Schizophrenia

ARTICLE OPEN

Low awareness of clozapine-induced agranulocytosis in a mixed-method survey of 354 patients and carers

Ebenezer Oloyede[1,2✉], Von-de-viel Nettey[3], Olubanke Dzahini[1], Ed Silva[4], Ninoslav Majkic[1], Patricia Montford[4], Agostina Secchi[3], Eromona Whiskey[1,5,6] and David Taylor[1,5,6]

Current preventative measures for clozapine-induced agranulocytosis (CIA) include indefinite haematological monitoring. Another safeguard against CIA is patient and carer education to identify and respond to potential symptoms of this adverse effect. Our aim was to explore how informed patients and carers are about the potential symptoms of CIA and what actions to take. An anonymous cross-sectional survey was distributed electronically to patients or family/carers prescribed clozapine across England. A mixed methods approach was used to assess how informed patients and carers are about CIA, identifying potential symptoms of CIA and the appropriate actions to take. Quantitative data were analysed using descriptive and inferential statistics, and qualitative responses were analysed thematically. A total of 354 individuals participated in the survey (310 patients and 44 unrelated family carers). Overall, 122 (35%) were aware that clozapine can cause agranulocytosis. The odds of awareness were significantly higher among carers (AOR = 2.90; 95% CI, 1.45–5.88) and lower among males (AOR = 0.60; 95% CI, 0.36–1.00), Black individuals (AOR = 0.33; 95% CI, 0.17–0.61) and individuals in the other ethnicity group (AOR = 0.39; 95% CI, 0.16–0.89). Among those who reported CIA awareness, 45 (37%) participants could name at least one of the signs or symptoms of CIA. A typology of responses to experiencing signs or symptoms of CIA were derived from the thematic analysis, categorised into seeking immediate medical attention (two subthemes), consulting healthcare professionals (four subthemes), uncertainty or lack of knowledge (two subthemes), involvement of family or care providers (two subthemes), self-care (three subthemes) and reluctance to seek help (two subthemes). Our results indicate that most patients and carers are unaware of CIA. There is a need to better inform patients and carers about CIA, about how to identify symptoms and the importance of consulting their treating clinician when suspicions arise. This is particularly important if calls for reduced haematological monitoring are implemented.

Schizophrenia (2025)11:129 ; https://doi.org/10.1038/s41537-025-00639-5

INTRODUCTION

Schizophrenia and related psychotic disorders are chronic, severe mental health conditions, estimated to affect 0.7–4% of the global population[1]. For approximately one-third of individuals experiencing an acute episode of psychosis, conventional antipsychotic treatments fail to provide adequate symptom reduction, a condition known as treatment-resistant schizophrenia (TRS)[2]. Clinical guidelines recommend clozapine in these cases, as it is regarded as more effective than other antipsychotic medications[3]. Clozapine-induced agranulocytosis (CIA) is a decrease in absolute neutrophil count (ANC) persistently below 0.5×10^9/L, increasing susceptibility to potentially life-threatening infections[4]. The standard preventative protocols for CIA in most countries include ongoing haematological monitoring and a heightened awareness of any newly emerging physical alterations or symptoms that may suggest an infection, including fever, sore throat, or other flu-like manifestations[5].

Epidemiological research has consistently shown that CIA occurs predominantly within the first few months of treatment, with recent data estimating an incidence of 0.9% that drops significantly after two years[6–8]. This reduced risk is further supported by observational studies suggesting it is safe to reduce blood monitoring to every three months once the initial high-risk period has passed[9,10]. The analysis of likely cases of CIA indicates a rapid decline in neutrophils over a week, casting doubt on the utility of ongoing mandatory fortnightly or monthly monitoring[11]. Furthermore, recent observational data suggests that 70% of CIA cases transition from a 'normal count' (ANC > 2.0×10^9/L) immediately to agranulocytosis (< 0.5×10^9/L) predominantly within the early stages of treatment[11]. While monitoring systems are undoubtedly effective, this body of evidence highlights their limitations and supports calls for a revision of haematological monitoring requirements after the early treatment phase to enhance patient access to clozapine[12,13].

