Medicines Adverse Reactions Committee

Meeting date	11/03/2021	Agenda item 3.2.2	
Title	**Clozapine monitoring frequency and duration.**		
Submitted by	Medsafe Pharmacovigilance Team	Paper type	For advice
Active ingredient Clozapine	**Product name** Clozaril tablets Clopine	**Sponsor** Mylan New Zealand Ltd Douglas Pharmaceuticals Limited	
PHARMAC funding	Tablets 25 mg – Clozaril, Clopine Tablets 50 mg – Clopine Tablets 100 mg – Clozaril, Clopine Tablets 200 mg – Clopine Suspension 50 mg/ml - Clopine		
Previous MARC meetings	Clozapine and cardiac safety 12 March 2003		
Prescriber Update	Clozapine – close monitoring required June 2015 https://medsafe.govt.nz/profs/PUArticles/June2015/June2015Clozapine.htm		
Classification	Prescription medicine		
Usage data	See section 2.4		
Advice sought	**The Committee is asked to advise whether:** • There is sufficient evidence that a change to the frequency and/or duration of haematological monitoring for patients taking clozapine would continue to mitigate the risks to patients, and if so, what change is supported by the evidence. • This topic requires further communication other than MARC's Remarks in *Prescriber Update*.		

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1 PURPOSE

During treatment with clozapine, white blood cell count (WBC) and absolute neutrophil count (ANC) are routinely monitored due to the risk of agranulocytosis. Blood levels are measured every week during the first 18 weeks of treatment, then at least every four weeks throughout treatment and for four weeks after discontinuation of clozapine. To this end the companies supplying the medicine are required by Medsafe to provide a database to enable tracking of blood test results.

In NZ, during the COVID-19 level 4 lockdown period in 2020, guidelines were issued by groups without reference to regulatory requirements stating that monitoring requirements for clozapine could be relaxed. The need to return to the regular monitoring schedule (concerning frequency and duration) has been questioned by some clinicians. A debate article was recently published, discussing the issue (1).

Arguments in favour of a change have been, for example, that haematological adverse reactions are uncommon after the first year of clozapine treatment, that regular blood testing is an additional burden, and that the current monitoring requirements may exclude some patients from treatment. Reasons against a change is that the risk of adverse reactions, such as neutropenia and agranulocytosis, may be fatal.

The aim of this paper is to discuss the haematological monitoring requirements for patients taking clozapine, and to examine the frequency, severity and timing of neutropenia adverse events during treatment.

As monitoring blood levels is an important way to decrease the risk of agranulocytosis, the committee is asked to advise whether the current evidence clearly shows that relaxation of these risk mitigating activities would continue to protect patients from these potentially life-threatening reactions.

2 BACKGROUND

2.1 Clozapine

2.1.1 Indication and uses

Clozapine is a second-generation antipsychotic medicine (SGA), also called an atypical antipsychotic medicine.

The provisionally approved indication for clozapine in New Zealand is schizophrenia in patients unresponsive to, or intolerant of, conventional antipsychotic drugs (2, 3). Non-responsiveness is defined in the data sheets as 'a lack of satisfactory clinical improvement despite the use of adequate doses of at least two marketed antipsychotics prescribed for adequate duration'. Non-responsiveness to conventional antipsychotics affects approximately one third of patients with schizophrenia (4).

Intolerance is defined as the impossibility of achieving adequate clinical benefit with classic antipsychotics because of severe and untreatable neurological adverse reactions (extrapyramidal side effects or tardive dyskinesia) (2, 3).

In addition, clozapine is used off-label for schizophrenia accompanied by persistent suicidal or self-injurious behaviour (5).

2.1.2 Mechanism of action

Clozapine has proven effective in relieving both positive and negative schizophrenic symptoms in short- and long-term trials (2, 3).

The therapeutic efficacy of clozapine is proposed to be mediated through antagonism of the dopamine type 2 (D2) and serotonin type 2A (5-HT2A) receptors. It does not bind as tight to dopamine D2 receptors as first-generation antipsychotic medications, such as haloperidol, which may explain its reduced potential for producing movement abnormalities.

In addition, clozapine acts as an antagonist at alpha-adrenergic, histamine H1, cholinergic, and other dopaminergic and serotonergic receptors. Postural dizziness, sedation, and increased appetite may reflect actions of clozapine at alpha-1, H1, and 5-HT2c receptors, respectively (5). Clozapine produces little or no prolactin elevation, thus avoiding adverse effects such as gynaecomastia, amenorrhoea, galactorrhoea, and impotence (2, 3).

A therapeutic response may take some time to develop, and a year of continuous treatment may be required before efficacy for the individual patient can determined (6).

2.1.3 **Pharmacokinetics**

Clozapine is well absorbed. First-pass metabolism reduces its bioavailability to 60 to 70 percent of the administered dose. Food has little effect on the bioavailability of clozapine. The elimination half-life of clozapine averages approximately 14 hours under steady state conditions, but there is substantial variability across individuals.

Clozapine is extensively metabolized by the cytochrome P450 system in the liver and excreted in both the urine and faeces. Cytochrome P450 1A2 is primarily responsible for clozapine metabolism. Agents that induce cytochrome CYP1A2 will increase the metabolism of clozapine and a higher dose will be needed. Agents that inhibit CYP1A2 (eg, theophylline, ciprofloxacin, fluvoxamine) decrease the metabolism of clozapine and may produce clinical toxicity at usual doses. Cytochrome-related problems can be avoided by monitoring clozapine plasma levels while gradually increasing clozapine from a low starting dose (5).

Note that smoking (but not nicotine replacement therapy or vaping) affects plasma levels of clozapine. Polycyclic aromatic hydrocarbons in tobacco smoke induce hepatic cytochrome P450 1A2 enzyme, increasing the rate of metabolism of clozapine, lowering the concentration of clozapine to approximately 80% those of non-smokers. Dose reduction is highly recommended in patients who quit or who are hospitalised and unable to smoke. Recommendations are to reduce the dose by about 36% within one week of quitting smoking followed by therapeutic monitoring and further adjustment over the next four weeks (7, 8).

2.1.4 **Safety of clozapine**

Given the pharmacokinetics of clozapine, differences of a few hours in the time of evening dosing and/or morning plasma sampling will lead to large differences in reported plasma levels (5, 9).

A variety of adverse reactions have been associated with clozapine treatment. The risk of some of these adverse reactions can be considerably decreased by active monitoring of the treatment. Monitoring of blood levels for white cell count (WBC) and absolute neutrophil count (ANC) are required and will be discussed in detail below. In addition, it is of great importance to continuously and in an active way ask patients about other adverse reactions, such as constipation, for example whenever a prescription is to be issued.

A large part of the spectrum of adverse reactions associated with clozapine treatment can be explained by the medicine's modes of action. Many of the adverse effects of clozapine commonly occur at the start of therapy and can be minimised by ensuring dose escalation is done gradually.

Below are descriptions of some adverse reactions associated with clozapine treatment.

2.1.4.1 Adverse reactions affecting the blood

Background

Clozapine can cause reversible neutropenia. If the drug is not withdrawn immediately, the neutropenia may progress to potentially fatal agranulocytosis. In the NZ data sheets, neutrophilia is listed as a common adverse

reaction (ie, affecting between 1% and 10% of patients) and agranulocytosis is listed as an uncommon adverse reaction (ie, affecting between 0.1% and 1% of patients) (2, 3).

Patients need to be advised to immediately report symptoms consistent with severe neutropenia or infection (eg, fever, weakness, lethargy, sore throat). Note that some patients are entirely asymptomatic despite very low neutrophil counts.

This adverse reaction was first signalled in Finland in 1975, which led to withdrawal of clozapine in some countries and to restrictions in its use and intense haematological monitoring in others. After studies showing efficacy of clozapine in severely ill schizophrenic patients unresponsive to adequate therapy with classical antipsychotics, the drug became available again in the UK and USA in 1990 with strict procedures for monitoring of white blood cell counts (4).

