Contents lists available at ScienceDirect

Schizophrenia Research

journal homepage: www.elsevier.com/locate/schres

Risk of clozapine-associated agranulocytosis and mandatory white blood cell monitoring: Can the regulations be relaxed?

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ARTICLE INFO

Keywords:
Clozapine
Pharmacovigilance
Weighing risks
Haematological monitoring
Agranulocytosis
Neutropenia

ABSTRACT

After the introduction of clozapine eight Finnish patients died after developing agranulocytosis. Clozapine was withdrawn from the market and only reintroduced with strict mandatory white blood cell monitoring as long as treatment lasts and thresholds at which clozapine must be discontinued definitively. The fear of agranulocytosis and the need for intensive blood monitoring is the single most important barrier for prescribers and patients alike and leads to underprescription of the only effective and approved medication for treatment-resistant schizophrenia. We summarize evidence that the risk of agranulocytosis is smaller than perceived at the time of reintroduction, is concentrated in the first 18 weeks of treatment, is not greater than with other antipsychotics thereafter and that frequent blood monitoring has not demonstrably decreased the rate of agranulocytosis. Therefore we propose 1) mandatory monitoring of the absolute neutrophil count (ANC) exclusively during the first 18 weeks of clozapine treatment, 2) that thereafter the prescriber and the well-informed patient decide together about further monitoring frequency, 3) that clozapine treatment must be stopped if the ANC falls below 1.0×10^9/L. Continuation of clozapine or a rechallenge are possible if prescriber and patient determine that the benefits outweigh the risks. 4) National registries which control the haematologic monitoring are unnecessary and do not help to reduce clozapine-induced agranulocytosis. They should at least be restricted to the first 18 weeks of clozapine use.

1. Introduction

Clozapine is the only effective and approved medication for treatment-resistant schizophrenia (TRS). Unfortunately it is underprescribed in many countries, a lamentable situation since underprescription of clozapine leads to poorer clinical outcomes and unnecessarily prolongs patients' suffering (Bogers et al., 2016). A systematic review found that the main reason for underprescription was concern on the part of prescribing physicians about the pharmacological characteristics of clozapine (mandatory blood monitoring and adverse effects) and – probably as a consequence of this concern – lack of personal prescribing experience (Verdoux et al., 2018). Undoubtedly the fear of agranulocytosis and the need for intensive blood monitoring is the single most important barrier for prescribers and patients alike (Gee et al., 2017; Farooq et al., 2019; Taylor et al., 2000). There is some evidence that, broadly speaking, the stringency of monitoring correlates with clozapine utilisation rates (Oloyede et al., 2022a).

In this article we will discuss the WCC and/or ANC cut-off points for determining whether any additional risk management, including the discontinuation of clozapine treatment with easing of restrictive haematological prohibition of rechallenge, is required, and also whether the available evidence actually justifies mandatory four-weekly WCC and/or ANC monitoring during maintenance treatment until four weeks after termination of clozapine treatment.

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[1] We are deeply saddened to report that Bert Bakker passed away after the completion of this review.

https://doi.org/10.1016/j.schres.2023.09.024
Received 31 May 2023; Received in revised form 11 September 2023; Accepted 12 September 2023

2. Short history of clozapine and haematological risks

Clozapine was first introduced in Europe in the 1970s. Unfortunately, a group of patients in Finland developed severe neutropenia, leading to eight deaths (Idänpään-Heikkilä et al., 1975). Shortly after this, a Sandoz-sponsored article proposed weekly haematological monitoring for the first 18 weeks, a similar recommendation to that for chlorpromazine at the time (Anderman and Griffith, 1977). After the events in Finland indicating the threat of agranulocytosis, clozapine was withdrawn from the market and only reintroduced, with mandatory white blood cell monitoring for an indefinite period, after Kane's landmark study showing that clozapine is efficacious in TRS (Kane et al., 1988). However, the basis for determining leukocyte or granulocyte cut-off readings to discontinue clozapine therapy and for the view that monitoring should continue indefinitely is unclear and has in fact been debated from the outset (Kleinerman, 1990). Moreover, the estimate at that time that 'approximately 1% to 2% of treated patients developed agranulocytosis' has been shown to be incorrect (see below) (Honigfeld et al., 1998). Later the manufacturers acknowledged that these thresholds were arbitrary and may unnecessarily restrict access to treatment for patients with benign ethnic neutropenia (BEN) (O'Sullivan and Lynch, 1996).

Neutropenia is generally defined as an absolute neutrophil count (ANC) of $<1.5 \times 10^9$/L and is often classified clinically as mild (1.0 to $<1.5 \times 10^9$/L), moderate (0.5 to $<1.0 \times 10^9$/L), or severe neutropenia ($<0.5 \times 10^9$/L) (National Cancer Institute, 2009; Oloyede et al., 2022b). Most publications on clozapine and neutropenia put severe neutropenia on a par with agranulocytosis. In this article we adhere to these definitions unless otherwise stated. ANC values above 1.0×10^9/L are generally sufficient to provide phagocytic defence, while counts below 0.5×10^9/L increase the risk of opportunistic infections. It should be noted that serious infections are likely to occur at counts lower than 0.2×10^9/L. Typically, agranulocytosis presents with fever, mouth ulcers, and sore throat, although some patients remain entirely asymptomatic despite very low neutrophil counts (Mijovic and MacCabe, 2020).

Recently there have been two reports linking clozapine use to haematological malignancies, of which 81 % were lymphomas (Tiihonen et al., 2022; Dawson et al., 2023). As Tiihonen et al. (2022) pointed out, the absolute risk difference between clozapine users and users of other antipsychotic drugs (0.2 %) is small compared with the previously observed absolute risk reduction in all-cause mortality (10.0 %).

3. Haematological monitoring worldwide

Remarkably, the haematological threshold for discontinuation of clozapine and the frequency and duration of haematological monitoring vary between different countries, even though all the countries draw on the same evidence base. An international survey of clozapine haematological monitoring in guidelines or regulations found substantial differences among the 102 countries included (Oloyede et al., 2022a). In 92 countries (90 %) routine haematological monitoring is included in guidelines or governmental regulations, but it is mandatory in only 42 countries (45 %). For example Ruan et al. (2023) reported for China that the package insert and the Chinese Psychiatric Association guideline do not provide specific recommendations on the frequency and duration of haematological monitoring. In their experience haematological monitoring varies from hospital to hospital. Eighty-five countries (83 %) include both the white cell count (WCC) and the absolute neutrophil count (ANC) in their monitoring. Sixty-two countries (61 %) recommend clozapine discontinuation based on specific haematological thresholds. The threshold haematological reading below which treatment interruption or discontinuation is recommended (often referred to as the 'red alert') varies widely between countries, ranging from an ANC reading of 0.5×10^9/L in Taiwan to 1.5×10^9/L in several other countries.

The Netherlands is the only country where the guideline (since 2006) provides the option of stopping with routine blood monitoring. If a mentally competent and adequately informed patient explicitly wants to stop having routine blood tests, this can be permitted after the first six months of clozapine treatment. Nevertheless, occasional checks of white blood cells (for instance 4 times a year) were still advised in order to detect a continuous slow decrease of granulocytes (Cohen and Monden, 2013; Dutch Clozapine Collaboration Group, 2013; Tamam et al., 2001; Raja et al., 2011). It should be noted that the Dutch guideline does not overrule the national regulations. In cases that deviate from the official regulations clozapine is prescribed off-label.

