Medicines Adverse Reactions Committee

Meeting date	12/09/2024	Agenda item	3.2.1
Title	**Review of clozapine safety and monitoring requirements: clozapine-induced neutropenia and agranulocytosis**		
Submitted by	Medsafe Pharmacovigilance Team	Paper type	For advice

Active ingredient	**Product name**	**Sponsor**
Clozapine	Clozaril	Viatris
Clozapine	Clopine	Douglas
Clozapine	Versacloz Oral suspension	Douglas

PHARMAC funding	Fully funded by PHARMAC (community schedule and hospital medicines list)
Previous MARC meetings	11 March 2021: Clozapine monitoring and frequency 4 December 2002: Clozapine and cardiac safety
Prescriber Update	Articles within the last 10 years: *Antipsychotics (general):* • Antipsychotic medicines: monitor cardiovascular risk (June 2020) • Antipsychotic-induced constipation – high impact for patients (June 2023) *Clozapine only:* • Clozapine – Close Monitoring Required (June 2015)
Classification	Prescription medicine
Usage data	See Section 3.3.
Advice sought	**The Committee is asked to advise:** • Are changes to the haematological monitoring requirements for clozapine needed? • If yes, what possible changes could be implemented to minimise the impact of the monitoring requirements to patients and healthcare professionals while maintaining the safe use of clozapine and manage the risk of clozapine-induced agranulocytosis.

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1 PURPOSE

Clozapine is a second generation (also called atypical) antipsychotic medicine used in treatment resistant schizophrenia.

While many people experience significant benefits from clozapine, treatment can also cause some significant side effects. There are a number of monitoring requirements for clozapine to manage the risk of these side effects.

Regular monitoring of blood cell counts is mandatory throughout clozapine treatment in New Zealand due to the risk of clozapine-induced neutropenia and agranulocytosis.

The purpose of this paper is to provide information about clozapine treatment, specifically focusing on haematological effects (clozapine-induced neutropenia (CIN) and clozapine-induced agranulocytosis (CIA)) and associated haematological monitoring as part of a review of clozapine safety and monitoring requirements.

2 BACKGROUND

2.1 Schizophrenia

2.1.1 Overview

Schizophrenia is a mental health condition that affects how the brain works [1].

The exact cause of schizophrenia is not yet fully understood. It is thought that an interaction between genes and a range of environmental factors may increase the risk of developing schizophrenia [1].

The onset of schizophrenia most often begins between the ages of 15 and 30 years of age. It tends to happen earlier among men than among women [2].

Diagnosis of schizophrenia is made by identifying symptoms and signs of the disorder. Symptoms vary between people and may be different at different times [1,2].

Table 1 outlines the symptoms of schizophrenia.

Table 1: Symptoms of schizophrenia

Symptoms	Examples
Psychotic symptoms (positive symptoms)	• See, hear, taste, smell or feel things that others can't (hallucinations) • develop unusual or strongly held beliefs (delusions) • have disorganised thinking and speech.
Mood and motivation problems (negative symptoms)	• Lack of motivation • Social withdrawal • Changes in mood • Loss of awareness
Thinking and memory problems (cognitive symptoms)	• Problems with memory or concentration • Difficult to do daily tasks, perform job or keep up with education

Source: Healthify He Puna Waiora. 2022. Health A – Z: Schizophrenia. 27 Oct 2022. URL: healthify.nz/health-a-z/s/schizophrenia/ (accessed 6 August 2024).

Schizophrenia is frequently associated with significant destress and impairment in personal, family, social, educational, occupational and other important areas of life [3].

People with schizophrenia are 2 to 3 times more likely to die early than the general population. This is often due to physical illnesses, such as cardiovascular, metabolic and infectious diseases, suicide and accidents [3,4].

It is estimated that the prevalence of tobacco smoking among people with schizophrenia is higher than the general population. The additive use of cannabis, stimulants and nicotine is disproportionately high among people with psychosis [4].

The social and economic costs of schizophrenia are disproportionately high, relative to its incidence and prevalence. Schizophrenia is associated with a greater burden of long-term disability than any other mental disorder [4].

In New Zealand, studies have reported a significantly increased prevalence and incidence of schizophrenia in Māori compared with the remainder of the NZ population [5].

2.1.2 Management

Early diagnosis and treatment are essential to reduce symptoms, maintain quality of life and prevent relapses in people with schizophrenia [4,6].

Treatment of schizophrenia includes both non-pharmacological approaches and antipsychotic medicines [6].

Second generation antipsychotics are recommended in preference to first generation antipsychotic medicines due to better tolerability and extrapyramidal side-effect profile. Generally, a low starting dose is used with gradual titration up to an effective level. If no response occurs after 6 – 8 weeks of treatment, changing to another antipsychotic is recommended [4].

2.1.3 Treatment resistant schizophrenia

Some individuals may experience treatment-resistant schizophrenia (TRS). TRS is usually defined as continued positive symptoms after trials of at least 2 different antipsychotics at moderate doses (usually at least 300mg chlorpromazine equivalent per day) for a reasonable period (usually at least 6 weeks) [4].

TRS is common, even in first-episode schizophrenia. It has been reported that 20 – 25% of patients with first episode schizophrenia are diagnosed with TRS, and an additional 10 – 20% of patients develop TRS after initially responding to antipsychotic treatment [6].

The prevalence of treatment resistance among patients in community psychiatric services has been reported to be 50 – 60% of patients with schizophrenia and related disorders [6].

TRS may be associated with a higher incidence of physical and psychiatric co-morbidities, more frequent and severe psychiatric symptoms and poor social functioning [6].

Family and caregivers play a key role in supporting people with TRS [6].

Clozapine can be a highly effective medicine in TRS [4,6].

2.1.4 Clozapine

2.1.4.1 Mechanism of action

The exact mechanism of action of clozapine is relatively unknown, however, it is documented that clozapine affects many receptors in the brain [7].

Clozapine is an antagonist at dopamine (D) receptors, with weak activity at D_1, D_2, D_3 and D_5 receptors and high affinity for D_4 receptor. Clozapine also binds to multiple serotonin receptors (5-HT), alpha 1 and alpha 2 receptors, M1-M5 muscarinic receptors and histamine (H1) receptors [7,8].

The therapeutic efficacy of clozapine is proposed to be via rapid dissociation from D_2 receptors and antagonistic activity at 5-HT2A receptors [7].

The major active metabolite of clozapine is N-desmethylclozapine (norclozapine), which has activity comparable to clozapine at the D_2 and 5-HT2A receptors as well as several other receptors [7].

Both norclozapine and clozapine can activate N-methyl-D-aspartate (NMDA) glutamate receptors [7].

Clozapine has been shown to be different from other antipsychotics in that it produces virtually no major extrapyramidal reactions such as acute dystonia and tardive dyskinesia, and low frequency of parkinsonian-like side effects and akathisia. In contrast to other antipsychotics, clozapine produces little or no prolactin elevation [7,8].

2.1.4.2 Use in treatment resistant schizophrenia

Clozapine is considered as first-line treatment for TRS because of superior efficacy specifically in people with TRS relative to other antipsychotics [4, 6].

Compared to other antipsychotics, clozapine is more effective in improving overall psychiatric symptoms, especially positive symptoms and preventing relapse in people with TRS [6].

Patients treated with clozapine also show improved adherence both to antipsychotics and medical treatments. This may influence the observed reduction in the rate of psychiatric and medical hospitalisations in patients treated with clozapine. Treatment has also been shown to be associated with a reduction in the number of community psychiatric clinic appointments required and psychiatric healthcare costs [6].

Clozapine treatment also reduces the risk of all-cause mortality and suicide mortality [6].

As per New Zealand and Australian guidelines, TRS should be recognised within 6-12 months of starting potentially effective antipsychotic treatment and confirmed as soon as possible [4].

A trial of clozapine should be considered for people with psychotic symptoms that are resistant to other antipsychotic agents. If possible, the trial should be continued for 12 months to allow for late responders. If there has been no response and/or side effects are severe, a change of treatment is suggested [4].

2.1.4.3 Dose

Cautious titration and a divided dosage schedule are necessary with starting clozapine to minimise the risks of hypotension, seizure and sedation [8].

The data sheet recommends that clozapine should be started at 12.5 mg once or twice on the first day, followed by 25 mg – 50mg on the second day. If well tolerated, the daily dose may then be increased slowly in increments of 25 mg to 50 mg in order to achieve a dose level of up to 300 mg/day within 2 to 3 weeks. Thereafter, if required, the daily dose may be further increased in increments of 50 mg to 100 mg at half-weekly or, preferably, weekly intervals [8].

In most patients, antipsychotic efficacy can be expected with 200 to 450 mg/day given in divided doses. Some patients may be treated with lower doses, and some patients may require doses up to 600 mg/day. A few patients may require larger doses. The maximum dose of clozapine is 900 mg/day. The dosage must be adjusted individually. For each patient the lowest effective dose should be used. Doses over 450 mg/day are associated with an increased risk of adverse reactions (in particular seizures) [8].

After achieving maximum therapeutic benefit, patients can be maintained effectively on lower doses. Careful downward titration is recommended to the lowest effective dose for the individual patient. Treatment should be maintained for at least 6 months [8].

Interruption of clozapine treatment for more than 2 days, requires re-titration as outlined in the data sheet. Depending on the duration of treatment interruption, changes to the frequency of haematological monitoring may be required [8].

Discontinuation of clozapine for reasons other than an abnormal blood count, or other serious side effect, should be done gradually to minimise the risk of withdrawal effects. A gradual reduction in dose over a 1- to 2- week period is recommended. Patients should be carefully observed for the recurrence of psychotic symptoms and symptoms related to cholinergic rebound [8].

Stopping clozapine suddenly can lead to physical and mental withdrawal effects which may occur within 2 – 3 days and usually within the first 2 weeks. Patients may experience rapid deterioration in their mental state with rebound psychosis and symptoms related to cholinergic rebound such as nausea, vomiting, diarrhoea, headache, restlessness, agitation and sweating [8].

2.1.4.4 Side effects

Antipsychotic medicines, including clozapine, are associated with a range of side effects. These include neurological, metabolic, sexual, endocrine and cardiovascular side effects [4].

It is important to routinely assess people taking antipsychotic medicines for side effects and consider appropriate intervention if necessary. Local clinical guidelines for monitoring people taking antipsychotic medicines should be followed [4].

Compared to other antipsychotics, clozapine additionally requires regular monitoring of white blood cell counts and neutrophils due to the risk of CIN and CIA [6].

A barrier to clozapine treatment is the concern of people with TSR and their carers about possible side effects and how to manage them [6].

Further information about other clozapine side effects is discussed in section 5.7.

Comments

Schizophrenia is complex condition that can significantly impact an individual's life.

People with schizophrenia are at increased risk of all-cause mortality.

The prevalence of schizophrenia in New Zealand is higher in Māori than non-Māori.

Antipsychotic medicines are used in the treatment of schizophrenia. Clozapine is superior to other antipsychotics in treatment of TRS and has many benefits.

As with other antipsychotic medicines, clozapine can cause significant side effects. Close monitoring is needed throughout treatment. Clozapine can cause toxicity in overdose. Clozapine is titrated slowly to help minimise side effects.

Contrary to treatment with other antipsychotics, clozapine requires mandatory blood tests to monitor white blood cell counts and neutrophils throughout the duration of treatment due to the risk of CIN and CIA. The monitoring requirements of clozapine have been cited as a barrier to clozapine use in TRS.

Clozapine requires careful dose titration when initiated and when treatment is interrupted for more than 2 days. Sudden cessation of clozapine may lead to recurrence or psychotic symptoms. This is an important consideration noting the haematological monitoring requirements, and possible interruptions in treatment.

Overseas, clozapine is also indicated for reducing suicidal behaviour (US) and in psychotic disorders occurring during the course of Parkinson's disease in cases where standard treatment has failed (Europe and UK). Other uses of clozapine include bipolar disorders, depressive disorders and borderline personality disorders. The same monitoring requirements apply irrespective of indication.

Use of clozapine for conditions other than in TRS is 'off label' (unapproved) use in New Zealand.

2.2 Clozapine induced neutropenia and agranulocytosis

Comments

Clozapine can cause significant side effects and requires close monitoring.

This report focuses on clozapine-induced neutropenia (CIN) and clozapine-induced agranulocytosis (CIA) and associated monitoring requirements only.

2.2.1 Background

The blood consists of red blood cells (erythrocytes), white blood cells (basophil, neutrophil, eosinophil, monocyte and lymphocyte) and platelets [9].