If monitoring requirements were to be revised, patient education on identifying and responding to CIA (by seeking medical care when suspected) is plausibly the most essential safeguards against potential complications associated with CIA[14]. Despite current concerns, there have been no attempts to explore patient and family/carers understanding around clozapine's association with agranulocytosis, its identification and action it warrants when suspected. Understanding this may assist care providers and policymakers to provide optimal support and resources for patients and key others in their networks. Therefore, our aim was to explore how informed people with lived experience of clozapine treatment, their family and carers, are about the potential signs and symptoms of CIA and what actions they should take.

[1]South London and Maudsley NHS Foundation Trust, London, UK. [2]Department of Psychiatry, University of Oxford, Oxford, UK. [3]Kent and Medway NHS and Social Care Partnership Trust, London, UK. [4]Mersey Care NHS Foundation Trust, Liverpool, UK. [5]King's College London, London, UK. [6]These authors contributed equally: Eromona Whiskey, David Taylor. ✉email: Ebenezer.oloyede@psych.ox.ac.uk

METHODS

This was an online survey of patients currently prescribed clozapine in three large mental health NHS trusts in England. ~2000 patients received clozapine treatment from the hospitals surveyed. We used the Checklist for Reporting Results of Internet E-Surveys (CRES) in designing the survey[15].

Survey design

The survey was developed by a multidisciplinary team consisting of specialist mental health pharmacists and nurses. It comprised 13 items divided into two sections: demographic information, such as age, ethnicity, the number of years prescribed clozapine ($n = 9$); and CIA, including its association with clozapine, identification, and actions to take when suspected ($n = 4$).

The survey was disseminated using Qualtrics XM (Provo, Utah, USA). A pilot study of clinicians ($n = 10$) was initially conducted within the South London and Maudsley (SLaM) National Health Service (NHS) Foundation Trust to assess item range and variance, as well as content and clarity. The final version (available on request) took a median of 5 min to complete (interquartile range: 3–9 min).

Participants

A total of three NHS Trusts in England were approached via email and asked to distribute the survey to patients or carers of those currently prescribed clozapine. The NHS Trusts were selected based on convenience sampling, based on existing research collaborations that facilitated access and engagement. The NHS Trusts were Kent and Medway NHS and Social Care Partnership Trust, Merseyside Care NHS Foundation Trust and South London and Maudsley NHS Foundation Trust. All three NHS Trusts agreed to disseminate the survey. The survey was accessible for five weeks. Eligible participants were aged 18 years or older and prescribed clozapine treatment or relatives of patients receiving clozapine treatment. Patients were initially approached in person by a pharmacist, pharmacy technician or nurse to explain the survey and discussion potential participation. Alternatively, the pharmacist, pharmacy technician or nurse approached the patient's main carer to discuss potential participation. To preserve respondent independence, either the patient or their carer was included in the study, but not both.

Ethical approval

Ethical approval was obtained from the SLaM Drug and Therapeutics Committee (DTC/2024/60). All participants provided informed electronic consent before beginning the online survey.

Data analysis

The demographic and clinical characteristics of participants were summarised descriptively using mean ± SD, medians, and ranges (minimum and maximum) for continuous variables and counts (percentage) for categorical ones. For carer respondents, all demographic and clinical data reported refer to the patient they support, rather than the carer themselves. Open-ended responses regarding signs and symptoms of CIA were categorised, counted and presented as frequencies.

Open-ended responses regarding response to potential signs or symptoms of CIA were analysed thematically. Thematic categories were constructed inductively from response data by two independent researchers (EO and VN). They then met to compare themes and subthemes and derive consensus. Following the creation of these themes and subthemes, the two researchers coded each response independently, then met to discuss any discrepancies and derive a consensus.

Unadjusted odds ratios (ORs) were calculated to examine the association between (i) participants' intention to seek medical attention and CIA knowledge, and (ii) the intention to seek medical attention and the ability to identify a symptom of CIA. Seeking medical attention was defined as any form of contact with a healthcare professional, e.g., via accident and emergency (A&E), pharmacist, or general practitioner (GP).

Binary logistic regression was used to determine the factors associated with awareness that clozapine can cause agranulocytosis (yes vs no/unsure). The following factors were included: patient or carer status, age, gender, ethnicity, NHS Trust, duration of clozapine use, benign ethnic neutropenia (BEN) monitoring, and previous haematological aberrations (none or at least one amber and/or red result). Under current UK guidelines, an amber result is defined as a white blood cell (WBC) count between ≥3.0 and $<3.5 \times 10^9$/L and/or an absolute neutrophil count (ANC) between ≥1.5 and $<2.0 \times 10^9$/L, warranting increased monitoring[16]. A red result is defined as a WBC count $<3.0 \times 10^9$/L and/or ANC $< 1.5 \times 10^9$/L, warranting treatment interruption. For individuals with confirmed BEN, these thresholds are adjusted downward by 0.5×10^9/L[17].

