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Original Article

Identifying clinically relevant agranulocytosis in people registered on the UK clozapine Central Non-Rechallenge Database: retrospective cohort study

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Background

Clozapine is the most effective antipsychotic for treatment-resistant psychosis. However, clozapine is underutilised in part because of potential agranulocytosis. Accumulating evidence indicates that below-threshold haematological readings in isolation are not diagnostic of life-threatening clozapine-induced agranulocytosis (CIA).

Aims

To examine the prevalence and timing of CIA using different diagnostic criteria and to explore demographic differences of CIA in patients registered on the UK Central Non-Rechallenge Database (CNRD).

Method

We analysed data of all patients registered on the UK Clozaril® Patient Monitoring Service Central Non-Rechallenge Database (at least one absolute neutrophil count (ANC) $< 1.5 \times 10^9$/L and/or white blood cell count $< 3.0 \times 10^9$/L) between May 2000 and February 2021. We calculated prevalence rates of agranulocytosis using threshold-based and pattern-based criteria, stratified by demographic factors (gender, age and ethnicity). Differences in epidemiology based on rechallenge status and clozapine indication were explored. The proportion of patients who recorded agranulocytosis from a normal ANC was explored.

Results

Of the 3029 patients registered on the CNRD with 283 726 blood measurements, 593 (19.6%) were determined to have threshold-based agranulocytosis and 348 (11.4%) pattern-based agranulocytosis. In the total sample (75 533), the prevalence of threshold-based agranulocytosis and pattern-based agranulocytosis was 0.8% and 0.5%, respectively. The median time to threshold-based agranulocytosis was 32 weeks (IQR 184) and 15 (IQR 170) weeks for pattern-based agranulocytosis. Among age groups, the prevalence of pattern-based agranulocytosis and threshold-based agranulocytosis was highest in the >48 age group. Prevalence rates were greatest for White (18%) and male individuals (13%), and lowest for Black individuals (0.1%). The proportion of people who were determined to have pattern-based agranulocytosis without passing through neutropenia was 70%.

Conclusions

Threshold-based definition of agranulocytosis may over-diagnose CIA. Monitoring schemes should take into consideration neutrophil patterns to correctly identify clinically relevant CIA. In marked contrast to previous studies, CIA occurred least in Black individuals and most in White individuals.

Keywords

Psychotic disorders/schizophrenia; antipsychotics.

Treatment-resistant psychosis (TRP) is broadly defined as a suboptimal response to at least two non-clozapine antipsychotics prescribed at an adequate dose and duration.[1] TRP affects approximately one-third of individuals diagnosed with psychosis and is one of the leading causes of disability worldwide. TRP is associated with severe long-term consequences on social and occupational functioning, with total treatment costs up to 11 times that of schizophrenia that is responsive to standard treatment.[2]

Since the seminal work by Kane and colleagues in the 1980s, clozapine has been regarded as the most effective antipsychotic in TRP, supported by evidence from randomised controlled trials and observational studies.[3,4] Despite this, clozapine is vastly underutilised,[5] and its initiation is often substantially delayed, partly owing to the stringent requirement of indefinite blood monitoring to detect the potentially fatal but rare risk of agranulocytosis.[6] This adverse effect was first identified in the 1970s during clozapine's pre-marketing development where fatalities among 18 Finnish individuals were ultimately linked to CIA.[7] The risk of CIA, assessed at a prevalence of approximately 0.4–0.8%[8] has for a long time distorted the perception among clinicians and patients of the risk versus benefit of this uniquely effective treatment.[9] For instance, after the Finnish epidemic, the notion of so-called 'clozapine-induced neutropenia' became widely accepted. However, evidence to date demonstrates that clozapine's association is strictly with agranulocytosis (i.e. severe neutropenia), and an association with milder forms of neutropenia has been largely assumed and indeed perpetuated by surveillance bias.

Clozapine monitoring schemes were originally established for the early detection of moderate neutropenia as a means of preventing the development of agranulocytosis and ultimately death.[10] However, several lines of evidence indicate that the threshold model for discontinuation substantially overestimates rates of potential CIA. Over-diagnosis of CIA or potential CIA in turn

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leads to unnecessary discontinuation of clozapine.[11,12] For example, evidence shows that 80% of people suspected of having clozapine-related dyscrasia can be safely restarted on treatment.[13] One explanation for this mismatch between assumed clozapine toxicity and success on re-exposure is that haematological phenotypes such as benign ethnic neutropenia (BEN) are often the cause of isolated neutropenic readings.[14] Unsurprisingly, clinicians have highlighted the need for revisions to the definition and criteria for identifying CIA.[15]

The basis of the current threshold monitoring system for clozapine is that agranulocytosis is defined by a single neutrophil count below 0.5×10^9 and the assumption that all such cases in people taking clozapine are caused by clozapine. However, an isolated below-threshold count may be neither pathological nor related to clozapine.[16] Examining the pattern of neutrophil count changes[17] is very probably a more accurate measure of clozapine-associated agranulocytosis. It is thus unsurprising that efforts to delineate risk factors for CIA (derived from a threshold monitoring system) have yielded contradictory findings. For instance, Alvir and colleagues identified an increased risk of agranulocytosis in females receiving clozapine.[18] However, since this study in 1993, no report has replicated these findings.[19] Munro et al suggested an increased risk in Asian individuals compared with White individuals,[20] but this too has not been replicated. Since then, other studies have generated diverging conclusions.

In this study, we aimed to determine the epidemiology and timing of CIA using pattern-based criteria, to investigate demographic differences of CIA in a large retrospective cohort study design.

