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Clozapine Response in Schizophrenia and Hematological Changes

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Abstract:

Background: Clozapine is the only effective medication for treatment-resistant schizophrenia; however, its mechanism of action remains unclear. The present study explored whether its effectiveness is related to changes in hematological measures after clozapine initiation.

Methods: Patients with treatment-resistant schizophrenia commenced on clozapine between January 2007 and December 2014 by the United Kingdom's largest mental health trust were identified from electronic patient records. Hematological data from these patients were obtained from a monitoring registry. White blood cell, neutrophil, and platelet count were assessed at baseline and during the early phase of clozapine treatment. Clozapine response at 3 months was defined as "much," or "very much" improved on the seven-point Clinical Global Impression—Improvement (CGI-I) subscale.

Results: In the total sample (n = 188), clozapine initiation was associated with a significant transient increase (peaking in weeks 3 to 4) in white blood cell, neutrophil, and platelet count ($P < 0.001$). There were 112 (59.6%) patients that responded to treatment; however, none of the hematological factors assessed at baseline, nor changes in these factors, were directly associated with treatment response.

Implications: Clozapine treatment is associated with transient hematological changes during the first month of treatment; however, there was no evidence that these were related to the therapeutic response.

Key Words: clozapine, psychosis, inflammation, hematology

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Treatment-resistant schizophrenia is defined as an inadequate response to treatment with at least 2 antipsychotics,¹ and occurs in around 30% of patients.² It is associated with particularly poor clinical outcomes, including greater functional impairment³ and hospitalization rates.⁴ Clozapine is the only effective intervention for treatment-resistant schizophrenia. The number of otherwise treatment-refractory patients who respond positively to clozapine is typically estimated to be between 30% and 45%;^{5–7} commonly defined as a reduction in positive symptoms by 20% or more.¹ Although clozapine has a unique pharmacological profile among antipsychotics,⁸ the reasons for its superior clinical efficacy are still unclear.⁹ Understanding its mechanism of action is important, because it may help to predict which patients are most likely to respond to clozapine, as well as potentially identify novel therapeutic targets for schizophrenia.

Clozapine has several hematological side effects.¹⁰ Approximately 4% of patients initiated on clozapine exhibit neutropenia of which 1% develop agranulocytosis, which has an associated case fatality rate of 2.1%.¹¹ The pharmacodynamic mechanisms underlying these hematological abnormalities are not fully understood; however, there is support for immunological factors playing an important role.^{12,13} Because of these risks, mandatory blood tests for patients initiated on clozapine have been introduced in many countries.¹⁴ In vivo and ex vivo studies have identified clozapine having complex immunomodulatory properties,^{15,16} including a transient increase in peripheral white blood cells (WBCs) after drug initiation,^{17,18} and there has been increasing interest as to whether clozapine's unique efficacy may be related to these immunomodulating effects.¹⁹ The primary aim of this study was to investigate whether response to clozapine, in patients with treatment-resistant schizophrenia, was associated with changes in hematological cell count.

MATERIALS AND METHODS

Study Design

A cohort design was used to study patients initiated on clozapine and under the care of South London and Maudsley (SLaM) NHS Foundation Trust; the largest mental health trust in the United Kingdom serving a population of 1.3 million.²⁰ The sample consisted of all patients initiated on clozapine for the first time between January 1, 2007, and December 31, 2014, meeting the eligibility criteria.

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Inclusion criteria required patients to be aged 18 to 65 years and have a clinical diagnosis of schizophrenia spectrum disorder (F2X) according to the International Classification of Diseases, 10th Edition (F20-F29, inclusive) and be treated with clozapine for a minimum of 12 weeks. Patients were required to have undergone a pre-clozapine blood test (up to 10 days before initiation). As our primary objective was to explore temporal changes in hematological indices during the window of interest, patients were also required to have undergone a minimum of 12 blood tests (for assessment of full blood count) during the first 12 weeks of treatment. This period was chosen to closely align with the 3-month period over which response to clozapine was assessed.