To assess whether continuous variables (age or duration of clozapine treatment) exhibited non-linear relationships with CIA awareness, cubic splines were used to determine if transforming these variables improved model fit based on likelihood ratio tests. Model goodness of fit was assessed using the Hosmer-Lemeshow test. Multicollinearity was examined using the variance inflation factor (VIF), with a cut-off of <2. Statistical significance was defined as a two-sided p value of <0.05. Results from logistic regression model were presented as ORs with 95% confidence intervals (CIs). All analyses and visualisations were conducted in *R*, version 4.4.1 (R Project for Statistical Computing).

Role of funding source

There was no funding source for this study. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

RESULTS

Sample characteristics

Among the three hospitals, 354 individuals (310 patients and independent 44 carers) completed the survey. The median age of patients was 46 years. A total of 73 (20%) patients had a previous haematological aberration while receiving clozapine treatment (none of which were cases of CIA) and 40 (11%) were monitored with modified BEN criteria (Table 1). The exact number of patients invited to participate in the survey is unknown, preventing a formal calculation of the response rate. However, ~2000 individuals were receiving clozapine in the study hospitals. Based on this estimate, the minimum response rate can be extrapolated to 16%. All patients who provided consent successfully completed the survey.

Clozapine and agranulocytosis

122 subjects (35%) indicated that they were aware that clozapine can cause agranulocytosis, while 174 subjects (49%) were unaware. A further 58 (16%) of respondents were 'unsure' (see Fig. 1).

When asked to name some of the signs and symptoms of agranulocytosis, 45 subjects (37%) who reported CIA awareness correctly identified a sign or symptom of agranulocytosis. All these respondents indicated that they were aware that clozapine can cause agranulocytosis in the previous question. The most common symptoms reported by participants were malaise,

including flu-like symptoms (40%), fever (27%), infection (22%) and sore throat or mouth (10%).

The median duration of treatment with clozapine in years for respondents who were aware of CIA was 5.5 (IQR: 3–15) compared to 7 (IQR: 7–10) for respondents who were unaware or unsure of CIA. When stratified by the presence or absence of previous haematological aberrations, among those who had a previous haematological aberration 30 (41%) were aware that clozapine caused agranulocytosis while 43 (59%) were not. Among patients who did not have a previous haematological aberration, 92 (32%) were aware that clozapine caused agranulocytosis while 189 (67%) were not. Among individuals who received modified BEN monitoring and were aware of CIA, 28 (70%) identified as Black or from other ethnic groups. Among individuals who identified as Black or from other ethnic groups and did not receive modified BEN monitoring, CIA awareness was 22%. A summary of responses in demographic groups can be found in the supplementary material.

Table 1. Characteristics of survey participants.

Characteristics	Carer (n = 44)*	Patient (n = 310)	Overall (n = 354)
Gender (n, %)			
Male	27 (61)	224 (72)	251 (71)
Female	17 (39)	86 (28)	103 (29)
Age (median years, IQR)	52 (36 - 60)	42 (35 - 47)	46 (36 - 55)
NHS Trust (n, %)			
South London and Maudsley	37 (84)	231 (75)	268 (76)
Merseyside	4 (9)	53 (17)	57 (16)
Kent	3 (7)	26 (8)	29 (8)
Clozapine duration median years, IQR	6 (2–15)	12.5 (3.5–20.5)	7 (4–15)
Ethnicity (n, %)			
Asian	0 (0)	22 (7)	22 (6)
Black	22 (50)	92 (30)	114 (32)
Caucasian	18 (41)	162 (5)	180 (51)
Other	4 (9)	34 (1)	38 (11)
BEN Monitoring (n, %)	4 (9)	36 (12)	40 (11)
Previous haematological aberration (n, %)	10 (23)	63 (20)	73 (21)
Amber result	6 (60)	52 (83)	58 (79)
Red result	0 (0)	8 (13)	8 (11)
Amber and red results	4 (40)	3 (5)	7 (10)

Note
*'Carers' denotes the patients under care.
Amber result: General criteria WBC ≥ 3.0 and < 3.5 AND/OR neutrophils ≥1.5 and <2.0, BEN criteria WBC ≥ 2.5 and <3.0 AND/OR neutrophils ≥1.0 and <1.5.
Red result: General criteria WBC < 3.0 AND/OR neutrophils <1.5, BEN criteria WBC < 2.5 AND/OR neutrophils <1.0.
Abbreviations
BEN: Benign ethnic neutropenia.
IQR: Interquartile range.
NHS: National Health Service.