Figure 1 outlines haematopoiesis, which is the process relating to the formation and development of blood cells [9].

Myeloid stems cells develop into red blood cells, white blood cells and platelets. Lymphoid stem cells develop into T-lymphocytes and B-lymphocytes [9].

Figure 1: Haematopoiesis cell development pathways

Source: Best Practice Advocacy Centre (Bpac). 2008. Complete Blood Count in Primary Care. May 2008. URL: bpac.org.nz/Supplement/2008/May/docs/bpac_cbc_in_primary_care.pdf (accessed 6 August 2024).

2.2.1.1 White blood cells

White blood cells (WBC), also known as leucocytes, are part of the immune system and help fight infections and diseases [9].

WBC include neutrophils, eosinophils, basophils, T-lymphocytes, B-lymphocytes and monocytes. A WBC count is a measure of the total numbers of WBC in the blood [9].

If the WBC count drops below the reference range (generally between 4.0 – 11.0 $x10^9$/L) there is increased risk of infection. A low WBC count is also called leukopenia [10].

Leukopenia may be caused by viral or bacterial infection, medical conditions (such as cancer, autoimmune disorders) or medicines (such as cancer treatment) [11].

Although the WBC count may provide a useful summary, the absolute count of each of the cell type is more useful than the total. The WBC count may be misleading, for example low neutrophils with an elevated lymphocyte count may produce a WBC count within reference range. As a result, the WBC should not be considered in isolation [9].

2.2.1.2 Neutrophils

A neutrophil is a type of WBC and plays an important role in the immune system [9].

For most adults, neutrophils account for approximately 70% of WBC [9]. The adult reference range for neutrophils is generally 2.0 – 7.5 $x10^9$/L (however the range may be different depending on different labs) [9,10].

As seen in Figure 1, neutrophils differentiate in bone marrow from hematopoietic cells via multiple intermediate progenitor cells into mature cells that enter the circulation. Neutrophil production is regulated by the granulocyte colony-stimulating factor (G-CSF). Mature neutrophils are continually released into the circulation with an estimate 10^{11} neutrophils exiting the bone marrow daily under basal conditions [12].

The average half-life of a non-activated neutrophil in the circulation is about 4 – 10 hours. Upon migration, outside the circulation, neutrophils survive for 1 – 2 days [9].

There is a large storage pool of mature neutrophils in the bone marrow, termed the bone marrow reserve. These neutrophils may be rapidly mobilised during an inflammatory episode or in response to infection, resulting in a rise in circulating neutrophil numbers [12].

Neutropenia is the term used to describe low neutrophil counts (referred to as the absolute neutrophil count, ANC). Neutropenia is further classified as mild (1.0 – 2.0 $x10^9$/L), moderate (0.5 – 1.0 $x10^9$/L) and severe (also called agranulocytosis) (< 0.5 $x10^9$/L) [9].

The risk of bacterial infection rises if the neutrophil count drops below $1.0x10^9$/L, and is most significant when the count falls below $0.5x10^9$/L [9].

<u>Causes of neutropenia</u>

Neutropenia is caused by a decreased production or increased peripheral destruction of neutrophils from a variety of causes [9].

The most frequent cause of low neutrophil count is viral infection. Acute changes are often noted within 1 – 2 days of infection and may persist for several weeks [9].

Other causes of neutropenia include conditions such as malignant disorders of bone marrow, auto-immune conditions and genetic neutropenia's [9].

Individuals from certain ethnic populations, who are otherwise healthy and not prone to repeated or severe infections, commonly demonstrate recurrent low ANC below $1.8x10^9$/L. This phenomenon is defined as Benign ethnic neutropenia (BEN) or benign familial neutropenia and has been linked to the atypical chemokine receptor 1 gene [13].

BEN most frequently occurs in individuals of African descent, with an estimated prevalence rate ranging from 25 – 50%. Case report evidence also suggests its occurrence in some Caucasian and Chinese populations [13].

Several medicines have been associated with medicine-induced neutropenia and agranulocytosis. The medicines most likely to be associated with neutropenia include chemotherapy and immunosuppressive medicines, antithyroid medicines, antibiotics, anti-rheumatics, antipsychotics and anti-convulsant. However, there are many other medicines that might cause neutropenia [9].

A low neutrophil count may also be discovered in some people as an incidental finding. In such cases, the patients are generally asymptomatic, and the clinical examination is unremarkable. The count is usually stable on follow up [9].

Lifestyle and environmental factors can also impact the number of circulating neutrophils and other blood cells in the body. Regular use of illicit drugs and acute alcohol intake can reduce neutrophil levels. Agranulocytosis has been linked to chronic use of cocaine [14].

Neutrophils also exhibit fluctuations over a 24-hour period with a gradual increase throughout the day [14].

Management of neutropenia

People who have symptomatic neutropenia may present with mouth ulcers, fever and signs of infection and require immediate medical assessment. If there are very low neutrophil counts, even simple infections can be serious and may lead to sepsis [9].

Careful assessment of the patient's condition is critical, and patients who are unwell and/or febrile with an ANC $<1x10^9$/L generally need urgent referral and haematologist input [9].

There are specific protocols for management of drug-induced neutropenia, such as clozapine. However, input from a haematologist is also recommended [9].

Comments

Neutrophils are important for fighting infections. People with very low neutrophil counts are at risk of severe, life-threatening infections.

There are many causes of neutropenia, including medical conditions and medicines.

Some people may experience fluctuations in neutrophil counts that may have no underlying cause.

Clozapine is commonly listed as a medicine associated with agranulocytosis.

2.2.2 Mechanism

CIA is an idiosyncratic drug reaction, affecting a small number of individuals exposed to clozapine, however, can be a fatal event [15].

CIA is proposed to have a distinct pattern, with a continuous, rapid fall of ANC within 2 – 15 days [16]. It has been described as an all-or-nothing event, with an emerging absence or near absence of circulating neutrophils. This is caused by their almost total chemical or immunological destruction or by the disabling of all neutrophil production by some means [16].

The exact mechanisms for CIA are not entirely understood [15].

Studies that have addressed immune-mediated mechanisms failed to demonstrate the presence of antibodies against neutrophils or their precursors [15].

A study that applied an adapted lymphocyte proliferation assay in patients with a history of CIA, compared with those on clozapine without haematological disorders and healthy controls, found significantly raised lymphocyte proliferation rates in patients with a history of CIA only [15].

The formation of reactive clozapine metabolites may be directly toxic to neutrophils [16]. One study found that N-desmethylclozapine was toxic to granulocyte progenitors and multipotent progenitor cells at concentrations

3 – 6-fold higher that those normally achieved during treatment. It was hypothesised that the toxicity of N-desmethylclozapine may be amplified by another metabolic intermediate, such as nitrenium ion [15].

Nitrenium ion binding triggers apoptosis of granulocytic cells. Another postulated mechanism is the irreversible binding of nitrenium ion with consequent alterations of granulocyte membrane, leading to formation of a neo-antigen and an immune response [15].

It has been proposed that the mechanisms of CIA and CIN are different [16]. Based on incidence figures, at least two thirds of cases of neutropenia identified in people on clozapine do not progress to agranulocytosis [16].

2.2.3 Risk factors

There is no evidence that CIN or CIA is dose dependent [15].

It has been suggested that the risk of developing agranulocytosis with clozapine is elevated within the initial stages of treatment. Neutropenia may occur at any time during treatment [17].

Some studies have identified that the risk of CIA increases with age and in females [18].

Use of clozapine with other medicines that are known to depress the bone marrow may increase the risk of neutropenia and agranulocytosis [8,17]. The data sheet recommends that such medicines should not be used concurrently with clozapine [8].

As per the data sheet, clozapine is contraindicated in individuals with a history of toxic or idiosyncratic agranulocytosis with the exception of agranulocytosis from previous chemotherapy [8].

People who have had previous CIA may experience a more severe haematological event if clozapine is rechallenged [19].

Patients with pre-existing haematological disorders may contribute to the occurrence of agranulocytosis [17].

The data sheet includes that patients with a history of primary bone marrow disorders may be treated only if the benefit outweighs the risk and should be carefully reviewed by a haematologist prior to starting clozapine [8].

Genetic factors may influence the development of CIA. Certain HLA alleles may increase the susceptibility to CIA by altering immune responses or increasing immune-mediated cytotoxicity [17].

2.2.4 Monitoring

Monitoring of WBC and ANC with clozapine throughout treatment to manage the risk of CIA is mandatory in many countries across the world, including New Zealand.

In NZ, people taking clozapine are required to have weekly blood tests for the first 18 weeks of treatment and then 4-weekly blood tests thereafter [8]. Section 3.2 and section 4 provide further information about the haematological monitoring requirements in NZ and overseas.

As well as checking WBC and ANC, patients taking clozapine, their family/caregivers and healthcare professionals should be alert for any symptoms of infection which may be related to underlying neutropenia including flu-like symptoms such as fever, mouth ulcers and sore throat. If this occurs, an additional blood test should be taken [8].

2.2.5 Management

As per the data sheet, individuals who experience WBC $<3.0 \times 10^9$/L and/or ANC $<1.5 \times 10^9$/L must stop clozapine and an additional blood test must be taken [8].

Repeat blood tests should be taken daily until WBC and ANC normalise. If the WBC falls further to $<2 \times 10^9$/L and/or the ANC falls below $< 1.0 \times 10^9$/L, management should be guided by a haematologist [8].

Individuals who experience neutropenia with clozapine must be closely monitored for presence of flu-like symptoms or other symptoms suggestive of infection. If febrile, or signs of sepsis or local infection develop, referral to hospital is likely necessary as well as prompt start of antibiotic treatment [8, 20].

Administration of granulocyte colony-stimulating factor (G-CSF), such as filgrastim, may be needed [8, 20].

Section 3.2.3 provides further information about monitoring and management of abnormal blood test results with clozapine treatment in NZ.

Comments

Regular haematological monitoring of WBC and ANC is mandatory throughout clozapine treatment in many countries, including New Zealand, to manage the risk of CIA with clozapine.

CIA is a serious side effect of clozapine. The mechanism is not clearly understood, however, is thought to relate to a rapid fall of neutrophil counts within 1 – 2 weeks.

Agranulocytosis can be life-threatening if not detected early. Individuals may be asymptomatic. Very low neutrophil counts increase the risk of infection, and severity of infections, including sepsis.

Not all people who experience leukopenia and/or neutropenia with clozapine may progress to agranulocytosis. In general, the frequency of mild/moderate neutropenia is higher than that of severe neutropenia. However, as a precautionary measure the data sheet recommends that clozapine is stopped if WBC $<3.0 \times 10^9$/L and/or ANC $<1.5 \times 10^9$/L is detected during treatment.

If CIA occurs, expert advice should be sought from a haematologist. Patients may require hospitalisation and treatment with G-CSF.

Medicine-induced agranulocytosis is an 'off label' use of currently approved and available G-CSF (filgrastim) products in NZ.

3 Clozapine in New Zealand

3.1 Provisional consent

Clozapine has provisional consent in NZ under Section 23 of the Medicines Act 1981. This means that there are legal restrictions for use of clozapine in New Zealand [21].

Table 2 outlines the requirements for clozapine provisional consent.

Table 2: Provisional consent requirements for clozapine in New Zealand

The medicine may only be prescribed by: • Registered medical practitioners as defined in the Health Practitioners Competence Assurance Act 2003 who are certified by the Medical Council of New Zealand as competent in the scope of practice of psychiatry (i.e. psychiatrists). • Medical practitioners or nurse practitioners, who are under the supervision of the persons referred to above. • Medical officers who are in the employment of a Te Whatu Ora and are under the supervision of persons who are registered medical practitioners as defined in the Health Practitioners Competence Assurance Act 2003 who are certified by the Medical Council of New Zealand as competent in the scope of practice of psychiatry. • Registered medical practitioners as defined in the Health Practitioners Competence Assurance Act 2003 who are registered with the Medical Council of New Zealand within the vocational scope of practice of general practice. The general practitioner must be continuing the prescribing of clozapine for a specific patient whose illness is well-controlled in collaboration, or following consultation, with a Community Mental Health Team.
Persons prescribing the medicine must comply with appropriate local treatment guidelines.
The medicine must be dispensed in accordance with appropriate local dispensing guidelines.
Sale or marketing of clozapine may only occur if the sponsor has an appropriate blood monitoring and patient record database in place.