Clinical data were extracted using the SLaM NHS Foundation Trust Biomedical Research Centre Clinical Record Interactive Search (CRIS).²¹ This tool searches a research repository of real-time, anonymized data derived from the electronic health records of patients treated within SLaM. Data are organized in the form of structured and unstructured free-text fields. Eligible patients were identified from CRIS using two natural language processing applications. The first identified patients with a diagnosis of schizophrenia spectrum disorder (F2X), and the second identified the subgroup of patients initiated on clozapine during the window of interest. These applications were developed using General Architecture for Text Engineering, a Java suite application which enables development of language processors capable of interpreting corpus linguistics and syntax, which has been extensively applied to mental health research.²²

As part of the United Kingdom's mandatory monitoring protocol, all patients initiated on clozapine underwent a baseline blood test for hematological indices (WBC, neutrophil, and platelet count) followed by weekly blood tests during the first 18 weeks of treatment. Using a patient-specific 7-digit code, clinical records identified through CRIS were linked to the Zaponex Treatment Access System (ZTAS); a dedicated hematological monitoring database for patients treated on clozapine (ZAPONEX; Teva UK, Harlow, United Kingdom). After titration, the regular prescribed daily dose of clozapine was decided by the treating clinician, based on clinical effectiveness and tolerability.

The study was performed under a preexisting approval for CRIS as a data resource for secondary analysis by Oxford Research Ethics Committee C (reference 18/SC/0372) and adhered to the Strengthening the Reporting of Observational Studies in Epidemiology guidelines for reporting cohort studies.²³

Data Extraction

Sex, ethnicity, age (at clozapine initiation), duration of psychosis, and schizophrenia subtype were extracted from structured fields. Clozapine dose (closest to 12 weeks after initiation), prescription of lithium (within 7 days before commencing clozapine, or during the window of interest), body mass index, and smoking status (both closest to clozapine initiation) were extracted using natural language processing applications. Of included patients, 30% also had variables extracted manually to verify accuracy. Potential confounders and effect modifiers were recorded from the clinical database. Values for WBC, neutrophil, and platelet count were retrieved from ZTAS. Retrospective clinical assessments were performed by two researchers based on electronic health records using the Clinical Global Impression (CGI) scale, a research-tool developed to assess change in global functioning relative to baseline.^{24,25} The CGI Improvement (CGI-I) subscale measures change in symptom severity from baseline on a seven-point Likert-type scale ranging from "very much improved" to "very much worse." The CGI-I scores for each patient were rated independently by

two researchers blind to hematological status with inter-rater agreement measured using intraclass correlation coefficient (ICC).

Primary Outcome—Treatment Response

The primary outcome was treatment response, as measured by the CGI-I score at 3 months after clozapine initiation. This interval was chosen based on evidence that treatment response is typically demonstrated by this period.^{26,27} A treatment responder was defined a priori as "very much improved" or "much improved" (CGI-I score of 1 to 2), whereas a non-responder was defined as "minimally improved" to "very much worse" (CGI-I score of 3 to 7).²⁵

Hematological Variables

The pre-clozapine full blood count test was used to characterize baseline WBC, neutrophil, and platelet count. Hematological changes after clozapine initiation were characterized in three ways. First, maximum values over the 12-week period, and the week in which they occurred, were ascertained for each patient. Second, area under the curve (AUC), following the trapezoidal rule method, was calculated to estimate change in cell count between adjacent blood test intervals. Cumulative AUC (based on the sum of all AUCs between blood test intervals between baseline and week 12) was then calculated to estimate clozapine associated change. For maximum cell count and cumulative AUC, absolute and adjusted values were derived. The adjusted maximum cell count was calculated by subtracting the pre-clozapine baseline cell count from the maximum value, whereas the adjusted cumulative AUC was calculated by multiplying the pre-clozapine baseline value by the number of blood test intervals (ie, 12) and then subtracting this value from the absolute cumulative AUC.

Data Analysis

Baseline demographic, clinical and hematological characteristics for the cohort were described for completeness and to clarify the external validity. Correlations between baseline WBC, neutrophil and platelet count were assessed using Pearson correlation coefficient. A repeated-measures analysis of variance, with cell count as the dependent variable and time as the independent variable, assessed change over time for all 3 cell types. A Bonferroni correction was applied to adjust for multiplicity. Clinicodemographic characteristics were compared across treatment response groups (responders vs non-responders) using a Student's *t* test for continuous variables and a χ^2 test for categorical variables. Univariable and multivariable (adjusted for age and clozapine dose) logistic regression analyses were performed to examine associations between hematological variables and treatment response. For all analyses, 95% CIs were calculated with an associated *P* value. Analysis was carried out using SPSS Statistics for Windows version 23 (IBM Corp. Released 2015. IBM SPSS Statistics for Windows, Version 23.0; IBM Corp, Armonk, NY).

Population Under Investigation and Missing Data

The population under investigation consisted of patients with treatment-resistant schizophrenia commenced on clozapine for a minimum of 3 months. A complete-case analysis approach was used with regards missing data of the key variables, namely, hematological variables and treatment response.