Univariable analysis

Within our cohort, the unadjusted odds of CIA awareness were higher among carers (OR = 2.33; 95% CI, 1.23–4.42, $p < 0.05$) compared to patients (Table 2 Supplementary material). The odds of being aware of CIA was lower among Black responders compared to White respondents (OR = 0.56; 95% CI, 0.34–0.93, $p < 0.05$).

Multivariable analysis

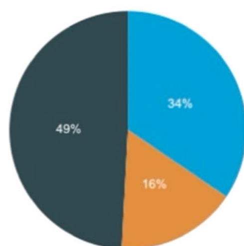
In the multivariable logistic regression analysis (Fig. 2) knowledge of CIA was associated with three variables: patient or carer status, ethnicity and gender. The odds of awareness were significantly higher among carers (AOR = 2.90; 95% CI, 1.45–5.88) and lower among males (AOR = 0.60; 95% CI, 0.36–1.00), individuals who identified as Black (AOR = 0.33; 95% CI, 0.17–0.61) or from Other ethnicity groups (AOR = 0.39; 95% CI, 0.16–0.89).

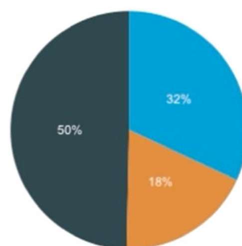
Relationship between CIA awareness and response

The question regarding responding to suspected agranulocytosis included 321 respondents (90%). Of those who would seek immediate medical attention or consult a healthcare professional, 41 (21%) were aware of CIA and could identify at least one of its symptoms. Amongst those who would take another action, 38 (24%) were aware of CIA and 4 (3%) could identify at least one of its symptoms. The odds ratio of seeking medical attention was greater in those who were aware of CIA (OR = 2.46; 95% CI, 1.33–4.58).

Responding to suspected agranulocytosis thematic analysis

Six major themes were identified regarding patient or carer response to potential signs or symptoms of CIA (Table 2). The most frequently mentioned theme was consulting healthcare professionals ($n = 139$, 43%), with the subthemes of GPs, specialised care teams, care coordinators and pharmacy. The second most common theme was uncertainty or lack of knowledge ($n = 81$, 25%), with the subthemes of unawareness of symptoms and general confusion. The third most common theme was seeking medical attention ($n = 59$, 18%), with the subthemes of emergency contact, urgent visit to A&E and escalating symptoms.





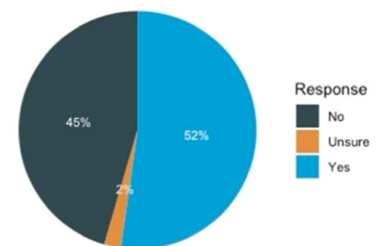


Fig. 1 Knowledge of clozapine-induced agranulocytosis.

Table 2. Representative quotes from thematic analysis on response to signs and/or symptoms of CIA.

Theme (%)	Subtheme	Participants' quotes
Seeking immediate medical attention (18)	Emergency contact	"Call 999" "Call the ambulance" "Contact emergency services" "Seek medical attention immediately"
	Urgent visit to A&E	"Go to A&E" " If unwell take to hospital"
Consulting healthcare professionals (43)	GP	"Contact GP", "We might tell GP if he is unwell"
	Specialised care teams	"Contact Clozapine team", "Talk to clozapine clinic" "Speak with psychiatric team"
	Care coordinators	"Talk to my care coordinator" "Contact care coordinator"
	Pharmacy	"Contact pharmacy for advice" "Go to pharmacist"
Uncertainty or lack of knowledge (25)	Unawareness of symptoms	"Does not know what to look for" "As a carer I have no idea that clozapine can cause a blood disorder or what to look for"
	General confusion	"Unsure" "Not sure what to do" "Don't know"
Involvement of family or caregivers (4)	Immediate family support	"Tell daughter", "Tell mum or dad" "Would talk to mum if unwell"
	Caregiver awareness	"Tell carers about symptoms" " Talk to staff at accommodation if he became unwell at all"
Self-care (5)	Hydration and rest	"Drink water" "Rest for a while" "Sleep it off"
	Use of over-the-counter medications	"Buy paracetamol from local pharmacy" "Use GSL meds"
	Natural healing	"Fight it off naturally" "Research how to deal with symptoms"
Reluctance to seek help (4)	Avoiding medical attention	"Doesn't tell anyone if unwell" "Keeps health private" "Won't usually tell anyone"
	Self-reliance or minimising symptoms	"Just get over it" "Body always fixes itself"