Method

Data sources

This retrospective observational study was based on data from the largest clozapine manufacturer in the UK – Viatris, monitored by the Clozaril® Patient Monitoring Service (CPMS) database from the period between May 2000 and February 2021 inclusive.

Definition of haematological monitoring

In accordance with the Medicines and Healthcare Products Regulatory Agency (MHRA), UK regulations for clozapine prescription include regular monitoring of haematological parameters for all individuals receiving Clozaril®, notably the white blood cell (WBC) count, and the absolute neutrophil count (ANC). In the UK, weekly monitoring is mandated for the first 18 weeks of clozapine treatment, and in weeks 19–52 monitoring is mandatory biweekly.[21] Thereafter, 4-weekly haematological monitoring is required indefinitely. Blood test results are categorised into one of the following three categories: green (WBC $>3.5 \times 10^9$/L, ANC $>2.0 \times 10^9$/L), amber (WBC 3.0–3.5×10^9/L, ANC 1.5–2.0×10^9/L) and red (WBC $<3.0 \times 10^9$/L, ANC $<1.5 \times 10^9$/L). Since 2002, ANC and/or WBC discontinuation thresholds were reduced by 0.5×10^9/L for those with confirmed BEN status.[21]

In the event of an amber blood test result, blood tests must be performed two times per week, until the WBC and/or ANC stabilises or increases. In the event of a red result, individuals are assessed for signs of infection, clozapine is stopped immediately and daily haematological monitoring is initiated until ANC and/or WBC is above threshold. In exceptional cases, clozapine manufacturers allow for re-exposure of clozapine (i.e. 'clozapine rechallenge') following discontinuation due to suspected CIA and thus registration on the Central Non-Rechallenge Database (CNRD), which has been fully described elsewhere.[13,21]

Study population

For individuals registered on the CNRD with at least one ANC $<1.5 \times 10^9$/L and/or WBC $<3.0 \times 10^9$/L (i.e. neutropenia), CPMS provided the WBC and absolute neutrophil count (ANC) data and individuals' sociodemographic information, i.e. gender, age, self-reported ethnicity, clozapine indication (i.e. TRP, off-label, other), date of blood test(s) and clozapine rechallenge status information. Self-reported ethnicity was stratified as follows: White, Black, Asian and Other. For the exploratory analysis between demographic/clinical factors and prevalence of CIA, age was stratified into quartiles (≤29, 30–40, 41–48 and >48 years). For people who were rechallenged on clozapine after experiencing agranulocytosis, only the first event was included in the primary analysis.

Measures

In this study, we calculated the prevalence of agranulocytosis, stratified by gender, age and ethnicity.

Individuals were diagnosed with CIA using two different ascertainment methods:

(a) At least one ANC $<0.5 \times 10^9$/L – threshold-based agranulocytosis
(b) Two consecutive ANC (over 2 or more days) $<0.5 \times 10^9$/L – pattern-based agranulocytosis as suggested by Taylor et al[22]

The number of people who were determined to have transient agranulocytosis were described. Transient agranulocytosis was defined as one ANC $<0.5 \times 10^9$/L followed by subsequent ANC $\geq 0.5 \times 10^9$/L. The number of individuals who transitioned from a normal ANC count ($\geq 1.5 \times 10^9$/L) to threshold-based and pattern-based agranulocytosis were recorded. The number of people who recorded pattern-based agranulocytosis within 14 days of a mild to moderate neutropenia (ANC 0.5–1.5×10^9/L) were recorded and stratified by ethnicity. The rationale for 14 days was to assess current monitoring requirements. Heat maps were produced to visually represent the impact of demographic and clinical factors on the proportion of individuals recording neutropenia, and threshold- and pattern-based agranulocytosis.

Statistical analysis

The statistical analyses were performed using SciPy software (version 1.12.0 for Windows).[23] The 20-year prevalence of agranulocytosis was calculated for the entire cohort and the CNRD sample using the threshold- and pattern-based criteria. The mean, s.d., median and interquartile range (IQR) were calculated for continuous data. Additional subgroup analyses were performed according to gender, age and ethnicity. Frequencies and percentages were calculated for categorical data.

Ethics approval statement

Consent was not obtained from all participants, as we used non-identifiable data provided by Clozaril® (Viatris) monitored by CPMS. Ethical approval was not required according to the UK HRA.

Results

Baseline characteristics

Between May 2002 and February 2021, 75 553 people were registered on the CPMS database for clozapine treatment – data on ethnicity were not available. In the same study period, 3029 were registered on the CPMS CNRD and included in this study. The mean age of the CNRD cohort was 39 years (s.d. 13) at clozapine

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initiation, and 62% were male. Overall, 85% identified as White, 9% as Black and 4% as Asian. The median number of blood samples per person was 93.7 (s.d. 83.7, range 1–900), and the mean observation period was 1909 days (~5.2 years) (s.d. 2043, range 0–7602 days). Of the people registered on the CNRD, 2436 (80%) had mild to moderate neutropenia, and 245 (8%) were determined to have transient agranulocytosis (see Supplementary Appendix available at https://doi.org/10.1192/bjp.2024.104). Clinical and demographic characteristics of the study population are shown in Table 1.

Agranulocytosis and prevalence

Table 2 outlines the prevalence of agranulocytosis in the CNRD cohort using threshold- and pattern-based criteria. In the total sample (75 533), prevalence of threshold-based agranulocytosis and pattern agranulocytosis was (0.8%) and (0.5%), respectively. The period prevalence of threshold-based agranulocytosis in the CNRD was 19.5%, compared with 11.4% using the pattern-based criterion. Overall, 43.3% of threshold-based agranulocytosis cases emerged during the first 18 weeks of clozapine treatment, and 53.3% during the first year, while these rates were 53.2 and 58.9%, respectively, for the pattern-based criterion (Supplementary Appendix).

