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Original Article

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Clozapine haematological monitoring for neutropenia: a global perspective

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Abstract

Aims. Clozapine is licensed for treatment-resistant psychosis and remains underutilised. This may be related to the stringent haematological monitoring requirements that are mandatory in most countries. We aimed to compare guidelines internationally and develop a novel Stringency Index. We hypothesised that the most stringent countries would have increased healthcare costs and reduced prescription rates.

Method. We conducted a literature review and survey of guidelines internationally. Guideline identification involved a literature review and consultation with clinical academics. We focused on the haematological monitoring parameters, frequency and thresholds for discontinuation and rechallenge after suspected clozapine-induced neutropenia. In addition, indicators reflecting monitoring guideline stringency were scored and visualised using a choropleth map. We developed a Stringency Index with an international panel of clozapine experts, through a modified-Delphi-survey. The Stringency Index was compared to health expenditure per-capita and clozapine prescription per 100 000 persons.

Results. One hundred two countries were included, from Europe ($n = 35$), Asia ($n = 24$), Africa ($n = 20$), South America ($n = 11$), North America ($n = 7$) and Oceania and Australia ($n = 5$). Guidelines differed in frequency of haematological monitoring and discontinuation thresholds. Overall, 5% of included countries had explicit guidelines for clozapine-rechallenge and 40% explicitly prohibited clozapine-rechallenge. Furthermore, 7% of included countries had modified discontinuation thresholds for benign ethnic neutropenia. None of the guidelines specified how long haematological monitoring should continue. The most stringent guidelines were in Europe, and the least stringent were in Africa and South America. There was a positive association ($r = 0.43$, $p < 0.001$) between a country's Stringency Index and healthcare expenditure per capita.

Conclusions. Recommendations on how haematological function should be monitored in patients treated with clozapine vary considerably between countries. It would be useful to standardise guidelines on haematological monitoring worldwide.

Introduction

Clozapine is licensed for the treatment of patients with schizophrenia who have failed to respond to two other antipsychotic medications, and is the only treatment that is effective in this subgroup, which is described as showing treatment resistance (Oloyede *et al.*, 2021a). Recently, there has been interest amongst national regulatory bodies and academics to expand clozapine use in treatment-resistant psychosis (TRP). This interest reflects an increased acknowledgement of its underutilisation, despite sustained evidence indicating its superior therapeutic benefits in this subgroup (Land *et al.*, 2017; Vermeulen *et al.*, 2019; Bhavsar *et al.*, 2020). Clozapine use is limited in part by the need for regular blood monitoring and the fear of severe neutropenia, a side effect that occurs in approximately 0.4% of treated patients, which can be fatal if undetected (Amsler *et al.*, 1977; Kelly *et al.*, 2018; Xiao-Hong *et al.*, 2020; Oloyede *et al.*, 2021a). Other factors associated with clozapine's underuse include adverse drug reactions such as weight gain, hypersalivation and acute hypersensitivity reactions such as clozapine-related drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome (de Filippis *et al.*, 2020; Parkes *et al.*, 2022).

A common strategy in healthcare to overcome health disparities and improve quality of care, while ensuring patient safety, is through developing evidence-based guidelines (Kredo *et al.*,

2016). Over recent decades, the number of guidelines for schizophrenia, including haematological monitoring in the context of clozapine treatment have increased in both high and middle-income countries (Warnez and Alessi-Severini, 2014; Nielsen *et al.*, 2016). Several recent investigations have shown that excessively rigid guidelines, that prioritise risk minimisation without balancing this against the superior efficacy of clozapine, can lead to clozapine being withheld from patients for whom it represents their only hope of recovery (Schulte, 2006; Myles *et al.*, 2018, 2019; Whiskey *et al.*, 2019; Schulte *et al.*, 2020; Oloyede *et al.*, 2021a, 2021b). Preliminary investigations and existing literature suggest there are marked variations in key recommendations around monitoring between countries (Nielsen *et al.*, 2016; Bachmann *et al.*, 2017; Whiskey *et al.*, 2021).

The aim of the present study was to provide a comprehensive review of these guidelines, comparing the stringency of clozapine haematological monitoring parameters and frequency, thresholds for discontinuation and rechallenge restrictions, with the extent of use.

Materials and methods

We identified and compared national guidelines for clozapine haematological monitoring to determine the level of variability in different countries. National or sub-national guidelines on prescribing, stopping and restarting clozapine were categorised as either regulations or recommendations. Conditions in guidelines for prescribing, stopping and restarting clozapine that were mandatory were defined as ‘regulations’. For example, in the United Kingdom (UK) haematological monitoring is mandated by the marketing authorisation of clozapine. Non-mandatory conditions were defined as ‘recommendations’.