Abbreviations
A&E: accident and emergency.
GSL: General Sales List.
GP: general practitioner.

DISCUSSION

Study findings

In this cross-sectional survey in 3 NHS hospitals, only 35% of patients or carers were aware that clozapine can cause life threatening agranulocytosis. Of these patients, only 37% were able to identify at least one of the signs or symptoms of agranulocytosis. A substantial proportion of respondents reported that they would not know what action to take if they experienced any signs or symptoms of agranulocytosis. The odds of awareness of CIA were significantly lower among patients (compared with carers), males and respondents from Black or Other ethnic groups. The odds of seeking medical attention were higher among individuals with knowledge of CIA and those who were able to identify symptom(s) of CIA. Our findings suggest that patients and caregivers require greater education about CIA and the necessary actions to take when it is suspected.

Comparison with other studies

To our knowledge, our study is the first to specifically explore patient and caregiver understanding of CIA. Previous studies on general patient perception of clozapine have largely reported positive experiences, however, there is limited evidence that suggests communication between clinicians and patients could be improved[18,19]. For example, our previous survey of patients and carers ($n = 8$) revealed poor communication and a lack of care planning following haematological abnormalities during clozapine treatment[20]. Studies from other medical specialties have specifically examined patient understanding regarding drug-induced neutropenia. For instance, in a survey of 473 patients with cancer, only 44% of respondents were informed of the infection risk associated with febrile neutropenia prior to starting chemotherapy[21]. Furthermore, in a cohort of 105 patients with malignant lymphoma, 64 (61%) reported receiving explanations about febrile neutropenia and as a result 61 (95%) felt that they understood

Variable		N	Odds ratio		p
Status	Patient	310		Reference	
	Carer/relative	44		2.90 (1.45, 5.88)	0.003
NHS Trust	South London and Maudsley	268		Reference	
	Kent and Medway	29		0.96 (0.41, 2.21)	0.927
	Mersey Care	57		0.55 (0.26, 1.11)	0.102
Age in years		354		0.99 (0.97, 1.01)	0.404
Gender	Female	103		Reference	
	Male	251		0.60 (0.36, 1.00)	0.049
Ethnicity	White	180		Reference	
	Asian	22		1.16 (0.45, 2.95)	0.756
	Black	114		0.33 (0.17, 0.61)	<0.001
	Other	38		0.39 (0.16, 0.89)	0.031
Clozapine Duration in years		354		1.00 (0.97, 1.03)	0.980
Modified BEN monitoring	No	314		Reference	
	Yes	40		1.78 (0.81, 3.85)	0.145
Prior haematological abberation	No	281		Reference	
	Yes	73		1.48 (0.83, 2.61)	0.182

Fig. 2 Association between demographic variables and reported knowledge of clozapine associated agranulocytosis.

febrile neutropenia "well or almost well"[22]. Interestingly, despite most participants reporting that they understood febrile neutropenia, Takamatsu and colleagues found that only half of the patients responded appropriately to febrile neutropenia[22]. Consistently, in our study, of those who were aware of CIA, only one in three respondents were able to identify some the symptoms of CIA. Such findings emphasise the importance of effective patient education. Recall bias may have contributed to an underreporting of CIA knowledge by our survey respondents, as suggested by the median treatment duration of 7 years amongst participants, which is significantly longer than the 2-year highest-risk period for CIA[6]. Nonetheless, this was not shown in the regression analysis (see Fig. 2) and exploratory analysis (see supplementary material table 4 and 5). Moreover, since patients currently undergo regular monitoring indefinitely, there is an expectation that they understand the rationale behind this monitoring irrespective of treatment duration.