Source: Medsafe. 2019. Product/Application Search – Medsafe Product Detail – Clozaril. 31 May 2019. URL: /www.medsafe.govt.nz/regulatory/ProductDetail.asp?ID=1580 (accessed 7 August 2024)

Comments
The use of clozapine is restricted in NZ to manage the benefits and risks of clozapine treatment.

3.1.1 Products available

There are currently 3 brands of clozapine approved and available in NZ as outlined in Table 3.

Table 3: Clozapine products in New Zealand

Product name	Sponsor	Dosage form	Strengths available
Clozaril	Viatris	Tablet	100mg, 25mg
Clopine	Douglas Pharmaceuticals Limited	Tablet	25mg, 50mg, 100mg, 200mg
Versacloz Oral Suspension	Douglas Pharmaceuticals Limited	Oral suspension	50mg/ml

Source: Medsafe. 2021. Product/Application search – Clozapine. 3 September 2021. URL: https://www.medsafe.govt.nz/regulatory/DbSearch.asp (accessed 7 August 2024)

Comments

Clopine and Versacloz oral suspensions are generic medicines. The reference product in NZ is Clozaril.

All brands above are fully funded by PHARMAC for use both in the community and in hospital.

3.1.2 Indication

Clozapine is indicated for treatment-resistant schizophrenia, i.e., patients with schizophrenia who are non-responsive to or intolerant of classic antipsychotics [8].

Non-responsiveness is defined as a lack of satisfactory clinical improvement despite the use of adequate doses of at least two marketed antipsychotics prescribed for adequate durations [8]

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) [8].

3.1.3 Prescribing and management of clozapine in clinical practice

Clozapine is initiated by a psychiatrist, generally within an inpatient setting due to the close monitoring requirements relating to starting treatment [22].

There are many people involved in looking after people taking clozapine including doctors, nurses, pharmacists, mental health teams, support workers and other healthcare professionals [22].

Depending on the individual and local protocols, clozapine prescriptions for people living in the community are provided either by secondary/tertiary or primary care [22].

A general practitioner may take over the role of continued prescribing of clozapine in those who are stable and are able to be discharged from secondary/tertiary care. Alternatively, clozapine may be managed by secondary/tertiary care and other medicines/medical conditions and overall health via general practice. Co-ordination of care between the mental health team and primary care teams is therefore required [22].

Some regions in New Zealand have dedicated clozapine clinics.

3.2 Clozapine haematological monitoring

Haematological monitoring of clozapine throughout treatment is a legal requirement in NZ. The aim of this monitoring is to minimise the risk of developing CIA with clozapine use.

As described above (Table 2), companies who market clozapine in NZ must have an appropriate blood monitoring and patient record database in place to monitor CIA [23].

The data sheet outlines the haematological monitoring requirements for clozapine products in NZ [8].

Comments

The blood monitoring and patient record data base are referred to as 'clozapine patient monitoring systems' (CPMS). These systems are based upon key principles that include close monitoring of WBC and ANC for people taking clozapine, immediate discontinuation if leukopenia/neutropenia occurs and exclusion from re-exposure to clozapine if previous CIA has occurred.

Clozaril was the first brand of clozapine approved under provisional consent in NZ in 1993. The haematological monitoring requirements (such as the frequency, duration and thresholds of WBC/ANC) of clozapine were submitted by the company in the application to market their medicine in NZ at this time.

Other brands of clozapine that are currently marketed in New Zealand are generic products and follow the same haematological monitoring requirements as the reference product Clozaril, however, have their own monitoring system.

3.2.1 Clozapine Patient Monitoring Systems

3.2.1.1 Background

Currently, CPMS in NZ are web-based electronic data bases where patients who are prescribed clozapine and healthcare professionals involved in the treatment, monitoring and dispensing of clozapine are registered. Blood test results are stored in CPMS and monitored by the relevant pharmaceutical company.

The pharmaceutical companies marketing clozapine are responsible for their respective CPMS. They interact with healthcare professionals to ensure that patients' WBC and ANC are closely monitored, and appropriate action is undertaken if needed [20].

Section 5.1 provides further background information as to why CPMS were introduced upon marketing of clozapine in different countries.

The CPMS for the available clozapine products in NZ are:

- CareLink Plus – Clozaril brand
- ClopineCentral – Clopine and Versacloz brand.

The CareLink Plus database is administered by Viatris and is in Australia. The ClopineCentral database is administered by Pfizer Australia Pty Ltd (Pfizer) in Australia [8, 24].

Both systems use a 'traffic light' category to assign blood test results. 'Green' results indicate that the WBC and ANC are within range and clozapine can be continued. 'Amber' and 'red' test results indicate abnormal blood test results that correspond to thresholds of WBC and ANC that are outlined in the clozapine data sheets [8,20]. See also Figure 2 below.

Blood test results are entered into the CPMS either manually or uploaded automatically via HealthLink. These results are displayed within the patient profile in the CPMS and categorised as either green, amber or red.

Pharmacists use the CPMS to check blood test results before dispensing clozapine and to add dispensing information for patients.

System alerts are sent to registered users for patients who have had red and amber blood test results recorded, and also if blood tests are overdue.

Annex 1 provides further information about CPMS in NZ.

Comments

It is important that the monitoring systems are fit for purpose as they play a pivotal role in managing the risk of CIA, and to align with provisional consent requirements.

Different regions in NZ use different brands of clozapine. Patients who change brands must be de-registered from one system and re-registered with the other system.

Both systems follow the same monitoring requirements for clozapine however follow their own internal protocols relating to monitoring via CPMS.

Healthcare professionals and staff of the CPMS interact regularly to manage patients with abnormal blood test results and overdue blood test results (see also section 3.2.5).

3.2.2 Haematological monitoring requirements

Below is a summary of the haematological monitoring requirements for clozapine as per the clozapine data sheets and additional information from Viatris healthcare professional resource for Clozaril [8,20,24].

Annex 2 outlines information in the Clozaril data sheet relating to CIA and monitoring requirements.

3.2.2.1 Frequency of monitoring

Table 4 outlines the required frequency of haematological monitoring for clozapine in NZ.

Table 4: Frequency of haematological monitoring for clozapine in New Zealand

Time period	Frequency	
Before treatment (within 10 days):	A WBC and differential blood count[a]	
During treatment	<u>Standard monitoring:</u> WBC and ANC performed weekly for 18 weeks, and thereafter at least every 4-weeks throughout treatment	
	<u>Additional blood tests:</u> Differential blood count if any symptoms or signs of infection WBC and differential blood count if WBC has dropped by a substantial amount[b] from baseline WBC between $3.5x10^9$ /L – $3x10^9$/L and/or ANC between $1.5x10^9$/L – $2x10^9$/L, increase monitoring to at least twice weekly	
Restarting treatment after interruption of clozapine for non-haematological reasons (including missed doses)	3 days or less	No change to current blood monitoring.
	>3 days but < 4 weeks	If on weekly monitoring: weekly monitoring for 6 weeks or as long as needed to reach 18 weeks. If on 4-weekly monitoring: weekly monitoring for 6 weeks. If no abnormality, resume 4-weekly monitoring.
	>4 weeks	Same as new patient.
After treatment	<u>Discontinued due to non-haematological reasons:</u> If on weekly testing: WBC and ANC checked weekly for 4 weeks after stopping. If on 4-weekly monitoring: WBC and ANC checked 1 month after stopping.	
	<u>Discontinued due to haematological reasons:</u> If WBC falls below $<3x10^9$/L and/or ANC falls below $1.5x10^9$/L, daily blood tests until normalised Haematological evaluation is continued for at least 4 weeks or until full recovery from haematological abnormality has occurred (whichever is greater)	

a. Differential blood count: a blood count that measures the percentage and types of WBCs.
b. A substantial drop is defined as a single drop of $3x10^9$/L or more in WBC or a cumulative drop of $3x10^9$/L more within 3 weeks.

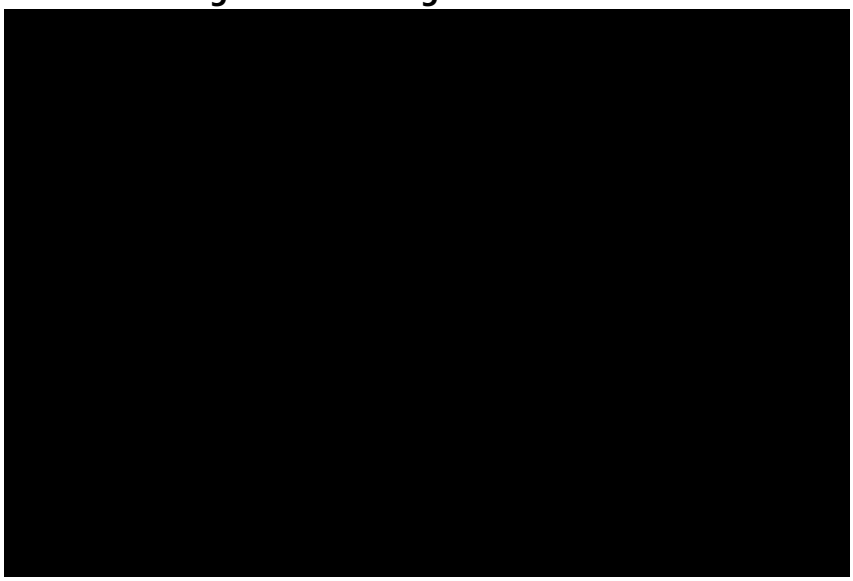
As per the NZ data sheet, re-titration is required if there has been missed doses for > 48 hours. Misses doses of clozapine also impact the frequency of monitoring, as highlighted in Table 4 above.

3.2.2.2 WBC and ANC thresholds

WBC and ANC results are categorised as per Figure 2 below.

Within 10 days prior to starting clozapine, the WBC and ANC must be within the 'green' range.

Figure 2: White blood cell and absolute neutrophil count thresholds for clozapine haematological monitoring



Source: Viatris. 2020. Clozaril Resources for psychiatrists, mental health staff, general practitioners and pharmacists. November 2020. (accessed 7 August 2024).

Comments

In June 2020, following a Medsafe review, the threshold of WBC and ANC levels for 'amber' and 'red' results after 18 weeks of treatment were updated to align with international standards (UK and EU).

Prior to this change lower WBC and ANC thresholds were used after 18 weeks of treatment:

- amber: WBC between 2.5 – 3 $x10^9$/L, ANC between 1 – 1.5$x10^9$/L
- red: WBC <2.5$x10^9$/L and ANC < 1$x10^9$/L.

After these changes, there may have been people taking clozapine who stopped treatment (as per data sheet recommendations) for 'red' results, whereas previously the results would have been in the 'amber' range and treatment could be continued.

3.2.2.3 Special monitoring

In some circumstances, the thresholds for monitoring may be adapted for certain individuals who are unable to adhere to the usual monitoring thresholds of ANC and WBC under the guidance of a consultant haematologist. This may include patients with BEN or patients receiving chemotherapy. Due to limitations within the CPMS, patients who have special monitoring requirements, specific reduced thresholds of WBC and/or ANC are documented separately. Manual alerts and follow ups are sent by the company.

3.2.3 Management of blood test results

Figure 3 outlines the management of blood test results as per the traffic light system.

Figure 3: Recommended action as per traffic light system

Source: Viatris. 2020. Clozaril Resources for psychiatrists, mental health staff, general practitioners and pharmacists. November 2020. (accessed 7 August 2024).

If a patient experiences a red blood test result, clozapine must be stopped. WBC counts and differential blood counts should then be performed daily until haematological recovery has occurred (green result) and patients should be carefully monitored for flu-like symptoms or other symptoms suggestive of infection.

It is recommended that the red result be confirmed by performing two blood counts on two consecutive days, however, clozapine should be discontinued after the first blood count.

Clinical management of agranulocytosis may be provided by a local haematologist.

Both companies have their own haematologist. Company haematologist input is needed for patients who experience a red result(s). The haematologist will advise what should be done based on the patients' medical history and current clinical status. Haematologist review may lead to continued prescribing if the patient is known to normally have low counts or a discontinuation in all other cases.

Individuals who experience a confirmed red result with clozapine must not be re-exposed to clozapine. Healthcare professionals need to contact the CPMS to confirm discontinuation or request a rechallenge (reviewed by company haematologist).

As well as checking the WBC and ANC for a particular blood test, the data sheet recommends also monitoring the trend of results. If during clozapine treatment, the 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. A substantial drop is defined as a single drop of 3.0 x 10^9/L or more in the WBC count or a cumulative drop of 3.0 x 10^9/L or more within 3 weeks.