To capture all guidelines, we used two approaches in parallel. The first was to search the literature for published international guidelines, and then hand-search the references of identified guidelines. The second approach was to directly contact clinicians or academics in each country who were active in psychosis research. To compare the content of the guidelines, information was categorised into three domains: haematological monitoring parameters, criteria for clozapine discontinuation and restrictions for rechallenge after suspected clozapine-induced neutropenia. Clozapine Rechallenge was defined as restarting clozapine treatment after meeting country-specific discontinuation criteria for suspected clozapine-induced neutropenia/agranulocytosis. Clozapine-induced neutropenia was defined as the country-specific neutrophil threshold for clozapine discontinuation. Indicators reflecting stringency of monitoring around clozapine use were scored and plotted on a choropleth map. The relationship between regulatory stringency and health expenditure and clozapine utilisation rates was evaluated using a scatter plot and Pearson’s correlation.

Search strategy and data extraction

Embase, Medline, PsychInfo and PubMed were searched up to 1st January 2021. The search terms, inclusion and exclusion criteria can be found in Supplementary Material (Table 1). The following search terms were used: Treatment*resistant psychosis* OR Treatment*refractory psychosis* OR Treatment*resistant schizophrenia OR Treatment*refractory schizophrenia OR clozapine AND algorithm OR guide* OR implementation OR monitor* protocol*. Exclusion criteria included non-specific worldwide or continental guidelines. Inclusion criteria were nationally or regionally recognised guidelines developed by their governing

body. The most recent version was selected if the guidelines were published in multiple versions. To determine eligibility, two authors (E.O and G.B) screened the titles, abstracts or summaries, followed by a full-text review and discrepancies were resolved by consensus. In addition, the references to guidelines were manually searched. The title and abstract were screened and the full text was reviewed to confirm eligibility.

As national or sub-national guidelines may not be published in academic journals, guidelines were also identified by personal communication with academic researchers in the field. Personal communication was prioritised for timely data collection as response times with regulatory bodies were slower during the initial stages of data collection. Researchers in the fields were initially selected based on authorship of key papers in the field identified by consensus (Falkai *et al.*, 2005; Gaebel *et al.*, 2005; Nielsen *et al.*, 2016; Bachmann *et al.*, 2017; Howes *et al.*, 2017; Siskind *et al.*, 2020; Wagner *et al.*, 2020; de Leon *et al.*, 2021) or membership of relevant organisations related to psychosis (e.g. Treatment-Resistant Schizophrenia: Treatment Response and Resistance in Psychosis [TRRIP] Working Group). Attempts were made to contact the first and senior authors to provide guidelines. Alternatively, email requests were made to psychiatry associations to provide contact details of an appropriate academic or clinician. The following psychiatry associations were contacted: African Association of Psychiatrists and Allied Professions, Asian Federation of Psychiatric Association and The Royal Australian and New Zealand College of Psychiatrists.

Data contributors were asked to confirm the information extracted and summarised in a table. Where national guidelines were not available, sub-national guidelines were requested from academic researchers. Furthermore, academic researchers were asked to confirm if guidelines previously identified from the literature review were the most recent version. In addition, academic researchers were asked to confirm whether information was referenced from the summaries of product characteristics (SmPC) of manufacturers providing clozapine in the respective country.

Stringency index

We developed a novel index to quantify the stringency of haematological monitoring during clozapine treatment. We used a modified Delphi methodology to arrive at a consensus. This methodology is well established for measuring international variability in clinical practice in other medical conditions (Hale *et al.*, 2020). Full details are provided in appendix 3.

Analysis and visualisation

The overall Stringency Index was plotted on a choropleth map to visualise variations between countries (Datawrapper, 2022). The Stringency Index was compared to health expenditure per capita (2018 constant in US dollars) (WHO, 2022) and clozapine prescription per 100 000 persons in countries with published data using scatter plots and Pearson correlation coefficient produced in R (R Core Team, 2022). Descriptive statistics were used to evaluate variability of the stringency indices by continent. The interquartile range (IQR) method was used to identify outliers in each continent, defined as values more than 1.5 times the IQR.