To date, this option has been applied in a minority of clozapine patients. A survey in two big Dutch mental health organizations found that 12 % of 268 and 24 % of 332 patients on maintenance treatment and their prescribers opt for three-monthly blood tests (Michielsen, 2023; van der Weide, 2023).

This frequency is in accordance with the recommendation of a group of clozapine experts that during the COVID-19 pandemic blood monitoring could be extended from 4-weekly to 12-weekly intervals to reduce the risk of exposure to the virus (Siskind et al., 2020). Recently a Delphi consensus guideline from the Treatment Response and Resistance in Psychosis (TRRIP) Working Group recommended (without further reasoning) reducing the frequency of WCC and ANC controls to every 6 months after five years of clozapine treatment, provided there is no previous history of neutropenia (Wagner et al., 2023).

In 2002 the European Medicines Agency (EMA) harmonised the summary of product characteristics for the member states of the European Economic Area mandating that WCC and ANC must be monitored weekly for the first 18 weeks and once every four weeks thereafter during treatment with clozapine (European Medicines Agency, 2023; see Supplementary Box S1 for Decision making on medicines in the European Union). If the WCC is lower than 3.0×10^9/L or the ANC lower than 1.5×10^9/L, clozapine must be stopped and rechallenge is prohibited. Although BEN is mentioned, the EMA has not established adapted thresholds for patients with this condition.

Both the EMA and the US Food and Drug Administration (FDA) state that clozapine must be discontinued after a first haematological result below a specified threshold ('red alert') but that this result should be confirmed within 24 h (European Medicines Agency, 2023; Food and Drug Administration, 2023). This is important to rule out laboratory errors, morning pseudoneutropenia or transient neutropenia in people with benign familial or ethnic neutropenia which may otherwise be mistaken for impending agranulocytosis. Johannsen et al. (2022) found that in 56 % of 38 neutropenic episodes with readings lower than 1.5×10^9/L the readings were found to be normal again when counts were repeated within one week.

In 2015 the FDA changed the treatment recommendations for clozapine dramatically so that patients are able to continue clozapine treatment with a lower ANC (FDA Drug Safety Communication, 2023). The ANC leading to treatment interruption was lowered from $<1.5 \times 10^9$/L to $<1.0 \times 10^9$/L and WCC monitoring was ceased altogether with monitoring limited to ANC. In addition, patients with BEN, who previously were not eligible for clozapine treatment, are now able to receive the medicine. Moreover, the revised prescribing information facilitates prescribers' ability to make individualised treatment decisions if they determine that the risk of psychiatric illness is greater than the risk of recurrent severe neutropenia, especially in patients for whom clozapine may be the antipsychotic of last resort (see for comparison with the EMA regulation Table 1). The FDA expected that these changes would allow continued treatment for a greater number of patients.

A British modelling study has confirmed this positive assumption (Oloyede et al., 2022b): it showed that in a cohort of all 3731 clozapine users who had been placed on the mandatory UK non-rechallenge database between 2002 and 2021 because of ANC $<1.5 \times 10^9$/L or WCC $<3.0 \times 10^9$/L, application of the lower FDA neutrophil thresholds and BEN criteria would have permitted continuation of clozapine treatment in 85 % of the cases who had to stop and were prohibited from ever trying the treatment again except in exceptional circumstances and

Table 1
Comparison of Leukocyte Monitoring in European Medicines Agency and US Food and Drug Administration Clozapine Guidelines.

	Current EMA guideline[a]		Current FDA guideline[b]		
	Criteria for all clozapine users[c]	Rule	Criteria for general clozapine users	Criteria for clozapine users with BEN	Rule
Normal range (green alert)					
WCC	$\geq 3.5 \times 10^9$/L	Continue clozapine without change of monitoring frequency: weekly for the first 18 weeks and once every four weeks thereafter.	Not mandatory	Not mandatory	
ANC	$\geq 2.0 \times 10^9$/L		$\geq 1.5 \times 10^9$/L	$\geq 1.0 \times 10^9$/L	Continue clozapine without change of monitoring frequency: weekly from initiation to 6 months, monthly after 12 months.
Mild neutropenia (amber alert)					
WCC	≥ 3.0 and $< 3.5 \times 10^9$/L	Continue clozapine with increased monitoring frequency (twice a week) until counts stabilise in the range of mild neutropenia or return to normal range.	Not mandatory	Not mandatory	
ANC	≥ 1.5 and $< 2.0 \times 10^9$/L		≥ 1.0 and $< 1.5 \times 10^9$/L[e]	≥ 0.5 and $< 1.0 \times 10^9$/L[e]	General clozapine users: Continue clozapine with increased monitoring frequency (3 times a week) until ANC returns to normal range and then return to patient's last "Normal Range" ANC monitoring interval. BEN: recommend haematology consultation but continue clozapine treatment with increased monitoring frequency (3 times a week) until ANC returns to $\geq 1.0 \times 10^9$/L or to $\geq$ patient's known baseline, once ANC $\geq 1.0 \times 10^9$/L or at $\geq$ patient's known baseline, check ANC weekly for 4 weeks, then return to patient's last "Normal BEN Range" ANC monitoring interval.
Moderate or severe neutropenia (red alert)					
WCC	$< 3.0 \times 10^9$/L[d]	Immediately stop clozapine, sample blood daily until haematological abnormality is resolved, monitor for infection. Do not re-expose the patient.	Not mandatory	Not mandatory	
ANC	$< 1.5 \times 10^9$/L[d]		$\geq 0.5 \times 10^9$/L and $< 1.0 \times 10^9$/L[e]		General clozapine users: recommend haematology consultation. Interrupt treatment for suspected clozapine-induced neutropenia. Sample blood daily until ANC $\geq 1.0 \times 10^9$/L, then check three times weekly until ANC $\geq 1.5 \times 10^9$/L, once ANC $\geq 1.5 \times 10^9$/L, check ANC weekly for 4 weeks, then return to patient's last "Normal Range" ANC monitoring interval. Resume treatment once ANC normalizes to $\geq 1.0 \times 10^9$/L.
			$< 0.5 \times 10^9$/L[e]	$< 0.5 \times 10^9$/L[e]	Recommend haematology consultation. Interrupt treatment for suspected clozapine-induced neutropenia. Sample blood daily until ANC is $\geq 1.0 \times 10^9$/L (general clozapine users) or $\geq 0.5 \times 10^9$/L (clozapine users with BEN), then check three times weekly until ANC $\geq 1.5 \times 10^9$/L (general clozapine users) or ANC $\geq$ patient's known baseline. Do not rechallenge unless prescriber determines benefits outweigh risks. If patient rechallenged, resume treatment as a new patient under "Normal Range" monitoring once ANC $\geq 1.0 \times 10^9$/L or at patient's known baseline

ANC: absolute neutrophil count, BEN: benign ethnic neutropenia, FDA: Food and Drug Administration, EMA European Medicines Agency, WCC: white cell count.
[a] WCC and ANC must be monitored weekly for the first 18 weeks and once every four weeks during treatment with clozapine thereafter.
[b] ANC must be monitored weekly from initiation to 6 months, every 2 weeks from 6 to 12 months and monthly after 12 months.
[c] The guideline does not specify adapted thresholds for BEN, but states: patients who have low white blood cell counts because of benign ethnic neutropenia should be given special consideration and may be started on clozapine with the agreement of a haematologist.
[d] Confirmation of the haematological values is recommended by performing two blood counts on two consecutive days: however, clozapine should be discontinued after the first blood count.
[e] Confirm all initial reports of ANC $< 1.5 \times 10^9$/L (ANC $< 1.0 \times 10^9$/L for BEN patients) with a repeat ANC measurement within 24 h.

under an off-licence agreement.