Group differences

In our study, we attempted to explore whether there were group differences in recognising CIA. Generally, carers were more likely to recognise CIA compared to patients, underlining the importance of including carers and family members in education about clozapine. Moreover, this may suggest that patients only receive counselling on CIA during treatment initiation when they are most unwell and less likely to retain information. Furthermore, individuals from Black and Other ethnic groups had significantly lower odds of being aware of the CIA. While this warrants further exploration, this may be related to limited health literacy amongst ethnic minorities, potentially exacerbated by language barriers and lower engagement with healthcare services[23]. A surprising finding from our study was the lack of association between previous haematological abnormalities and awareness of CIA, despite such patients undergoing increased monitoring and/or treatment interruption. This may suggest that re-education did not occur after a haematological aberration or that healthcare professionals assumed patient awareness without explicitly confirming it[20]. Together, these findings underline the need for better patient education and for regularly reassessment of patient understanding when clinical stability has been achieved.

When patients report symptoms of infection (e.g., flu-like symptoms, sore throat, high temperature) an urgent full blood count is indicated. The thematic analysis revealed that a substantial portion of respondents (43%) would appropriately consult a healthcare professional if experiencing potential symptoms of agranulocytosis, with the most common options being GPs, community clozapine clinics, pharmacies or care coordinators. An additional 18% reported that they would seek immediate medical attention, with the most common options being A&E or calling emergency services. While not completely inappropriate, attendance to A&E would only be a potential consideration if routine services were unreachable.

A substantial minority reported reliance on self-care or a reluctance to seek help. This discrepancy may be attributed to the broad and non-specific nature of CIA symptoms, which often resemble less severe or non-life-threatening clozapine adverse effects such as fever or an increased risk of infections[24]. Additionally, the median clozapine duration of 7 years among respondents may have contributed to a sense of reduced urgency or concern regarding adverse effects. However, it was concerning that 25% of respondents expressed uncertainty or a lack of knowledge regarding how to manage potential CIA symptoms, considering the potentially urgent nature of CIA. Of note, there was a positive association between seeking medical attention and awareness of CIA and the ability to identify a symptom of CIA. Overall, these findings underscore the importance of reinforcing the need for medical attention while ensuring that patients and caregivers are not deterred from continuing clozapine treatment[19]. Notably thematic categories such as self-care, reluctance

to seek help, and uncertainty or lack of knowledge may overlap in meaning and motivation. Participants' responses often reflected multiple, intertwined perspectives, which is a recognised complexity in qualitative analysis and highlights the nuanced nature of patient and carer experiences.

Clinical implications

Haematological monitoring is essential for the early detection and prevention of potential CIA. However, the duration of monitoring and the criteria for discontinuation are poorly defined, presenting a significant barrier to treatment access[12]. Current literature overwhelmingly indicates that most cases of life-threatening agranulocytosis occur within the first few years of treatment[6,7]. As such, the current stringent approach of indefinite monitoring has been described as impractical from a patient or service perspective. Instead, as proposed by others, policymakers should consider restricting monitoring to the highest-risk period[25]. To achieve this, it is imperative that patients and carers are well informed of the risks and the actions to take to prevent mortality from CIA. Moreover, encouraging patients to request an urgent FBC if they have potential symptoms of CIA, such as fever or sore throat, will likely help prevent fatalities even when haematological monitoring is in force. This recommendation is supported by the understanding that individuals with fatal agranulocytosis typically present initially with signs of infection, including febrile or upper respiratory symptoms[14]. Educational initiatives for the public regarding clozapine treatment and the risks are limited[26,27]. Given the findings from our survey, policymakers should prioritise effective education for patients and their family members to make clozapine a safer treatment. Patient and carer education should be delivered before treatment initiation and reinforced routinely at each scheduled haematological consultation. While the effectiveness of patient and caregiver education in preventing complications associated with CIA is yet to be established, patient and carer empowerment is increasingly endorsed by healthcare professionals in other medical specialties. Recognition of agranulocytosis symptoms is a key component of the safe use of clozapine when blood monitoring intervals exceed the typical time course for the development of agranulocytosis. A potential solution, as used in other conditions such as epilepsy, may be the use of electronic alert cards to remind patients and carers of symptoms related to CIA and other potentially serious adverse effects, such as clozapine-induced gastrointestinal hypomotility (CIGH). These e-cards may also be useful to non-psychiatric healthcare providers who may have limited knowledge of clozapine and its risks. This approach is particularly important given our data showing that many patients or carers would first consult their GP or community pharmacist if CIA is suspected. Alternatively, home-based ANC testing could be explored, particularly considering respondents reporting a preference for self-management or hesitance to seek medical care. Future research is warranted to investigate patient and carer awareness of other potentially serious adverse effects, such as CIGH, which carries a higher mortality rate than CIA[28]. Educational materials for individuals taking clozapine should emphasise the importance of early recognition and timely medical intervention given the potential severity.