Results

The search and selection of guidelines

In total, 954 records were identified through the search of Embase, Medline, PsychInfo and PubMed. After de-duplication and title

and abstract screening, 15 guidelines were screened for eligibility. Guidelines from seven countries were included (Disayavanish *et al.*, 2000; Gaebel *et al.*, 2005; Schulte *et al.*, 2010; SIGN, 2013; NICE, 2014; Galletly *et al.*, 2016; Remington *et al.*, 2017; Keepers *et al.*, 2020; Japanese Society of Neuropsychopharmacology, 2021). These were from Australia, Canada, Japan, Netherlands, New Zealand, Thailand and the UK. Only the Australian, New Zealand and Dutch guidelines provided specific monitoring requirements and parameters for clozapine in the guidelines identified from the literature search. In addition, 132 clinicians and academics were approached directly, yielding a further 95 guidelines. The survey response rate for guideline identification was 98% (130 respondents). A total of 102 countries were included in the final review (see Supplementary Material, Table 2 for summary). The response rate from clinicians and academics for data confirmation was 73% (95 respondents). The data source was mandatory regulations (national or sub-national) in 40 (39%) of the countries and recommendations in 60 (59%) countries.

Haematological monitoring

Guidelines from 92 (90%) countries included routine haematological monitoring. This was mandatory (i.e., 'no blood, no drug') in 42 (45%) countries. Guidelines from 85 countries (83%) included both the white cell count (WCC) and the absolute neutrophil count (ANC) in this monitoring. Only five (5%) countries mandated or recommended ANC monitoring, based on United States (US) Food and Drug Administration (FDA) regulation revisions in 2015. These countries were Chile, Israel, Lebanon, South Africa and the US. Two countries (Armenia and Colombia) recommended WCC monitoring but not ANC monitoring. None of the countries provided explicit recommendations about when it was appropriate to stop haematological monitoring. In the Netherlands many psychiatrists and individuals receiving clozapine treatment agree to off-label use, where monitoring is stopped, or reduced to four times a year (Schulte *et al.*, 2010). Seven (7%) countries have modified clozapine monitoring criteria for those diagnosed with benign ethnic neutropenia (BEN). These countries were Canada, Iceland, Israel, Qatar, South Africa, United Kingdom and the USA.

Clozapine discontinuation

Sixty-two (61%) countries recommended clozapine discontinuation for a specified criterion based on haematological thresholds. Recommendation for treatment interruption or discontinuation after a below threshold haematological reading differed between countries. For example, 31 (30%) countries did not have explicit guidance regarding thresholds requiring clozapine discontinuation and were dependent on clinician judgement. Eight countries (in Asia and Europe) adopted a graded approach dependent on the length of treatment. The lowest ANC threshold for discontinuation was $0.5 \text{ mm}^3/\text{L}$ in Taiwan, while the highest was $1.5 \text{ mm}^3/\text{L}$ (in several countries). The lowest threshold WCC threshold for discontinuation was $1.0 \text{ mm}^3/\text{L}$ in Taiwan, while the highest limit was $4.0 \text{ mm}^3/\text{L}$ (in Armenia).

Clozapine rechallenge

Forty-one (40%) countries prohibited clozapine rechallenge after suspected clozapine-induced neutropenia. Seven (7%) countries partially restricted clozapine rechallenge. Specifically, guidelines

from three countries (Argentina, Singapore, Turkey) recommended clozapine rechallenge based on the previous ANC/WCC count not indicating severe neutropenia. Brazil and Qatar required consultation with a haematologist prior to rechallenge. Australia, Canada and the United Kingdom required a manufacturer off-licence agreement. An off-licence agreement indicates that the use of clozapine is outside of the marketing authorisation and that the benefits of clozapine treatment outweigh any possible risks to the patient. In practice, this often involves liaison with a haematologist but this is not a pre-requisite.

Clozapine haematological monitoring stringency Index

Figure 1 plots the clozapine Stringency Index for each country on a choropleth map. Within continents, Africa, North America followed by Europe showed the least variability between member countries as measured by standard deviation (Supplementary Material, Table 3). Asia showed the greatest international variability. Outliers in Asia were Japan (where stringency was scored 100), while Iceland and Bulgaria (where stringency was scored 42 and 43) were outliers in Europe. There was a nonsignificant negative correlation ($R = -0.32$, $p = 0.2$) between a country's Stringency Index and clozapine prescription rates per 100 000 persons (Fig. 2a). In contrast, there was a significant positive correlation ($R = 0.43$, $p < 0.001$) between a country's Stringency Index and healthcare expenditure per capita (Fig. 2b).