Definitions of reactions and blood count measurement units

Leukopenia is an umbrella term referring to a reduction in any of the white blood cell types. Neutropenia is a type of leukopenia but refers specifically to a decrease in neutrophils, the most common type of white blood cell. Neutropenia is defined as an absolute neutrophil count (ANC) <1500/microL (=<1500/µL) (10).

Agranulocytosis is an acute, potentially life-threatening idiosyncratic reaction characterized by a profound decrease in neutrophil count and susceptibility to infection. The definition of agranulocytosis differs depending on source, between ANC <500/microL (10) or ANC <100/microL (11).

The units stated for ANC and WBC can vary depending on source and country. As an example, neutrophilia is defined as an ANC of <1500/microL (see above). This is the same as <1500/µL, <1500/mm^3 and <1.5 x 10^9/L. A WBC of <3000/microL is the same as <3000/ µL, <3000/mm^3 and <3.0 x 10^9/L. The units used in this report are aligned with the source information.

Epidemiology

The risk of clozapine-associated neutropenia is generally considered to be 1-2% and the risk is considered to be higher in early treatment than later (12). Females are generally considered to have a higher risk of drug-induced neutropenia.

The risk of agranulocytosis (defined as <500/microL) associated with clozapine treatment is reported to be 0.8% (3, 11) in the first year and 0.7% (11) in the second year. Lower incidences have been reported from China where clozapine is widely used as a first-line antipsychotic (3). A meta-analysis from 2019 reported a 0.4% risk of clozapine-associated agranulocytosis (13), but differences in the definition of agranulocytosis and in monitoring protocols limit the accuracy of this estimate. Late onset of clozapine-associated agranulocytosis is considered to be rare (11).

Risk factors and genetics

Females may have a slightly higher risk of drug-induced neutropenia and agranulocytosis (4).

Genetic variation involving HLA-DQB1, HLA-B, and SLCO1B3/SLCO1B7 may also be associated with clozapine-induced neutropenia/agranulocytosis (4).

Mechanism

The mechanism for clozapine-induced agranulocytosis is unclear and may be the result of direct toxicity or an immune-mediated mechanism. Agranulocytosis and neutropenia do not appear to be dose-related effects (4).

Management

If agranulocytosis develops, clozapine must be stopped immediately (if it has not already been stopped due to monitoring results). Use of granulocyte colony-stimulating factor (G-CSF) may reduce the duration of agranulocytosis (4).

About 1–3% of patients on CZP develop mild/moderate neutropenia, which may or may not progress to agranulocytosis (4).

Once a patient develops a neutrophil count < 1.5 × 10^9/l (or < 1.0 × 10^9/l in BEN patients in the US), they are typically not treated with clozapine again. Nevertheless, under special circumstances, psychiatrists may undertake a re-challenge with clozapine (4).

2.1.4.2 Other adverse reactions

Myocarditis/cardiomyopathy

Tachycardia that persists at rest, accompanied by arrhythmias, shortness of breath or signs and symptoms of heart failure, may rarely occur during the first month of treatment and very rarely thereafter. Mortality rates as high as 50% have been reported. If the diagnosis of myocarditis is confirmed, clozapine should be discontinued.

Cardiomyopathy usually occurs later in clozapine treatment than myocarditis. If patients are diagnosed with cardiomyopathy while on Clozapine treatment, there is potential to develop mitral valve incompetence (2, 3, 14).

Constipation and other gastrointestinal reactions

The risk of constipation is greater with clozapine than other medicines used to treat schizophrenia, probably on account of its anticholinergic properties (15). Constipation can develop at any stage of treatment and has been estimated to occur in 14% to 60% of patients. The risk is likely to be dose related. Severe constipation can cause bowel obstruction, sepsis and death. More deaths are caused by clozapine-induced ileus/megacolon than by agranulocytosis (14). Severe, sometimes fatal complications of constipation have been associated with a delayed diagnosis, but as there is no blood test for it, monitoring relies on questioning

It is essential to actively question patients about bowel habits, over the whole treatment period, for example whenever a prescription is to be issued. A patient may not feel or be aware of constipation symptoms, which include fewer bowel movements than normal, especially if less than three times a week, hard or dry stools, or difficulty passing gas. Symptoms associated with serious bowel problems include nausea, bloating or belly swelling, belly pain, and vomiting. Action may need to be taken urgently, not after waiting to see if symptoms settle without the use of a laxative (15). Many patients require routine use of a laxative, and this is often commenced during clozapine initiation.

Weight gain

SGAs, such as clozapine, generally induce more weight gain than classical first-generation antipsychotics (16).

Sedation

Sedation can be a therapeutic target in the acute treatment of patients presenting with agitation or severe behavioral symptoms but is also a safety concern and should be avoided in the long-term treatment due to its relationship with adverse effects on cognitive performance, physical activity/sedentary behavior/body weight, and patients' satisfaction with therapy. (16).

Metabolic syndrome and its components

Clozapine increases the risk of metabolic syndrome. Patients with metabolic syndrome are at an increased risk of cardiovascular disease (16).

Seizures

Clozapine seems to be associated with a higher seizure risk in patients with schizophrenia compared to other SGAs (16).

Pneumonia and sialorrhea

Pneumonia: suggestions of an increased incidence of pneumonia, which persists after CLO is withdrawn and returns when it is reintroduced. This has been associated with sialorrhea (excess salivation), which is a bit of a paradox as clozapine has anticholinergic effects and 'should rather' cause dry mouth. The risk is thought to be dose related and is higher in the first weeks of therapy and in elderly patients (16).

Comments: The monthly blood monitoring of clozapine also means that the medicine is dispensed monthly. This monthly interaction with healthcare professionals provides an opportunity for monitoring of the other reactions.

2.1.5 **Dosing of clozapine**

Clozapine dosing should be individualised to ensure the lowest effective dose is used. Treatment with clozapine should only be started in patients with a normal WBC and ANC blood test results within the preceding 10 days (see section 2.2 Monitoring of clozapine treatment). The clozapine dose is started low and slowly increased to achieve a therapeutic dose over 2-3 weeks. Further dose titrations, if needed, should also be undertaken gradually. The recommended starting dose and dose increments are detailed in the clozapine data sheets (2, 3).

2.2 Monitoring of clozapine treatment

Patients taking clozapine are monitored for symptoms and signs of neutropenia and agranulocytosis. Regular blood tests are mandatory to detect blood dyscrasias and for continued supply of the medicine. Monitoring requirements are detailed in the NZ data sheets (2, 3).

All patients prescribed clozapine must be registered in a patient monitoring system, where all blood monitoring results are collected. There are separate systems for the two available brands of clozapine, run by the respective companies. Prescribing physicians must also be registered in the system to access the monitoring results.

Clozapine can only be dispensed from pharmacies that are contracted with the DHB to do so, and staff need to be trained. Dispensing is prohibited if a blood test with a satisfactory result has not been performed in the previous three days. Pharmacists are required to contact the patient's prescriber or general practitioner if the test result is abnormal (6).

The monitoring includes white blood cell (WBC) and differential blood counts (which includes the absolute neutrophil counts (ANC)). The monitoring requirements are shown in Table 1.

Table 1. Monitoring requirement for clozapine in New Zealand (2, 3)

Before start of treatment

WBC and ANC must be performed within 10 days prior to starting clozapine treatment. Only patients with

normal leukocyte and absolute neutrophil counts (WBC ≥ 3500/mm3 (3.5 x 10^9/L), and ANC ≥ 2000/mm3 (2.0 x 10^9/L)) can receive clozapine.

During treatment

Regular WBC count and ANC must be monitored weekly for 18 weeks, and thereafter at least every four weeks throughout treatment, and for 4 weeks after discontinuation of clozapine. Patients must be reminded to contact the treating physician immediately if any kind of infection begins to develop, particularly flu-like symptoms, which may be indicative of neutropenia.

If, during clozapine therapy, either the WBC count or the ANC falls during treatment, specific action needs to be taken, see table below.