Limitations

While this study provides valuable insights, it has certain limitations that merit further discussion. The main limitation is the uncertainty regarding the generalisability of our findings beyond the included sample. Although the study encompassed three NHS mental health trusts, there are ~54 such Trusts across England, and it remains unclear whether our sample is representative of the broader UK context or applicable internationally. Additionally, the Trusts were selected based on convenience, which introduces the possibility of systematic differences from other Trusts, such as variations in patient demographics, resource availability, and levels of clinician engagement. Another limitation of our study is that we were unable to objectively explore whether patients received counselling on CIA and what actions to take. This is particularly relevant if information was provided prior to clozapine initiation, when patients are more likely to be symptomatic and may experience information-processing challenges. Nevertheless, health care professionals such as psychiatrists, pharmacists and psychologists should consider collaborative efforts to better educate patients and family members regarding CIA on a regular basis. As the survey was about clozapine and agranulocytosis, those with some knowledge of the topic might have been more likely to participate, leading to potential bias. Future work is required to determine the effectiveness of patient and caregiver education in preventing complications associated with CIA. Lastly, it is possible that some healthcare professionals may be unaware of CIA symptoms, contributing to low awareness among patients; however, this warrants further investigation[26].

CONCLUSION

People taking clozapine are largely unaware of the risk of CIA. There is a recognised need to better inform patients and carers about CIA, including how to identify symptoms and the importance of consulting their treating clinician if concerns arise. Patient awareness will become particularly important if recommendations for reduced haematological monitoring are implemented.

DATA AVAILABILITY

The data that support the findings of this study cannot be made publicly available for confidentiality reasons. Data are however available from the corresponding author upon reasonable request.

Received: 16 April 2025; Accepted: 11 June 2025;
Published online: 30 October 2025

REFERENCES

1. Saha, S. et al. A systematic review of the prevalence of schizophrenia. *PLoS Med.* **2**, e141 (2005).
2. Howes, O. D. et al. Treatment-resistant schizophrenia: treatment response and resistance in psychosis (TRRIP) working group consensus guidelines on diagnosis and terminology. *Am. J. Psychiatry* **174**, 216–229 (2017).
3. Kane, J. M. et al. Clozapine for the treatment-resistant schizophrenic: results of a US multicenter trial. *Psychopharmacology* **99**, 60–63 (1989).
4. Xiao-Hong, L. et al. The prevalence of agranulocytosis and related death in clozapine-treated patients: a comprehensive meta-analysis of observational studies. *Psychol. Med.* **50**, 583–594 (2020).
5. Oloyede, E. et al. Clozapine haematological monitoring for neutropenia: a global perspective. *Epidemiol. Psychiatr. Sci.* **31**, e83 (2022).
6. Northwood, K. et al. Evaluating the epidemiology of clozapine-associated neutropenia among people on clozapine across Australia and Aotearoa New Zealand: a retrospective cohort study. *Lancet Psychiatry* **11**, 27–35 (2024).
7. Rubio, J. M. et al. Long-term persistence of the risk of agranulocytosis with clozapine compared with other antipsychotics: a nationwide cohort and case–control study in Finland. *Lancet Psychiatry* **11**, 443–450 (2024).
8. Brandt, A. S. et al. The timing and severity of clozapine-associated neutropenia in the US: is the risk overstated? *Schizophrenia Res.* **272**, 104–109 (2024).
9. Oloyede, E. et al. Clinical impact of reducing the frequency of clozapine monitoring: controlled mirror-image cohort study. *Brit. J. Psychiatry* **382**, 388 (2023).
10. Taylor, D. et al. The safety of 12-weekly monitoring of neutrophil count in long-term clozapine patients. *Acta Psychiatrica Scandinavica* **10**, 13818 (2025).
11. Taylor, D. et al. Distinctive pattern of neutrophil count change in clozapine-associated, life-threatening agranulocytosis. *Schizophrenia* **8**, 21 (2022).
12. Oloyede, E., Taylor, D. & MacCabe, J. J. International variation in clozapine hematologic monitoring—a call for action. *JAMA Psychiatry* **80**, 535–536 (2023).