Discussion

We found marked international variability in the recommendations for haematological monitoring during clozapine treatment, the discontinuation of treatment and clozapine rechallenge. Moreover, only 7% of countries have modified clozapine monitoring criteria for patients with BEN. There was a direct correlation ($R = 0.43$, $p < 0.001$) between a country's Stringency Index and healthcare expenditure per capita. To our knowledge, this is the largest study to assess national differences in clozapine haematological monitoring guidelines, and the first to compare haematological thresholds for discontinuation between countries. Our findings complement a previous study by Nielsen *et al.*, 2016 that investigated broader aspects of international guidelines of clozapine use (Nielsen *et al.*, 2016), and are of particular interest in the context of growing concerns about the underutilisation of clozapine in TRP. Several authors have called for the easing of restrictive guidelines, such as those mandating lifelong, frequent haematological monitoring or prohibiting rechallenge after haematological values fall below a particular threshold (Schulte *et al.*, 2020; Siskind and Nielsen, 2020; Oloyede *et al.*, 2021a).

Geographical variations in haematological monitoring requirements

Clinical guidelines represent an important step towards the dissemination and implementation of evidence-based clinical practice, and this includes clozapine treatment in TRP (Woolf *et al.*, 1999). In our review, we found that the dissemination of haematological monitoring guidelines was lower in low- and middle-income countries. Moreover, as demonstrated in Fig. 1, there was a non-significant positive correlation between a country's Stringency Index and healthcare expenditure per capita. This variability in guideline availability may be attributed to

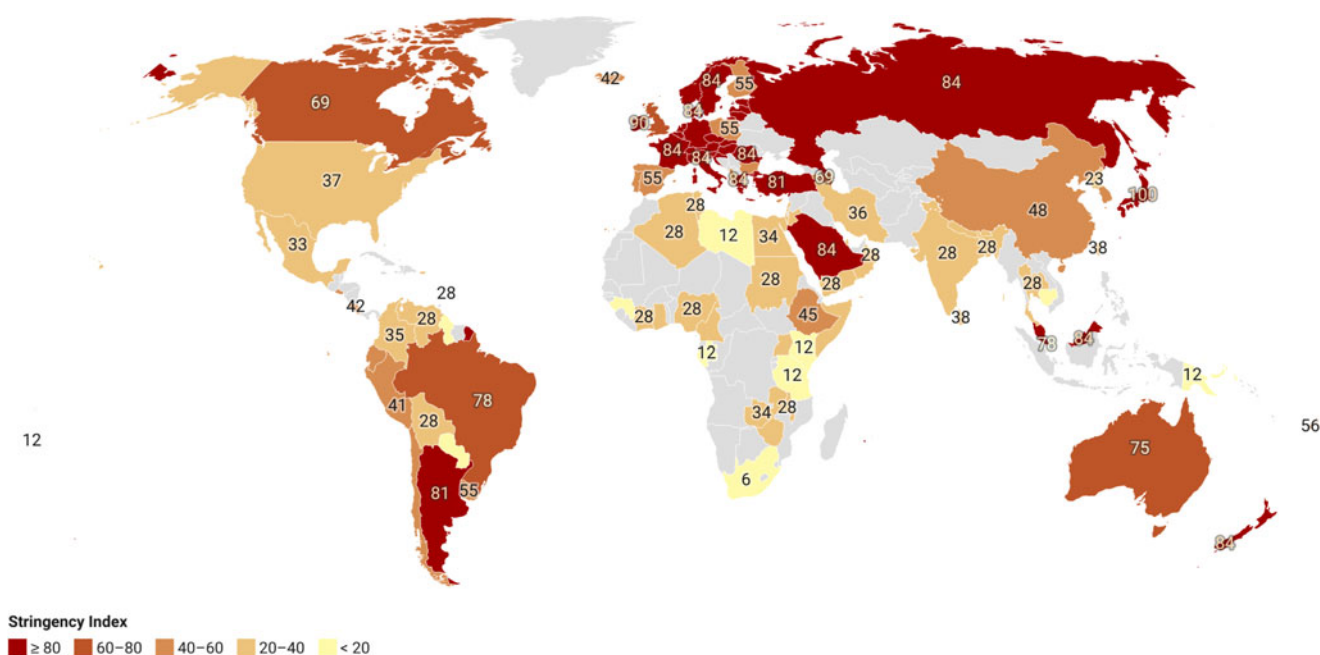


Fig. 1. Choropleth map of clozapine haematological monitoring Stringency Index. Red indicates highest stringency and yellow the lowest stringency. Grey indicates no data.

reduced resources in these countries and/or a lower rate of clozapine prescription (Woolf *et al.*, 1999).