4. Call for less restrictive haematological regulations

The true incidence of life-threatening, clozapine-induced agranulocytosis (LTCIA) is largely unknown, because it is assumed that the frequent monitoring prevents patients with neutropenia from developing agranulocytosis (Taylor et al., 2022). It is also unclear whether all patients with ANC $<0.5 \times 10^9$/L are in fact suffering from LTCIA, because there are scarcely any accurate data on the actual number of neutropenic sepsis episodes and consequent hospitalisations, including outcomes such as overall survival. Moreover, there are so few longitudinal data for the general population with similar frequent monitoring that it is impossible to make a proper comparison with clozapine users.

Taylor et al. (2022) have noted that the perceived association of clozapine with neutropenia may be a result of surveillance bias, with intensive blood monitoring revealing random, clinically silent and non-pathological episodes of neutropenia occurring coincidentally to the use of clozapine. Moreover, not all agranulocytosis is necessarily caused by clozapine. In Finland, during the week prior to the onset of agranulocytosis 40 % of all reported clozapine users with agranulocytosis had received not only clozapine, but also other medication associated with agranulocytosis (Lahdelma and Appelberg, 2012). Other reasons for neutropenia may be undiagnosed BEN, vitamin deficiencies (vitamin B12 and folic acid) or viral infections.

In the light of new findings (discussed below), several authors have called for the easing of the regulations (Lee, 1990; Zhang et al., 1996; Schulte, 2006; Shrivastava and Shah, 2009; Nooijen et al., 2011; Lahdelma and Appelberg, 2012; Cohen and Monden, 2013; Ingimarsson et al., 2016; Myles et al., 2018, 2019; Siskind and Nielsen, 2020;

Oloyede et al., 2021; Taylor et al., 2022; Leung et al., 2022).

5. Incidence and risk of neutropenia and agranulocytosis

Myles et al. (2018) examined the epidemiology of clozapine-associated neutropenia. They included 108 studies with >450,000 patients whose blood had been monitored while they were treated with clozapine. In high-quality studies the rate of mild neutropenia (ANC $<1.5 \times 10^9$/L) found was 3.9 %, of agranulocytosis (ANC $<0.5 \times 10^9$/L) 0.7 % and of mortality from complications of agranulocytosis 0.013 %, or 1 in 7700 treated patients. The case fatality rate for agranulocytosis was 2.1 %. The authors concluded that approximately 75 % of people developing mild neutropenia will not progress to moderate neutropenia or agranulocytosis. These rates of neutropenia are very reassuring, given that they are of the same order of magnitude as the point prevalence previously reported in otherwise healthy members of the community of between 0.4 % and 4.5 % for ANC $<1.5 \times 10^9$/L, and between 0.08 % and 0.57 % for ANC $<1.0 \times 10^9$/L (Hsieh et al., 2007). It is interesting that the data showed no difference in rates of agranulocytosis before and after 1990 (at which point mandatory haematological monitoring was introduced). The authors therefore concluded that their evidence indirectly suggests that monitoring programs facilitating early clozapine discontinuation due to mild or moderate neutropenia do not necessarily result in reduced progression to agranulocytosis.

Another meta-analysis, including many otherwise uncovered studies from China, supported this conclusion (Li et al., 2020). In Chinese studies of clozapine users undergoing strict monitoring the rate of severe agranulocytosis (ANC $<0.1 \times 10^9$/L, which suggests that these were true LTCIA cases) was 0.4 % (95 % CI 0.3–0.6 %) and in studies of patients without strict monitoring 0.5 % (95 % CI 0.3–0.8 %). Interestingly, the estimated incidence at the time of the first report on clozapine-associated agranulocytosis in Finland was also 0.4 % (eight of an estimated 2000 clozapine users, 95 % CI 0.19–0.80 %) (Idänpään-Heikkilä et al., 1975). In a reaction to the alarming Finnish report, in 1975 Sandoz published findings on agranulocytosis among clozapine users (Griffith and Saameli, 1975). At that time there was no extensive haematological monitoring, so that the cases found were true LTCIA cases. In clinical trials they found four cases of agranulocytosis in 2900 clozapine users (0.14 %, 95 % CI 0.04–0.37 %), two of them 'with a very questionable causal relationship', and from post-marketing reports in 22 countries outside Finland 18 cases (0.3 per 1000 clozapine users).

Myles et al. (2019) also compared rates of neutropenia in controlled studies of clozapine or other antipsychotic medications which included subjects from initiation of clozapine or the comparator medication. The data based on 1260 subjects exposed to clozapine (2981 person-years) and 1596 subjects exposed to comparator antipsychotics (4942 person-years) did not support a stronger association with clozapine for mild or severe neutropenia (agranulocytosis). The authors concluded 'that either all antipsychotic drugs should be subjected to haematological monitoring or monitoring isolated to clozapine is not justified'.

It might be objected that a higher agranulocytosis risk with clozapine during the first 18 weeks of treatment may become 'diluted' during follow-up. The risk ratio for agranulocytosis was 1.65 (95 % CI, 0.58 %–4.71 %) (Myles et al., 2019). Nevertheless, at least for clozapine use thereafter the finding is valid, certainly if it is taken into account that blood monitoring in the clozapine group in many studies was more intensive than in the comparator group, yielding a risk of observation bias towards a higher relative risk of neutropenia in the clozapine arm.

The reassuring findings of these systematic reviews and meta-analyses are supported by smaller studies with different methodologies. In Iceland no WCC monitoring is mandated during clozapine treatment. In a cohort of 201 clozapine users the median number of days between neutrophil measurements during the first 18 weeks of treatment was 25 days and thereafter 124 days (Ingimarsson et al., 2016). Thirty-four cases of neutropenia were identified during clozapine treatment, with an average follow-up time of 9.2 years. Most of these cases, 24 individuals, developed mild neutropenia (ANC 1.5–1.9 $\times 10^9$/L). None of these progressed to agranulocytosis. The remaining ten patients developed neutropenia in a range of 0.5–1.4 $\times 10^9$/L. Three of these patients stopped taking clozapine, while six of them continued on clozapine for at least a year without developing agranulocytosis. Only one 56-year-old patient developed agranulocytosis (ANC $< 0.5 \times 10^9$/L). Clozapine was identified as the most likely contributing factor, but since agranulocytosis occurred 28 years after the patient had started on clozapine, unknown age-related causes cannot be ruled out. This means that at least 30 of 34 patients with mild or moderate neutropenia failed to develop clozapine-associated agranulocytosis, which is consistent with the above-mentioned conclusion that approximately 75 % of people developing mild neutropenia will not progress to moderate neutropenia or agranulocytosis. Unexpectedly, in this study 410 schizophrenia patients on other antipsychotics had a similar risk of developing agranulocytosis to those on clozapine; however, when the outcome under scrutiny was neutrophils in the range of 0–1.9 $\times 10^9$/L then neutropenia was associated with more frequent testing.

