. One such scenario is clozapine rechallenge, an off-licence process permitted by manufacturers under exceptional circumstances. Rechallenge is typically only considered when the risk of untreated psychiatric illness outweighs the potential risk of agranulocytosis, particularly in patients for whom no other antipsychotic has provided meaningful clinical benefit.[9] This decision is made on a case-by-case basis, usually involving a multidisciplinary team and close collaboration with a consultant haematologist, and is informed by comprehensive assessment, including haematological profiling, blood film analysis, and review of haematinics.[4]

Despite growing interest in clozapine rechallenge, evidence on rechallenge outcomes remains limited by small sample sizes and heterogeneous methodologies. Adding to this complexity, ANC thresholds for discontinuation differ between countries, which means that criteria for rechallenge vary internationally.[2] To address this gap, we conducted a retrospective observational study evaluating rechallenge outcomes among patients previously registered on the UK CNRD due to mild to severe neutropenia. Our objective was to estimate the incidence proportion and incidence rate of unsuccessful rechallenge, examine factors associated with rechallenge failure, and characterise patients who either had rechallenge failure or developed agranulocytosis (severe neutropenia) after re-exposure.

Methods

Data source and study sample

We analysed data from the UK CNRD. Non-identifiable data were provided by the two largest manufacturers of clozapine and the associated haematological monitoring service in the UK: Clozaril (Mylan) monitored by Clozaril Patient Monitoring Service and Zaponex (Leyden Delta, Nijmegen, Netherlands) monitored by Zaponex Treatment Access System.[9] According to current Medicines and Healthcare products Regulatory Agency criteria, red results (neutropenia), necessitating clozapine discontinuation, are defined as a WCC of less than $3{\cdot}0\times10^9$/L with or without an ANC of less than $1{\cdot}5\times10^9$/L. Amber results are defined as a WCC of less than $3{\cdot}5\times10^9$/L and greater than or equal to $3{\cdot}0\times10^9$/L with or without an ANC of less than $2{\cdot}0\times10^9$/L and greater than or equal to $1{\cdot}5\times10^9$/L.

Green results are defined as a WCC of greater than or equal to $3{\cdot}5\times10^9$/L and an ANC greater than or equal to $2{\cdot}0\times10^9$/L. For patients with confirmed ACKR1/DARC-associated neutropenia (ADAN), all thresholds are lowered by $0{\cdot}5\times10^9$/L.

Ethical approval was not required according to the UK Health Research Authority and informed consent was not required as only non-identifiable information was used. STROBE reporting guidelines were followed (appendix p 39).[10]

We identified patients in the UK and Ireland who were registered with the Clozaril Patient Monitoring Service between May 2, 2000, and Feb 27, 2021, and Zaponex Treatment Access System between April 5, 2004, and Dec 12, 2025. The formal rechallenge process began in 1998. Our study focused on the period from Jan 1, 2013, to Dec 12, 2025, as the criteria for CNRD registration were revised in 2013, ensuring that all included patients were assessed under the same registration criteria. Specifically, we included patients who recorded a confirmed red result within this period, which was defined as an initial red result followed by another red result within the next 2 days.[4] In such cases, patients would be automatically registered on the CNRD. Additionally, clozapine registries can place patients on the CNRD in the absence of follow-up monitoring after an initial red result. Before 2013, the Medicines and Healthcare products Regulatory Agency criterion for CNRD registration was a single red result. Patients registered on the CNRD under previous criteria remain in the database but might be re-prescribed clozapine without undergoing the formal rechallenge process. For patients with more than one rechallenge attempt, only the first rechallenge was included in the primary analysis. Data on demographic factors (ie, age, sex [male or female], and ethnicity), clozapine treatment (ie, registration date, ADAN status, and indication), and haematological history (ie, ANC, WCC, and platelets) were extracted from the databases.