The observed geographical variations in monitoring standards could reflect ethnic differences in the risk of clozapine-induced blood dyscrasias (de Leon *et al.*, 2021). Nonetheless, there is mixed evidence regarding an increased risk in Asian populations (Munro *et al.*, 1999; Shapiro *et al.*, 1999; Sing *et al.*, 2017; Xiao-Hong *et al.*, 2020). There is clearer evidence regarding BEN, a phenotype seen predominantly in populations of African ancestry who have low ANC values of less than $1.5 \text{ mm}^3/\text{L}$ without

an increase in adverse clinical outcomes (Oloyede *et al.*, 2021b), which is associated with the Duffy-Null genotype (Legge *et al.*, 2019). From our review, many national guidelines mentioned identifying BEN in liaison with a haematologist in their guidance but did not include modified monitoring parameters. Moreover, contrary to expectations, in continents where BEN prevalence is reportedly highest (Africa and Middle East) there was little or no mention of BEN in monitoring guidelines (Supplementary Material, Table 2 and Fig. 1) (Manu *et al.*, 2016). Revisions concerning these monitoring parameters are warranted to overcome

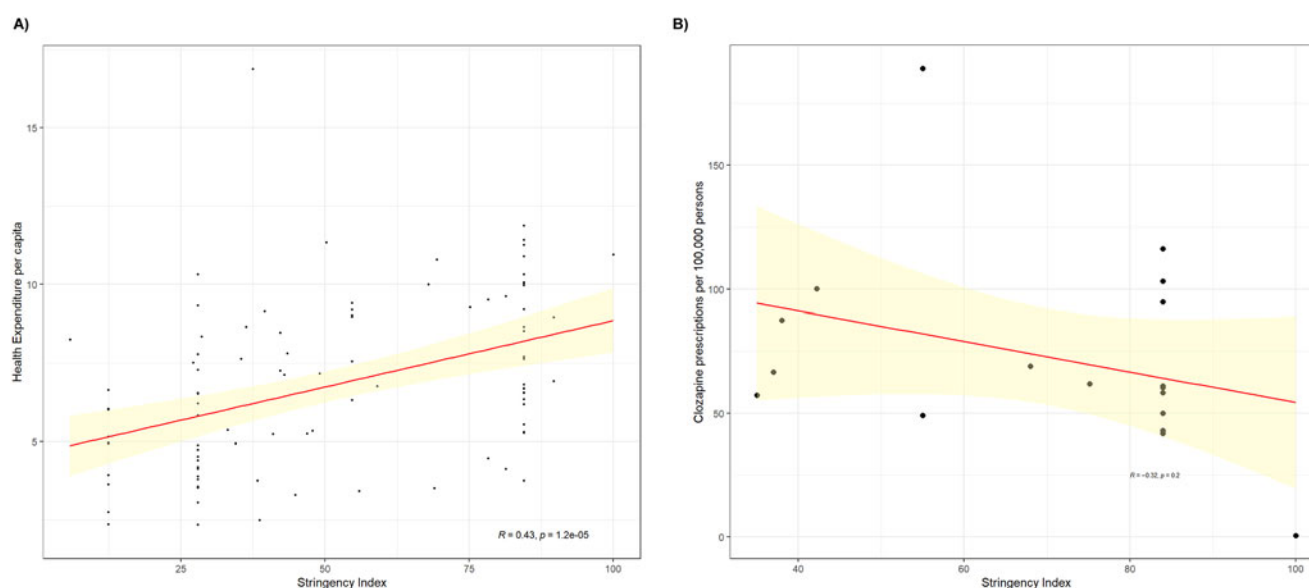


Fig. 2. (a) Scatter plot and Pearson's correlation coefficient for the clozapine Stringency Index and health expenditure per capita. Data was not available for Hong Kong, North Korea, Somalia and Taiwan. (b) Scatter plot and Pearson's correlation coefficient for the clozapine Stringency Index and clozapine utilisation rates in 18 countries. The yellow shaded area indicates confidence interval at the 95% level.

racial and ethnic disparities in clozapine use, particularly in countries where a high frequency of inter-ethnic admixture exists (Oloyede *et al.*, 2021b; de Freitas *et al.*, 2022). This is also emphasised by evidence suggesting that benign neutropenia (i.e. constitutional neutropenia) also occurs in Caucasian and Chinese populations (Cutting and Lang, 1964; Kyle and Linman, 1968; Dancey and Brubaker, 1980; Mant *et al.*, 1987; Pathak *et al.*, 2009). On a practical level, the identification of BEN may be complicated in some countries due to limited access to haematologists, however, the emergence of cost-effective genetic tests may improve this (Oloyede *et al.*, 2021b).