These results from Iceland are in accordance with other findings: Hummer et al. (1992) showed that 22 % (95 % CI 7.5 %–36.5 %) of 68 patients on clozapine developed temporary neutropenia ($<2.0 \times 10^9$/L) which recovered within two weeks with continued clozapine therapy. Transient (2–5 days) neutropenia and weekly benign variations of the neutrophil count, not necessitating the discontinuation of clozapine treatment, have also been reported in five Asian patients (Ahn et al., 2004). A registry-based retrospective cohort study of 520 patients using a within-subject design to compare incidence rates of neutropenia ($<1.5 \times 10^9$/L) in 773 person-years with clozapine exposure with 1014 person-years without clozapine exposure found no significant difference (Johannsen et al., 2022). In a database of 742 clozapine users Tirupati and Gordon (2021) detected 37 patients with a first episode of neutropenia (ANC between 1.0 and $<1.5 \times 10^9$/L) after a median treatment duration of 31 months (range 1–143 months). After consultation with a haematologist clozapine treatment was continued in 15 patients and in 16 others resumed after a maximum interruption of 2 days. The haematologist recommended lowering the ANC red alert threshold from <1.5 to $<1.0 \times 10^9$/L for twelve of the 31 patients. This change helped to avoid treatment interruption in these patients. Treatment was later discontinued in two patients with severe hepatic disease when the counts dropped below 1.0×10^9/L. Because these events emerged after treatment had continued for 49 and 82 months respectively and leukocytopenia, especially neutropenia, is often found in advanced chronic liver disease (Minemura et al., 2009), it seems likely that clozapine was not the only cause of this decline.

6. Rechallenge after red alert

Rechallenge was favourable in 128/203 patients with earlier clozapine-associated neutropenia (63.0 %, 95 % CI, 56.0 %–69.6 %), but only in 3/17 after agranulocytosis (17.7 %, 95 % CI, 4.7 %–44.2 %) (Manu et al., 2018). These data were recently replicated in a large British sample of all rechallenged patients on the biggest (mandatory) clozapine registry (Oloyede et al., 2022b). The patients had previously been placed on the non-rechallenge registry because of WCC $<3.0 \times 10^9$/L or ANC $<1.5 \times 10^9$/L. Rechallenge was successful in 419 of 519 subjects (81 %).

It remains unclear why a rechallenge does not lead to the same result as with the first clozapine treatment. In the British national non-rechallenge registry median time from initiation of clozapine to agranulocytosis was considerably shorter than median time to mild or moderate neutropenia (3.4 months versus 23.5 months) (Oloyede et al., 2022b), supporting the view that the two are clinically distinct. Another possible explanation is that clozapine was not the cause of the haematological abnormalities. For example, several publications show that co-prescribed valproate increases the risk of neutropenia and agranulocytosis (Imbarlina et al., 2004; Meyer et al., 2015; Malik et al., 2018). In

clozapine-associated neutropenia, a negative outcome of rechallenge with clozapine is more likely in the case of very rapid onset, long duration and long recovery time of neutropenia, and co-prescription of valproate (Meyer et al., 2015; Silva et al., 2020). If a second blood dyscrasia occurs, it often has a more rapid onset and is more severe and longer lasting than the first (Dunk et al., 2006). To minimise risk, liaising with a haematologist, slow retitration of clozapine and the use of lithium (in cases of mild clozapine-associated neutropenia) or Granulocyte Colony Stimulating Factor (G-CSF, in cases of moderate or severe clozapine-associated neutropenia) to enhance haematopoiesis is recommended (Kanaan and Kerwin, 2006; Verdoux et al., 2023; Wagner et al., 2023).

7. Risk of agranulocytosis over time and in different countries

Analysis of five cohorts of the large mandatory haematological clozapine registries in the US, the UK/Ireland and Australia with 6375 up to 138,844 participants per cohort showed that the period of highest agranulocytosis risk was between weeks 6 and 18 of clozapine treatment, with incidence decreasing markedly thereafter (see Supplementary Table S1, S2 and Fig. S1) (Munro et al., 1999; Schulte, 2006). For example, in the initial monitoring system cohorts of the US, the UK/Ireland and Australia the agranulocytosis risk per thousand patient-years in the first 18 weeks of treatment was 7.89, 24.8 and 8.27 respectively, decreased in week 19 to 52 to 0.59, 1.16 and 2.17 respectively, and after the first treatment year was 0.39, 0.31 and 0.52 respectively. Interestingly, there is a striking difference in the agranulocytosis risk in different countries, varying by a factor of three. Nevertheless, the incidence of agranulocytosis during the first 18 weeks of treatment with clozapine is still higher by a factor of 100 to 1000 than the annual incidence of idiosyncratic drug-induced agranulocytosis in the general population at 1.6–15.4 cases per million (Andrès and Maloisel, 2008). However, it should be noted that these cases in the general population are generally not detected by frequent monitoring and an unknown proportion may remain undetected.

Myles et al. (2018) found an overall agranulocytosis risk of 0.7 % in all clozapine users, with only 16 % of the cases occurring after 18 weeks and 11 % after the first year. Therefore, the risk of agranulocytosis after 18 weeks is 0.11 % and after the first year 0.077 %, similar to the risk of agranulocytosis associated with phenothiazines: 0.083 % (95 % CI 0.3–0.20 %) in a cohort with frequent blood monitoring and 0.14 % (95 % CI <0.013–0.89 %) in an earlier cohort without regularly blood counts (Mandel and Gross, 1968; Pisciotta, 1978).

These findings support serious doubt whether clozapine carries a higher risk of agranulocytosis than other antipsychotics, at least after the initial 18-week treatment period when the risk in clozapine treatment is 100 to 1000 times higher compared to other drug-induced agranulocytosis. The vast majority of neutropenic events in clozapine users remit and do not progress to agranulocytosis. At the very most, monitoring might detect agranulocytosis somewhat earlier. However, this is probably only true for weekly or fortnightly checks, since real agranulocytosis caused by clozapine at the beginning of treatment is usually a rapid process developing from normal to ANC $<0.5 \times 10^9$/L within a week (median 8.4 days, range 2–15 days) (Taylor et al., 2022). A slow decline of WCC and ANC over many months may occur very rarely after years of clozapine use, but there is no difference in risk between clozapine and other antipsychotics (Tamam et al., 2001; Raja et al., 2011; Cohen and Monden, 2013; Myles et al., 2019).