Table 1. Blood monitoring thresholds during clozapine treatment.

Blood cell count		**Action required**
WBC/mm³ (/L)	**ANC/mm³ (/L)**	
≥ 3500 (≥ 3.5 x 10^9)	≥ 2000 (≥ 2.0 x 10^9)	Continue clozapine treatment
Between ≥ 3000 and < 3500 (3.0 x 10^9 and 3.5 x 10^9)	Between ≥ 1500 and < 2000 (1.5 x 10^9 and 2.0 x 10^9)	Continue clozapine treatment, sample blood twice weekly until counts stabilise or increase.
< 3000 (< 3.0 x 10^9)	< 1500 (< 1.5 x 10^9)	Immediately stop clozapine treatment, sample blood daily until haematological abnormality is resolved, monitor for infection. Do not re-expose the patient.

In addition:

- If WBC count is found to have dropped by a substantial amount from baseline, a repeat WBC count and a differential blood count should be performed. Immediate discontinuation of clozapine is mandatory if the WBC count is less than 3000/mm^3 (3.0 x 10^9/L) or the ANC is less than 1500/mm^3 (1.5 x 10^9/L). WBC counts and differential blood counts should then be performed daily, and patients carefully monitored for symptoms suggestive of infection. Following discontinuation of clozapine, haematological evaluation is required.
- If clozapine has been withdrawn and WBC count falls further to below 2000/mm^3 (2.0 x 10^9/L) and/or the ANC falls below 1000/mm^3 (1.0 x 10^9/L), the management must be guided by an experienced haematologist. If possible, the patient should be referred to a specialised haematological unit, where protective isolation and the administration of GM-CSF (granulocyte-macrophage colony stimulating factor) or G-CSF (granulocyte colony stimulating factor) may be indicated.

Comments: In 2019, following a data sheet review for clozapine, Medsafe requested the sponsors to align the blood monitoring thresholds for the WBC and ANC with international standards (Table 1).

2.3 Recommendations in different countries

2.3.1 Monitoring frequency and duration

Table 2. Clozapine monitoring frequency and duration.

Country PI for Clozaril	Clozapine monitoring frequency
NZ (updated 10 Aug 2020) (2)	WBC and ANC to be measured within 10 days prior to starting clozapine treatment, weekly for 18 weeks, and thereafter at least every four weeks throughout treatment, and for 4 weeks after discontinuation.
Australia (updated Dec 2019) (17)	As above.
EMA, UK (updated May 2020) (18)	As above.
Canada (updated Jan 2020) (19)	WBC count and ANC to be measured before starting treatment and then: • Weekly for first 26 weeks of treatment. • Every second week for next 26 weeks. • Thereafter every month throughout treatment until 4 weeks after discontinuation.
US (updated March 2020) (20)	Obtain a complete blood count (CBC), including the ANC value, prior to initiating treatment and then monitor ANC (not WBC): • Weekly during the first 6 months of treatment. • Every 2 weeks for the next 6 months. • Every 4 weeks thereafter.

Comments: Canada and the US monitor clozapine more frequently than NZ between week 19 and week 52 as they monitor every 2 weeks during that period.

2.3.2 **Thresholds**

Table 3. Comparison of thresholds for increasing blood monitoring to twice a week

Country PI	**WBC/mm^3**	**ANC/mm^3**
NZ (2)	Between ≥ 3000 and < 3500 until counts stabilise or increase.	Between ≥ 1500 and < 2000 until counts stabilise or increase.
Australia (17)	Like EMA	Like EMA
EMA, UK (18)	3000 - 3500 until patient stabilise within the range 3000-3500 or higher	1500 – 2000 until patient stabilise within the range 1500 – 2000 or higher
Canada** (19)	2000 – 3500	1500 - 2000
US*** (20)	-	<u>General patient population:</u> 1000 – 1500/microL increase monitoring to 3 times weekly 500 – 1000 interrupt treatment, monitor once a day until 1000 /microL, then 3 times weekly until 1500/microL <u>Patients with Benign Ethnic Neutropenia (BEN)****:</u> 500 – 1000/microL increase monitoring to 3 times weekly Less than 500: interrupt treatment, monitor once a day until 500 /microL, then 3 times weekly

** Monitor weekly for 26 weeks, every 2 weeks for 26 weeks and then every 4 weeks.

*** Monitor weekly for 6 months, every 2 weeks for 6 months and then monthly.

**** Benign Ethnic Neutropenia see below.

Table 4. Comparison of thresholds for immediate discontinuation of clozapine

Country PI	**WBC/mm^3**	**ANC/mm^3**
NZ (2)	If less than 3000	If less than 1500
Australia (17)	If less than 3000	If less than 1500
EMA*, UK (18)	If less than 3000	If less than 1500
Canada (19)	If less than 2000	If less than 1500
US (20)	-	If less than 500 / microL. Do not rechallenge unless prescriber determines benefits outweigh risks. The same for patients with BEN****.

* Also includes this text: If Clozapine has been withdrawn and either a further drop in the WBC count below 2000/mm3 (2.0x109/l) occurs or the ANC falls below 1000/mm3 (1.0x109/l), the management of this condition must be guided by an experienced haematologist.
**** Benign Ethnic Neutropenia see below.

The monitoring thresholds in the US are very different from the other countries. The FDA changed the guidelines for monitoring in 2015 because of concerns about clozapine being underutilized in the management of treatment-resistant schizophrenia (21). Monitoring WBC was excluded and the ANC threshold for treatment interruption was lowered from 1500/microL to 1000/microL with the purpose to allow continued treatment for a greater number of patients.

FDA states in their communication that the revised prescribing information facilitates prescribers' ability to make individualized 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.

Another reason for changed guidelines was for patients with benign ethnic neutropenia (BEN), who previously were not eligible for clozapine treatment, to be able to receive the medicine. BEN is defined as neutropenia (< 1.5 × 109/L) with no apparent cause. This is common in individuals of African or Afro-Caribbean descent, but also some Arab ethnic groups and Yemenite Jews. BEN does not confer an increased risk of infection. There are special lower threshold guidelines for patients with BEN (21).

The effect of the changes in the FDA guidelines were evaluated in 2017 but no special consequences of the changes could be confirmed (22). See section 3.1.8.

Comments: Note that ANC < 1500/microL (ANC < 1000/microL for people with BEN) in the US guidelines requires monitoring 3 times weekly.

2.4 Usage

Usage of clozapine has decreased, but only slightly, over the last 5 years. The number of times clozapine was dispensed from a pharmacy in 2015 was 195,000 and in 2019 it was 189,000.

Source: Ministry of Health's Pharmaceutical Collection (accessed 25 February 2021).

Figure 1, 2 and 3 below shows different aspects of dispensing of clozapine in the last 3 years, and especially in 2019. The number of patients receiving clozapine was 4,300 in 2017, 4,270 in 2018 and 4,200 in 2019. The source is Qlik (see also section 4 below), accessed 25 February 2021.

Figure 1. Number of dispensings of clozapine year 2107 to 2019.

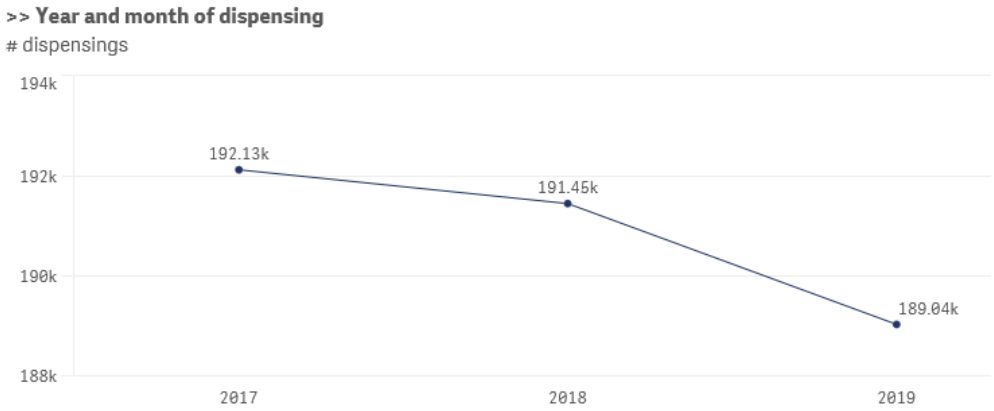


Figure 2. Number of different strengths of clozapine dispensed in 2019.