Procedures and outcomes

We calculated both the incidence proportion and incidence rate of unsuccessful rechallenge after CNRD registration. Incidence proportion of unsuccessful rechallenge was defined as the proportion of patients who were re-registered on the CNRD within the first 6 months of rechallenge or who recorded at least one red result within the first 6 months of treatment (to enable comparison with earlier studies).[11,12] Patients who had fewer than 6 months of post-rechallenge blood monitoring were classified as successful in the absence of CNRD re-registration during their observed follow-up. Reasons for cessation of monitoring before 6 months were not available. The 6-month cutoff was selected as this reflects the highest risk period for clozapine-induced agranulocytosis and enabled comparison with other studies.[13]

The CNRD episode (index or rechallenge) was defined as the period between the first and last consecutive red result that led to registration on the CNRD. We examined latency, severity, and duration of these episodes both before and after rechallenge. Latency was defined as the time from clozapine initiation to CNRD registration. Severity was based on the lowest recorded ANC and duration was the interval between the first and last red result. For latency analyses, any gap more than 6 weeks between blood tests was treated as a treatment break, with latency measured from when treatment restarted. The 6-week threshold was selected on the basis of standard monitoring protocols, which require patients to revert to weekly monitoring when this interval has been exceeded.

See Online for appendix

We calculated the incidence proportion and incidence rate of severe neutropenia (agranulocytosis) both during initial clozapine exposure and after rechallenge. Patients who developed severe neutropenia (agranulocytosis) were stratified into two groups. Threshold-based agranulocytosis was defined by at least one ANC less than $0{\cdot}5\times10^9$/L. Pattern-based agranulocytosis was defined by two consecutive ANCs (over 2 or more days) less than $0{\cdot}5\times10^9$/L with the second value lower than the first.[14] The rationale for using pattern-based criteria was that previous studies have suggested that threshold-based criteria might overestimate the incidence of clozapine-induced agranulocytosis due to transient fluctuations or laboratory errors.[15] Patients who developed agranulocytosis during their index clozapine exposure were also evaluated to determine whether agranulocytosis recurred upon rechallenge.

Statistical analysis

Baseline patient demographic and clozapine characteristics were summarised using descriptive statistics. Median (IQR) values were calculated for continuous data and frequencies and percentages calculated for categorical data. Incidence rates were calculated as the number of unsuccessful rechallenges per 1000 person-months. Person-months were defined as the months contributed by each patient from the date of rechallenge to a haematological event, loss of follow-up blood test data, or administrative censoring at 6 months.

To describe the effect of incomplete follow-up within the 6-month rechallenge period, we calculated and plotted cumulative incidence risks of CNRD re-registration as the event of interest and exit from monitoring as a competing risk. Exit from monitoring was treated as a competing risk under the worse-case assumption as reasons for exit were unavailable.

For regression analyses, we used univariate Cox proportional hazards models to estimate hazard ratios (HRs) and 95% CIs for factors associated with unsuccessful rechallenge. Participants without CNRD re-registration were right-censored at their last recorded follow-up or administratively at 6 months. The competing

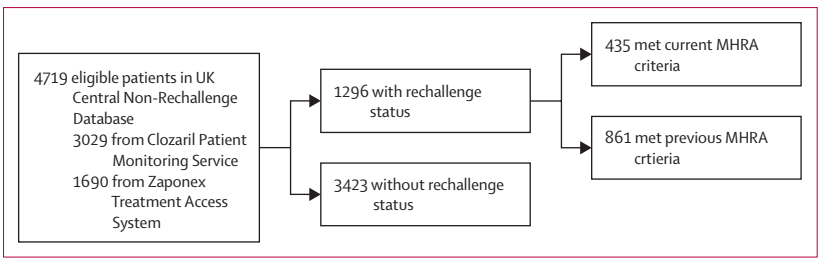

Figure 1: **Study flowchart**
MHRA=Medicines and Healthcare products Regulatory Agency.

risk of exit from monitoring was censored at the time of the last blood test date.

To assess whether factors associated with unsuccessful rechallenge were also associated with incomplete follow-up, we conducted secondary univariate Cox models with the outcome defined as failure to complete 6 months of post-rechallenge monitoring in the absence of CNRD re-registration. In this analysis, participants who had CNRD re-registration within 6 months were treated as non-events and individuals with follow-up extending to within 6 months were administratively censored at that timepoint. This analysis was undertaken to explore the potential for differential follow-up rather than as a primary outcome analysis.