8. Risk of LTCIA with less haematological monitoring

If we assume that without haematological monitoring between week 19 and 52 all cases with WCC $< 3.0 \times 10^9$/L or ANC $< 2.0 \times 10^9$/L would progress to agranulocytosis and we multiply this figure by 5 % (which is the present-day mortality rate of drug-induced agranulocytosis in the general population treated with intravenous broad-spectrum antibiotic therapy and hematopoietic growth factors), the mortality rate per 1000 patient-years if haematological monitoring were to be stopped can be calculated to be 0.78 and 1.31 per 1000 patient-years respectively (see Supplementary Box S2). It is clear that this calculation overestimates the risk, since in 75 % of cases mild leukopenia will probably not progress to agranulocytosis and even cases with ANC $< 0.5 \times 10^9$/L may not be true cases of LTCIA (Myles et al., 2018; Taylor et al., 2022). Correcting the figures for mild leukopenia by a factor of 0.25 results in lower, more reliable estimates of LTCIA mortality rates, namely 0.34 and 0.53 per 1000 patient-years respectively. The mortality rate without haematological monitoring after the first year of treatment can be calculated to be roughly one half (between 0.18 and 0.29 per 1000 patient-years).

Interestingly, there is some experience with lowering the frequency of haematological monitoring: lowering the monitoring frequency in the US from weekly to fortnightly checks after the first 6 months showed no increase in agranulocytosis rates (see Supplementary Table S1). In fact, after the first year the agranulocytosis rate had decreased by more than two thirds (from 0.39/1000 patient-years to 0.11/1000 patient-years; $p = 0.002$) Schulte, 2006). And in the UK, where a change was made from fortnightly to monthly checks after week 52 no significant differences in the incidence of severe leukopenia and agranulocytosis were found.

During the COVID-19 pandemic 459 long-term clozapine users in a large London National Health Service trust were included in a 1-year mirror-image study with 12-weekly blood monitoring instead of the usual 4-weekly monitoring and compared to 110 controls with the usual 4-weekly monitoring (Oloyede et al., 2023). There was an incidence of four mild to moderate neutropenia events per 1000 person-years in the intervention group, compared with nine events per 1000 person-years in the comparison group (IRR 0.48; 95 % CI 0.002–28.15, $P = 0.29$). In neither group did agranulocytosis occur. The authors concluded that no evidence was found that the incidence of severe neutropenia increased in those receiving 12-weekly monitoring.

9. Risks of agranulocytosis in perspective

Mortality due to agranulocytosis in clozapine users can be compared to other risks of antipsychotics. The risk of sudden cardiac death attributable to the use of antipsychotics is approximately 90 per 1000 person-years (Ray et al., 2009). An analysis of pharmacovigilance data of fatal adverse clozapine reactions of the top four reporting countries (US, UK, Canada and Australia) found that agranulocytosis was only in the 35th place (221 cases), whereas cardiac arrest was in the 4th place (919 cases) and sudden death in the 6th (663 cases) (De Las Cuevas et al., 2023). To the best of our knowledge mandatory ECG controls before and during treatment with antipsychotics have not been established anywhere, even though this risk is at least 50 times higher than that of mortality caused by LTCIA, if mandatory haematological monitoring were to be abolished after week 18 of clozapine treatment.

Furthermore, there is the risk of not being treated with clozapine or stopping with clozapine for example because a clozapine user does not want to comply with never-ending blood tests. Unfortunately, there are no reasonable therapeutic alternatives for clozapine in patients with TRS. The clinical risk for a patient of being taken off clozapine unnecessarily is the mean difference in clinical state between being on or off clozapine as measured with the CGI—S, namely moderately ill or seriously ill for the group as a whole (Oloyede et al., 2021). For some patients discontinuation of clozapine means a return to long-term hospitalisation on a closed ward or high risk of suicide.

Clozapine has clear and relevant beneficial effects, as shown by several studies: in a 20-year follow-up study of a nationwide cohort of 62,250 patients with schizophrenia clozapine was associated with the most beneficial mortality outcome of 19 antipsychotics in terms of all-cause (adjusted hazard ratio [aHR] = 0.39, 95 % CI: 0.36–0.43), cardiovascular (aHR = 0.55, 95 % CI: 0.47–0.64) and suicide mortality (aHR = 0.21, 95 % CI: 0.15–0.29) vs. non-use of any antipsychotic

(Taipale et al., 2020). The cumulative mortality rates during maximum follow-up of 20 years were.

46.2 % for no antipsychotic use, 25.7 % for any antipsychotic use, and 15.6 % for clozapine use. Although a similar Danish study replicated the antisuicidal effect of clozapine (van der Zalm et al., 2021), this study did not find a significant difference in all-cause or cardiovascular mortality between clozapine and other antipsychotic users. However, when the study populations were restricted to patients with TRS, both in Denmark and in the UK, the aHRs for all-cause mortality of clozapine versus other antipsychotics were in line with the Finnish results (Wimberley et al., 2017; Cho et al., 2019). Several studies have found evidence that all-cause or suicide mortality is increased after discontinuation of clozapine (Walker et al., 1997; Patchan et al., 2015; Wimberley et al., 2017; van der Zalm et al., 2021). In our opinion, in patients with TRS the agranulocytosis risk is offset by reduced all-cause and suicide mortality.

10. Proposal for relaxing haematological monitoring rules

To summarise, we can state that the risk of agranulocytosis with clozapine is highest in the first 18 weeks of treatment (see supplementary table S1), but that there is no evidence that agranulocytosis occurs more frequently with clozapine than with other antipsychotics (Myles et al., 2019), particularly after the first 18 weeks. Frequent mandatory blood tests do not demonstrably lower the risk (Ingimarsson et al., 2016; Myles et al., 2018; Li et al., 2020), and reducing the frequency of blood tests does not lead to a higher risk of agranulocytosis (Schulte, 2006; Oloyede et al., 2023). Regulations such as those of the FDA and in particular of the EMA unnecessarily burden clozapine users and their prescribers and deter them from using clozapine (Verdoux et al., 2018; Gee et al., 2017; Taylor et al., 2000; Farooq et al., 2019). Furthermore, patients are at risk of having to stop taking clozapine unnecessarily in case of neutropenia (Oloyede et al., 2022a; Oloyede et al., 2022b), which increases their all-cause and suicide mortality (Walker et al., 1997; Patchan et al., 2015; Wimberley et al., 2017; Taipale et al., 2020; van der Zalm et al., 2021).

We have therefore formulated the suggestions listed below with regard to haematological monitoring with clozapine treatment. We realise that every choice of a specific frequency of blood tests and thresholds for raising that frequency or discontinuing clozapine is somewhat arbitrary.

1. Exclusively during the first 18 weeks the ANC will be monitored weekly in accordance with the FDA regulations, with separate thresholds for BEN (see Table 1).
2. After the first 18 weeks of clozapine treatment haematologic monitoring is no longer mandatory. The prescriber informs the patient about the remaining very low risk of agranulocytosis and haematological malignancies. They decide together about further monitoring frequency of ANC or WCC respectively for these two low-risk clozapine associated conditions – for instance, quarterly, yearly, or stopping blood tests altogether. The patient is reminded that immediate ANC checks are necessary if there is any clinical suspicion of agranulocytosis. If the patient is not capable of making a treatment decision, a legal representative or guardian will have to decide in the patient's best interests.
3. In accordance with the FDA regulations, clozapine treatment must be stopped if the ANC falls below 1.0×10^9/L (below 0.5×10^9/L in case of BEN). Continuation of clozapine or a rechallenge are possible if prescriber and patient determine that the benefits outweigh the risks. It should be borne in mind that the lower the ANC was, the lower the chance of successful rechallenge will be.
4. So long as the clozapine regulations have not been relaxed, the prescriber and patient may decide to adopt these propositions and clozapine may be prescribed according to the national regulations for off-label use.
5. Mandatory national clozapine programs such as the US Risk Evaluation and Mitigation Strategy (REMS) program which registers and monitors the blood tests of all patients on clozapine are unnecessary and do not help to reduce LTCIA. They should at least be restricted to the first 18 weeks of clozapine use. The majority of countries including those of the European Union rely on the responsibility of prescribers. Absolute compliance with strict haematological regulations must be weighed against 'patient access issues for clozapine' which the FDA have admitted (Leung et al., 2022).