Among ethnic groups, the prevalence was highest among White individuals (10.7%) and lowest in Black individuals (0.1%). In general, the prevalence rates were highest in the >48 age group. Prevalence of pattern-based agranulocytosis was slightly higher among males (7.3) compared with females (4.1).

As shown in Table 3, most people transitioned from a normal ANC count to agranulocytosis with threshold-based (73%) and pattern-based (70%) criteria.

Agranulocytosis timing

The median time to pattern-based agranulocytosis was 0.28 (IQR 3.25) years and 0.62 (IQR 3.52) years for threshold-based agranulocytosis. Overall, 43% of people recorded threshold-based agranulocytosis in the first 18 weeks of treatment. The corresponding figure for pattern-based agranulocytosis was 53.16% (see Supplementary Appendix). For threshold-based criteria, 55% of individuals recorded agranulocytosis at 1 year and 76% by 4 years. For pattern-based criteria, 58% of individuals recorded agranulocytosis at 1 year and 80% by 4 years (see Supplementary Appendix). Figure 1 displays the cumulative frequency of neutropenia and agranulocytosis stratified by threshold and pattern-based criteria for the entire cohort.

Agranulocytosis demographic differences

The heatmaps in Fig. 2 present the (a) prevalence of haematological events and (b) median time in days to the haematological event, stratified by ethnicity, gender and age quantiles. Haematological events including neutropenia, threshold-based agranulocytosis and pattern-based agranulocytosis.

Table 1 Sociodemographic and clinical characteristics of people registered on the Central Non-Rechallenge Database (CNRD)

Characteristic	Threshold agranulocytosis[a] (*n* = 593)	Pattern agranulocytosis (*n* = 348)	All patients (*n* = 3029)
Gender (%)			
Female	201 (34)	128 (36)	1141 (38)
Male	392 (66)	220 (63)	1888 (62)
Age at clozapine initiation			
(Years ± s.d.)	43 (13)	46 (13)	39 (13)
(Quantile 1: ≤29)	106 (17.9)	35 (10.1)	833 (27.5)
(Quantile 2: 30–40)	145 (24.5)	83 (23.9)	787 (26.0)
(Quantile 3: 41–48)	123 (20.7)	69 (19.8)	585 (19.3)
(Quantile 4: >48)	219 (36.9)	161 (46.3)	824 (27.2)
Duration of clozapine treatment (years ± s.d.)	2.6 (3.7)	2.3 (3.5)	2.9 (3.7)
Clozapine indication (%)			
TRP	513 (87)	303 (87)	2644 (87)
Off-label	59 (10)	28 (8)	237 (8)
Other	21 (4)	17 (5)	148 (5)
Ethnicity (%)			
White	539 (91)	324 (93)	2569 (85)
Black	23 (4)	3 (1)	276 (9)
Asian	22 (4)	16 (5)	117 (4)
Other	9 (2)	5 (1)	67 (2)
Rechallenged (%)	93 (16)	59 (17)	584 (19)
Haematological measurements median (IQR)	19 (52)	16 (43)	33 (64)
Haematological characteristics at baseline (%)			
White cell count, mean (s.d.)	7.6 (2.5)	7.7 (2.6)	6.8 (2.6)
White cell count, median (IQR)	7.3 (2.9)	7.4 (2.9)	6.3 (2.8)
Absolute neutrophil count, mean (s.d.)	4.9 (2.1)	5.0 (2.1)	4.2 (2.0)
Absolute neutrophil count, median (IQR)	4.5 (2.5)	4.6 (2.5)	3.8 (2.4)
Platelet count, mean (s.d.)	246 (81)	242 (79)	235 (80)
Platelet count, median (IQR)	238 (79)	236 (82)	230 (87)
Haematological characteristics at haematological event (%)			
White cell count, mean (s.d.)	3.1 (3.1)	1.9 (1.2)	3.3 (1.5)
White cell count, median (IQR)	2.1 (1.6)	1.8 (1.0)	2.9 (1.0)
Absolute neutrophil count, mean (s.d.)	0.2 (0.2)	0.3 (0.1)	1.2 (0.4)
Absolute neutrophil count, median (IQR)	0.3 (0.3)	0.3 (0.2)	1.3 (0.4)
Platelet count, mean (s.d.)	225 (120)	231 (118)	196 (93)
Platelet count, median (IQR)	230 (119)	238 (123)	196 (101)

a. Threshold-based agranulocytosis cohort includes individuals who registered pattern-based agranulocytosis. See Supplementary Appendix for distinct group characteristics. TRP, treatment-resistant psychosis; IQR, interquartile range.

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Table 2 Prevalence (ever) of agranulocytosis (threshold-based *v.* pattern-based) in the Central Non-Rechallenge Database (CNRD) sample

		CNRD prevalence (%)	
Ethnicity	Subgroup	Threshold-based criterion	Pattern-based criterion
White (*N* = 2569)	All	17.78	10.68
	Male	11.68	6.66
	Female	6.10	4.02
Black (*N* = 276)	All	0.75	0.09
	Male	0.52	0.06
	Female	0.23	0.03
Asian (*N* = 117)	All	0.71	0.42
	Male	0.52	0.39
	Female	0.19	0.03
Other (*N* = 57)	All	0.28	0.16
	Male	0.19	0.13
	Female	0.09	0.03
All (*N* = 3029)	All	19.52	11.35
	Male	12.91	7.24
	Female	6.61	4.11

Discussion

Summary of findings

To our knowledge, our study is the first to examine how diagnostic criteria for agranulocytosis affect estimated prevalence rates in people prohibited from receiving clozapine treatment. Overall, we found a substantial difference in the prevalence when a pattern-based criterion for CIA was applied. Review of a large and diverse cohort enabled us, for the first time, to demonstrate the relevance of diagnostic criteria when examining demographic differences in the epidemiology of CIA. In marked contrast to previous studies, CIA (as pattern-based criterion) was least likely to occur in Black individuals, warranting further exploration. In recent years, there has been considerable discussion as to the appropriate classification of agranulocytosis in people receiving clozapine. Our data provide added evidence that the current haematological threshold model overestimates the incidence of CIA.