The following variables were included based on clinical relevance, previous literature, and opportunistic availability. Demographic factors were sex and ethnicity (collapsed as White *vs* Other due to small numbers in non-White groups). The pre-index CNRD haematological factor was median ANC across the first four measurements recorded at clozapine initiation. Index CNRD episode factors were agranulocytosis at or before the index CNRD episode and time to index CNRD registration. Rechallenge-specific factors were age at rechallenge and the time interval from index CNRD registration to the rechallenge date. ADAN status was excluded due to low representation in the cohort (n=70, 16%) and inconsistent clinical identification across clinicians. The median of the first four ANC measurements before the index CNRD episode was a proxy for baseline neutrophil status to reduce the influence of transient variation and assess whether lower baseline ANC affects rechallenge outcomes. Continuous variables were modelled per unit increase in their natural scale (eg, per 1×10^9/L for ANC). For time-related variables, we used 30-day increments.

The proportional hazards assumption was evaluated using the Grambsch and Therneau test of proportional hazards. For covariates that broke the proportional hazard assumption, Cox proportional hazards models were fitted with a time interaction. Linearity for continuous covariates was assessed using martingale residual plots. When non-linearity was suggested, continuous covariates were modelled using restricted cubic splines. To increase robustness of findings and estimated HRs, we repeated the analyses using multivariate regularised Cox models with ridge regression.[16] Lambda was tuned in a five-fold cross-validation framework with the largest value of lambda such that error is within 1 standard error of the cross-validated errors for minimum lambda (lambda 1SE) applied to a final model fitted on all available data. 95% CIs were estimated over 1000 bootstrap samples which reflect the variability of the penalised coefficients under repeated sampling, including the bias introduced by shrinkage (boot version 2.3–31).

Statistical significance was set at $p<0\cdot05$ (two-sided). Analyses were conducted using R (version 4.5.2), using the survival package (version 3.8–6) for proportional hazards models, cmprsk (version 2.2–12) for descriptive competing risk cumulative incidence estimates, and tidyverse packages (version 2.0.0) for data handling and visualisation.

Role of the funding source
There was no funding source for this study.

Results

Of the 4719 patients registered on the CNRD, 1296 (27%) patients underwent a clozapine rechallenge (figure 1). Of these 1296 patients, 435 (9%) recorded a confirmed red result and were included in this study. At the index CNRD episode, 278 (64%) were male and 157 (36%) were female (table 1). The cohort comprised 321 (74%) White patients, 70 (16%) Black patients, 30 (7%) Asian patients, and 14 (3%) patients of other ethnicities. Before the rechallenge, 91 (21%) patients had a red result before their index CNRD episode (median 1 [IQR 1–2]) and 319 (74%) had at least one amber result beforehand (5 [2–11]). The index CNRD episode lasted a median of 3 days (IQR 2–4), with a median ANC of $1\cdot3\times10^9$/L (IQR 1·1–1·4). 40 (9%) patients had agranulocytosis in the index event.

The rechallenged cohort and non-rechallenged cohort differed descriptively (table 1). The rechallenged cohort included 321 (74%) White patients (*vs* 2785 [81%] White patients in the non-rechallenged cohort), 70 (16%) Black patients (*vs* 390 [11%] Black patients), and a higher prevalence of ADAN monitoring (70 [16%] in the rechallenged cohort *vs* 58 [2%] in the non-rechallenged cohort). The rechallenged cohort had longer clozapine duration than the non-rechallenged cohort (median 9 years [IQR 4–13] *vs* 2 years [0–5]). Median age at clozapine initiation (34 years [IQR 26–46] *vs* 41 years [30–51]) and at CNRD registration (43 years [IQR 32–53] *vs* 46 years [IQR 35–56]) was lower in the rechallenged cohort compared with the non-rechallenged cohort. Median follow-up after rechallenge was 2·2 years (IQR 0·5–4·9), yielding a total of 1336 person-years.