11. Conclusion

Unfortunately, there are no randomised, clinical trials comparing mortality rates of different screening strategies for clozapine-induced agranulocytosis. A comparison of current clozapine monitoring to screening for cancer may help to form opinion. Broadly speaking, medical screening is beneficial if the prevalence of the medical condition being screened for is high, the preclinical phase for intervention is long and the risk caused by false positive results is low. Clozapine-induced agranulocytosis does not seem a good candidate, particularly not after the first 18 weeks of treatment.

In our opinion the stringency of the haematological monitoring of clozapine users is disproportionate. A better balance between risks and benefits could be achieved by relaxing the monitoring requirements. We are convinced that these changes would simplify clozapine monitoring and enable more patients to start and continue treatment without endangering their health. Furthermore, we expect that an additional advantage of the changes would be a decrease in the exaggerated fear of agranulocytosis in prescribers and patients and as a result an increase of clozapine prescription, with lower all-cause and suicide mortality in clozapine users.

Funding

This article was completed without any external funding. No commercial organizations had any role in the writing of this paper for publication.

CRediT authorship contribution statement

P.S., S.V., B.B, J.B., A.J. and D.C. contributed to the conception and design of the study. P.S. analysed the data. All authors interpreted the data and contributed to the drafting and revision of the manuscript.

Declaration of competing interest

No one of the authors has competing interests to declare. I declare for all authors that we have not received any financial support for the preparation of the article.

Acknowledgment

The authors would like to honour their fellow board member Bert Bakker, retired internist, who suddenly passed away after the completion of this review. He had been a member of our board since the foundation of the Dutch Clozapine Collaboration Group 25 years ago. As an internist, Bert was indispensable because of his expertise regarding the development and treatment of unwanted effects of clozapine. The collaboration group wrote a guideline for appropriate measures to limit side effects and complications as much as possible. Without Bert this would have been impossible. He was a co-author of many articles by the collaboration group, gave many lectures and advised psychiatrists, nurses, patients and family members with respect to their questions about this special medicine.

Bert was full of humour, an inspired physician and very approachable, for both his patients and his colleagues. All those years he did this

work selflessly and in his spare time. Even after retiring he continued to serve the cause with as much dedication as ever. By doing so he not only saved lives, but also helped to significantly improve the quality of the lives of a very large number of people suffering from psychosis.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.schres.2023.09.024.

References

Ahn, Y.M., Jeong, S.H., Jang, H.S., et al., 2004. Experience of maintaining clozapine medication in patients with 'red-alert zone' neutropenia: long-term follow-up results. Int. Clin. Psychopharmacol. 19, 97–101. https://doi.org/10.1097/00004850-200403000-00007. 15076018.

Anderman, B., Griffith, R.W., 1977. Clozapine-induced agranulocytosis: a situation report up to august 1976. Eur. J. Clin. Pharmacol. 11, 199–201. https://doi.org/10.1007/BF00606410.

Andrès, E., Maloisel, F., 2008. Idiosyncratic drug-induced agranulocytosis or acute neutropenia. Curr. Opin. Hematol. 15 (1), 15–21. https://doi.org/10.1097/MOH.0b013e3282f15fb9 (PMID: 18043241).

Bogers, J.P., Schulte, P.F., Van Dijk, D., et al., 2016. Clozapine underutilization in the treatment of schizophrenia: how can clozapine prescription rates be improved? J. Clin. Psychopharmacol. 36, 109–111. https://doi.org/10.1097/JCP.0000000000000478 (PMID: 26872120).

Cho, J., Hayes, R.D., Jewell, A., et al., 2019. Clozapine and all-cause mortality in treatment-resistant schizophrenia: a historical cohort study. Acta Psychiatr. Scand. 139 (3), 237–247. https://doi.org/10.1111/acps.12989.

Cohen, D., Monden, M., 2013. White blood cell monitoring during long-term clozapine treatment. Am. J. Psychiatry 170 (4), 366–369. https://doi.org/10.1176/appi.ajp.2012.12081036 (PMID: 23545791).

Dawson, J.L., Sluggett, J.K., Procter, N.G., et al., 2023. Hematological and other cancers in people using clozapine: analysis of Australian spontaneous reports between 1995 and 2020. J. Clin. Psychopharmacol. 43 (4), 333–338. https://doi.org/10.1097/JCP.0000000000001699.

De Las Cuevas, C., Sanz, E.J., de Leon, J., 2023. Adverse drug reactions and their fatal outcomes in clozapine patients in VigiBase: comparing the top four reporting countries (US, UK, Canada and Australia). In: Schizophrenia Research, S0920-9964(23)00184-6. Advance Online Publication. https://doi.org/10.1016/j.schres.2023.05.004.

Dunk, L.R., Annan, L.J., Andrews, C.D., 2006. Rechallenge with clozapine following leucopenia or neutropenia during previous therapy. Br. J. Psychiatry J. Ment. Sci. 188, 255–263. https://doi.org/10.1192/bjp.188.3.255.

Dutch Clozapine Collaboration Group, 2013. Guideline for the use of clozapine. https://www.clozapinepluswerkgroep.nl/wp-content/uploads/2013/07/Guideline-for-the-use-of-Clozapine-2013.pdf (accessed at 22nd of May, 2023).

European Medicines Agency, 2023. CPMP summary information on referral opinion following arbitration pursuant to article 30 of Council directive 2001/83/EC for Leponex and associated names. https://www.ema.europa.eu/en/documents/referral/summary-information-referral-opinion-following-arbitration-pursuant-article-30-council-directive/83/ec-leponex-associated-names-international-non-proprietary-name-inn-clozapine-background-inform_en.pdf (accessed at 29th of May, 2023).

Farooq, S., Choudry, A., Cohen, D., et al., 2019. Barriers to using clozapine in treatment-resistant schizophrenia: systematic review. BJPsych Bull. 43, 8–16. https://doi.org/10.1192/bjb.2018.67.

FDA Drug Safety Communication, 2023. FDA modifies monitoring for neutropenia associated with schizophrenia medicine clozapine; approves new shared REMS program for all clozapine medicines. https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-modifies-monitoring-neutropenia-associated-schizophrenia-medicine (accessed at 29th of May, 2023).

Food and Drug Administration, 2023. Clozaril (clozapine) tablets, Safety Labeling Change Order 4/28/2023. https://www.fda.gov/media/167933/download (accessed at 29th of May, 2023).

Gee, S.H., Shergill, S.S., Taylor, D.M., 2017. Patient attitudes to clozapine initiation. Int Clin Psychopharmacol. 32, 337–342. https://doi.org/10.1097/YIC.0000000000000188 (Erratum in: Int Clin Psychopharmacol. 2019, 34, 273. PMID: 28704228).