Comments

The data sheet recommends that if a patient experiences a red result, clozapine is stopped. If the red result is confirmed by a follow up blood test the next day, clozapine must not be restarted.

The threshold cut-offs for red results include any severity of neutropenia, of which not all may not be clinically significant. Some patients may experience mild neutropenia that does not progress to agranulocytosis, while other patients might have clinically significant reductions in neutrophil counts and

experience agranulocytosis. There may be instances where a patient experiences a red result quickly followed by a green or amber result, as opposed to a severe sustained drop in ANC with accompanying symptoms. As per the current monitoring requirements, all of these possible scenarios are managed in the same way through clozapine cessation and daily blood monitoring (see also Table 4).

Company haematologist input is required for all red blood tests results as per CPMS protocols. In clinical practice, the company is unable to stop clozapine recommencement without company haematologist approval if the treating team decides to rechallenge.

People taking clozapine who experience a red result interrupt or permanently stop clozapine treatment. There may be periods of time without any antipsychotic treatment. As mentioned previously, there may be no alternative to clozapine for TRS for some individuals.

Other ethnic groups, such as African Americans, may experience BEN. There are no current BEN criteria for clozapine in NZ, which may create an equality issue as patients with BEN are likely to experience increased frequency of red and amber blood test results.

3.2.4 Clozapine dispensing

3.2.4.1 Clozapine dispensing in community pharmacy

A community pharmacy must have a contract with Te Whatu Ora (Health New Zealand) to dispense clozapine as part of the Integrated Community Pharmacy Service Agreement [25].

A generic protocol for the dispensing of clozapine by community pharmacies for the integrated community pharmacy services agreement is available for community pharmacies on the Te Whatu Ora website (effective from 1 October 2018). This protocol was last updated in 2018 [26].

The protocol outlines the requirements of the pharmacist and pharmacy when dispensing clozapine to ensure safe dispensing of clozapine and that appropriate processes are in place for monitoring of blood tests. Pharmacists are required to undertake several actions, including checking the blood test results of the patients. If a result is abnormal, the pharmacist must take appropriate action, such as contacting the prescriber and community mental health teams [26].

Each pharmacy should have a pharmacy specific standard operating procedure (SOP) for dispensing specific to local procedures of their region.

Only a pharmacist who has undergone the required training can dispense clozapine from an accredited community pharmacy [25, 26]. The training course is provided by the Pharmaceutical Society of New Zealand (PSNZ) and funded by Te Whatu Ora. It includes an initial course and a refresher course [27].

The total amount of clozapine to be dispensed at a time is generally equal to one blood test cycle for a patient (i.e.. 7 days for patients on weekly monitoring, and 28-days for patients on 4-weekly monitoring). In some cases, the prescriber may request that the medicine is dispensed more frequently that the blood test monitoring frequency [26].

There may be some circumstances were the blood test date and/or supply amount is changed, such as travelling overseas or when a blood test has not been taken on the correct day [26].

Local guidelines for clozapine offer advice relating to haematological monitoring in situations such as public holidays and travel, and where a patient has not had their blood test taken within the usual recommended timeframe [28].

As per the Viatris Clozaril healthcare professional resources, under special circumstances, the company may approve a dispensation [20].

Patients on weekly monitoring may apply to extend their blood test up to 2 days and 14 days for patients on 4-weekly monitoring. Dispensation for longer periods of time must be approved by the company haematologist [20].

Comments

The quantity of clozapine supply is relative to the monitoring frequency and date of blood test.

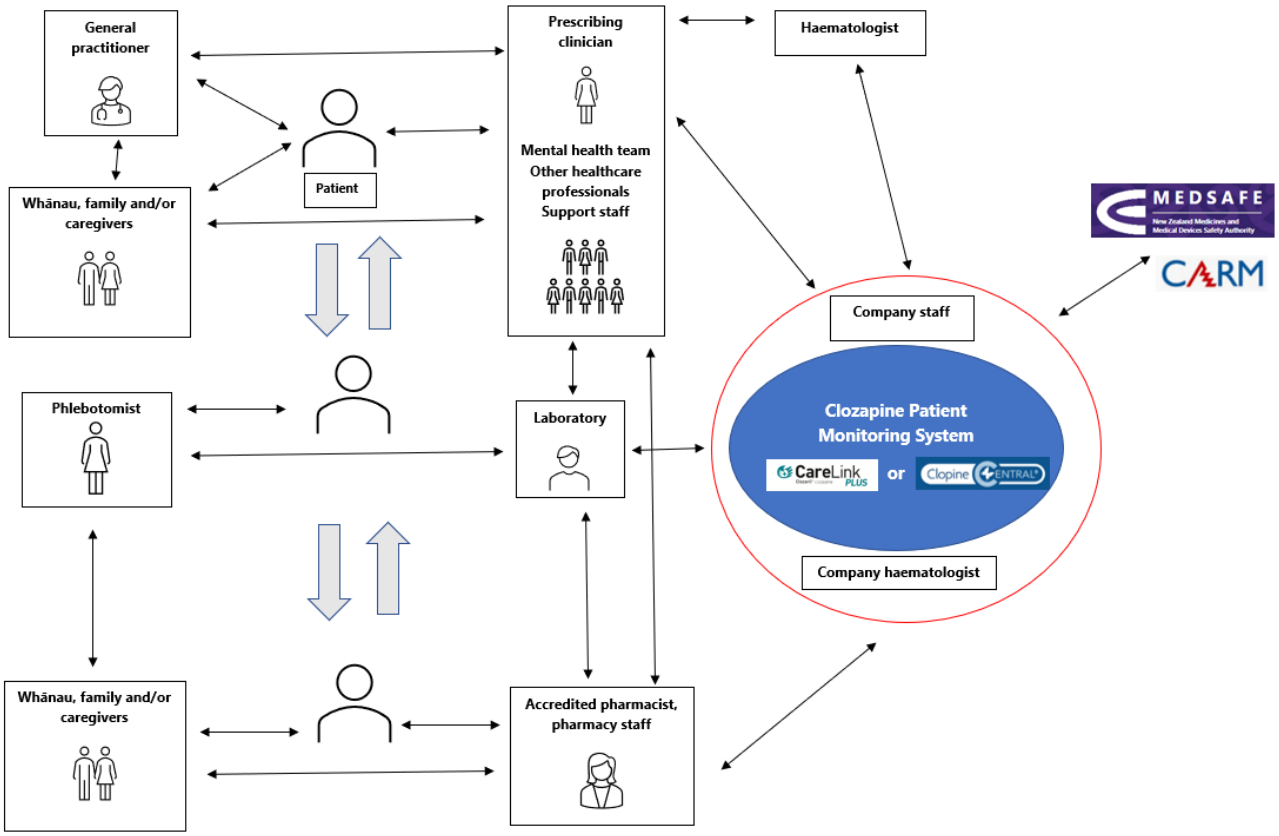
In practice, delays in blood test results may impact timely dispensing of clozapine.

Extensions to blood test due dates may be made in conjunction with the company.

3.2.5 Haematological monitoring flow chart

Figure 4 below outlines a flow chart of the multiple interactions that may take place with clozapine relating to the haematological monitoring requirements as discussed in the sections above.

Figure 4: Interactions relating to clozapine haematological monitoring requirements



3.3 Usage

3.3.1 Pharmaceutical collection

[redacted]

[redacted]

[redacted]

[redacted]

3.3.2 Pharmaceutical web tool

Publicly available community pharmacy dispensing information is available via the pharmaceutical web tool, on the Te Whatu Ora website [29].

Table 7 outlines information from community pharmacy dispensing records relative to the dosage form of clozapine in 2022.

A total of 4216 people were dispensed clozapine in a community pharmacy in 2022.

Table 7: Number of people dispensed clozapine in 2022, by dosage form

Dosage form (funded brand(s) available)	Number of people
25mg tablet (Clozaril or Clopine)	2605
50mg tablet (Clopine only)	121
100mg tablet (Clozaril or Clopine)	3920
200mg tablet (Clopine only)	164
Liquid (Versacloz only)	51

Source: Te Whatu Ora. 2023. Pharmaceutical Data web tool version 24 August 2023 (data extracted from the Pharmaceutical Collection on 08 June 2023). URL: https://tewhatuora.shinyapps.io/pharmaceutical-data-web-tool/ (accessed 7 August 2024)

Comments

[redacted].

4 Clozapine haematological monitoring (overseas)

This section provides information on clozapine haematological monitoring requirements in different countries.

4.1 International monitoring requirements

Oloyede et al (2022) reviewed international guidelines for clozapine haematological monitoring parameters and frequency, thresholds for discontinuation and rechallenge restrictions from 102 countries [30].

Guidelines from 92 (90%) of countries included routine haematological monitoring. This was mandatory in 42 countries [30].

Guidelines from 85 countries included both WBC and ANC monitoring. A total of 5 countries mandated or recommended ANC monitoring only (Chile, Israel, Lebanon, South Africa, US). There were 2 countries that recommended WBC only (Armenia, Colombia) [30].

A total of 7 countries have modified clozapine monitoring criteria for those diagnosed with BEN (Canada, Iceland, Isreal, Qatar, South Africa, UK, US). It was found that many national guidelines mentioned identifying BEN in liaison with a haematologist in their guidance but did not include modified monitoring parameters [30].

None of the countries provided explicit recommendations about a time when it would be appropriate to stop haematological monitoring [30].

There were 62 countries that recommended clozapine discontinuation for a specified criterion based on haematological thresholds [30].

Table 8 outlines the monitoring requirements from a selection of countries, adapted from Oloyede et al (2022).

The authors of this study call for evidence-based and standardised international guidelines, with more information on duration of monitoring, discontinuation of clozapine in patients with BEN and restarting of clozapine following neutropenia [30].

Table 8: Clozapine monitoring requirements in different countries

Source: Adapted from Oloyede E, Blackman G, Whiskey E, et al. 2022. Clozapine haematological monitoring for neutropenia: a global perspective. *Epidemiol Psychiatr Sci* 31: e83. DOI: 10.1017/s204579602200066x (accessed 7 August 2024).

Comments

This study reviewed clozapine haematological requirements in many different countries and highlighted international variability in the recommendations for haematological monitoring during clozapine treatment, the discontinuation of treatment and clozapine rechallenge.

All countries that have mandatory monitoring, require that haematological monitoring to continue throughout treatment. The most commonly seen monitoring frequency across multiple countries was weekly for 18 weeks then 4-weekly. Ireland, UK, Canada and US require fortnightly monitoring between 18 and 52 weeks.

Some countries such as the UK, Canada and US have specific monitoring protocols for patients with BEN.

A commonly noted threshold for discontinuation of clozapine was when WBC are $<3x10^9$L and/or ANC are $<1.5x10^9$/L. However, lower thresholds of WBC and ANC are used in some countries.

4.2 Australia

4.2.1 Summary

Similar to NZ, pharmaceutical companies are required to provide a CPMS as a condition of registration of clozapine products in Australia [31].

Annex 2 outlines information about CIA and monitoring requirements currently present in the Clozaril PI.

Each brand of clozapine has its own monitoring system in Australia. These currently include Clopine Central (Clopine brand, Pfizer), Clozaril Patient Monitoring System (Clozaril brand, Viatris) and Juno Connected (Clozitor, Juno Pharmaceuticals). Treatment centres, individual patients, prescribers and pharmacists must also be registered with a CPMS [31,32].

Monitoring of WBC and ANC with clozapine is mandatory in Australia. The frequency, thresholds of ANC and WBC and the duration of monitoring is the same as New Zealand. Australia also uses the 'traffic light' system for management of blood test results within the CPMS. If a 'red' result occurs, clozapine must be stopped and telephone contact with the CPMS haematologist is mandatory [31, 32].

The WBC and ANC must be checked by a pharmacist before clozapine is dispensed [31].

Clinical guidelines are available in Australia that provide local information about clozapine haematological monitoring requirements, management of abnormal blood test results and dispensing information [31].

Comments

Similar to NZ, haematological monitoring with clozapine is mandatory in Australia. The CPMS in Australian managed by Viatris and Pfizer, these companies also manage the CPMS for Clozaril and Clopine in NZ.

Both countries have the same monitoring requirements for clozapine as outlined in the prescribing information.

Annex 2 outlines differences and similarities on review of the Clozaril data sheet and Clozaril PI information related to CIA and monitoring requirements.