The median time to clozapine rechallenge from index CNRD registration was 27 days (IQR 7–149), with a range of 1 day to 3650 days. The number of patients re-registered on the CNRD within 6 months of clozapine rechallenge was 29 (7%) patients, with a median time to re-registration

	Rechallenged cohort using current criteria (n=435)	Rechallenged cohort using previous criteria (n=861)	Non-rechallenged cohort (n=3423)	All patients (n=4719)
Sex				
Female	157 (36%)	296 (34%)	1294 (38%)	1747 (37%)
Male	278 (64%)	565 (66%)	2129 (62%)	2972 (63%)
Age at clozapine initiation, years	34 (26–46)	34 (26–45)	41 (30–51)	39 (29–49)
Age at CNRD registration, years	43 (32–53)	36 (27–46)	46 (35–56)	44 (33–55)
Median clozapine duration, years	9 (4–13)	5 (2–9)	2 (0–5)	3 (1–7)
ADAN status	70 (16%)	111 (13%)	58 (2%)	239 (5%)
Ethnicity				
White	321 (74%)	653 (76%)	2785 (81%)	3759 (80%)
Black	70 (16%)	145 (17%)	390 (11%)	605 (13%)
Asian	30 (7%)	40 (5%)	162 (5%)	232 (5%)
Other	14 (3%)	23 (3%)	86 (3%)	123 (3%)
Agranulocytosis by CNRD registration*	40 (9%)	51 (6%)	586 (17%)	677 (14%)
Haematological characteristics, ×10⁹/L				
White cell count at CNRD registration	2·9 (2·6–3·4)	3·1 (2·7–3·7)	2·9 (2·6–3·6)	2·9 (2·6–3·6)
Absolute neutrophil cell count at CNRD registration	1·3 (1·1–1·4)	1·3 (1·1–1·4)	1·3 (1·0–1·4)	1·3 (1·0–1·4)
Platelet count at CNRD registration	177 (133–226)	196 (149–243)	198 (146–251)	195 (145–247)

Data are n (%) or median (IQR). ADAN=ACKR1/DARC-associated neutropenia. CNRD=Central Non-Rechallenge Database. *Includes patients who recorded agranulocytosis before their CNRD episode (eg, a single red result) and at the time of CNRD registration.

Table 1: **Baseline sociodemographic and clinical characteristics of patients rechallenged on clozapine**

of 57 days (IQR 27–84). Additionally, the number of patients with a red result within 6 months of clozapine rechallenge was 111 (26%) patients, with a median time of 83 days (IQR 26–260; appendix p 1). The incidence rate of unsuccessful clozapine rechallenge was 1·35 per 1000 person-months (95% CI 0·9–1·94). A further 87 (20%) patients did not complete 6 months of post-rechallenge monitoring in the absence of CNRD re-registration. Among these, 34 (39%) patients had a haematological abnormality during rechallenge, including 12 (14%) with a single red result and 32 (37%) with at least one amber result. At the last recorded blood test, two (2%) patients had a red result, four (5%) had an amber result, and the remainder had green results. Table 2 provides a summary of outcomes after clozapine rechallenge. Among the 29 (7%) patients who re-registered onto the CNRD within 6 months of rechallenge, the subsequent neutropenic episode was longer (median 6 days [IQR 3–15] *vs* 4 days [2–8]) and neutrophil count nadir was lower (median $1{\cdot}0\times10^9$/L [IQR 0·9–1·1] *vs* $1{\cdot}5\times10^9$/L [1·3–1·7]) compared with their index episodes. A detailed summary is provided in the appendix (pp 1–4).

The cumulative incidence function plot for time to re-registration onto the CNRD is shown in figure 2, accounting for the competing risk of end of follow-up before 6 months. The cumulative incidence of re-registration increased gradually over follow-up and reached 7% by 6 months. Re-registrations occurred predominantly within the first 3 months after clozapine rechallenge, with a slower rate of increase thereafter.