Griffith, R.W., Saameli, K., 1975. Letter: clozapine and agranulocytosis. Lancet. 2 (7936), 657. https://doi.org/10.1016/s0140-6736(75)90135-x (PMID: 52022).

Honigfeld, G., Arellano, F., Sethi, J., et al., 1998. Reducing clozapine-related morbidity and mortality: 5 years of experience with the Clozaril National Registry. J. Clin. Psychiatry 59 (Suppl. 3), 3–7 (PMID: 9541331).

Hsieh, M.M., Everhart, J.E., Byrd-Holt, D.D., et al., 2007. Prevalence of neutropenia in the U.S. population: age, sex, smoking status, and ethnic differences. Ann. Intern. Med. 146, 486–492. https://doi.org/10.7326/0003-4819-146-7-200704030-00004 (PMID: 17404350).

Hummer, M., Kurz, M., Barnas, C., et al., 1992. Transient neutropenia induced by clozapine. Psychopharmacol. Bull. 28, 287–290 (PMID: 1480732).

Idänpään-Heikkilä, J., Alhava, E., Olkinuora, M., et al., 1975. Letter: clozapine and agranulocytosis. Lancet 27;2 (7935), 611. https://doi.org/10.1016/s0140-6736(75)90206-8 (PMID: 51442).

Imbarlina, M.J., Sarkar, S., Marwah, S., et al., 2004. Leukopenia in clozapine treated patients may be induced by other drugs: a case series. Eur. Psychiatry 19 (8), 506–509. https://doi.org/10.1016/j.eurpsy.2004.09.007.

Ingimarsson, O., MacCabe, J.H., Haraldsson, M., et al., 2016. Neutropenia and agranulocytosis during treatment of schizophrenia with clozapine versus other antipsychotics: an observational study in Iceland. BMC Psychiatry 12;16 (1), 441. https://doi.org/10.1186/s12888-016-1167-0 (PMID: 27955666; PMCID: PMC5153901).

Johannsen, C.F., Petersen, T.S., Nielsen, J., et al., 2022. Clozapine- and non-clozapine-associated neutropenia in patients with schizophrenia: a retrospective cohort study. Ther Adv Psychopharmacol. 12 https://doi.org/10.1177/20451253211072341 (20451253211072341, PMID: 35273789; PMCID: PMC8902187).

Kanaan, R.A., Kerwin, R.W., 2006. Lithium and clozapine rechallenge: a retrospective case analysis. J. Clin. Psychiatry 67, 756–760. https://doi.org/10.4088/jcp.v67n0509.

Kane, J., Honigfeld, G., Singer, J., et al., 1988. Clozapine for the treatment-resistant schizophrenic. A double-blind comparison with chlorpromazine. Arch Gen Psychiatry. 45, 789–796. https://doi.org/10.1001/archpsyc.1988.01800330013001 (PMID: 3046553).

Kleinerman, M.J., 1990. Controversy grows over monitoring system for new schizophrenia drug. JAMA 264 (19), 2488–2491 (doi:10.1001/jama.1990.03450190018006. Erratum in: JAMA 1991 Apr 17;265(15):1953. PMID: 2232010).

Lahdelma, L., Appelberg, B., 2012. Clozapine-induced agranulocytosis in Finland, 1982-2007: long-term monitoring of patients is still warranted. J. Clin. Psychiatry 73, 837–842. https://doi.org/10.4088/JCP.11m07244.

Lee, H., 1990. Pharmacists outraged by clozaril system. Journal of Pharmacy Practice 3, 6–8.

Leung, J.G., de Leon, J., Frye, M.A., et al., 2022. The modernization of clozapine: a recapitulation of the past in the United States and the view forward. J Clin Psychopharmacol. 42, 565–580. https://doi.org/10.1097/JCP.0000000000001606.

Li, X.H., Zhong, X.M., Lu, L., et al., 2020. The prevalence of agranulocytosis and related death in clozapine-treated patients: a comprehensive meta-analysis of observational studies. Psychol. Med. 50, 583–594. https://doi.org/10.1017/S0033291719000369.

Malik, S., Lally, J., Ajnakina, O., et al., 2018. Sodium valproate and clozapine induced neutropenia: a case control study using register data. Schizophr. Res. 195, 267–273. https://doi.org/10.1016/j.schres.2017.08.041.

Mandel, A., Gross, M., 1968. Agranulocytosis and phenothiazines. Dis. Nerv. Syst. 29 (1), 32–36 (PMID: 5635744).

Manu, P., Lapitskaya, Y., Shaikh, A., et al., 2018. Clozapine rechallenge after major adverse effects: clinical guidelines based on 259 cases. Am. J. Ther. 25 (2), e218–e223. https://doi.org/10.1097/MJT.0000000000000715 (PMID: 29505490).

Meyer, N., Gee, S., Whiskey, E., et al., 2015. Optimizing outcomes in clozapine rechallenge following neutropenia: a cohort analysis. J. Clin. Psychiatry 76 (11), e1410–e1416. https://doi.org/10.4088/JCP.14m09326.

Michielsen, E., 2023. Clinical Chemist at Diagnostiek voor U in Eindhoven, Personal Communication, 2 August.

Mijovic, A., MacCabe, J.H., 2020. Clozapine-induced agranulocytosis. Ann Hematol. 99, 2477–2482. https://doi.org/10.1007/s00277-020-04215-y.

Minemura, M., Tajiri, K., Shimizu, Y., 2009. Systemic abnormalities in liver disease. World J Gastroenterol. 15 (24), 2960–2974. https://doi.org/10.3748/wjg.15.2960 (PMID: 19554648; PMCID: PMC2702103).

Munro, J., O'Sullivan, D., Andrews, C., et al., 1999. Active monitoring of 12,760 clozapine recipients in the UK and Ireland. Beyond pharmacovigilance. Br J Psychiatry. 175, 576–580. https://doi.org/10.1192/bjp.175.6.576 (PMID: 10789357).

Myles, N., Myles, H., Xia, S., et al., 2018. Meta-analysis examining the epidemiology of clozapine-associated neutropenia. Acta Psychiatr. Scand. 138, 101–109. https://doi.org/10.1111/acps.12898.

Myles, N., Myles, H., Xia, S., et al., 2019. 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 53, 403–412. https://doi.org/10.1177/0004867419833166.

National Cancer Institute, 2009. Common terminology criteria for adverse events v4.0. In: Report for the National Institutes of Health, Publication No. 09-7473, 28 May. Bethesda, MD: National Cancer Institute..

Nooijen, P.M., Carvalho, F., Flanagan, R.J., 2011. Haematological toxicity of clozapine and some other drugs used in psychiatry. Hum. Psychopharmacol. 26, 112–119. https://doi.org/10.1002/hup.1181.

Oloyede, E., Casetta, C., Dzahini, O., et al., 2021. There is life after the UK clozapine central non-rechallenge database. Schizophr Bull. 47 (4), 1088–1098. https://doi.org/10.1093/schbul/sbab006 (PMID: 33543755; PMCID: PMC8266568).

Oloyede, E., Blackman, G., Whiskey, E., et al., 2022a. Clozapine haematological monitoring for neutropenia: a global perspective. Epidemiol Psychiatr Sci. 25 (31), e83 https://doi.org/10.1017/S204579602200066X (PMID: 36426600; PMCID: PMC9714212).