Utilisation rates and clozapine-induced agranulocytosis mortality rates

While our data provides a clearer perspective on clozapine haematological monitoring guidelines internationally, one important consideration that remains unanswered is the impact of these variations on clozapine utilisation rates. In a previous study, Bachmann *et al.*, 2017 compared clozapine usage internationally, (Bachmann *et al.*, 2017) and a similar study was conducted by Whiskey *et al.*, 2021, reporting clozapine usage in the UK (Whiskey *et al.*, 2021). Combining data from both studies, clozapine usage rates were highest in Finland, New Zealand, Iceland and the Netherlands (Bachmann *et al.*, 2017). Interestingly, as shown in Fig. 2, these countries were among those with the least stringent clozapine guidelines. Conversely, clozapine use is significantly lower in Japan which until recently has relatively strict national guidelines. These data suggest that the stringency of monitoring is broadly related to usage rates, and this assertion is further supported by evidence that frequent monitoring is a factor that leads both patients and clinicians to discontinue clozapine (Black *et al.*, 1996; Legge *et al.*, 2016). Furthermore, previous studies have suggested that flexible neutrophil monitoring may contribute to long-term clozapine maintenance (Davis *et al.*, 2014; Ingimarsson *et al.*, 2016). Nevertheless, such conclusions are limited by the absence of data for clozapine utilisation rates in some countries included in our study.

Beyond clozapine usage rates, the safety implications of flexible haematological monitoring, particularly around the risk of severe neutropenia, are equally important (Boxer, 2012). Encouragingly, recent meta-analytic data found no significant difference in the prevalence of clozapine-induced severe neutropenia across 12 countries in five continents, with or without strict monitoring (Xiao-Hong *et al.*, 2020). Therefore, these data would seemingly suggest that achieving optimum stringency of monitoring does not affect mortality rates secondary to clozapine-induced severe neutropenia. Notably, an early analysis suggested reduced mortality with the implementation of clozapine national registries with mandatory haematological monitoring requirements. However this study was flawed due to an assumption that 1% of patients treated with clozapine develop severe neutropenia with expected fatality rates of 20% (based on the antidepressant mianserin) (Honigfeld, 1996). However, meta-analytic evidence suggests that the rate of severe neutropenia is closer to 0.4% and estimated that fatalities are closer to 10%, even without strict monitoring, thus overestimating the impact of stringent monitoring (Myles *et al.*, 2018; Xiao-Hong *et al.*, 2020). Moreover, a recent case series has demonstrated how monitoring schemes should aim to identify true clozapine-induced severe neutropenia as opposed to threshold-defined nominal severe neutropenia (Taylor *et al.*, 2022). In addition, several recent meta-analyses have shown that

the risk of clozapine-induced severe neutropenia is highest in the first 6 months (Myles *et al.*, 2018; Myles *et al.*, 2019). Cumulatively, this casts doubts on the clinical utility of stringent haematological monitoring beyond the first six months of treatment, especially when considering the impact of premature discontinuation of clozapine on morbidity (Schulte, 2006; Shrivastava and Shah, 2009; Rettenbacher *et al.*, 2010; Myles *et al.*, 2018, 2019; Luykx *et al.*, 2020; Schulte *et al.*, 2020; Siskind and Nielsen, 2020; Johannsen *et al.*, 2022).

Clozapine rechallenge criteria

The current literature emphasises the need to encourage continued clozapine treatment in responsive patients when it is safe to do so (Shah *et al.*, 2018; Luykx *et al.*, 2020). Nevertheless, there are occasions where treatment discontinuation is necessary, and this includes the case of a true clozapine-induced blood dyscrasia (Legge *et al.*, 2016; Blackman and Oloyede, 2021; Blackman *et al.*, 2021). Studies suggest that treatment is often interrupted in the absence of strong evidence of a haematological aberration (Davis *et al.*, 2014; Oloyede *et al.*, 2021a). This raises the question of whether it is appropriate to rechallenge such patients with clozapine. Encouragingly, most studies indicate that rechallenging is feasible when the neutropenia is not severe or emerged within the first few months of treatment (Manu *et al.*, 2012; Meyer *et al.*, 2015; Silva *et al.*, 2020; Oloyede *et al.*, 2021a). However, our review found that only a small minority of countries (5%) permit rechallenge, with the majority either imposing a lifelong prohibition on rechallenge after suspected clozapine-induced blood dyscrasias or providing no guidance on the issue. Balanced criteria from a mental and physical health perspective for clozapine rechallenge such as those used in Turkey and Singapore, based on the index ANC count, can conceivably achieve optimal outcomes for patients in regard to safety and therapeutic benefits (Schulte *et al.*, 2010).