	Sample number (n=435)
Cases of threshold-based agranulocytosis	17 (4%)
Cases of pattern-based agranulocytosis	8 (2%)
Duration of rechallenge, years	2·2 (0·5–4·9)
Number of patients placed back on CNRD within 6 months of rechallenge	29 (7%)
Time to CNRD re-registration, days	57 (27–84)
Neutropenia duration, days	6 (3–15)
Neutropenia severity, ANC	1·0 (0·86–1·1)

Data are n (%) or median (IQR). ANC=absolute neutrophil count. CNRD=Central Non-Rechallenge Database.

Table 2: **Summary of outcomes after clozapine rechallenge**

A substantially larger proportion of patients had a competing event than had re-registration, with the cumulative incidence of end of follow-up before 6 months reaching 20%. The cumulative incidence of all-cause exit by 6 months was 27%.

Overall, 17 (4%) patients had threshold-based agranulocytosis after clozapine rechallenge, with a median time to agranulocytosis of 144 days (IQR 30–670). Two (11%) patients recorded agranulocytosis both before and after clozapine rechallenge. Ten (59%) patients recorded agranulocytosis within the first 6 months, with an incidence rate of 4·6 per 1000 person-months (95% CI 2·2–9·0). The median time to their index CNRD registration was 44 days (IQR 14–1012). Amongst these 17 patients, eight (47%) patients had pattern-based agranulocytosis, with a median time to onset

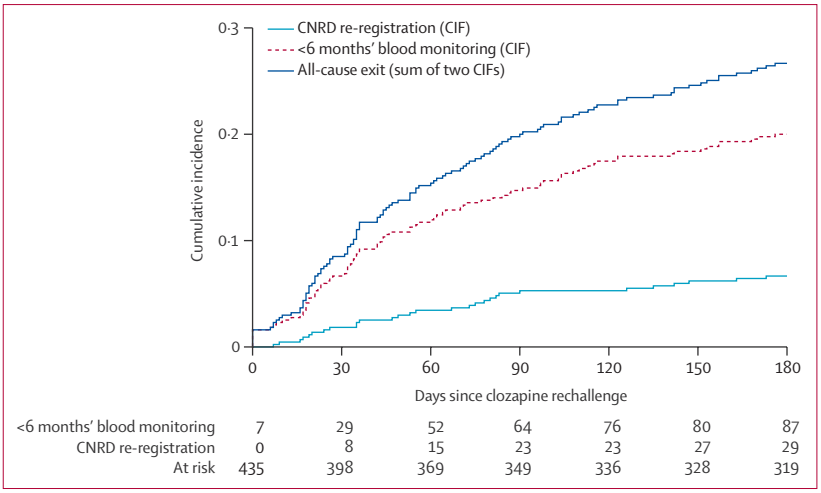

***Figure 2*: Cumulative incidence of re-registration on the CNRD after clozapine rechallenge**
CIF=cumulative incidence function. CNRD=Central Non-Rechallenge Database.

	Unadjusted HR (95% CI)	Adjusted HR (95% CI)
Sex (male *vs* female)	2·74 (1·05–7·18)	2·16 (1·11–4·02)
Age at rechallenge per year	1·04 (1·01–1·08)	1·06 (1·01–1·11)
Age at rechallenge per year × time*	0·99 (0·98–1·01)	0·99 (0·98–1·00)
Ethnicity (Other *vs* White)	0·43 (0·15–1·25)	0·67 (0·32–1·15)
Baseline ANC, per 1×10⁹/L	1·45 (1·21–1·72)	1·38 (1·09–1·61)
Index agranulocytosis (yes *vs* no)	2·38 (0·906–6·230)	1·85 (0·67–3·77)
Time to index CNRD per 30 days	1·00 (1·00–1·01)	1·00 (1·00–1·00)
Time to rechallenge from index CNRD per 30 days	1·00 (0·98–1·02)	1·00 (0·99–1·01)

ANC=absolute neutrophil count. CNRD=Central Non-Rechallenge Database. HR=hazard ratio. *Time-varying effect to address the proportional hazards violation.