The NZ data sheet includes additional advice relating to monitoring relating to substantial drops of WBC and information about use of G-CSF.

4.3 United Kingdom

There are national-specific recommendations for haematological monitoring of clozapine in the UK which is regulated by the Medicines Health and Regulatory Authority (MHRA) [33].

Annex 2 outlines information about CIA and monitoring requirements currently present in the Clozaril UK SmPC.

4.3.1 Clozapine patient monitoring systems

Similar to NZ, the use of clozapine in the UK is restricted to patients registered with a CPMS specific to the brand prescribed [34].

The following 3 brands of clozapine and associated monitoring services are available in the UK [34]:

- Clozaril tablets: Clozaril Patient Monitoring System (CPMS)
- Zaponex tablets and orodispersible tablets: Zaponex Treatment Access System (ZTAS)
- Denzapine tablets and oral suspension: Denzapine Monitoring System (DMS)

Patients using clozapine in the UK must be registered with one of the 3 systems. The patient, prescriber, a nominated pharmacist and the pharmacy that supplies clozapine must all be registered the relevant monitoring service [33, 34].

All patients must be under the supervision of an appropriate specialist and supply of clozapine is restricted to hospital and community pharmacies registered with the CPMS. Clozapine is not sold to or distributed through wholesalers [33].

Clozapine is not normally prescribed or supplied in primary care but there are exceptions [34]. A pharmacist checks the blood test results before clozapine is dispensed.

4.3.2 Haematological monitoring requirements

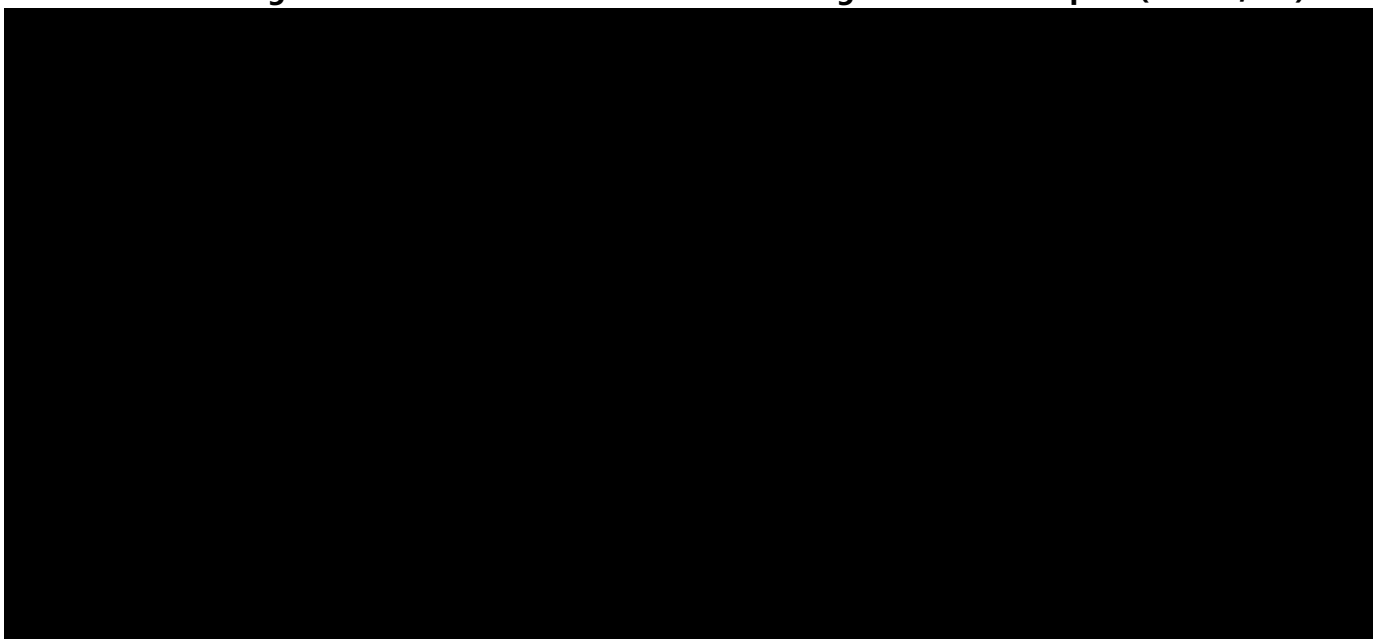
As per national-specific official recommendations, WBC and ANC is monitored weekly for the first 18 weeks of treatment and at 2-week intervals between weeks 18 and 52 during clozapine treatment [33].

After 1 year, patients with stable neutrophil counts may be monitored at least at 4-week intervals [33].

Monitoring must continue throughout treatment and for at least 4 weeks after clozapine discontinuation [33]. As seen in NZ and Australia CPSM, blood tests results are categorised into green, amber or red according to WBC and ANC thresholds [34].

Table 9 outlines the current UK MHRA clozapine monitoring requirements for WBC and ANC thresholds. The UK have specific criteria for BEN patients [13].

Table 9: Categorisation of blood test results and management for clozapine (MHRA, UK)



Source: Oloyede E, Dzahini O, Barnes N, et al. 2021. Benign ethnic neutropenia: an analysis of prevalence, timing and identification accuracy in two large inner-city NHS hospitals. *BMC Psychiatry* 21(1): 502. DOI: 10.1186/s12888-021-03514-6 (accessed 7 August 2024).

For patients to be registered with the CPMS with the BEN monitoring criteria, a letter is required from the registered consultant psychiatrist confirming that a haematologist has agreed to a probable diagnosis of BEN [35].

If a patient has a 'red' result, clozapine is interrupted. The patient should be checked for any signs of an infection. A follow-up blood test is taken on the next 2 days following the date of the red alert sample. If either of these follow up blood counts is in the red range, then the red result is confirmed, and clozapine is contraindicated. The individual must not restart clozapine treatment [36].

If neither follow-up sample is red, the red result is unconfirmed and the patient may resume clozapine. Clozapine can only be restarted once the second follow up result is obtained. Following an unconfirmed red additional monitoring is needed as a precaution if the follow up results are either amber or green, but still low for that patient, whether clozapine is restarted or not [36].

Clozapine rechallenge is contraindicated in patients who experienced a confirmed red result. These patients are entered into the Central Non-Rechallenge Database (CNRD) which is shared between the 3 UK clozapine providers [36].

Manufacturers of clozapine allow for the re-exposure of clozapine following CNRD registration under an off-license agreement. The decision for clozapine re-challenge is undertaken by a multidisciplinary team, in close liaison with a consultant haematologist. Patients who are typically rechallenged if it is determined that the risk of psychiatric illness is greater than the risk of recurrent neutropenia, especially in patients for whom no other antipsychotic medicine has shown any meaningful improvement in their psychotic

symptoms. The final decision is driven by a comprehensive assessment, which includes extensive information gathered from various sources [37].

Comments

The Clozaril UK SmPC and Clozaril data sheet contain similar information about CIA and monitoring requirements. Similar use of CPMS and requirements for clozapine dispensing are also noted between the UK and NZ.

The main differences noted between UK and NZ information include:

- Fortnightly monitoring between weeks 18 – 52 (UK) vs 4-weekly monitoring between weeks 18 – 52 (NZ)
- BEN criteria (UK) vs no BEN criteria (NZ)
- Centralised non-rechallenge database (UK) vs no centralised non-rechallenge database (NZ)
- Additional monitoring for substantial drop of WBC (NZ) vs not in monitoring recommendations (UK)
- Additional contraindication that treatment must not be started concurrently with substances known to have a substantial potential for causing agranulocytosis (UK) vs use with drugs known to have a substantial potential to depress bone marrow function should not be used concurrently with clozapine (warning) (NZ).

Changes to monitoring requirements of clozapine in the UK overtime have included lower haematological cut-off points for patients with BEN (since 2002) and requirement of 2 consecutive red results for a 'confirmed' red result (since 2013, previously a single red result). In addition, re-challenge may be possible under special benefit/risk circumstances even if previously contraindicated.

4.4 United States

4.4.1 Clozapine patient monitoring systems

In 2015, the Food and Drug Administration (FDA) made changes to the requirements for clozapine monitoring, prescribing, dispensing and receiving clozapine, to address safety concerns and current knowledge about CIA (referred to as clozapine-induced severe neutropenia by FDA). These changes were in response to the underutilisation of clozapine and to decrease barriers preventing people to start or remain on clozapine [38].

Changes included how clozapine-induced severe neutropenia is monitored and managed, and introduction of a new, shared risk evaluation and mitigation strategy (REMS) called the Clozapine REMs program [38].

REMS is a program of the FDA for the monitoring of medicines with high potential for serious adverse effects. The Clozapine REMS program replaced 6 existing CPMS maintained by individual clozapine manufactures [38].

The main changes were that only ANC is monitored (previously both WBC and ANC), patients can continue clozapine in mild neutropenia (unlike the previous guidance where clozapine would be stopped), and clozapine is discontinued in cases of moderate or severe neutropenia only. In addition, restarting clozapine is allowed even after cases of severe neutropenia if the benefits of re-exposure outweighed the risks. Specific parameters for clozapine users with BEN were also established [38].

4.4.2 Haematological monitoring requirements

Table 10 outlines the clozapine monitoring requirements from the Clozaril label [39].

In summary, ANC are monitored weekly for 6 months. After 6 months, if the ANC remains equal or greater that 1.5 $x10^9$/L then the monitoring frequency may be reduced to every 2 weeks. If the ANC remains equal or greater that 1.5 $x10^9$/L for the second 6 months of continued therapy, then the monitoring frequency may be reduced to once every 4 weeks thereafter [39].

All initial reports of ANC less than 1.5$x10^9$/L should be confirmed with a repeat ANC measurement within 24 hours [39].

If clozapine is stopped for reasons unrelated to neutropenia, the Clozaril label recommends continuation of the existing ANC monitoring for general population patients until their ANC is ≥1.5 x109/L and for BEN patients until their ANC is ≥1.0 x109/L 1000/µL or above their baseline. Additional ANC monitoring is required for any patient reporting onset of fever (temperature of 38.5°C or 101.3°F, or greater) during the 2 weeks after discontinuation [39].

Additional information in the Clozaril FDA label for management of all patients with a fever or with neutropenia [39]:

- Fever: interrupt clozapine as a precautionary measure in any patient who develops fever (temperature of 38.5°C or greater), and obtain a ANC level.
- ANC less than 1.0$x10^9$/L: if fever occurs in any patient with an ANC less than 1.0$x10^9$/L, initiate appropriate work-up and treatment of infection.
- Consider haematology consult

The current FDA recommendations for clozapine, allow rechallenge in patients who experienced CIA if clinically appropriate. The label includes that for some patients who experienced severe CIN, the risk of serious psychiatric illness from discontinuing clozapine treatment may be greater that the risk of rechallenge (e.g. patients with severe schizophrenic illness who have no treatment options other than clozapine). A haematology consultation may be useful in deciding to rechallenge a patient. In general, do not rechallenge patients who develop severe neutropenia with clozapine [39].

If a patient is to be rechallenged, the clinician should consider the ANC thresholds, the patients' medical and psychiatric history, a discussion with the patient and caregiver about the benefits and risks of rechallenge, and the severity and characteristics of the neutropenic episode [39].

The Clozaril label includes that it is unclear if concurrent use of other drugs known to cause neutropenia increases the risk or severity of CIN. There is no strong scientific rationale to avoid clozapine treatment in patients concurrently treated with these drugs [39].

If clozapine is used concurrently with an agent known to cause neutropenia (e.g., some chemotherapeutic agents), consider monitoring patients more closely than the treatment guidelines provided. Consult with the treating oncologist in patients receiving concomitant chemotherapy [39].