Proposed solution: internationally standardised guidelines

Haematological Monitoring is an intrinsic component of treatment with clozapine (Farooq *et al.*, 2019; Schulte *et al.*, 2020). Our review shows that most countries require that this continues throughout the duration of treatment. This approach has been adopted in most SmPCs, despite the lack of supporting evidence. This practice began over 30 years ago after a group of patients in Finland developed severe neutropenia leading to eight deaths (Hippius, 1999; Crilly, 2007). While the early detection of clozapine-induced agranulocytosis (CIA) has undoubtedly avoided many clinical complications (Copolov *et al.*, 1998; Munro *et al.*, 1999; Deliliers, 2000), two issues remain outstanding: the haematological threshold for discontinuation, and for how long haematological monitoring is necessary (Atkin *et al.*, 1996). Concerning the first issue, the haematological thresholds originally used by the clozapine patent holder appear to have been set with a margin of safety. However, the manufacturers have since acknowledged that these limits were arbitrarily defined and are not consistent with clinical and scientific knowledge of immune system functioning, and therefore may unnecessarily restrict access to treatment (O'Sullivan and Lynch, 1996). Regarding the second issue, shortly after the aforementioned events in Finland, a Sandoz-sponsored article proposed weekly haematological monitoring for the first 18 weeks, similar to previous recommendations for chlorpromazine (Pisciotta *et al.*,

1958; Amsler *et al.*, 1977; Anderman and Griffith, 1977). However, the basis of the view that monitoring should continue indefinitely is unclear. As described by Kleinerman in 1990, this controversy is not new (Kleinerman, 1990). In a letter to the manufacturers, authors described the monitoring practices as ‘clinically, scientifically and economically unjustified’. Indefinite monitoring is increasingly questioned from both a safety and a health economics perspective (Lee, 1990; Zhang *et al.*, 1996; Shrivastava and Shah, 2009; Nooijen *et al.*, 2011; Lahdelma and Appelberg, 2012; Cohen and Monden, 2013; Myles *et al.*, 2018, 2019). Routine monitoring increases the likelihood of detecting transient fluctuations in neutrophil count that are unrelated to clozapine treatment, particularly when patients have been established on treatment for many years and have unrecognised haematological phenotypes such as benign neutropenia (Oloyede *et al.*, 2021a, 2021b; Taylor *et al.*, 2022). To this end, limiting monitoring to the first few months of treatment, as used in Bulgaria, Mexico and Colombia, is arguably the most evidence-based approach. While cases of late-onset CIA have been previously reported, these events are rare (Lahdelma and Appelberg, 2012; Cohen and Monden, 2013). Moreover, other medications that increase the risk of neutropenia, such as carbamazepine are not subject to the same monitoring requirements (Ibáñez *et al.*, 2005).

So what could be the solution to restrictive monitoring guidelines? There is a clear need to balance the benefits of mandatory haematological monitoring against the risk that these become barriers to the initiation and continuity of clozapine treatment. Noteworthy initiatives to address this issue have been made. For example, due to the low incidence of CIA, the Netherlands Clozapine Collaboration group allows haematological monitoring for neutropenia to be stopped or reduced to 3-monthly monitoring (off-label) after the first 6 months of clozapine treatment (Cohen and Monden, 2013). This has not led to an increase in mortality secondary to clozapine-induced severe neutropenia (van der Klauw *et al.*, 1998; Schulte, 2006). Furthermore, in 2015 the US FDA updated its clozapine guidelines, decreasing the ANC cut-off for clozapine cessation to a lower threshold compared to many other countries (Sultan *et al.*, 2017; Oloyede *et al.*, 2022). In addition, the requirements for monitoring WCC were removed (Whiskey *et al.*, 2019) and patients with BEN were permitted to commence clozapine treatment under lower thresholds than in most countries.