***Table 3*: Univariate and multivariate HR model for re-registration on the CNRD**

of 31 days (IQR 25–78 days). A more detailed demographic summary of patients who developed agranulocytosis before and after clozapine rechallenge is provided in the appendix (pp 6–8).

Within our cohort, unsuccessful rechallenge within 6 months was significantly associated with male sex (adjusted HR 2·16 [95% CI 1·11–4·02]) and higher baseline ANC (1·38 per 1×10⁹/L [1·09–1·61]; table 3). Age at rechallenge showed evidence of a time interaction (main effect adjusted HR 1·06 per year [95% CI 1·01–1·11]; time interaction HR 0·99 [95% CI 0·98–1·00]), although the overall effect was small. Ethnicity (Other *vs* White: adjusted HR 0·67 [95% CI 0·32–1·15]), index agranulocytosis (1·85 [0·67–3·77]), and the time-based covariates (time to index CNRD per 30 days adjusted HR 1·00 per year [95% CI 1·00–1·00] and time to rechallenge per 30 days adjusted HR 1·00 per year [95% CI 0·99–1·01]) were not significantly associated with unsuccessful rechallenge.

In multivariable analyses of failure to complete 6 months of post-rechallenge monitoring, none of the covariates showed meaningful associations (appendix p 33). Overall, there was little evidence that factors linked to unsuccessful rechallenge influenced follow-up completion within the 6-month monitoring period.

Discussion

To our knowledge, this study represents the largest UK-based analysis of clozapine rechallenge following suspected neutropenia. Among 435 patients with CNRD registration, 319 (74%) of those rechallenged were still receiving clozapine 6 months after re-initiation, underscoring the feasibility of rechallenge in carefully selected cases. Higher baseline neutrophil status, older age, and male sex were the only factors significantly associated with unsuccessful outcomes. These findings highlight that current monitoring systems lack specificity, contributing to false positives and unnecessary treatment discontinuations.

Earlier studies often defined successful rechallenge as the absence of any subsequent neutropenic event—that is, no single WCC or ANC result necessitating clozapine discontinuation irrespective of duration or severity. This definition reflected prevailing discontinuation criteria and, where applicable, CNRD registration requirements during the study period. Using this broader definition, 111 patients (26%) in our cohort had a further neutropenia event. Our findings are consistent with those of Dunk and collegues,[11] who reported that 21 (38%) of 53 patients developed an additional neutropenia after rechallenge, and an Argentinian study[12] which found that six (32%) of 19 patients had recurrent neutropenia. Meyer and colleagues[13] similarly reported that four (21%) of 19 patients had repeated neutropenia after rechallenge, although this was within a tertiary service specialising in clozapine rechallenge. Using the revised criterion of a confirmed red result, our study identified only 29 (7%) patients for whom treatment was unsuccessful within 6 months of rechallenge.

A key limitation of earlier studies is the lack of consideration of the timing of neutropenic events. The high-risk period for clozapine-induced agranulocytosis is generally within the first 18 weeks of treatment.[17] Our cohort had a substantially longer interval between clozapine initiation and CNRD registration (median time of 9 years [IQR 4–13]), compared with earlier studies that reported median intervals of 0·8 and 1·0 years.[11,12] This finding suggests that late-onset neutropenia is less likely to reflect true clozapine-induced agranulocytosis, supporting the rationale for rechallenge in such cases. Current studies have similarly provided inconsistent findings regarding the severity and duration of neutropenia on rechallenge. For instance, Dunk and colleagues[11] reported that among 20 patients, the second episode of blood dyscrasia lasted longer in 60% (p=0·037) and was more severe (p<0·001) and occurred more rapidly (p<0·001) in 85%. By contrast, Prokopez and colleagues[12] found that the second episode was less severe in five (83%) of six cases. In our cohort, the

duration was longer and severity of neutropenic events worse (median duration increased from 4 days [IQR 2–8] to 6 days [3–15] and median ANC decreased from $1·5×10^9$/L [1·3–1·7] to $1·0×10^9$/L [0·9–1·1]). These discrepancies might reflect differences in population characteristics, monitoring practices, and the use of adjunctive treatments.[18] Notably, in our study, time to CNRD registration after rechallenge was markedly shorter (median 57 days [IQR 27–84] *vs* 3 years [1–8] during initial exposure), suggesting an immune-mediated mechanism of increased severity.[11,12]