Comparison with other studies

To date, no published study has specifically examined the impact of diagnostic criteria on prevalence rates of CIA in individuals deemed at high risk. Nonetheless it can be said that CIA epidemiology remains incompletely understood, likely because of broad diagnostic criteria (ANC < 0.5×10^9/L) and heterogeneity of the patient populations studied, and the varied duration of patient follow-up. In a meta-analysis comprising over 260 000 people across 12 countries, the pooled prevalence of agranulocytosis was 0.4% (95% CI 0.3–0.6%). By comparison, recent literature by Northwood et al reported a CIA prevalence of 1.2 and 0.8% deemed unrelated to clozapine.[18,20] Personal communications with CPMS revealed that 75 533 people were registered for clozapine use within our study period, providing an estimated prevalence of 0.8% with threshold-based criterion and 0.5% with pattern-based criterion. While direct comparisons with our cohort are only speculative, our somewhat higher threshold-based prevalence compared with the meta-analysis may be attributed to differences in follow-up periods. For instance, the follow-up periods of most studies included in the meta-analysis by Li et al[8] were considerably shorter than the 20-year time span in our study. Notably, in their subgroup analysis, the authors noted a slightly higher pooled prevalence (0.5% *v.* 0.4%) of moderate neutropenia (<1.0×10^9/L) compared with agranulocytosis (<0.5×10^9/L). Still, it is likely that application of pattern-based diagnostic criteria in existing studies would have yielded comparable results to the present study and improve the quality of epidemiological and clinical studies concerning CIA in the future.

Table 3 Proportion of individuals that transitioned from neutropenia or a normal absolute neutrophil count (ANC) to clozapine-induced agranulocytosis (CIA) (threshold-based *v.* pattern-based) in the Central Non-Rechallenge Database (CNRD) sample

	Agranulocytosis (%)			
	Threshold-based criterion (n = 593)		Pattern-based criterion (n = 348)	
Ethnicity	Normal ANC to CIA	Neutropenia to CIA	Normal ANC to CIA	Neutropenia to CIA
All (%)	430 (73)	163 (27)	242 (70)	106 (30)
White (%)	394 (66)	145 (24)	224 (64)	100 (29)
Black (%)	14 (2)	9 (2)	2 (1)	1 (0)
Asian (%)	16 (3)	6 (1)	13 (4)	3 (1)
Other (%)	6 (1)	3 (1)	3 (1)	2 (1)

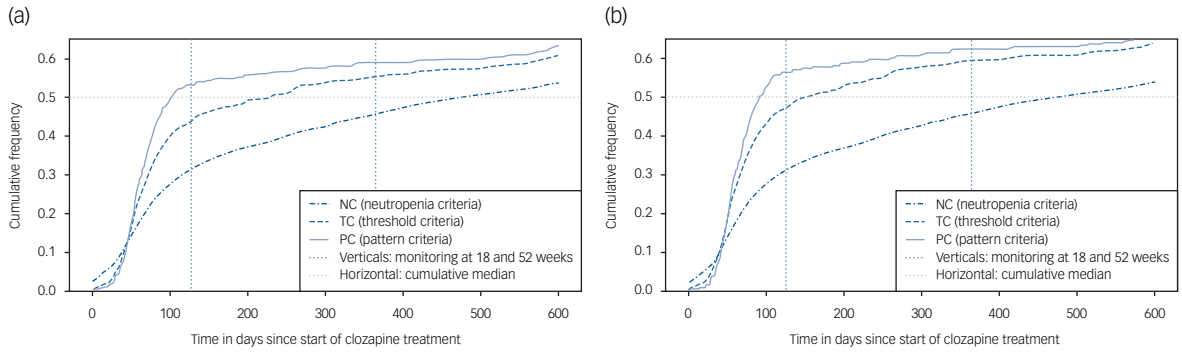

Fig. 1 Cumulative frequency of haematological events (neutropenia, threshold-based and pattern-based agranulocytosis) in people registered on the Central Non-Rechallenge Database (CNRD): (a) includes all recorded clozapine indications and (b) restricted to only people with treatment-resistant psychosis.