Sensitivity Analysis

In secondary analysis, statistical tests were repeated after excluding patients with clinically elevated WBCs at baseline ($>11 \times 10^9/L$), to explore the possible impact of non-clozapine

related factors mediating hematological profile, such as a concomitant infection.

RESULTS

Population Characteristics

A total of 188 patients with treatment-resistant schizophrenia initiated on clozapine during the defined window met eligibility criteria. The mean age of included patients was 36.0 years (SD = 10.1) and 32.5% (61/188) were women. All patients followed a standard clozapine titration, starting at 12.5 mg daily in accordance with the Maudsley Prescribing Guidelines in Psychiatry.²⁸ The mean clozapine dose at 12 weeks was 310 mg (SD = 132 mg). Table 1 summarizes the demographic and clinical characteristics of the sample.

Hematological Characteristics of the Whole Sample

The mean interval between blood tests was 6.9 days (SD = 2.0); in line with patients undergoing a weekly blood test, as per guidelines.²⁸ At baseline, 25 (13.3%) patients had a WBC count above the reference range ($>11.0 \times 10^9/L$). There was a mild positive correlation between platelet count and WBC ($r^2 = 0.10$), as well as neutrophil count ($r^2 = 0.08$).

Peak cell count, based on modal average, occurred in the third week of treatment for WBC and neutrophils, and the fourth week of treatment for platelets (see Fig. 1). A Bonferonni-corrected repeated measures analysis of variance revealed peak cell count was significantly elevated from baseline for WBC (MD, 3.0; 95% CI, 2.6–3.4; $P < 0.001$), neutrophil (MD, 2.7; 95% CI, 2.4–3.07; $P < 0.001$), and platelet count (MD, 84.3; 95% CI, 72.6–95.9; $P < 0.001$). By the 12th week of treatment, there was no significant difference from baseline for any of the cell types ($P > 0.05$).

One hundred and twelve (59.6%) patients responded to treatment, based on CGI-I score at 3 months with excellent interrater agreement observed (ICC, 0.91; 95% CI, 0.87–0.94). Table 1

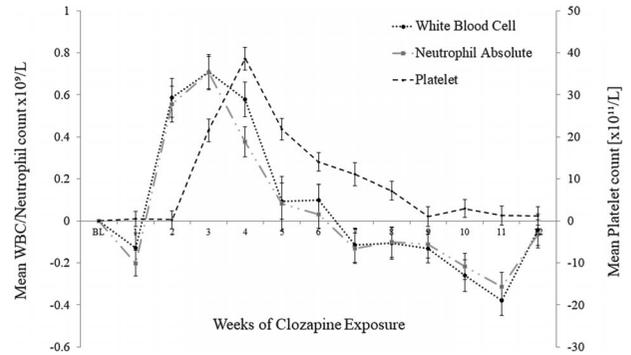


FIGURE 1. Temporal profile of WBC, neutrophil (left y axis), and platelet (right y axis) counts for all patients initiated on clozapine displayed as change from baseline. Error bars represent ± 1 standard error.

describes the demographic and clinical characteristics stratified by treatment response. The only difference between the groups was sex, with women (72.1%) more likely to respond than men (53.5%) ($P = 0.02$).

Hematological Variables and Treatment Response

Mean cell count for WBC, neutrophils and platelets for responders and non-responders are plotted in Figure 2. In logistic regression models, baseline and peak cell count were not significantly associated with treatment response. In addition, cumulative AUC did not significantly predict treatment response.

DISCUSSION

Summary of Main Findings

To our knowledge, this is the largest study to have investigated the relationship between hematological measures and the response

TABLE 1. Demographic and Clinical Characteristics (Whole Cohort and Stratified by Treatment Response)