Haematological monitoring during clozapine treatment aims to prevent agranulocytosis and its sequelae, including life-threatening infections.[2] By most definitions, drug-induced agranulocytosis is an ANC of less than $0·5×10^9$/L. In our cohort, 40 (9%) patients had agranulocytosis during first exposure to clozapine. Conventional guidance recommends against rechallenge in such cases, as clozapine is presumed causative and weak evidence suggests re-exposure might precipitate a more rapid and severe recurrence. For instance, Safferman and colleagues[19] reported quicker recurrence among nine patients rechallenged after leukopenia or agranulocytosis. However, their study did not specify how many had true agranulocytosis versus leucopenia, the latter of which might result from alternative causes, such as viral infections or nutritional deficiencies. This distinction is important given emerging evidence that clozapine itself might increase infection risk. Our findings support this interpretation: only two of the 40 patients who had agranulocytosis during initial exposure developed agranulocytosis again over a median follow-up of 1·4 years after rechallenge. Considering that their median time to onset during first exposure was 6 years (IQR 3–11), clozapine was unlikely to have been the primary cause.[20] Furthermore, previous work indicates that some ANC results of less than $0·5×10^9$/L might be spurious, related to ADAN, concomitant medications (eg, valproate), or laboratory error.[11,13,21] As expected, the incidence proportion of agranulocytosis was lower among patients selected for rechallenge than in the broader CNRD population (40 [9%] *vs* 586 [17%]). These findings underscore that agranulocytosis status should not be considered in isolation and that latency should also guide rechallenge decisions.

Conversely, 17 patients recorded agranulocytosis rapidly after rechallenge (median onset 144 days [IQR 30–670]), suggesting a true clozapine effect. Apart from the two individuals aforementioned, these patients did not have agranulocytosis initially, indicating that early discontinuation criteria might have been effective in preventing impending agranulocytosis at first exposure. This assertion is supported by the median time to initial CNRD registration of 44 days for these patients. Descriptively, unsuccessful rechallenges more frequently exhibited both pattern-based and early threshold-based agranulocytosis, with larger differences seen for early cases. A limitation of our study is the absence of data on the use of adjunctive strategies such as granulocyte colony-stimulating factor (G-CSF)[18,22] and lithium,[13,23] which are increasingly used to mitigate clozapine-induced agranulocytosis during rechallenge. To distinguish spurious from true agranulocytosis, we applied recently suggested pattern-based criteria.[15] Among the 17 patients who developed agranulocytosis after rechallenge, eight (47%) had pattern-based episodes, compared with only 11 (27%) in the initial-exposure group, supporting evidence that pattern-based criteria might be a more reliable indicator of true clozapine-induced agranulocytosis.[24]

From a clinical perspective, a central question remains: which patients are suitable candidates for clozapine rechallenge after suspected neutropenia? Although Prokopez and colleagues[12] found no significant demographic or clinical differences between patients who developed a second neutropenia and those who did not, our findings could suggest otherwise. Specifically, our study found that a higher ANC status during initial exposure was associated with unsuccessful outcomes. This finding might be explained by ADAN or constitutional neutropenia. Weak evidence suggests that Black patients are less likely to develop clozapine-induced agranulocytosis compared with other ethnic groups and that the lower neutrophil counts could confer a protective effect, although further investigation is required.[7] Given that ADAN is often under-recognised in clinical practice and ethnicity alone is an unreliable predictor of atypical chemokine receptor 1 status, in this instance, median ANC likely served as a more reliable proxy for baseline neutrophil status.[21,25–27] Meyer and colleagues[13] found that lower baseline ANC predicted successful rechallenge and observed that patients with shorter initial clozapine exposure were more likely to be successfully rechallenged, suggesting that early discontinuation might have been driven by constitutionally low neutrophil counts rather than true clozapine toxicity. Notably, patients with ADAN in our sample were more likely to undergo clozapine rechallenge. Although uncertain, ADAN was probably recognised at rechallenge in many cases, reinforcing evidence that unrecognised ADAN contributes to unnecessary clozapine discontinuation and ethnic disparities in access.[25] Alternatively, ADAN-adjusted monitoring might have been used strategically to prevent red results regardless of confirmed atypical chemokine receptor 1 status.[25] Furthermore, our analysis showed a higher risk of neutropenia among male patients and with increasing age, although both findings should be interpreted cautiously. The association with sex could reflect residual confounding such as greater use of valproate in this subgroup or a broader predisposition to infection rather than a direct clozapine-related effect.[17,28]