13. Schulte, P. F. J. et al. Risk of clozapine-associated agranulocytosis and mandatory white blood cell monitoring: can the regulations be relaxed?. *Schizophr Res.* **268**, 74–81 (2023).
14. Mylan. Clozaril 25 mg tablets (2020, accessed 14th January 2023).
15. Eysenbach, G. Improving the quality of web surveys: the checklist for reporting results of internet E-Surveys CHERRIES. J. Med. Internet Res. 6, e34 (2004).
16. Oloyede, E. et al. Relaxation of the criteria for entry to the UK Clozapine Central Non-Rechallenge Database: a modelling study. *Lancet Psychiatry* **9**, 636–644 (2022).
17. Oloyede, E. et al. Benign ethnic neutropenia: an analysis of prevalence, timing and identification accuracy in two large inner-city NHS hospitals. *BMC Psychiatry* **21**, 502 (2021).
18. Murphy, K. et al. Clozapine and shared care: the consumer experience. *Aust. J. Prim. Health* **24**, 455–462 (2018).
19. Parkes, S. et al. Patient's experiences of clozapine for treatment-resistant schizophrenia: a systematic review. *Schizophrenia Bulletin Open* **3**, sgac042 (2022).
20. Oloyede, E. et al. The lived experience of clozapine discontinuation in patients and carers following suspected clozapine-induced neutropenia. *BMC Psychiatry* **23**, 413 (2023).
21. Leonard, K. A European survey relating to cancer therapy and neutropenic infections: Nurse and patient viewpoints. *Eur. J. Oncol. Nurs.* **16**, 380–386 (2012).
22. Takamatsu, Y., Yoshida, I. & Yoshida, M. An internet-based survey exploring the awareness of febrile neutropenia in patients with malignant lymphoma. *Support. Care Cancer* **28**, 4509–4516 (2020).
23. Mantwill, S., Monestel-Umaña, S. & Schulz, P. J. The relationship between health literacy and health disparities: a systematic review. *PloS one* **10**, e0145455 (2015).
24. Mace, S. et al. Incident infection during the first year of treatment - A comparison of clozapine and paliperidone palmitate long-acting injection. *J. Psychopharmacol.* **36**, 232–237 (2022).
25. Verdoux, H. et al. The time has come for revising the rules of clozapine blood monitoring in Europe. A joint expert statement from the European Clozapine task force. *Eur. Psychiatry* **68**, e17 (2025).
26. Oloyede, E. et al. What are the barriers and facilitators of clozapine use in early psychosis? A survey of UK early intervention clinicians. *Schizophrenia***9**, 26 (2023).
27. Oloyede, E., et al. Clozapine for treatment resistance in early psychosis: a survey of UK clinicians' training, knowledge and confidence. *Therapeutic Adv. Psychopharmacol.* **12**, 20451253221141222 (2022).
28. Cohen, D. et al. Beyond white blood cell monitoring: screening in the initial phase of clozapine therapy. *J. Clin. psychiatry* **73**, 1887 (2012).

ACKNOWLEDGEMENTS

We would like to thank the patients and carers interviewed during the study. The study did not receive direct funding.

AUTHOR CONTRIBUTIONS

E.O., E.W., and D.T. contributed to the conception and design of the study. E.O., V.N., N.M., P.M., and A.S. collected the date. E.O. analysed the data and E.O., O.D., and D.T. interpreted the data. E.O. wrote the main manuscript text. All authors contributed to the drafting and revision of the manuscript.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41537-025-00639-5.

Correspondence and requests for materials should be addressed to Ebenezer Oloyede.

Reprints and permission information is available at http://www.nature.com/reprints

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Open Access This article is licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License, which permits any non-commercial use, sharing, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if you modified the licensed material. You do not have permission under this licence to share adapted material derived from this article or parts of it. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit http://creativecommons.org/licenses/by-nc-nd/4.0/.

© The Author(s) 2025