Table 10: Clozaril treatment recommendations based on absolute neutrophil count (ANC) monitoring for the general population and BEN criteria (FDA Clozaril Label)

ANC level	Treatment recommendation	Monitoring
General population		
Normal range ≥1.5 x10^9/L	Initiate treatment If treatment is interrupted: <30 days: continue monitoring as before ≥ 30 days: monitor as if new patient	Weekly from initiation to 6 months Every 2 weeks from 6 to 12 months Monthly after 12 months
Mild neutropenia 1.0 – 1.499 x10^9/L	Continue treatment	3x week until ANC ≥1.5 x10^9/L Once ANC ≥1.5 x10^9/L returns to patients last 'normal range' ANC monitoring interval if clinically appropriate.
Moderate neutropenia 0.5 – 0.999 x10^9/L	Recommend haematology consultation Interrupt treatment for suspected clozapine induced neutropenia Resume once ANC ≥1.0 x10^9/L	Daily until ANC ≥1.0 x10^9/L 3x weekly until ANC ≥1.5 x10^9/L Once ANC ≥1.5 x10^9/L, check ANC weekly for 4 weeks, then return to patients last 'normal range' ANC monitoring interval if clinically appropriate.
Severe neutropenia < 0.5x10^9/L	Recommend haematology consultation Interrupt treatment for suspected clozapine-induced neutropenia Do not rechallenge unless prescriber determines benefits outweigh risks	Daily until ANC ≥1.0 x10^9/L 3x weekly until ANC ≥1.5 x10^9/L If patient is re-challenged, resume treatment as new patient under 'normal range' range once ANC ≥1.5 x10^9/L
BEN criteria		
Normal BEN range Established baseline ≥1.0 x10^9/L	Initiate treatment If treatment is interrupted: <30 days: continue monitoring as before ≥ 30 days: monitor as if new patient	Weekly from initiation to 6 months Every 2 weeks from 6 to 12 months Monthly after 12 months
BEN neutropenia 0.5 – 0.999 x10^9/L	Recommend haematology consultation Continue treatment.	3x weekly until ANC ≥1.0 x10^9/L or ≥ patients known baseline Once ANC ≥1.0 x10^9/L, or at patients known baseline, check ANC weekly for 4 weeks, then return to patients last 'normal BEN range' ANC monitoring interval if clinically appropriate.
BEN severe neutropenia < 0.5x10^9/L	Recommend haematology consultation Interrupt treatment for suspected clozapine-induced neutropenia Do not rechallenge unwell prescriber determines benefits outweigh risks	Daily until ANC ≥0.5 x10^9/L 3x weekly until ANC ≥patients baseline If patient is re-challenged, resume treatment as new patient under 'normal range' range once ANC ≥1.0 x10^9/L

Source: Novartis Pharmaceuticals Corporation. 2023. Clozaril Label. May 2023. URL: www.accessdata.fda.gov/drugsatfda_docs/label/2023/019758s103lbl.pdf (accessed 21 August 2024).

Comments

The FDA monitoring system monitors ANC only and has lower thresholds for discontinuation. Clozapine may be continued in mild neutropenia with increased monitoring, as opposed to NZ requirements where clozapine is stopped in mild neutropenia.

Clozapine may also be rechallenged in previous CIA if risks outweigh the benefit. Re-exposure to clozapine after a confirmed red result is not recommended as per the data sheet.

Changes to the FDA criteria in 2015 enabled more patients to initiate and continue treatment due to lower thresholds for clozapine discontinuation.

The FDA are hosting the Drug Safety and Risk Management Advisory Committee and Psychopharmacological Drugs Advisory Committee meeting in fall 2024. There they will discuss the re-evaluation of the Clozapine Risk Evaluation and Mitigation Strategy (REMS) and possible changes to minimise burden on patients, pharmacist and prescribers while still maintaining safe use of clozapine.

As part of this re-evaluation, the FDA have funded/conducted 3 studies relating to clozapine monitoring, clinical outcomes and adherence to monitoring requirements.

5 LITERATURE

This section provides information from the literature relating to CIN, CIA, haematological monitoring and other information related to the topic.

Comments

Medsafe have previously reviewed the topic of clozapine monitoring frequency and duration at the Medicines Adverse Reaction Committee (MARC) March 2021 meeting. Minutes from the meeting are available here.

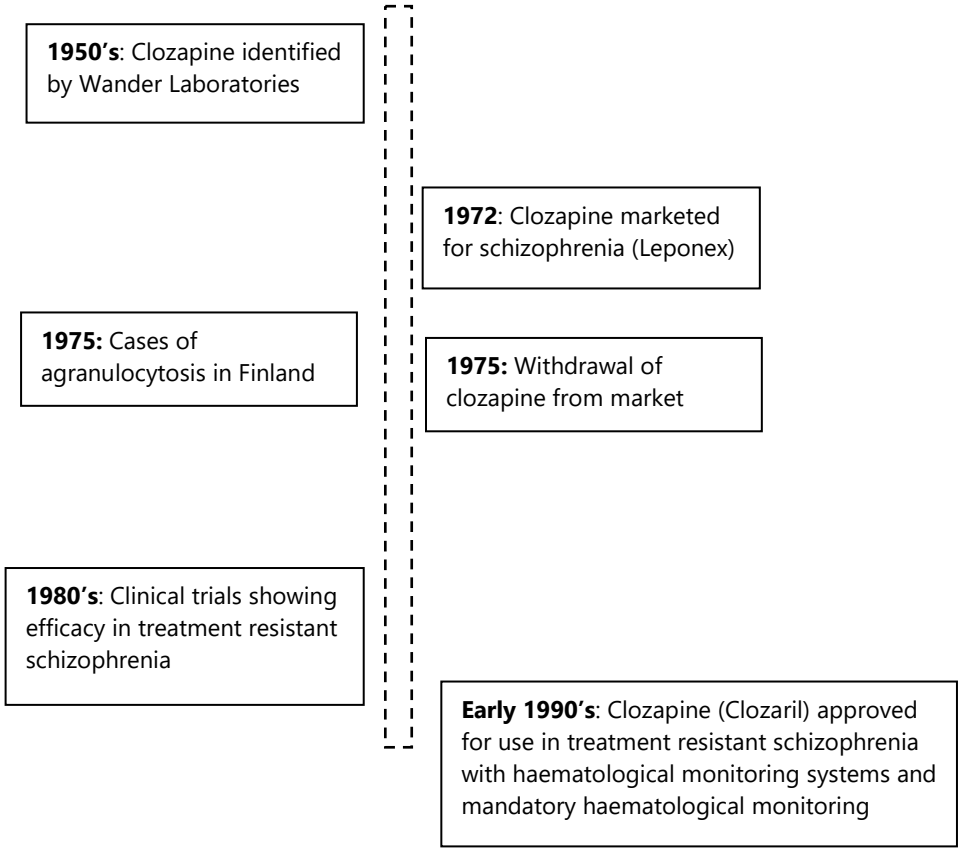
Since this meeting, there has been new research undertaken for this topic.

Articles that were previously reviewed have not been included in this report. Please refer to **Annex 3** for a copy of the report that was presented at the meeting.

5.1 Early use of clozapine and cases of clozapine-induced agranulocytosis

Figure 10 provides a summary of important timelines in the history of clozapine.

Figure 10: Brief timeline of the history of clozapine



Source: Hippius H. 1999. A historical perspective of clozapine. *J Clin Psychiatry* 60 Suppl 12: 22-3. (accessed 9 August 2024). Alphs LD and Anand R. 1999. Clozapine: the commitment to patient safety. *J Clin Psychiatry* 60 Suppl 12: 39-42. (accessed 9 August 2024)

In 1972, clozapine under the brand name 'Leponex' was marketed in several European countries [40, 41]. During clinical trials and marketing, sporadic cases of agranulocytosis were reported with a frequency within the range of what was known for other neuroleptics [42].

In 1975 there was a sudden outbreak of cases of agranulocytosis in Finland among patients taking Leponex, of which some were fatal [41]. Clozapine was withdrawn from the market. Experts from the Finnish Health authorities and from Sandoz (pharmaceutical company of Leponex) investigated the cases in Finland to identify any local factors that might have explained or predicted these events [41, 42].

It was established that the cases were identical with those reported in patients on clozapine outside Finland and with those occurring with tricyclic neuroleptics. It was recommended that in patients under treatment with clozapine, leucocytes should be determined once a week, body temperature measured daily and signs of infection monitoring regularly during the first 18 weeks of treatment (the period of which 90% of the cases reported to have occurred) [41]. Clozapine was reintroduced in some European countries under rigorous controlled conditions [40].

A retrospective analysis of cases of reported to the Sandoz Drug Monitoring Centre between 1973 and 1990 found that of the 366 cases of neutropenia (ANC < $1.5x10^9$/L) 75% of cases occurred during the initial 18 weeks of clozapine treatment [43].

It was recognized at the time that regular monitoring of blood counts with clozapine was necessary to identify early detection of the fall in WBC allowing prompt discontinuation of clozapine and recovery, and minimise further progression to agranulocytosis, onset of infection and associated risk of death [43, 44 ,45]. The risk of fatality is increased with detection of agranulocytosis after the onset of secondary infection [43].

During the 1980's, the results of the US Clozaril Multicentre Study, a double-blind comparison with chlorpromazine, indicated that clozapine produce significantly greater improvement on the Brief Psychiatric Rating Scale, Clinical Global Impressions scale and Nurses Observation Scale for inpatient evaluation in a very well-defined group of patients with TRS. This improvement included negative as well as positive symptoms [46].

Data from clinical trials for clozapine efficacy in TRS, together with a proposal for a mandatory haematological monitoring service for all patients as an early warning system to minimize the risk of agranulocytosis, enabled Clozapine (Clozaril brand (Sandoz/Novartis)) to be approved in in the early 1990's in UK, US, Canada and Australia [47, 48, 49].

While the monitoring requirements of clozapine were slightly variable across regulatory approvals, a 'no blood, no drug' policy was mandated [46].

Comments

The history of clozapine provides relevant background relating to the current requirements for haematological monitoring. Clozapine was reintroduced with mandatory haematological monitoring to balance the risks of agranulocytosis with effectiveness of treatment for TRS.

Early clinical trials may have been too small and of limited study duration to detect the true incidence of CIA. As use of clozapine increased post-market, the incidence of cases increased, and some were fatal.

Companies that marketed clozapine at this time established monitoring systems for their products as part of regulatory approval. These systems were based upon the same key principles including weekly WBC/ANC during the initial months of treatment, immediate discontinuation of clozapine if leukopenia/neutropenia occurred and exclusion from re-exposure to clozapine if CIA occurs.

5.2 Frequency of clozapine-induced neutropenia and agranulocytosis

5.2.1 Neutropenia and agranulocytosis in patients receiving clozapine in UK and Ireland – Atkin et al (1996) [48]

This study examined the incidence of neutropenia (ANC 0.5 – 1.5 x10^9/L) and agranulocytosis (ANC < 0.5 x10^9/L) from patients registered in the Clozaril Patient Monitoring Service in UK and Ireland between 7 January 1990 and 3 July 1994.

A total of 6316 patients were registered in CPMS and received at least 1 blood test. The mean age of patients was 37 years and two-thirds of patients were male.

The study identified a total of 182 cases of neutropenia, 48 cases of agranulocytosis and 6 cases of thrombocytopenia. Agranulocytosis was reversible in all but 2 fatal cases. Both of these cases occurred within the first 12 weeks of treatment and were a result of uncontrolled sepsis despite treatment. There were no fatalities due to complications of neutropenia.

A defined period of increased risk for developing neutropenia and agranulocytosis was seen in the first 6 – 18 weeks of clozapine treatment (Figure 11). A total of 43/48 agranulocytosis cases developed within the first 18 weeks of treatment. The earliest time to onset of agranulocytosis was 5 weeks and the last case occurred at 16 months. A total of 2 patients developed agranulocytosis after the first year of treatment. In 1 case, agranulocytosis occurred 11 weeks after stopping clozapine while the patient was taking other anti-psychotics.

Figure 11: Frequency of agranulocytosis and neutropenia

Table 11 outlines the risk of agranulocytosis and neutropenia over time for study participants. The incidence of agranulocytosis decreased by a factor of 10 from the first year of treatment to the second year (from 0.7% to 0.07%) which was significant (p = < 0.05). Similarly, the incidence of neutropenia significantly decreased from 2.3% in the first year of treatment to between 0.5% and 0.7% in the second to fourth years of treatment (=<0.005).

Table 11: The risk of clozapine – associated agranulocytosis and neutropenia over time

The cumulative incidence was 2.9% for neutropenia and 0.8% for agranulocytosis over the study period.

On review of the cases of neutropenia and agranulocytosis, no correlation between dose and gender was identified. The incidence of agranulocytosis marginally increased with increasing age. There was no increased risk of neutropenia with age.

People of African and Afro-Caribbean ethnicity were more likely to develop both pre-treatment neutropenia and neutropenia during treatment.

A total of 4.3% of patients stopped clozapine for haematological reasons.

5.2.2 Active monitoring of 12,760 clozapine recipients in the UK and Ireland – Munro et al, 1999 [50]

This study also reviewed patients registered in the Clozaril Patient Monitoring Service in the UK and Ireland however for a longer time period. Data from 12,760 patients from January 1990 to April 1997 was analysed.