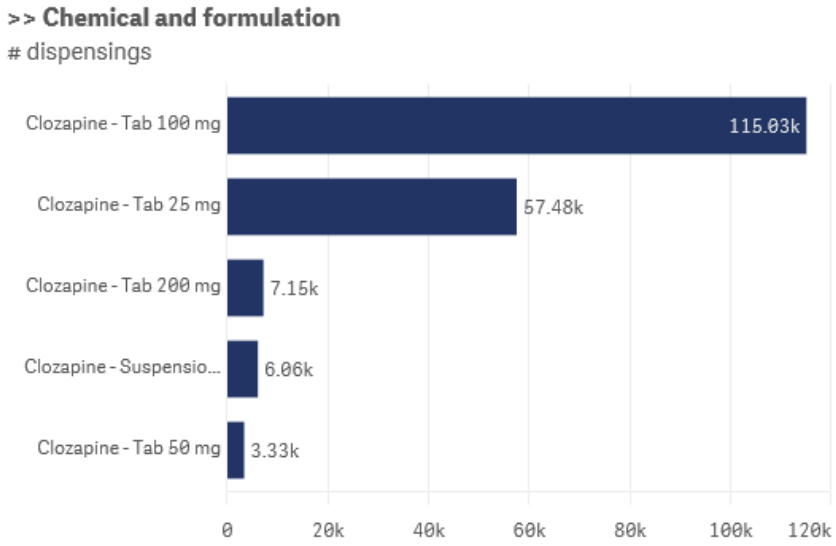
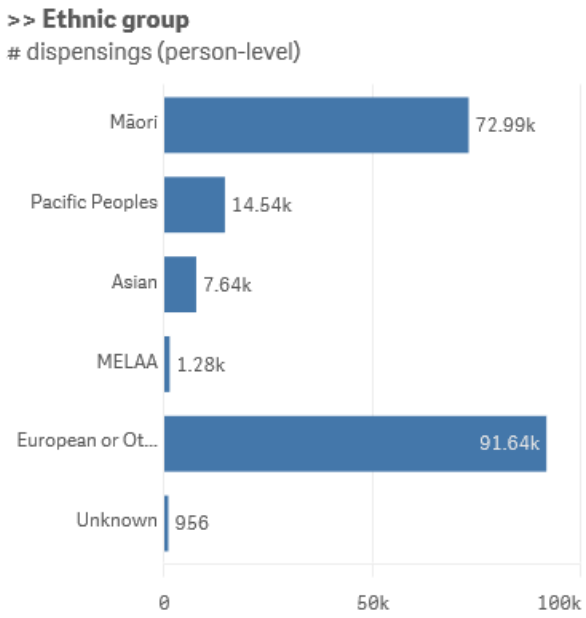


Figure 3. Ethnicity of patients receiving clozapine in 2019.



3 SCIENTIFIC INFORMATION

3.1 Published literature

A summary of recent publications is presented below, grouped as studies and meta-analyses, case reports and discussion papers.

Studies and meta-analyses

3.1.1 **Myles N et al 2019 (23)**

The aim of this Australian meta-analysis was to assess the strength of the association between clozapine and neutropenia when compared to other antipsychotic medicines.

Methods:
The search terms used were: [clozapine OR clopine OR Clozaril OR zaponex] AND [neutropenia OR agranulocytosis]. Random-effects meta-analysis using 'Mantel–Haenszel risk ratio' was used to assess the strength of the effect size. Because of the rarity of events, nonfixed empirical continuity corrections were used to impute data for studies with no events in both treatment groups. The definition of neutropenia was an ANC < 1500 /microL. Severity of neutropenia was stratified as mild (1000–1500 /microL), moderate (500–1000 /microL) and severe (<500 /microL). Risk of bias was assessed using the 'Newcastle–Ottawa' scale across three domains: selection, comparability and outcomes.

Results:
A total of 20 randomised controlled trials (RCT) or cohort studies were identified that reported rates of neutropenia associated with clozapine and other antipsychotic medicines. Of these, 17 were RCT-studies. The total sample size of subjects exposed to clozapine was 1260 (mean number per sample = 63), comprising 2981 person-years. The total sample size of subjects exposed to comparator antipsychotics was 1596 (mean number per sample = 80), comprising 4942 person-years. Median follow-up was 3.5 (range = 1–108) months. Five of the studies had a low risk of bias and 15 had high risk of bias.

The risk ratio was not significantly increased in clozapine-exposed groups compared to exposure to other antipsychotic medications (Mantel–Haenszel risk ratio = 1.45, 95% confidence interval = [0.87, 2.42]). This also applied to severe neutropenia (absolute neutrophil count < 500 per microL) when compared to other antipsychotics (Mantel– Haenszel risk ratio = 1.65, 95% confidence interval = [0.58, 4.71]). See also Figure 4.

Figure 4. Forest plot. Lower absolute MH risk ratio indicates a lower relative risk of neutropenia in clozapine-exposed subjects relative to comparator-exposed subjects and higher risk indicates a higher risk of neutropenia in clozapine-exposed subjects.

The authors discuss that part of the risk of neutropenia associated with clozapine may be a class effect of antipsychotics or results from a vulnerability carried by patients with psychosis. The also discuss that neutropenia occurs as a benign and transient finding in the general population (and that ANC threshold of <1500 and <1000 between 0.38% and 4.5% and between 0.08% and 0.57%, respectively has been reported).

Conclusion:
The authors conclude that data from these studies do not support the belief that clozapine has a stronger association with neutropenia than other antipsychotic medications, implying that either all antipsychotic drugs should be subjected to haematological monitoring or clozapine should not be monitored either.
However, they also state that there is insufficient evidence to support abandoning monitoring of clozapine entirely.

Comments: The meta-analysis has several limitations (also pointed out by the authors), such as neutropenia not being the primary outcome in the included studies, no knowledge how the other antipsychotics were monitored, limited knowledge on dosing, and the fact that many studies reported zero events in both treatment arms. The follow up time of the patients was short.

Figure 2 shows that overall, there is a higher risk of neutropenia in patients on clozapine compared to other antipsychotic medicines. However, the risk ratio is uncertain as the lower bound of the confidence interval crosses 1. None of the included studies provide strong evidence of either high or low risk as the CIs in all studies cross 1 (either as the upper or lower bound). One study (Rosenheck 1997) heavily dominates the analysis.

Also, note that combining many small studies to study safety does not provide good evidence as one study in a population the same size as each small study may have randomly not included at risk patients, whereas the one larger study is less subject to this risk – especially if the effect of interest was not an outcome of the study.

The results have a high level of uncertainty.

This study does not answer any questions about monitoring frequency or duration.

3.1.2 **Myles N et al 2018 (12)**

In this Australian meta-analysis, the objective was to determine the cumulative incidence of mild, moderate and severe neutropenia, the incidence of death related to severe neutropenia, case fatality rate of neutropenia and the longitudinal incidence of neutropenia following exposure to clozapine.

Methods:

Systematic searches for publications were conducted with the search terminology [clozapine OR clopine OR zaponex OR clozaril] AND [neutropenia OR agranulocytosis]. The abstracts and titles of identified articles were reviewed by two authors to identify studies that may have reported on the epidemiology of clozapine-associated neutropenia. Criterion for the longitudinal incidence was reported sample size of subjects exposed to clozapine and number of neutropenia events occurring at time intervals of follow-up, to calculate cumulative incidence of clozapine-associated neutropenia over time.