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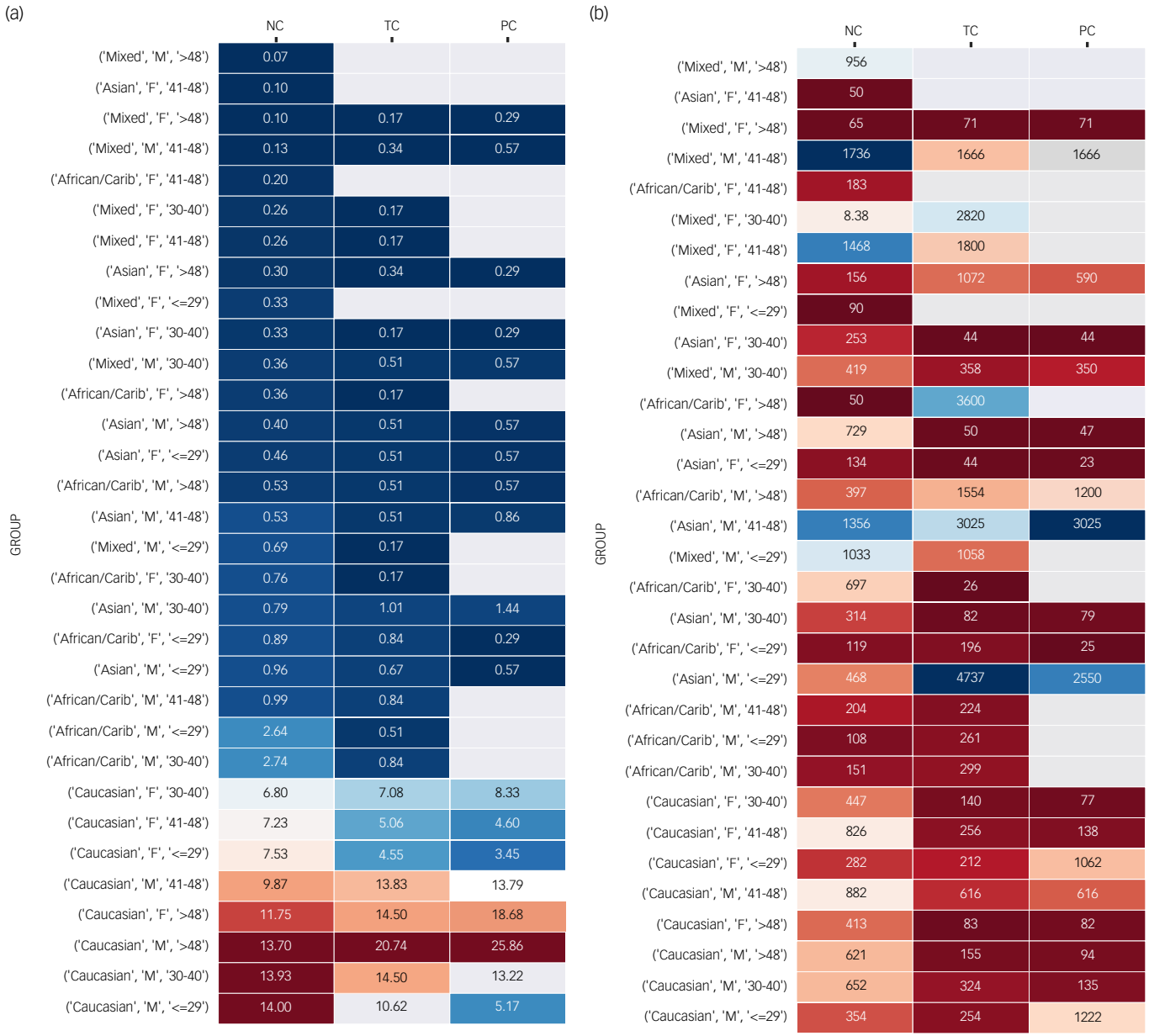

Fig. 2 Heatmaps represent (a) the prevalence and (b) the median time of different haematological events (neutropenia, threshold-based and pattern-based agranulocytosis) for different demographic groups (ethnicity, gender, age). See the Supplementary Appendix for a more detailed version which includes clozapine indication and clozapine rechallenge status. For figure (a), blue represents low prevalence and burgundy represents high prevalence. For figure (b), blue represents longer medians and burgundy represents short medians. Areas in white represent no event in the respective demographic group.

Earlier evidence indicates that the risk of CIA is greatest in the first 18 weeks of clozapine treatment and is significantly reduced after 1 year, with its incidence falling to 0.07% in the second year.[24] More recently, it has been similarly shown that the weekly incidence rate for CIA peaked at 9 weeks (0.128%), falling to a rolling average weekly incidence of 0·001% by 2 years. Consistent with those observations, we observed that a large proportion of agranulocytosis cases occurred within the first year (55% with threshold-based criterion). This was notably more pronounced when using a pattern-based criterion (59% with pattern-based criterion), again underlying how stringent diagnostic criteria may reduce false positive rates. Despite existing reports, a somewhat unexpected finding in our study was the large proportion of people who recorded agranulocytosis beyond two years (37%). Overall, these findings should be interpreted with caution as we were limited in our ability to determine non-clozapine causes for these apparent haematological aberrations, such as chemotherapy.

Risk factors for clozapine-induced agranulocytosis (CIA)

Previous studies on risk factors and prevalence for CIA and its outcome have found inconsistent and diverging conclusions. For example, in their study on CIA incidence and risk factors in the US, Alvir et al[18] reported a slightly higher risk in females (RR 1.60, 95% CI 0.99–2.58, after adjustment for age), whereas these findings were not seen in Denmark,[25] Germany[26] or Italy.[19] By contrast – at least when using the threshold-based criterion – prevalence was higher in males than females (19.5% compared with 12.9%) for CIA in our study. The reason for this is unclear; however, epidemiological data from a US cohort of children and adolescents treated with clozapine described an increased risk of moderate neutropenia in males.[27] Moreover, it is plausible that there was a greater proportion of non-clozapine causes of agranulocytosis in males, such as infection or concomitant medication such as valproate in our sample.