It is paramount that regulatory bodies on a global scale take actions to improve access to the only proven treatment for this severely debilitating and costly disorder (Schulte *et al.*, 2020). Our direct communications with academic experts in low- and middle-income countries revealed inequality in access to clozapine care due to costly haematological monitoring requirements, despite clozapine being listed as an essential drug by the World Health Organisation (Barbui and Purgato, 2014). This is further supported by a recent study by Todesco *et al.* who conducted a cross-country analysis of selection, availability, prices and affordability of essential medicines for mental health conditions. From their findings, clozapine was considered an essential medicine in most high-income countries, but only in a minority of low-income countries (Todesco *et al.*, 2022). Consistent evidence has shown overly stringent monitoring requirements to be a prominent barrier to prescribing or utilising clozapine in patients with TRP (Farooq *et al.*, 2019). The result of which are worse long-term outcomes for this debilitating disorder, including lower long-term all-cause mortality rates (Vermeulen *et al.*, 2019), reduced violent offending (Bhavsar *et al.*, 2020) and

readmission rates (Land *et al.*, 2017). This evidence merits that guidelines should take a more balanced approach in which mental, as well as physical health outcomes are considered. In this regard, we propose that an alignment of some of the aforementioned measures fosters this goal.

Collaborative efforts to standardise monitoring could help overcome the lack of haematological monitoring guidelines in some countries by providing accessible, evidence based monitoring guidelines. Such efforts may prove important to improve access to treatment (Barbui and Purgato, 2014). Notably, a similar collaborative approach to guideline development is seen in Europe with countries regulated by the European Medicines Agency. However, as some guidelines are not consistent with present evidence, countries such as Iceland and the Netherlands have taken steps to adopt monitoring standards that often run contrary to manufacturer recommendations to alleviate the effect of restrictive guidelines (Ingimarsson *et al.*, 2016; de Leon *et al.*, 2021). In particular, in Iceland, haematological monitoring after the first 18 weeks of treatment (when the risk of severe neutropenia is highest) (Alvir *et al.*, 1993; Atkin *et al.*, 1996) is conducted approximately every four months as opposed to recommended monthly intervals. Furthermore, there is evidence that clozapine can be safely continued even after ANC levels that would have mandated treatment discontinuation in other countries. From a clinical standpoint, recent literature has demonstrated that this reduced neutrophil measurement did not lead to more frequent cases of severe neutropenia (Ingimarsson *et al.*, 2016). Assuming that the available scientific evidence underpinning haematological monitoring is broadly generalisable, it should be feasible to produce consistent, evidence-based international recommendations, irrespective of the country. With the need to reduce barriers to clozapine initiation, maintenance and increase patient acceptability, the revision and standardisation of prescribing and monitoring regulations across countries should be prioritised (Black *et al.*, 1996; Kelly *et al.*, 2018; Farooq *et al.*, 2019).

Strengths and limitations

Several important limitations need to be considered. First, reviewed guidelines may not be representative of the situation in countries that were not reviewed in our study. Nevertheless, our study includes over 50% of countries worldwide, covering all populated continents, suggesting representability. Second, our review included four countries where only sub-national guidelines were available present. Therefore, it is plausible that there is considerable variation in practice between regions of the same country. We therefore consulted with at least two academics from different regions of these countries. However, our study is limited by reliance on academics for guidelines and data provision opposed to regulatory bodies. Third, the Stringency Index does not measure the effectiveness of any of the monitoring guidelines, therefore, it is not possible to make definite conclusions on which regulation should be favoured on an international scale. Rather, our data provide a basis for future empirical analyses across countries using a combination of regulatory parameters from different countries. The fourth concerns the exploration of the association between monitoring stringency and clozapine use. As only 18 countries were included, this may have been insufficiently powered. Furthermore, while health expenditure is a reliable measure of healthcare spending, it was not possible to quantify the spending on clozapine treatment management specifically. Caution should be exercised in attributing a causal relationship from this

ecological study due to ecological fallacy and requires confirmation in individual-level case-control or cohort studies. Fifth, we have assumed that national guidelines on clozapine monitoring have a significant influence on clinical practice, but could not assess this directly. It is thus possible that clinical practice may vary from that recommended in guidelines, such as the off-label reduction in haematological monitoring seen in the Netherlands. Finally, our review focuses primarily on haematological monitoring in relation to agranulocytosis and not general tolerability nor all haematological aspects such as clozapine-related DRESS syndrome.

Conclusion

There are wide variations in the guidelines for clozapine monitoring between countries. There is also a general lack of guidance on the duration of haematological monitoring, the discontinuation of clozapine in patients with BEN, and the restarting of clozapine following neutropenia. A single evidence-based and standardised international guideline, with more information on the three latter items could help to address the under-utilisation of clozapine in the management of patients with schizophrenia whilst simultaneously addressing safety concerns.

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