To determine the reporting strength of the studies, the authors developed a four-point rating scale derived from the Newcastle-Ottawa rating scale. Studies were given points if they:

1. Did not classify events based on discontinuation data alone (assumption that patients discontinued because of neutropenia).
2. Specified neutropenia as an outcome in the study methods.
3. Specified thresholds of neutropenia in the study methods.
4. Reported patient follow-up of greater than 18 weeks.

Studies with a quality score of four were considered to have high strength and those with lower score had low strength.

The definition of neutropenia was an ANC less than 1500 /microL. Neutropenia was stratified as mild (1000–1499 /microL), moderate (500–999 /microL) or severe (<500 /microL).

For the analysis of neutropenia, meta-analytically estimated event rates were used as the measure of effect size. For the analysis of longitudinal rates, meta-analytically estimated events per 100 person-years of exposure at time points of follow-up were used as the measure of effect size. Many studies reported zero events but were assigned a nominal effect size value equivalent to the crude event rate across all studies included for the relevant analysis.

Results:

A total of 108 studies reporting on 119 592 subjects were identified that included analysable data. All the studies were included in the analysis of rates of neutropenia, 82 studies were included in the analysis of death

rates and seven studies were included in the longitudinal analysis. Nineteen of the total 108 studies were rated high strength and the rest low.

Incidence of clozapine-associated neutropenia was 3.8% (95% CI: 2.7–5.2%) at a threshold of <1500 with high between-sample heterogeneity (I^2 = 97%, P < 0.01). Incidence was 1.3% at a threshold of <1000 with small between-sample heterogeneity that was not significant. Incidence of neutropenia at a threshold of <500 was 0.9% (95% CI: 0.7–1.1%) with high between-sample heterogeneity (I^2 = 88%, P < 0.01). Corresponding numbers if only the high-quality studies were analysed were: 3.9% 95% (CI: 3.0–5.2%) for the threshold <1500, 0.9% (CI: 0.8–1.1%) for the threshold <1000 and 0.7% (CI: 0.6–0.8%) for the threshold <500.

The incidence of death related to neutropenia following prescription of clozapine was 0.013% (95% CI: 0.01–0.017%). The case fatality rate of severe neutropenia was 2.1% (95% CI: 1.6–2.8%).

The longitudinal analysis included a total of 31 462 subjects and reported on the cumulative incidence of severe neutropenia (ANC of <500) at lengthening time points of follow-up. Mean follow-up was 76 months (range 12–204, SD = 60), but meta-analysable data were only available up to 48 months of follow-up. The peak incidence of severe neutropenia occurred at one month of exposure and declined after that: 38% of total events occurred by 1 month, 56% at 2 months, 84% at 4.5 months, 89% at 12 months, 89% at 24 months, 96% at 36 months and 96% at 48 months. Heterogeneity was low across samples at follow-up.

Comments: The reporting score for 19 of the included studies were rated high strength and the rest low.

The authors discuss that given the 1.3% estimate of moderate neutropenia (ANC < 1000), approximately 75% of people developing mild neutropenia will not progress to moderate or severe neutropenia. However, in many countries, clozapine is discontinued when ANC is lower than 1500 and it is unknown if they would have developed more severe neutropenia. Therefore, a more appropriate measure would be patients that discontinued treatment.

This meta-analysis is based on diverse range of studies with different methodologies, and there are limitations for each study type. The analysis mainly contains studies reporting registry data or retrospective/prospective study data. There is a high risk that useful data around cases are missing as well as confounding factors being present, especially in the retrospective situation, which make conclusions uncertain. Of the total, 82% of the articles were rated low reporting strength.

The heterogenicity between samples was high if all studies were included in the analysis. Because of the rarity of neutropenia etc, many of the studies included zero events and were assigned a nominal effect size value. In the studies included in the longitudinal analysis, events were reported at non-standardised time points which makes the analysis weaker.

Note that 11% of the cases of severe neutropenia occurred after more than 12 months of treatment.

The authors comment that further research is required to determine whether less strict haematological monitoring of clozapine is safe.

3.1.3 **Sultan RS et al 2017 (22)**

The purpose was to analyse the effect of the changes in FDA guidelines for clozapine monitoring. In 2015, FDA lowered the threshold of the absolute neutrophil count for treatment interruption from 1,500/microL to 1,000/microL and removed white blood cell count thresholds from the monitoring algorithm.

The study was retrospective. The authors analysed outpatient prescribing records for antipsychotic medicines in the Veterans Integrated Service Network 7 database between 1999 and 2012. Two cohorts were included, a general clozapine treatment cohort (individuals who received a clozapine prescription during the study period) and a clozapine initiation cohort (individuals who had new treatment episodes of clozapine and monitored events that occurred within the first year of the treatment).

For the general clozapine treatment cohort, the proportion of patients with a schizophrenia diagnosis per year who received any clozapine treatment during the study period was determined, total clozapine treatment exposure, and rate of agranulocytosis.

Using the clozapine initiation cohort, the authors assessed the complete blood count monitoring results under the old and new guidelines to determine the percentage of the cohort with ≥ 1 haematologic event.

From a sample of 14,620 individuals with schizophrenia, 246 patients received any clozapine treatment between 1999 and 2012. Of these, 160 were eligible for the initiation cohort.

No agranulocytosis was observed during the study period. Under the former recommendations, 5 patients in the clozapine initiation cohort (n=160, 3.1%; 95% CI, 0.43–5.83) qualified for treatment interruption during the first year of clozapine treatment, while only 1 patient (0.6%) qualified under the current recommendations.

Comments: In this study, the authors assessed the ANC results for a cohort of patients who were treated according to the older guidelines to see how many patients would have met the criteria for treatment interruption under the new recommendations. Not surprisingly, they found that fewer patients would have required treatment interruption under the new, lower ANC threshold.

The study includes very few patients and events, and it does not provide information on the frequency (under either the old or new guidelines) of treatment-interrupting ANC levels beyond one year. It also can't say what the outcome would have been for the four patients who, under the new guidelines, would not have required treatment interruption.

3.1.4 **Ingimarsson O et al, 2016 (24)**

This observational study was a part of a wider ongoing longitudinal study of schizophrenia in Iceland. In most countries, even mild neutropenia results in mandatory discontinuation of clozapine but Iceland has less stringent clozapine monitoring. Therefore, data on haematological outcomes of patients who continue clozapine treatment following neutropenia can be gathered. The risk of agranulocytosis and neutropenia during treatment with clozapine was compared with other antipsychotics among patients with schizophrenia.

Aim:
To analyse the risk of neutropenia and progression to agranulocytosis in a sample of patients with schizophrenia in Iceland, where it is not mandatory to provide blood samples at certain intervals in order to get clozapine dispensed.

Methods:
Two hundred-and one patients with schizophrenia treated with clozapine and 410 patients with schizophrenia who had never been on clozapine but had been treated with other antipsychotics were identified. They constituted the total amount of patients with schizophrenia being treated at Landspitali University Hospital (LUH) department of psychiatry in Reykjavik who were alive on 1 January 2003.

Neutrophil counts and the frequency of neutrophil measurements were examined. The frequency of measurements, which only included patients using clozapine for the first time, was calculated by dividing the total time on clozapine treatment by the number of neutrophil measurements. The frequency during the first 18 weeks was analysed separately.

Results:
Neutrophils were measured weekly or more often during the first 18 weeks for only 12 out of 83 patients (14.4%). The mean number of days between neutrophil measurements during the first 18 weeks of clozapine treatment was 25 days (median 18 days) but after the first 18 weeks on the medicine, the median interval increased to 124 days.

Thirty-four cases of neutropenia were identified during clozapine treatment with an average follow up time of 9.2 years. Of these, 24 individuals developed mild neutropenia (1500–1900 neutrophils/mm^3). None of them progressed to agranulocytosis.