With respect to ethnicity, Munro et al found an increased risk in Asian individuals compared with White individuals.[20] However, an earlier study in the same setting reported no difference between ethnic groups regarding agranulocytosis.[24] The authors suggested an increased risk of neutropenia in Black individuals; however, this is likely related to undetected BEN. Interestingly, in the absence of ethnicity data, Northwood et al found that a low baseline ANC ($<2.5 \times 10^9$/L) predicted an increased risk of minor neutropenia and serious neutropenia unrelated to clozapine, but not increased risk of serious neutropenia related to clozapine. Considering the predominant prevalence of BEN in Black populations, it is likely that these data corroborate our hypothesis of a reduced risk of CIA in this population. Overall, our findings warrant further investigations to characterise clinical and genetic risk factors for CIA. Of note, our study found an increased prevalence of agranulocytosis in White individuals, which is probably because of a genuinely lower risk of CIA in Black individuals. An alternative influence could be earlier treatment discontinuation (as described by Atkins et al)[24] and thus reduced exposure time in Black individuals; nevertheless, further studies are required to elucidate this. Of note, the increased prevalence in older people from our study is consistent with existing literature. Remarkably, the increased prevalence of CIA in White individuals is striking in its similarity to the findings of the risk of agranulocytosis with phenothiazines in the late 1950s.[28]

Clinical implications

Agranulocytosis, also known as severe neutropenia, is an acute condition involving severe and dangerously low neutrophil counts that place people at a high risk of severe infection. When assessing whether a below-threshold haematological reading is indicative of CIA, current literature emphasises consideration of factors such as the length of clozapine exposure, concomitant medication and possible infections. However, little attention is paid to the actual diagnostic criteria for agranulocytosis. By most standards, agranulocytosis is defined as a neutrophil count of less than 0.5×10^9/L. A subthreshold ANC always provokes clozapine cessation, as mandated by official monitoring programmes. However, this is often done prematurely – serious infections are most likely to occur at counts of $<0.2 \times 10^9$/L. Emerging evidence has demonstrated a distinct pattern of continuous and rapid neutrophil count decline to zero or near zero in those with clinically relevant CIA.[22] Consistently, in our cohort, 70% of people transitioned from a normal ANC to agranulocytosis without passing through neutropenia, casting further doubt on the utility of fortnightly and certainly monthly monitoring beyond the highest period. While not explored in this study, it is certainly plausible that the remaining 30% of people were identified by weekly monitoring.

Taking this into consideration, our study showed a clinically important difference in prevalent CIA using pattern-based compared with threshold-based diagnostic criteria, which could have important implications for epidemiologic surveillance and patient prognosis. Current monitoring schemes require clozapine to be discontinued in the event of an ANC $<1.5 \times 10^9$/L, with the aim of preventing agranulocytosis by detecting early a fall in ANC. As shown in the Supplementary Appendix, in 1 in 10 people registered on the CNRD, there was a single event of an ANC count $<0.5 \times 10^9$/L, which is then followed by a spontaneous and prompt normalisation of the ANC. Nevertheless, in most cases such a single event which will inevitably lead to clozapine discontinuation, which in turn puts people at a high risk of severe psychotic relapse from avoidable clozapine discontinuation, reduced responsiveness and discontinuation symptoms.[29]

Based on the current findings and to avoid the above-mentioned adverse consequences, it is important that monitoring schemes and regulatory bodies take consideration of neutrophil patterns to correctly discriminate between clozapine and non-CIA. It is plausible that use of pattern-based criteria may improve understanding of risk factors for true CIA and reduce ethnic disparities in clozapine prescription by emphasising the misconceptions about the increased risk of CIA among Black individuals. Overall, a pattern-based classification for CIA may represent a fundamentally important step towards reduced treatment discontinuation and improved care for those with TRP.

Strengths and limitations

This study has several strengths and limitations that require acknowledgement. A major strength of our study is the large sample size that spans an observation period of more than 20 years. Moreover, our cohort is ethnically diverse, with nearly 10% of individuals being of Black ethnicity.

This study has some considerable limitations that need to be accounted for. The main weakness is the need to estimate total number of people receiving clozapine over the observation period. Only the CNRD group had the exact number of people known. In addition, the prevalence estimates, which are based on people from the UK and Ireland, may not generalise to other populations with different ethnicity mixes. A further limitation is that no data on the outcomes of individuals with agranulocytosis (i.e. death) were available, and that information on somatic comorbidities or concomitant medication, which might influence/increase the risk of agranulocytosis (e.g. valproate[30]), was lacking. In addition, people who recorded threshold- and pattern-based

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agranulocytosis ceased clozapine at the initial instance of neutropenia. Thus, we are unable to determine if clozapine cessation prevented some people from transitioning from threshold- to pattern-based agranulocytosis. Despite our efforts to improve the diagnostic accuracy of CIA through pattern-based criteria, we could not confirm that all cases of severe neutropenia in our sample are necessarily associated with clozapine treatment;[25] for example, it is plausible that individuals with BEN may occasionally be misdiagnosed as having CIA by pattern-based agranulocytosis. Finally, we were not able to confirm that all individuals studied were first-starters of clozapine; that is, some may have previous been prescribed clozapine by another clozapine supplier. However, the key finding from our study was that pattern-based criteria give a substantially lower estimate of CIA risk than threshold-based criteria.

Current threshold-based definitions of agranulocytosis over-diagnose cases of potentially CIA. This study demonstrates that a pattern-based definition of agranulocytosis yields markedly lower incidence and prevalence rates of clozapine-associated agranulocytosis. The use of pattern-based criteria for CIA may lead to better patient outcomes through lower clozapine discontinuation rates. Our findings of White ethnicity as having greatest agranulocytosis prevalence warrant further exploration.

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Supplementary material

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Data availability

The data that support the findings of this study are available from Clozaril® Patient Monitoring Services. Restrictions apply to the availability of these data, which were used under licence for this study.