Oloyede, E., Whiskey, E., Casetta, C., et al., 2022b. Relaxation of the criteria for entry to the UK clozapine central non-rechallenge database: a modelling study. Lancet Psychiatry 9, 636–644. https://doi.org/10.1016/S2215-0366(22)00188-2.

Oloyede, E., Dzahini, O., Abolou, Z., et al., 2023. Clinical impact of reducing the frequency of clozapine monitoring: controlled mirror-image cohort study. Br. J. Psychiatry 24, 1–7. https://doi.org/10.1192/bjp.2023.44.

O'Sullivan, D.P., Lynch, K.P., 1996. Reply from clozaril patient monitoring service. BMJ 313, 1262.

Patchan, K.M., Richardson, C., Vyas, G., Kelly, D.L., 2015. The risk of suicide after clozapine discontinuation: cause for concern. Annals of clinical psychiatry: official journal of the American Academy of Clinical Psychiatrists 27 (4), 253–256.

Pisciotta, V., 1978. Drug-induced agranulocytosis. Drugs. 15 (2), 132–143. https://doi.org/10.2165/00003495-197815020-00003 (PMID: 342230).

Raja, M., Azzoni, A., Maisto, G., 2011. Late onset neutropenia associated with clozapine. J. Clin. Psychopharmacol. 31, 780–781.

Ray, W.A., Chung, C.P., Murray, K.T., et al., 2009. Atypical antipsychotic drugs and the risk of sudden cardiac death. N Engl J Med. 15;360 (3), 225–235. https://doi.org/10.1056/NEJMoa0806994 (Erratum in: N Engl J Med. 2009 Oct 29;361(18):1814. PMID: 19144938; PMCID: PMC2713724).

Ruan, C.J., Wang, C.Y., Zang, Y.N., Liu, C.G., Dong, F., Li, A.N., Wan, Z., Guo, W., Wang, G., 2023. A brief history of clozapine in China with a look forward. Schizophrenia Research (S0920-9964(23)00142-1. Advance online publication. doi: 10.1016/j.schres.2023.03.048).

Schulte, P.F.J., 2006. The risk of clozapine-associated agranulocytosis and mandatory white blood cell monitoring. Ann. Pharmacother. 4, 683–688. https://doi.org/10.1345/aph.1G396.

Shrivastava, A., Shah, N., 2009. Prescribing practices of clozapine in India: results of a opinion survey of psychiatrists. Indian J Psychiatry 51, 225–226. https://doi.org/10.4103/0019-5545.55097 (PMID: 19881056; PMCID: PMC2772230).

Silva, E., Higgins, M., Hammer, B., et al., 2020. Clozapine rechallenge and initiation despite neutropenia - a practical, step-by-step guide. BMC Psychiatry 20 (1), 279. https://doi.org/10.1186/s12888-020-02592-2 (PMID: 32503471; PMCID: PMC7275543).

Siskind, D., Nielsen, J., 2020. Clozapine: a fine balance. Acta Psychiatr. Scand. 141, 175–177. https://doi.org/10.1111/acps.13159. 32096227.

Siskind, D., Honer, W.G., Clark, S., et al., 2020. Consensus statement on the use of clozapine during the COVID-19 pandemic. J. Psychiatry Neurosci. 45, 222–223. https://doi.org/10.1503/jpn.200061 (PMID: 32297722; PMCID: PMC7828973).

Taipale, H., Tanskanen, A., Mehtälä, J., et al., 2020. 20-year follow-up study of physical morbidity and mortality in relationship to antipsychotic treatment in a nationwide cohort of 62,250 patients with schizophrenia (FIN20). World Psychiatry 19, 61–68. https://doi.org/10.1002/wps.20699 (PMID: 31922669; PMCID: PMC6953552).

Tamam, L., Kulan, E., Ozpoyraz, N., 2001. Late-onset neutropenia during clozapine treatment. Psychiatry & Clin Neuroscience 55, 547–548.

Taylor, D., Shapland, L., Laverick, G., et al., 2000. Clozapine – a survey of patient perceptions. Psychiatr. Bull. 24, 450–452. https://doi.org/10.1192/pb.24.12.450.

Taylor, D., Vallianatou, K., Whiskey, E., et al., 2022. Distinctive pattern of neutrophil count change in clozapine-associated, life-threatening agranulocytosis. Schizophrenia (Heidelb) 14;8 (1), 21. https://doi.org/10.1038/s41537-022-00232-0 (PMID: 35288577; PMCID: PMC8920060).

Tiihonen, J., Tanskanen, A., Bell, J.S., et al., 2022. Long-term treatment with clozapine and other antipsychotic drugs and the risk of haematological malignancies in people with schizophrenia: a nationwide case-control and cohort study in Finland. Lancet Psychiatry 9 (5), 353–362. https://doi.org/10.1016/S2215-0366(22)00044-X.

Verdoux, H., Quiles, C., Bachmann, C.J., et al., 2018. Prescriber and institutional barriers and facilitators of clozapine use: a systematic review. Schizophr. Res. 201, 10–19. https://doi.org/10.1016/j.schres.2018.05.046.

Verdoux, H., Quiles, C., de Leon, J., 2023. Risks and benefits of clozapine and lithium co-prescribing: a systematic review and expert recommendations. Schizophrenia research (S0920-9964(23)00126-3. Advance online publication. doi:10.1016/j.schres.2023.03.032).

Wagner, E., Siskind, D., Falkai, P., et al., 2023. Clozapine optimization: a delphi consensus guideline from the treatment response and resistance in psychosis working group. Schizophr. Bull. 49 (4), 962–972. https://doi.org/10.1093/schbul/sbad030.

Walker, A.M., Lanza, L.L., Arellano, F., Rothman, K.J., 1997. Mortality in current and former users of clozapine. Epidemiology (Cambridge, Mass.) 8 (6), 671–677. https://doi.org/10.1097/00001648-199710000-00010.

Tirupati, S., Gordon, T., 2021. Continuation of treatment with clozapine after an episode of neutropenia. J. Clin. Psychopharmacol. 41, 320–322. https://doi.org/10.1097/JCP.0000000000001371. 33657071.

van der Weide, J., 2023. Clinical Chemist at the Clinical Chemistry Laboratory, St. Jansdal Hospital, in Harderwijk, Personal Communication, 22 March.

Wimberley, T., MacCabe, J.H., Laursen, T.M., et al., 2017. Mortality and self-harm in association with clozapine in treatment-resistant schizophrenia. Am. J. Psychiatry 174 (10), 990–998. https://doi.org/10.1176/appi.ajp.2017.16091097.

van der Zalm, Y., Foldager, L., Termorshuizen, F., et al., 2021. Clozapine and mortality: a comparison with other antipsychotics in a nationwide Danish cohort study. Acta Psychiatr. Scand. 143 (3), 216–226. https://doi.org/10.1111/acps.13267.

Zhang, M., Owen, R.R., Pope, S.K., et al., 1996. Cost-effectiveness of clozapine monitoring after the first 6 months. Arch. Gen. Psychiatry 53, 954–958. https://doi.org/10.1001/archpsyc.1996.01830100104013 (PMID: 8857873).