The remaining 10 patients developed neutropenia in the range 500–1400 /mm^3 of whom one developed agranulocytosis, three stopped clozapine use and 6 patients continued clozapine for at least a year, all without developing agranulocytosis. The patient who developed agranulocytosis had been on clozapine for over 28 years and recovered fully.
The authors also found that schizophrenia patients on other antipsychotics had an equal risk of developing moderate to severe neutropenia as those on clozapine, based on just nine patient cases (4.8%) in the clozapine group and 23 (5.8%) in the group treated with other (unknown) antipsychotic medicines. The risk of developing agranulocytosis in the long term was also similar, based on 1 case in the clozapine group and 4 in the 'other antipsychotics' group. However, in all the cases in the 'other antipsychotics' group there were other factors that may have contributed more to the agranulocytosis. Mild neutropenia was more common in patients on clozapine.

Comments: This study gives an interesting insight into how the monitoring frequency can work in practice in a country. However, the low number of patients included makes it hard to draw any conclusions from the results.

The authors conclude that consideration could be given to reducing the lower limit of the amber range, whereby clozapine can be continued with additional monitoring, from 1500 to 1000. They do not directly suggest a change in monitoring frequency but do not express any disadvantages with the Icelandic approach to have guidelines but not make them mandatory.

The equal risk of developing neutropenia for other antipsychotics seen in the study is very uncertain as it is based on so few cases. In addition, there are other factors involved in these cases, such as cancer treatment, that may have contributed more to development of agranulocytosis and there is a lack of information, such as which other antipsychotic medicines are used.

3.1.5 **Drew L et al 2013 (25)**

The aim of this Australian retrospective study was to estimate the maximum incidence of agranulocytosis which clozapine would have caused between 2006 and 2010 had there been no blood monitoring system; and to determine the number of clozapine-associated cases of agranulocytosis and related deaths recorded between 1993 and 2011.

Methods:

Pharmaceutical companies are required to report all cases of white blood cell deficiency (WBCD) associated with clozapine use in Australia to the Therapeutic Goods Administration (TGA). WBCD includes a diagnosis of agranulocytosis, neutropenia, leucopenia, pancytopenia or unspecified white blood cell disorder.

The case line listing of reports from TGA were examined for the period March 1993 to October 2011. All cases of WBCD during period 2006-2010 and all cases of agranulocytosis and all deaths associated with WBCD during 1993-2011 were examined. The figure of 11,000 was used as the population on clozapine each year from 2006–2010 to calculate annual incidence rates.

The TGA cases provide data on the actual incidence of WBCD which – had it not been identified with immediate withdrawal of clozapine – could have become agranulocytosis, and for deaths due to agranulocytosis.

Results:

Two hundred and nine cases of clozapine associated WBCD were recorded during 2006-2011. Agranulocytosis was diagnosed in 33 cases. In 2/3 of the 209 cases the outcome was uncertain, and some of those may have progressed to agranulocytosis.

In 47 out of the 209 cases, the duration of treatment before the event happened was not recorded. These 47 cases were allocated to each time grouping proportional to the representation of that time group amongst cases with a record of duration of treatment. On this basis, WBCD occurred within the first year of clozapine use in 114 cases. Some 95 cases (45% of all cases) occurred after 1 year (1–5 years in 58 cases; longer in 37 cases). Three cases beyond 5 years had other serious co-morbidities. Twenty one of the 33 cases (63%) of agranulocytosis occurred within a year of commencing clozapine. Concomitant medicine use was recorded in 1/3 of the cases, including use of other medicines with known association with white cell deficiency. In 26 cases, WBCD was probably caused by something other than clozapine.

Between 1993 and 2011 there were 141 recorded cases of agranulocytosis, and four deaths (out of ten) were considered possibly clozapine associated.

The authors estimated that at least 20% of patients may have had BEN and should be excluded, and they also exclude the 26 cases where WBCD was probably caused by something other than clozapine. They conclude that during 2006–2010, without any monitoring system, the maximum annual incidence of agranulocytosis caused by clozapine would have been 0.26%. They also conclude that as 141 cases of agranulocytosis, including four deaths, were recorded in association with clozapine use between 1993 and 2011. The monitoring system could, according to them, have successfully prevented relatively few deaths.

Comments: This study captures adverse event reports from companies.

It is not stated if the 26 reports where WBCD was probably caused by something else, than clozapine had actually been assessed for causality and, if so, by whom.

The estimations calculations that are made add a lot of uncertainty to the results. Note though that in 45% of the cases (although after the allocation of the cases where TTO was not reported), WBCD occurred after one year of treatment with clozapine.

Case reports of late neutropenia/agranulocytosis

3.1.6 **Bullock SA and Bescoby-Chambersa NJC 2020 (26)**

UK: A 41-year-old gentleman with paranoid schizophrenia, well established on clozapine for 6 years, presented to clinic for routine monitoring and was noted to look unwell. His full blood count was remarkable with a white blood cell count of 3.47 (normal range 4–11 × 10^9/L) and neutrophils of 0.07 (normal range 2–7.5 × 10^9/L). A diagnosis of clozapine induced neutropenia was confirmed. His blood tests normalised within a week and he was started on aripiprazole. During this period his mental health remained stable and there were no signs of a relapse.

The authors note that the lifetime incidence of clozapine-associated agranulocytosis (neutrophils <0.5 × 10^9/L) is well documented as approximately 0.7%–0.8%. Most cases, 70-90%, occur within the first 18 weeks of treatment. However, it can still occur, and this case highlights the importance of monitoring services to ensure that serious complications can be detected and treated appropriately.

3.1.7 **Singh A et al 2016 (27)**

India: A 32-year-old man with treatment resistant schizophrenia was started on clozapine. As he showed partial response to clozapine, trifluoperazine 9 months later. After 35 months he developed fever and agranulocytosis was diagnosed. There was no history of administration of any antibiotics, chemotherapeutic

agent, radiotherapy, anti-epileptic medications, and no other cause, such as malignancy or autoimmune disease, was found.

The leucopenia and neutropenia were attributed clozapine and the infection secondary to the neutropenia. He was found positive for HLA DR4 (DRB1*04) and HLA DQB1*02:01, 1*02:02,1*03:02. He was managed with granulocyte colony-stimulating factor (G-CSF) and broad-spectrum antibiotics and the leucocyte and neutrophil count was normalized after a week. Re-challenge with clozapine was not done, instead he was treated with trifluoperazine and olanzapine with partial response.

The authors discuss that patients may have genetic vulnerabilities (this patient was positive for HLA DR4 which could increase the risk of developing agranulocytosis, also after a long treatment period with clozapine.

3.1.8 **Panesar N et al 2011 (28)**

Australia: A 37-year-old man had a history of schizoaffective disorder spanning over the last seventeen years and neuroleptic malignant syndrome (NMS). He had been treated with clozapine for many years. He had previously developed neutropenia in response to antipsychotics.

After being diagnosed with tuberculosis in 2007, he received treatment with isoniazid, pyrazinamide, rifampicin and ethambutol for nine months while taking clozapine. During this time, he developed neutropenia ($0.5x10^9$/l) and leukopenia ($2.7x10^9$/l) and clozapine was ceased. This resulted in a psychotic relapse and clozapine was carefully re-instated.

It was suggested that the late onset neutropenia occurred due to a combined treatment of clozapine with isoniazid and rifampicin, which are also known to cause neutropenia.

3.1.9 **Raja M et al 2011 (29)**

Italy: A 65-year-old man developed progressive neutropenia in May 2010 after 10 years of treatment with clozapine. Before the start of neutropenia there had been no sign of infection. On October 20, 2010, he was admitted to hospital for severe neutropenia and discontinuation of clozapine. Hematological monitoring confirmed worsening neutropenia, see figure 5 below.

The patient's psychiatric symptoms were in full remission. In the previous months, besides clozapine, he had initiated metformin for diabetes and had consumed scopolamine, sporadically. Neither of these medicines have been associated with hematological risks. No other cause of neutropenia was found.