Author contributions

E.O.: conceptualisation, methodology, validation, writing – original draft; C.J.B.: conceptualisation, methodology, writing – original draft; O.D.: methodology, writing – review & editing; J.M.L.A.: data curation, formal analysis, writing – review & editing; S.D.S.: methodology, data curation, software, formal analysis, writing – review & editing; K.V.: resources, writing – review & editing; B.F.: methodology, software, formal analysis, writing – review & editing; E.W.: resources, writing – review & editing; D.T.: conceptualisation, methodology, validation, writing – review & editing. All authors have reviewed the manuscript draft critically for important intellectual content and approved the final version to be published, and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Declaration of interest

None.

Transparency declaration

This manuscript is an honest, accurate and transparent account of the study being reported; no important aspects of the study have been omitted; and any discrepancies from the study as planned have been explained.

References

1 Howes OD, McCutcheon R, Agid O, de Bartolomeis A, van Beveren NJ, Birnbaum ML, et al. Treatment-resistant schizophrenia: treatment response and resistance in psychosis (TRRIP) working group consensus guidelines on diagnosis and terminology. *Am J Psychiatry* 2017; **174**(3): 216–29.

2 Kennedy JL, Altar CA, Taylor DL, Degtiar I, Hornberger JC. The social and economic burden of treatment-resistant schizophrenia: a systematic literature review. *Int Clin Psychopharmacol* 2014; **29**(2): 63–76.

3 Siskind D, Siskind V, Kisely S. Clozapine response rates among people with treatment-resistant schizophrenia: data from a systematic review and meta-analysis. *Can J Psychiatry* 2017; **62**(11): 772–7.

4 Leucht S, Cipriani A, Spineli L, Mavridis D, Orey D, Richter F, et al. Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple-treatments meta-analysis. *Lancet* 2013; **382**(9896): 951–62.

5 Bachmann CJ, Aagaard L, Bernardo M, Brandt L, Cartabia M, Clavenna A, et al. International trends in clozapine use: a study in 17 countries. *Acta Psychiatr Scand* 2017; **136**(1): 37–51.

6 Farooq S, Choudry A, Cohen D, Naeem F, Ayub M. Barriers to using clozapine in treatment-resistant schizophrenia: systematic review. *BJPsych Bull* 2019; **43**(1): 8–16.

7 Crilly J. The history of clozapine and its emergence in the US market: a review and analysis. *History Psychiatry* 2007; **18**(1): 39–60.

8 Li X-H, Zhong X-M, Lu L, Zheng W, Wang S-B, Rao W-W, et al. The prevalence of agranulocytosis and related death in clozapine-treated patients: a comprehensive meta-analysis of observational studies. *Psychol Med* 2020; **50**(4): 583–94.

9 Parkes S, Mantell B, Oloyede E, Blackman G. Patients' experiences of clozapine for treatment-resistant schizophrenia: a systematic review. *Schizophr BullOpen* 2022; **3**(1): sgac042.

10 Oloyede E, Blackman G, Whiskey E, Bachmann C, Dzahini O, Shergill S, et al. Clozapine haematological monitoring for neutropenia: a global perspective. *Epidemiol Psychiatr Sci* 2022; **31**: e83.

11 Myles N, Myles H, Xia S, Large M, Bird R, Galletly C, et al. A meta-analysis of controlled studies comparing the association between clozapine and other antipsychotic medications and the development of neutropenia. *Aust N Z J Psychiatry* 2019; **53**(5): 403–12.

12 Myles N, Myles H, Xia S, Large M, Kisely S, Galletly C, et al. Meta-analysis examining the epidemiology of clozapine-associated neutropenia. *Acta Psychiatr Scand* 2018; **138**(2): 101–9.

13 Oloyede E, Whiskey E, Casetta C, Dzahini O, Dunnett D, Gandhi S, et al. Relaxation of the criteria for entry to the UK clozapine Central Non-Rechallenge Database: a modelling study. *Lancet Psychiatry* 2022; **9**(8): 636–44.

14 Manu P, Sarvaiya N, Rogozea LM, Kane JM, Correll CU. Benign ethnic neutropenia and clozapine use: a systematic review of the evidence and treatment recommendations. *J Clin Psychiatry* 2016; **77**(7): e909–16.

15 Oloyede E, Taylor D, MacCabe J. International variation in clozapine hematologic monitoring – a call for action. *JAMA Psychiatry* 2023; 80(6): 535–6.

16 van Staa TP, Boulton F, Cooper C, Hagenbeek A, Inskip H, Leufkens HG. Neutropenia and agranulocytosis in England and Wales: incidence and risk factors. *Am J Hematol* 2003; **72**(4): 248–54.

17 Taylor D, Vallianatou K, Whiskey E, Dzahini O, MacCabe J. Distinctive pattern of neutrophil count change in clozapine-associated, life-threatening agranulocytosis. *NPJ Schizophr* 2022; **8**(1): 21.

18 Alvir JM, Lieberman JA, Safferman AZ, Schwimmer JL, Schaaf JA. Clozapine-induced agranulocytosis. Incidence and risk factors in the United States. *N Engl J Med* 1993; **329**(3): 162–7.

19 Deliliers GL. Blood dyscrasias in clozapine-treated patients in Italy. *Haematologica* 2000; **85**(3): 233–7.

20 Munro J, O'Sullivan D, Andrews C, Arana A, Mortimer A, Kerwin R. Active monitoring of 12,760 clozapine recipients in the UK and Ireland. Beyond pharmacovigilance. *Br J Psychiatry* 1999; **175**: 576–80.