	All Patients (N = 188)	Responders (n = 112, 59.6%)	Non-responders (n = 76, 40.4%)	Mean Difference (95% CI)	P
Sex (F/M), n (%)	61 (32.5)/127 (67.6)	44 (39.3)/68 (60.7)	17 (22.4)/59 (77.6)		0.02*
Age (SD), years	36 (10.1)	35.9 (10.6)	36.1 (9.4)	0.2 (-1.8, 2.1)	0.90
Clozapine dose (SD), mg	310.1 (132.1)	295.4 (127.6)	331.2 (136.2)	35.8 (33.9, 37.8)	0.09
Lithium (yes/no), n (%)	13 (6.9)	8 (7.1)	5 (6.6)	N/A	0.88
BMI (SD) (kg/m ²)	28.3 (6.4)	28.6 (6.6)	28.2 (6.1)	0.4 (-1.6, 2.4)	0.72
Ethnicity n (%)					
White	79 (42)	48 (42.9)	31 (40.8)		
Black	83 (44.2)	47 (42.0)	36 (47.4)		0.70
Other	26 (13.8)	17 (15.2)	9 (11.8)		
Smoking (yes/no) n (%)	148 (78.7)/ 40 (21.3)	88 (78.6) / 24 (21.4)	60 (79) / 16 (21.1)		0.95
Diagnosis n (%)					
Schizophrenia	170 (90.4)	104 (91.2)	66 (89.2)		
Other F2X diagnosis	18 (9.6)	10 (8.8)	8 (10.8)		
Duration of psychosis (SD), years	3.3 (2.7)	3.4 (2.8)	2.9 (2.7)	0.5 (-0.8,1.9)	0.42

Mean and standard deviation reported for continuous variables (age, clozapine dose, BMI, duration of psychosis). Count and percentages reported for categorical variables (sex, lithium use, ethnicity, smoking, primary psychiatric diagnosis). The duration of psychosis was defined as the interval from first diagnosis of a psychotic disorder to clozapine initiation. For continuous variables, the mean difference between treatment responders and non-responders was calculated alongside 95% CI. P values indicate the results of Student t test for continuous variables and χ^2 test for categorical variables comparing responder and non-responder subsamples.

BMI, body mass index.

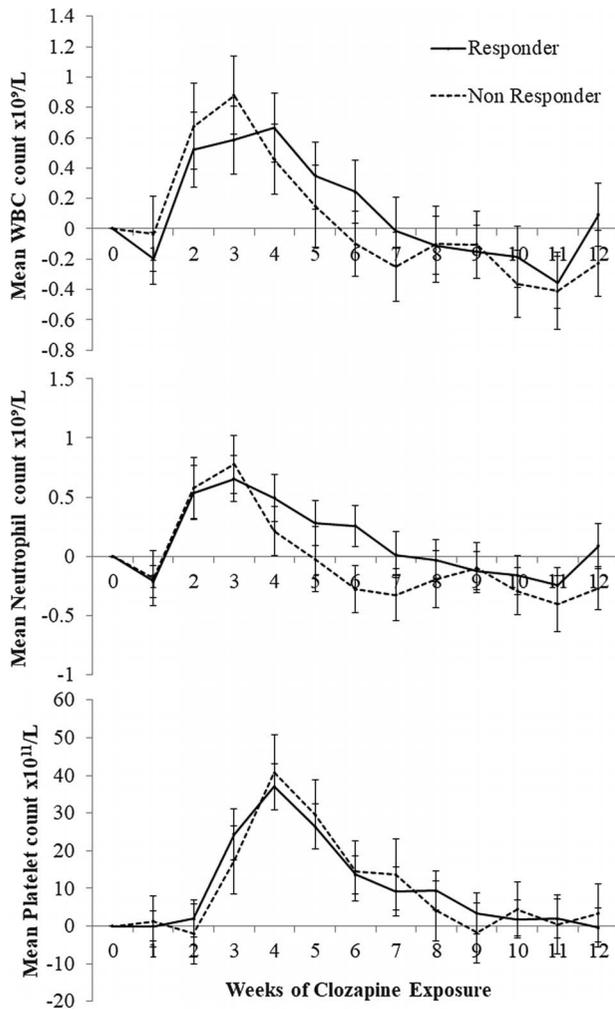


FIGURE 2. Temporal profile of WBC (top panel), neutrophil (middle panel), and platelet (lower panel) counts by treatment response as change from baseline. Error bars represent ± 1 standard error.

to clozapine. We did not find a relationship between WBC, neutrophil count or platelet count and treatment response at 12 weeks.

Early Hematological Effects of Clozapine

Consistent with data from previous clinical studies,^{17,18} there was a transient rise in the level of WBCs, neutrophils, and platelets after clozapine initiation. Cell counts peaked in weeks 3 to 4; however, by the 12th week of treatment, cell counts did not differ significantly from baseline. Although an observational study cannot provide evidence of causality, the close temporal relationship with the start of treatment is consistent with these hematological changes being clozapine-induced. How clozapine could give rise to this response remains to be fully explained, although the growth factor, granulocyte-colony stimulating factor (G-CSF) has been postulated to play a role.²⁹ The rise across hematological cell types is consistent with clozapine acting on cells before differentiation,¹⁷ although interpretation is limited by the restricted number of cell types assessed.