He was treated with risperidone and then switched (for akathisia) to olanzapine and quetiapine. His clinical status remained stable and in the beginning of November his neutrophils started to normalise.

The authors discuss that there seemed to be a trend of decline in WBC count for 7 months before the development of neutropenia that might have progressed into a state of agranulocytosis if no intervention had been conducted.

Figure 5. WBC and neutrophils over time.

3.1.10 **Latif Z et al 2009 (30)**

Ireland: A patient with a 28-year history of schizophrenia had been treated with a wide range of antipsychotic medicines since diagnosis. She had not experienced any clinically significant symptomatic relief until she commenced treatment on clozapine. After 6 years of successful treatment, she developed leukopenia and clozapine was discontinued.

When the article was published, she was maintained on two antipsychotic medicines and a mood stabilizer; however, her symptom control had not improved since the discontinuation of clozapine therapy.

Comments: There is limited literature in the form of published case reports of late onset neutropenia and late onset agranulocytosis. In some reports, the patients have concomitant treatment that may carry a risk of blood dyscrasia but in other reports no other cause has been found. The authors stress the need for stringent mandatory requirements for monthly blood monitoring of clozapine, even after many years of treatment.

Published discussion papers

3.1.11 **Nielssen O 2020 (1)**

This is an Australian debate article. They start by referring to the two meta analyses from Myles et al described above.

In Myles 2018 (12), the authors found rates of mild neutropenia (neutrophil count [NC] < 1500) of 3.8%, severe neutropenia (NC < 500) of 0.7% and mortality from complications of agranulocytosis of 0.013%. Those rates of neutropenia are close to the point prevalence in otherwise healthy members of the community of between 0.4% and 4.5% for NC < 1500, and between 0.08% and 0.57% for NC < 1000 presented by Hsieh et al. 2007 (31). A total of 25,222 subjects participated in the study by Hsieh with the aim to estimate neutrophil counts in the U.S. population based on a single measurement.

Nielssen at al notes that 89% of events in the analysis by Myles occurred in the first 12 months of treatment. They also discuss that the annual rate of suicide alone of people with schizophrenia is an order of magnitude greater than the mortality from the complications of clozapine.

In Myles 2019 (23), no significant difference was found between the rates of neutropenia for those treated with clozapine compared to some other antipsychotics.

Therefore, they ask:

- Should routine haematological monitoring be performed of all patients on antipsychotic medicines? Probably no they answer, based on risk ratios and confidence intervals reported in the studies comparing other antipsychotics with clozapine, and the absence of clinical evidence of an association between other antipsychotics and neutropenia
- Are health resources wasted and mentally ill patients subjected to excessive regimentation and discomfort by insisting on indefinite haematological monitoring? They answer yes, at least after the first year. This is based on the risk ratios identified by meta-analysis and the actual mortality from complications of agranulocytosis in patients treated with clozapine.
- Are patients deprived of the best available treatment for schizophrenia by doctors estimating their likely compliance with blood monitoring? They refer to data from New South Wales Forensic showing that among patients who receive optimal rehabilitation, 43% are treated with clozapine, whereas only 3.9% of a large sample of homeless people with psychotic illness have ever received that treatment.
- On the other hand, the regular review by doctors and nurses at clozapine clinics may be part of the therapeutic effect of clozapine, and it would be a shame if an unintended consequence of a change in monitoring regimes was less frequent review of patients with severe forms of schizophrenia.

Comments: Hsieh et al reported that neutrophil counts NC < 1000 were observed in fewer than 1% of the overall sample (0.57% in black participants, 0.11% in white participants, and 0.08% in Mexican-American participants) which is lower than Myles rate of severe neutropenia (NC < 500).

Patients who are less likely to adhere to routine blood tests, may also be less likely to comply to treatment and be less likely to access health care if they become unwell with febrile neutropenia.

Note that patients reviewed in studies typically are patients who are continuously monitored during clozapine treatment, due to the current monitoring requirements. Patients with no monitoring would be a different situation.

Another risk with less frequent review is that other potentially dangerous adverse events, such as gastrointestinal effects, may be missed.

3.1.12 [redacted]

Comment: Note that US guidelines were changed to lower thresholds and exclude monitoring of WBC but there was no change in monitoring frequency or duration. The monitoring frequency in the US is higher than in NZ between 18 weeks and 6 months of treatment with clozapine.

3.2 Company reports

[redacted]

3.2.1 Douglas Pharmaceuticals Ltd

[redacted]

3.2.2 Mylan New Zealand Ltd

[redacted]

[redacted]

3.3 CARM data

Centre for Adverse Reactions Monitoring (CARM) was asked to do a search for all spontaneous reports received by them for clozapine up to 31 December 2020.

CARM was also asked for clozapine cases and adverse reactions affecting blood and lymph reported in the last 5 years (01 January 2016 to 31 December 2020), specifically when the patient had been treated with clozapine for more than 1 year.

Reaction terms used were:

Neutropenia Neutrophils decreased Neutrophilia
Agranulocytosis
Granulocytopenia
Leucopenia Leukocytosis
Lymphocytosis

WBC Abnormal NOS WBC count decreased

The search resulted in:

Total reported clozapine cases (all reactions) to 31/12/2020:	2142
Of these:	
Clozapine cases (all reactions) reported 01/01/2016 to 31/12/2020	530
Of these:	
Cases (all reactions) where clozapine treatment > 1 year	336
Of these:	
Cases involving blood and lymph effects	104

The 104 cases that met all the criteria (reported in the last 5 years, on treatment more than 1 year, reporting reactions of blood and lymph effects) were summarised. The reported reaction (which could be more than one per case) was neutropenia in 47 cases, leukopenia in 4 cases and agranulocytosis in 3 cases. Reactions reported in the rest of the cases, were for example neutrophilia and leucocytosis.

Cases reporting neutropenia, leukopenia or agranulocytosis

Fifty-one cases, who met all the criteria, were reported by pharmaceutical companies and 3 by hospital doctors.

The ethnicities of the patients were:

Maori:	15
European:	30
Asian:	2
Pasifica:	5
Indian:	1
Unknown:	1

The ages of the patients are shown in Figure 6.

Figure 6: Ages of the patients when the reaction occurred, by 10-year age brackets.

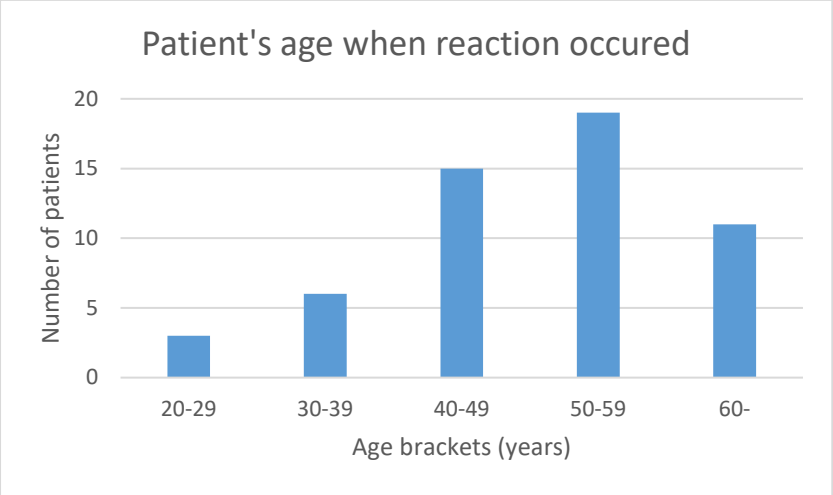
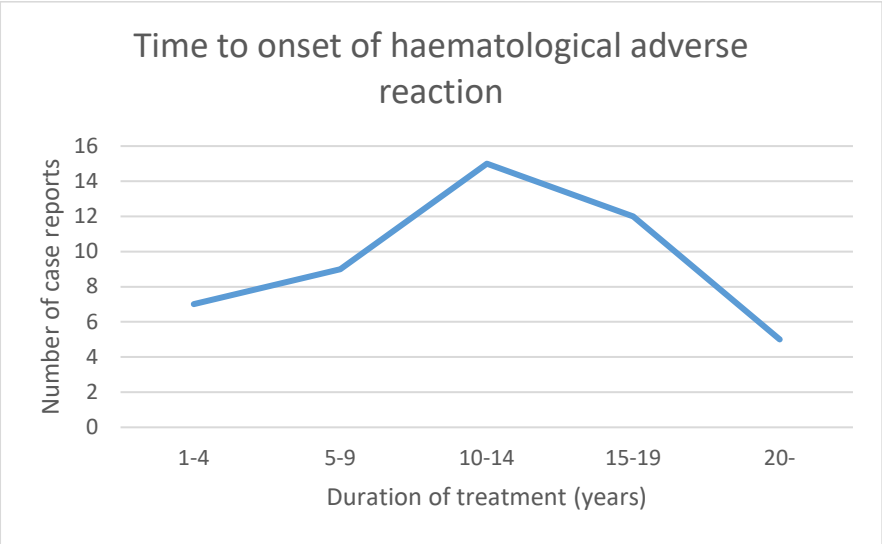