21 Oloyede E, Casetta C, Dzahini O, Segev A, Gaughran F, Shergill S, et al. There is life after the UK clozapine Central Non-Rechallenge Database. *Schizophr Bull* 2021; **47**(4): 1088–98.

22 Taylor D, Vallianatou K, Whiskey E, Dzahini O, MacCabe J. Distinctive pattern of neutrophil count change in clozapine-associated, life-threatening agranulocytosis. *Schizophrenia* 2022; **8**(1): 21.

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23 Virtanen P, Gommers R, Oliphant TE, Haberland M, Reddy T, Cournapeau D, et al. Scipy 1.0: fundamental algorithms for scientific computing in Python. *Nat Methods* 2020; **17**(3): 261–72.

24 Atkin K, Kendall F, Gould D, Freeman H, Liberman J, O'Sullivan D. Neutropenia and agranulocytosis in patients receiving clozapine in the UK and Ireland. *Br J Psychiatry* 1996; **169**(4): 483–8.

25 Johannsen C-F, Petersen TS, Nielsen J, Jørgensen A, Jimenez-Solem E, Fink-Jensen A. Clozapine-and non-clozapine-associated neutropenia in patients with schizophrenia: a retrospective cohort study. *Ther Adv Psychopharmacol* 2022; **12**: 20451253211072341.

26 Stübner S, Grohmann R, Engel R, Bandelow B, Ludwig WD, Wagner G, et al. Blood dyscrasias induced by psychotropic drugs. *Pharmacopsychiatry* 2004; **37**(Suppl 1): S70–8.

27 Maher KN, Tan M, Tossell JW, Weisinger B, Gochman P, Miller R, et al. Risk factors for neutropenia in clozapine-treated children and adolescents with childhood-onset schizophrenia. *J Child Adolesc Psychopharmacol* 2013; **23**(2): 110–6.

28 Lambo TA. Chlorpromazine jaundice. *BM J* 1957; **2**(5052): 1048.

29 Blackman G, Oloyede E, Horowitz M, Harland R, Taylor D, MacCabe J, et al. Reducing the risk of withdrawal symptoms and relapse following clozapine discontinuation—is it feasible to develop evidence-based guidelines? *Schizophr Bull* 2022; **48**(1): 176–89.

30 Lally J, Malik S, Krivoy A, Whiskey E, Taylor DM, Gaughran FP, et al. The use of granulocyte colony-stimulating factor in clozapine rechallenge: a systematic review. *J Clin Psychopharmacol* 2017; **37**(5): 600–4.

Psychiatry in music

The Velvet Underground's performance for the New York Society for Clinical Psychiatry in 1966

Nicholas Griffin, Alexander Smith and Michael Liebrenz

The Velvet Underground bestowed an enduring legacy, influencing avant-garde aesthetics and punk and post-punk genres. They employed experimental soundscapes, blurring boundaries between audience and performers, as exemplified in their 1966 show for the New York Society for Clinical Psychiatry (now the New York State Psychiatric Association).

At the Society's 43rd annual banquet, at the decadent Delmonico hotel, artist Andy Warhol was asked to provide the entertainment. The Society's programme chair explained the intentions behind this invitation to the media: 'creativity and the artist have always held a fascination for the serious student of human behaviour'. Warhol arranged an extravagant show for the psychiatrists, debuting his Exploding Plastic Inevitable collective. Within this ensemble, the Velvets (then managed by Warhol) performed alongside collaborators including actor Edie Sedgwick and singer Nico, in her first of numerous appearances with the group.

Led by singer, Lou Reed, the Underground delivered a high-decibel set against a backdrop of cinematic torture scenes. Warhol recalled, 'the doors flew open' and the filmmakers, Jonas Mekas and Barbara Rubin, with a 'crew of people with cameras and bright lights came storming into the room'. They interrogated the audience with sexually provocative questions, subsequently asking 'Why are you embarrassed? You're a psychiatrist; you're not supposed to get embarrassed!'.

Distorting the therapeutic relationship, one Velvet member, John Cale, labelled the performance 'Lou's revenge'; during adolescence Reed had received electroconvulsive therapy, possibly for suspected homosexuality. For the psychiatrists, many of whom left during the show, Reed conceded 'they had a sense of humour, up to a point'. The *New York Times* reported first-hand accounts of a 'spontaneous eruption of the Id' and a 'message of super-reality'. Others were less generous, calling the event 'ridiculous, outrageous, painful' and noting '[i]t seemed like a whole prison ward had escaped'.

However, in the performance, the band did not relinquish its status as a psychiatric subject. Among the setlist was 'Heroin', Reed's ambiguous ode to first-hand experiences of heroin use. Comprising phenomenological perspectives, the song's first word, 'I', foregrounds the individual using heroin. Interestingly, as demonstrated by the lyrics, the psychiatrists appeared to be a relevant (if not the intended) addressee: 'you can't help me, not you guys / or all your sweet girls with all your sweet talk'. Reflecting antipsychiatric sentiments in the 1960s and beyond, 'Heroin' conveys a rupturing of therapeutic logic, accentuating injurious drug use over health and recovery. 'Heroin', the song proclaims, 'it's my wife and it's my life' and 'thank God that I just don't care'.

Of course, heroin use entails severe consequences. Sedgwick died of an overdose in 1971, aged 27, as did another Warhol collaborator, Jean-Michel Basquiat, in 1988. A lineage of artists affected by substance use disorders seems the inverse of the vitality inherent in the Velvet's performances. This exemplifies the shared concerns of art and psychiatry across the full spectrum of human emotions and behaviours.

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