During the study period, in 1996, the frequency of monitoring after 1 year was reduced to every 4 weeks (previously 2-weeky).

In the study population, there were 8,533 males and 4,227 females. The majority of participants were Caucasian (89%). Most participants were aged between 25 – 35 years of age. Clozapine treatment durations ranged from 1 day to 7.6 years.

Neutropenia was defined as ANC 0.5-1.5 x 10^9/L and agranulocytosis as ANC less than 0.5 x 10^9/L.

The cumulative incidence of agranulocytosis was 0.73% (93 patients). Peak risk occurred at 6 – 18 weeks with an incidence of 0.7% (76 patients). The earliest time to onset of agranulocytosis was 4 weeks. A total of 2 cases of agranulocytosis were fatal.

The cumulative incidence of neutropenia was 2.7%. Peak risk occurred at 6 – 18 weeks with an incidence of 1.27%. A total of 344 patients discontinued clozapine due to neutropenia, with 49% stopping within the first 18 weeks and 76% in the first year.

For each ten-year increase in age starting on clozapine, the risk of developing agranulocytosis increased by 53% (p=0.0001, HR 1.528, 95% CI 1.315 – 1.777) (Figure 12).

Figure 12: Frequency of participants who discontinued clozapine due to agranulocytosis and neutropenia, by age

In contrast, for each 10-year increase in age starting on clozapine the risk of developing neutropenia decreased by 17% (p=0.0003, HR 0.834, CI 0.756 – 0.919).

The authors comment that the bone marrow of younger people may be more resistant to CIA. In elderly people, clozapine metabolism may occur through different pathways that may cause increased haemopoietic toxicity.

Compared with Caucasians, Asian subjects had 2.4 times higher risk of developing agranulocytosis (p=0.03, HR 2.388 95% CI 1.098 – 5.194). The risk of neutropenia was 77% higher in African-Caribbean subjects than in Caucasians but was not significantly different in Oriental/mixed-race or Asians. Compared to Caucasians, African-Caribbeans had significantly lower baseline WBC and neutrophils. The authors note how racial metabolic enzymes differences may alter the toxicity of drug metabolites.

Higher clozapine doses were not found to increase the risk of neutropenia or agranulocytosis.

The influence of baseline WBC on developing neutropenia was highly significant (p=0.0001, HR 0.687, 95% CI 0.583 – 0.809). For each $1x10^9$/L decrease in initial WBC, the risk of developing neutropenia increased by 31%. Caucasians and African-Caribbeans who developed neutropenia had lower baseline mean neutrophil and WBC counts than those who did not develop neutropenia.

The authors compared individuals who were on 2-weekly monitoring with those on 4 weekly monitoring after at least 1 year of clozapine treatment. Of the 5199 patients who were monitored 4-weekly, 68% had a treatment duration of at least 2 years and 48% has a treatment duration of greater than 3 years.

Table 12 compares the 2 monitoring regimes according to agranulocytosis and neutropenia frequency in patients treated for at least 1 year. Those that were on more frequent monitoring had a higher number of neutropenia and agranulocytosis cases.

Table 12: Comparison of safety in clozapine patients between those monitored at 2-weekly intervals and those monitored at 4-weekly intervals after at least 1 year of treatment

[redacted]

Comments

Review of the Clozaril Patient Monitoring Service in the UK and Ireland during the 1990's identified a peak risk period of agranulocytosis between the first 6 – 18 weeks of treatment. The risk of agranulocytosis after 1 year decreased by a factor of 10.

This study highlighted how mandatory haematological monitoring of clozapine was effective in reducing the risk of mortality associated with CIA, as the majority of cases of were reversible. Fatal cases of agranulocytosis still occurred, highlighting the importance of monitoring at high-risk periods.

There were a higher number of neutropenia cases compared to agranulocytosis cases. While a higher number of both neutropenia and agranulocytosis cases occurred during the first 18 weeks, higher numbers of neutropenia cases continued to be reported after this time period compared with cases of agranulocytosis. Of note, patients required weekly monitoring for the first 18 weeks.

It was noted that the number of people who had been on clozapine for longer periods decreased overtime, which may have been influential. In addition, people who experience neutropenia and/or agranulocytosis generally stop clozapine and are then removed from the data set.

The risk of developing agranulocytosis was found to be higher with increasing age. This same pattern was not seen for neutropenia.

Different ethnic groups may be more likely to experience neutropenia and agranulocytosis with clozapine.

Higher frequency of monitoring (2-weekly versus 4-weekly) of ANC after 1 year led to increased number of neutropenia and agranulocytosis cases. This difference could possibly highlight cases that may not be attributable to clozapine, however, the authors did not comment on this.

There are limitations to using CPMS for data analysis. These systems were not designed to be used for retrospective reviews. In addition, there is no information on factors that might influence WBC/ANC counts such as other medical conditions, concomitant medicines and viral illnesses. It is possible that not all cases of neutropenia and agranulocytosis identified in patients in these registries are directly attributable to clozapine treatment. Also, these studies do not provide any information about clozapine rechallenge, or if the person had a history of neutropenia on clozapine or had previously been on clozapine treatment.

5.2.3 Clozapine-induced agranulocytosis in Finland, 1982 – 2007: Long-Term monitoring of patients is still warranted – Lahdelma & Appelberg, 2012 [51]

This was a retrospective longitudinal study that evaluated all the cases of CIA (neutrophil count <0.5x10^9/L) in Finland reported to the Finnish National Agency for Medicines from 17 December 1982 to 31 December 2007.

A total of 163 patients with CIA were identified. Table 13 outlines the demographics and treatment characteristics at the onset of agranulocytosis. Of the 163 cases, 47.9% involved females and 52.1% males. The mean age was 44.6 years. The mean duration of clozapine treatment to onset of CIA was 332 days (median 59 days).

Table 13: Characteristics of patients at the onset of clozapine-induced agranulocytosis

[redacted]

Concomitant medicine information was described in the medical records of 151 patients. A total of 60 patients had received medicines reported to be associated with agranulocytosis during the week prior to onset of agranulocytosis which included chlorpromazine, doxepin, carbamazepine, lamotrigine, fluoxetine, olanzapine, ibuprofen, cefuroxime, trimethoprim and omeprazole. Data on patients receiving concomitant potentially inducing agranulocytosis is shown in table 14.

Table 14: Characteristics of patients with comedication potentially inducing agranulocytosis, with onset of agranulocytosis within 126 days after treatment initiation and with onset of agranulocytosis >365 days after treatment

[redacted]

When treatment duration of cases was known (155 cases), a total of 123 cases occurred within 5 months of starting clozapine and 130 cases occurred within 12 months (Figure 13).

Figure 13: Number of patients with agranulocytosis (n=155), by onset time since starting clozapine

[redacted]

There were 119/155 cases of CIA that occurred within 18 weeks (126 days). From these 119 cases, information on concomitant medicines was found in patient records in 115 cases. Of these patients, 41.7% had received concomitant medicine that has been associated with agranulocytosis. There were 2 cases where patients receiving comedication developed agranulocytosis very quickly when clozapine was started, including carbamazepine (after 2 days) and chlorpromazine (after 3 days).

Information on the presence or absence of infection was available for total of 111/119 patients who experienced CIA within 18 weeks. A total of 80.2% had a concomitant infection during agranulocytosis.

A total of 24 cases developed agranulocytosis more than 1 year after starting clozapine. The presence or absence of infection was reported in 19 cases, of which 68.4% reported an infection. A total of 6/22 patients had received concomitant medicines associated with agranulocytosis. The latest onset of agranulocytosis occurred 22 years after the start of clozapine therapy.

There were 5 patients who died of complications due to agranulocytosis (table 15). These patients were a mean of 13 years older than the patients who survived agranulocytosis. A female patient developed fatal agranulocytosis nearly a year after clozapine initiation. An infection was reported in all of the fatal cases. Concomitant medicines associated with agranulocytosis were reported in 4/5 patients and included chlorpromazine, doxepin, propranolol and olanzapine.

Table 15: Characteristics of patients with fatal agranulocytosis (n=5)

[redacted]

On review of the cases, the authors found that women and men were affected equally. However, women who developed agranulocytosis were significantly older than the men. This may reflect the earlier onset of schizophrenia in men but is also in line with earlier findings indicating that an increased risk of agranulocytosis is linked with older age and female sex.

Another finding was that women in this study developed agranulocytosis earlier after clozapine initiation than men. The explanation for this is unclear, however, it is possible that the older age of women may contribute to earlier onset.

The authors found that concomitant medicines associated with agranulocytosis were common in the cases, despite recommendations to avoid such medicines. A total of 40% of all patents in the week prior to onset of agranulocytosis, had received other medicines linked with agranulocytosis. This may possibly point towards a synergistic mechanism.

Comments

Similar to previous studies, this review of CIA cases in Finland identified that the majority of cases occurs within 1 year. The median onset was 59 days (approximately 8 – 9 weeks). A small number of CIA developed more than 1 year after starting clozapine, including a case that occurred 22 years after the start of treatment.

Concomitant treatment with other potentially agranulocytosis-inducing medicine was common in cases identified and may be a risk factor, especially for rapidly developing and fatal agranulocytosis. It is not known if the agranulocytosis in these cases was related to clozapine, the concomitant medicine(s) or an interaction between the 2 medicines.

This study did not provide any information relating to possible other causes of agranulocytosis. Some data was unable to be verified or was missing.

5.2.4 Frequency of neutropenia over time in patients on clozapine – Govind et al, 2022 [52]

[This article is a preprint and has not been peer-reviewed]

This study evaluated the frequency of confirmed 'red' results (defined as 2 blood test results of ANC < $1.5x10^9$/L and/or WBC <$3x10^9$'L) overtime using the results from Zaponex Treatment Access System (ZTAS) (a CPMS) and Clinical Record Interactive Search (CRIS) in the UK, between 2 May 2000 and 1 October 2019.

Review of the CRIS and ZTAS, identified 1,988 patients with 3,167 probable clozapine treatment periods. A total of 1,891 (60%) of the treatment periods had identifiable start dates. Of these, 75 treatments were stopped due to confirmed red results.

The total of 56/75 confirmed red results occurred during the first 6 months of treatment. After 6 months, the incidence of confirmed red results was sporadic (Figure 13). A total of 60 cases occurred in the first year.

Figure 13: Frequency of confirmed red results over time

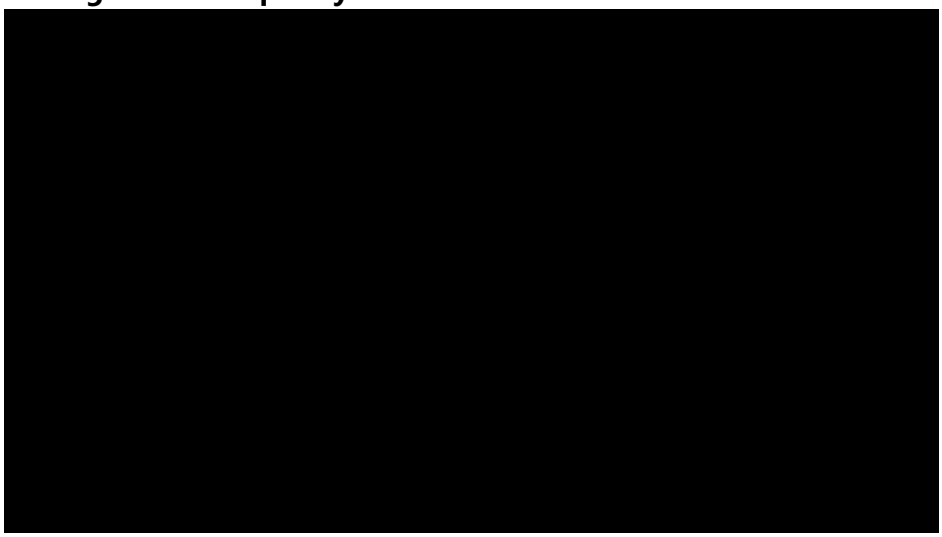
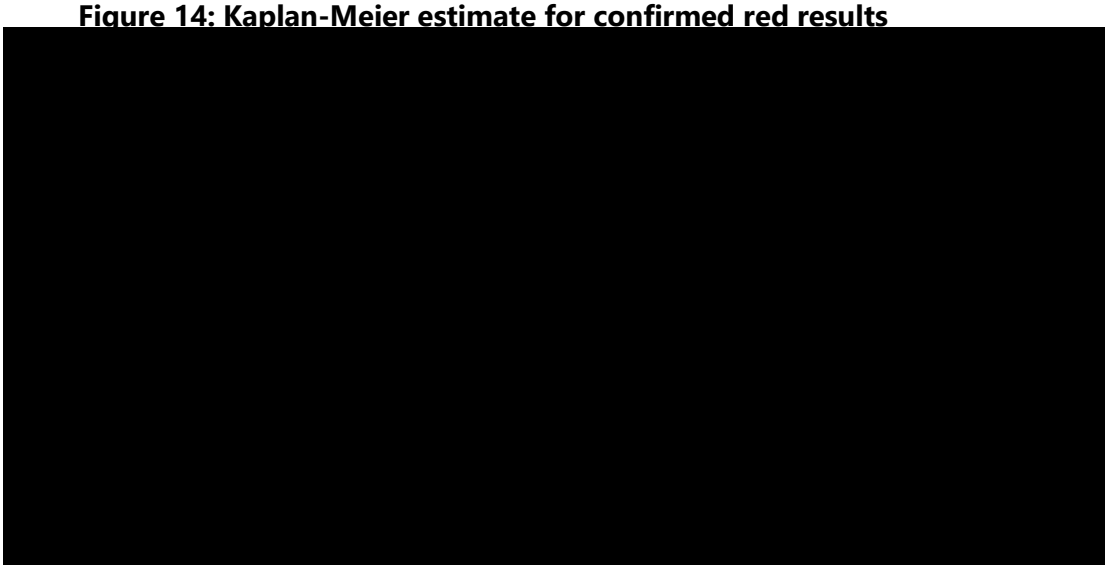