Figure 7 shows duration of clozapine treatment before the adverse reaction occurred (ie, time to onset), at intervals post one year of treatment.

Figure 7. Time to reaction.



See Annexe 1 for a summary of the 104 cases (the 54 case reports of neutropenia, leukopenia or agranulocytosis and the 50 case reports of other adverse reactions from blood/lymph).

Comment: As a comparison, the total number of the blood reactions (any time to onset) reported between 2016 and 2020 was 167.

Nearly all cases reported to CARM came from the pharmaceutical companies. However, Medsafe has not checked whether the cases reported to the company's and those reported to CARM are identical.

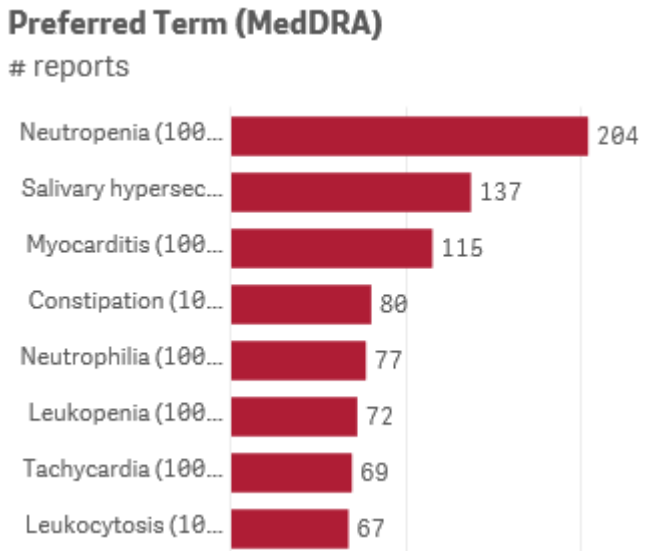
Reported cases to CARM and from the companies do not tally. One reason may be that the companies are only required to report serious adverse reactions to CARM, and these numbers may include not serious reactions.

4 Qlik

The Ministry of Health's Qlik application for suspected adverse reactions to medicines uses data from the Suspected Medicine Adverse Reaction Database (SMARS). The SMARS database contains all valid suspected medicine reaction reports made to CARM since April 1965. The database does not include reports assessed by CARM to be non-causally related to the suspect medicine.

The total number of reported clozapine reactions up to 2020 was 1,295. The figure below shows the 8 most reported reactions.

Figure 8. The most reported reactions to clozapine up to 2020.



In the past five years (2016 and 2020), 308 reactions were reported with clozapine as a suspect medicine, and 133 of them were related to blood and lymphatic system disorders.

Neutropenia

A total of 58 cases were reported during 2016-2020, and 22 of those were classified as serious.

Minimum days to onset was 0 days, median days to onset 1760 days (4.8 years) and maximum days to onset was 9286 days (25.4 years). First quartile: 33 days and third quartile: 4381 days (12 years).

Agranulocytosis

A total of 5 cases were reported during 2016-2020.

Minimum days to onset was 118 days, median days to onset 204 days and maximum days to onset was 8580 days (23.5 years).

Comments: The numbers from CARM and Qlik do not always match because the Qlik app only include reports assessed by CARM to have a causal association with the suspect medicine. However, the reports of most interest for this paper (cases of neutropenia and agranulocytosis) have a high degree of similarity between the two sources. Many of the reports of neutropenia and agranulocytosis occurred beyond one year of treatment with clozapine.

[redacted]

[redacted]

6 DISCUSSION AND CONCLUSIONS

Clozapine is an antipsychotic medicine, with a unique role in treatment-refractory schizophrenia. However, the risk of adverse reactions that may be fatal, such as neutropenia and agranulocytosis, may limit its use. In the NZ data sheets, neutrophilia is listed as a common (ie, 1-10% of patients) adverse reaction and agranulocytosis is listed as an uncommon (ie, 0.1-1% of patients) adverse reaction.

Regular blood monitoring is currently required during the whole clozapine treatment period to ensure early detection of adverse reactions affecting the blood. In that way, treatment can be interrupted or discontinued before infection is established, and fatalities could be reduced.

Reduced monitoring by either decreasing the frequency of monitoring or completely stopping the monitoring after the first year of treatment has been suggested. Some reasons argued for a change include that haematological adverse reactions are uncommon after the first year of clozapine treatment, that regular blood testing is an additional burden both for patients and healthcare professionals, and that the current requirements may exclude patients (for example those who live in areas where clozapine monitoring systems are practically hard to manage or patients who have a hard time adjusting to regular monitoring).

The current NZ guidelines for clozapine monitoring do not differ from international standards regarding frequency. In the US, the thresholds for and ANC (when testing twice a week (sometimes three times a week) or treatment discontinuation is needed) are lower and WBC monitoring has been excluded. The monitoring frequency in the US and in Canada is similar to NZ except between 18 weeks and 6 months of treatment when it is higher. However, in all jurisdictions covered by this report, monitoring is done every 4 weeks after the first 12 months.

Case reports of late onset of neutropenia and agranulocytosis have been published as discussed in section 3.1. In some reports, the patients had concomitant treatment that may carry a risk of blood dyscrasia but in other reports no other cause was found.

A small Icelandic study (24) found a low risk of agranulocytosis during clozapine treatment, but the authors were using this as an argument for lowering of monitoring thresholds rather than changing monitoring frequency.

In a meta-analysis (23) the authors concluded that clozapine does not have a stronger association with neutropenia than other antipsychotic medications and therefore all or none should be monitored (but they also state that evidence is insufficient to abandon clozapine monitoring). Another meta-analysis (12) by the same authors concludes that severe neutropenia associated with clozapine is a rare event and occurs early. However, the results in both meta- analyses have a high level of uncertainty.

[redacted]

A total of 54 cases of neutropenia (47), leukopenia (4) or agranulocytosis (3) where the patient had been on clozapine treatment for more than one year have been reported to CARM in the last 5 years. The highest number of reactions occurred between 10 and 14 years of clozapine treatment. More reactions affecting the blood or lymph were reported for patients who had been on clozapine treatment for more than one year compared to less than one year.

There are other potentially severe adverse reactions associated with clozapine treatment. For example, more deaths are caused by clozapine-induced ileus/megacolon than by agranulocytosis (14). Regular interactions with healthcare professionals provide an opportunity to assess the patient's wellbeing and enquire about other possible adverse reactions, besides their blood count status.

7 ADVICE SOUGHT

The Committee is asked to advise whether:

- There is sufficient evidence that a change to the frequency and/or duration of haematological monitoring for patients taking clozapine would continue to mitigate the risks to patients, and if so, what change is supported by the evidence.
- This topic requires further communication other than MARC's Remarks in *Prescriber Update*.

8 ANNEXES

1. CARM report – neutropenia, agranulocytosis

9 REFERENCES

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