Clozapine is an antagonist of dopaminergic, serotonergic, adrenergic, histaminergic, and muscarinic receptors.³⁰ Clozapine also has a range of effects on the immune system, including elevating interleukin (IL)-4 and IL-2 receptor levels and reducing IL-10 and interferon- γ levels.^{15,31} Evidence suggests that clozapine

may exert these effects by binding to neurotransmitter receptors within bone marrow and peripheral hematological cells.³²

Immune System and Predictors of Treatment Response

Converging lines of evidence support a role for the immune system in schizophrenia.³³ Immune activation, as a result of infections in early life, is a risk factor for later psychosis^{34,35} as are several autoimmune diseases.³⁶ Genome-wide association studies indicate that the strongest genetic association with schizophrenia involves the major histocompatibility complex locus.³⁷ Patients experiencing acute psychosis have also been shown to have elevated inflammatory markers.^{38,39}

Although it has been speculated that the immunomodulatory properties of clozapine may play a role in its unique efficacy,¹⁹ this was not supported by our findings. To our knowledge, only one study has investigated the relationship between peripheral hematological markers and clozapine response. This study found an association between a reduction in positive psychotic symptoms and a lower neutrophil count at 8 weeks, whereas a reduction in negative symptoms was associated with lower WBC count.⁴⁰ In contrast, we did not find an association between changes in WBC (or neutrophil) count and treatment response, although we did not assess changes in positive and negative symptoms separately.

The finding that women were more likely to respond to clozapine than men is consistent with previous research,⁴¹ although the reason for this remains unclear. The metabolism of clozapine is known to differ by sex, with women exhibiting higher plasma concentrations when controlling for dose.^{42,43} It is, therefore, possible that the sex effect may reflect differences in circulating clozapine concentration. In the present study, male patients were also more likely to be smokers, which may have also contributed toward lower clozapine plasma concentrations.⁴⁴⁻⁴⁶

Strengths

This is the largest study to date to have explored the relationship between hematological markers and treatment response to clozapine. The serial measurement of hematological markers at weekly intervals provided a high degree of temporal resolution. In addition, patients were identified from a monitoring database; therefore, the sample can be considered highly representative of the patient population. As all patients in the United Kingdom are required (as per national guidelines) to undergo regular hematological testing while on clozapine, a high level of data completeness was ascertained. Finally, we were able to model hematological changes relative to each patient's pre-clozapine blood test, thereby providing an individualized reference point to measure change.

Limitations

The study was limited to a small number of hematological markers. A wider array of indices would have been informative to further elucidate the immune response associated with clozapine. Measurement of acute-phase proteins, differential WBC count and cytokine levels are recommended for inclusion in future research.⁴⁷ Assessment of treatment response was performed retrospectively, based on electronic patient records. However, we were able to demonstrate a high level of concordance between raters, and treatment response was assessed blind to hematological indices. Although the pre-clozapine blood test provided an individualized reference point, natural variations in hematological markers are likely to have introduced a degree of imprecision. We excluded patients whose clozapine was discontinued before 3 months, which may have biased the sample in favor of treatment responders. Data on the use of other antipsychotic medication was unavailable,

therefore, the potential effects of cross-titration could not be explored. A power analysis was not performed; therefore, it is possible that our study was underpowered to detect a difference between groups. Plasma clozapine levels were not available for analysis. Finally, the study was retrospective, naturalistic and did not include a comparator group.¹⁸ Therefore, there were several potential confounders, such as concomitant medication, which could not be controlled.

Contributions

Although several studies have investigated the hematological effects of clozapine in relation to its side effects, this is the largest study to have explored the association between hematological profile and treatment response in some detail and with statistical rigor. As such, the study contributes toward a better understanding of the mechanism of action of clozapine. At present, assessment of treatment response to antipsychotic medication in patients with schizophrenia can only be determined empirically, after a lengthy trial of medication. The identification of candidate biological markers to predict treatment response, so-called treatment biomarkers, would be a major advance in moving toward a personalized approach to psychiatry. This is particularly relevant with regards commencing clozapine, where at present, patients who do not respond are nevertheless exposed to potentially serious side effects.

CONCLUSIONS

The study identified a transient increase in WBC, neutrophil, and platelet count closely associated with clozapine initiation in a sample of patients with treatment-resistant schizophrenia. Although the study provides evidence in support of clozapine having early hematological effects, despite thorough investigation, these changes were not found to predict treatment response.

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