Our findings support that clozapine rechallenge is often successful and should be considered in carefully selected patients, particularly when the initial event was

outside of the highest risk period and alternative causes of neutropenia have been identified. Future research should address refining risk stratification through statistical modelling, validating pattern-based criteria for true clozapine-induced agranulocytosis, and evaluating when adjunctive strategies such as G-CSF and lithium are indicated in improving rechallenge success. Recent revisions to monitoring criteria by the EMA[3] might reduce the need for such adjunctive treatments and help prevent unnecessary adverse effects.

There are limitations that warrant mention. First, the observational design introduces potential bias and misclassification of clozapine-induced neutropenia cannot be ruled out. Our survival analyses assume non-informative censoring, although we could not verify this directly. In our cohort, 20% of patients did not complete 6-month monitoring without CNRD re-registration, and the reasons for early discontinuation were not available, raising the possibility of informative censoring. Second, detailed information on adjunctive strategies such as G-CSF or lithium (both of which could influence rechallenge outcomes) was unavailable. Additionally, some patients might have discontinued clozapine before recording agranulocytosis, suggesting that cases could have gone undetected. Third, patients who were rechallenged were likely selected on the basis of consultant judgement and thorough risk assessment, including specialist haematology input, which limits the generalisability, particularly given that our cohort represents only 9% of patients registered on the CNRD. Moreover, the likelihood of rechallenge and its outcomes might have been influenced by specialist hospitals with relevant expertise. Fourth, the small sample size, few outcome events, and high attrition limit statistical power and the ability to adjust for confounding. Effect estimates should be interpreted with caution and findings should be considered exploratory and hypothesis generating rather than establishing definitive risk factors. Fifth, the absence of mortality data or medical interventions such as antibiotics and G-CSF makes it impossible to fully assess the risks associated with rechallenge. Finally, our study is limited by no involvement of people with lived experience in the design and interpretation of this study.

In summary, our findings indicate that clozapine rechallenge after neutropenia is feasible in selected patients, with only 7% of patients with recurrent neutropenia requiring CNRD registration and the majority remaining on clozapine at the end of follow-up. Our findings support a more individualised, risk-based approach to rechallenge decisions rather than automatic permanent discontinuation, while highlighting the need for future guideline revisions to balance haematological safety with the substantial risks of undertreating treatment-resistant schizophrenia.

Contributors

EO conceived the study. EO, OD, and EW designed the study. EO and DO had access to raw data. EO and DO collected and verified the data. EO and DO analysed the data and EO, OD, EW, and DT interpreted the data. EO wrote the initial manuscript text. All authors contributed to the drafting and revision of the manuscript. All authors had final responsibility for the decision to submit for publication.

Declaration of interests

DT has received research funding from Janssen and Otsuka; consultancy payments from Viatris, Merck, and Idorsia; and holds shares in 428Pharma and Myogenes. JM has received investigator-initiated research funding from H Lundbeck. He has received research funding for clinical trials from H Lundbeck, Bristol Myers Squibb, and Newron Pharmaceuticals. He has participated in advisory boards for H Lundbeck, LB Pharma, Newron Pharmaceuticals, and Teva UK. DS has received grant support from the National Health and Medical Research Council (GNT1194635). All other authors declare no competing interests.

Data sharing

The data that support the findings of this study are available from the corresponding author, EO, upon reasonable request.

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