Figure 14 shows a Kaplan-Meier survival plot of the length of clozapine treatment to get confirmed red results. This plot was generated using the 1,891 treatments that had known start dates. The plot demonstrates 3 distinct phases of risk for getting a confirmed red result. The risk is highest in the first 6 months of treatment, then reduces to reasonably constant level from after 6 months to 7 years of treatment, and after 7 years the risk is almost zero. After 7 years, there was only 1 incidence of a confirmed red result, and that was at 10.4 years.

Figure 14: Kaplan-Meier estimate for confirmed red results



The authors calculate an incidence rate of confirmed red results of 47 (95% CI 36 – 60) per 1,000 person years in the first year, compared with 5 (95% CI: 2-12) per 1,000 person years in the second year.

Comments

This study reviewed red blood test results of patients within a CPMS in the UK. Cases of agranulocytosis were not further defined. This article has not been peer-reviewed.

The authors comment that this review found a relatively higher risk of a confirmed red result at the beginning of clozapine treatment which was significantly reduced after 6 months of treatment. This result is consistent with previous studies highlighting increased risks of neutropenia and agranulocytosis within the first 18 weeks.

The authors state that the explanation of this pattern could be that there are 2 distinct biological mechanisms, and that clozapine-induced immunological response occurs in the first 6 months of clozapine treatment and afterwards, the occurrence of the confirmed red results is random.

The authors discuss how as clozapine treatment progresses over time, the risk-benefit ratio of monitoring changes significantly. This may suggest that application of the discontinuation rules based on thresholds may not be appropriate after 6 months of treatment. An alternative system could be proposed where a confirmed red result after 6 months triggers, a haematology review aimed to determine whether the neutropenia was likely related to clozapine or not and advise on the likely risks with clozapine rechallenge.

5.2.5 The prevalence of agranulocytosis and related death in clozapine-treated patients: a comprehensive meta-analysis of observational studies – Li et al, 2020 [53]

This meta-analysis examined the prevalence of agranulocytosis and related death, and their associated factors in clozapine-treated patients.

A total of 36 studies were identified conducted between 1984 and 2018, which included 260,948 patients across 12 countries in 5 continents. Sample sizes ranged from 147 to 99,502. The mean age of patients varied between 15 and 51.2 years. There were 8 studies that were based on clozapine monitoring systems.

The prevalence of agranulocytosis ranged from 0.1% to 2.7% in the 36 studies, with a pooled prevalence of 0.4% (95% CI 0.3 – 0.6%).

In the 30 studies that reported deaths caused by CIA (n=33), the pooled prevalence of death was 0.05% (95% CI 0.03 – 0.09%). Among patients with agranulocytosis, the pooled prevalence of death was 10.0% (95% CI 6.1 – 15.8%).

A total of 13 studies reported the mean length of clozapine exposure when agranulocytosis occurred (9.8 weeks), and 9 of these studies reported the mean length with standard deviation (5.4 weeks +/- 3.3 weeks). There were 4 studies reporting that 53.7 – 87.5% of agranulocytosis occurred in the first 18 weeks of clozapine treatment. Insufficient data was available to calculate proportion of agranulocytosis within the first 12 months of clozapine treatment.

Comments

This meta-analysis also identified that cases of CIA are more likely to occur during the initial stages of treatment.

This study calculated pooled prevalence; however, the prevalence of CIA is thought to be dependent on treatment duration and therefore the use of pooled prevalence may not be a significant outcome measure.

Studies used in this review had different monitoring requirements and definitions of CIA and comparison across studies should be made with caution.

5.2.6 Evaluating the epidemiology of clozapine-associated neutropenia among people on clozapine across Australia and Aotearoa New Zealand: a retrospective cohort study – Northwood et al, 2024 [54]

Full article available in **Annex 4.**

This study was a retrospective cohort study which reviewed data for all people enrolled in the Viatris CPMS across Australia and NZ between 6 June 1990 and 25 October 2022. Patients enrolled from earlier or alternative patient monitoring systems maintained their initial commencement date.

The aim of this study was to determine the epidemiology and timing of clozapine-associated neutropenia outcomes to investigate variables that might contribute to the odds of neutropenia and to determine risk of competing neutropenic events during clozapine treatment.

Participants were excluded if they commenced clozapine before 1990, did not have a blood test within 2 weeks of commencement date or had no follow up.

Patients were categorised based on the type of neutropenic event:

- Isolated minor neutropenia event (ANC between 1 – 1.5 $x10^9$/L).
- Serious neutropenic event (ANC < 1 $x10^9$/L) resulting in cessation of clozapine (cessation of clozapine within 6 weeks of event).
- Serious neutropenic event (ANC < 1 $x10^9$/L) unrelated to clozapine (recommencement or continued clozapine and without clozapine cessation within 6 weeks of the event). Clinical information on alternative causes were provided for some of these cases.

Results

Of the 33,074 people within the Viatris CPMS, 26,630 unique patients were eligible for inclusion. This included 6086 NZ patients and 20,544 Australian patients, encompassing 2,635,075 unique blood test results.

Table 16 outlines the demographics of participants. From the total cohort, 66% were male and 33.9% were female. Median follow-up time was 195 weeks (IQR 36 – 525). A total of 78.8% (20,979) of patients ceased clozapine for any cause during follow up, and 2.14% (571) ceased for any severity of neutropenia.

In the whole cohort (26,630), 536 (2.0%) patients had a serious neutropenic event. In 313 of those cases clozapine was ceased as a result and in 223 cases the event was unrelated to clozapine.

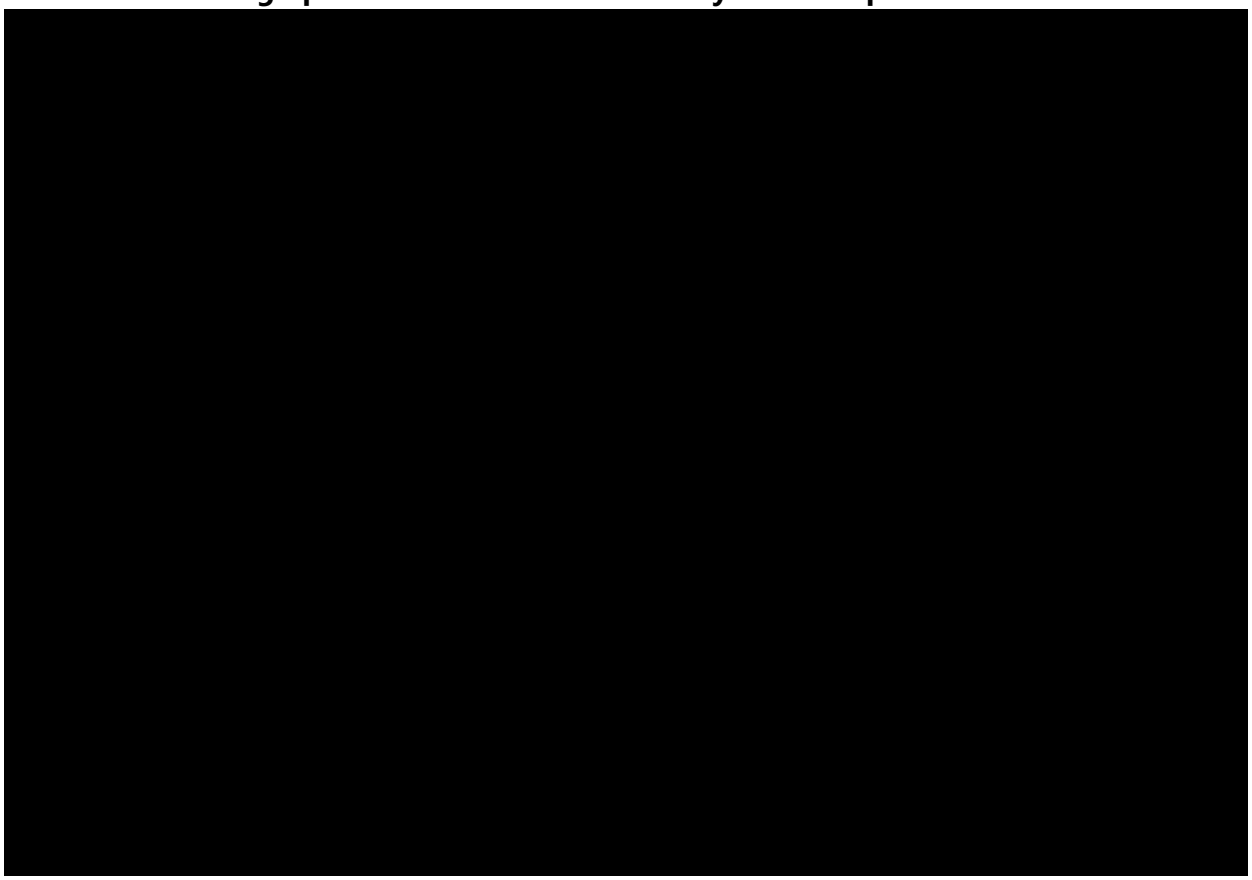
A total of 1146 (4.3%) of patients had a minor neutropenic event. A review of available adverse events reports did not identify any conclusive deaths from neutropenia.

No patients with suspected clozapine-induced serious neutropenia were rechallenged. Alternative causes of serious neutropenia included COVID-19 infection, chemotherapy or interferon treatment and BEN.

When adjusted for person-years of exposure, the event rate was 0.90 per 100 person years for a minor neutropenic event and 0.18 per 100 person-years of exposure for a serious neutropenic event leading to clozapine cessation.

Information on whether participants had previous clozapine exposure was available for the Australian cohort only, where 15,973 (77.7%) of the patients had not previously been exposed to clozapine. Patients with previous exposure were less likely to develop minor neutropenia (OR 0.59, 95% CI 0.51-0.69, p<0.0001) and serious neutropenia leading to cessation (OR 0.19, 95% CI 0.12 – 0.31, p<0.0001), but not less likely to develop serious neutropenia unrelated to clozapine (OR 0.89, 95% CI 0.61 – 1.29, p=0.53).

Table 16: Demographic characteristics and history of neutropenia



The following results focus on the group of patients with no previous exposure to clozapine.

The mean time to minor neutropenia was 46.1 weeks (IQR 10.9 – 191.1) and serious neutropenia was 17.0 weeks (IQR 9 – 102.5), and serious neutropenia unrelated to clozapine was 184.9 weeks (IQR 28.1 – 360.7).

History of drug-induced neutropenia or a previous diagnosis of BEN were statistically significant factors in determining the risk of serious neutropenia unrelated to clozapine (Table 17). Age had no association with any outcome. Compared with female gender, male gender was associated with lower odds for minor neutropenia and serious neutropenia leading to cessation, but not for serious neutropenia unrelated to clozapine. A baseline ANC of below 2.5 $x10^9$ /L was associated with increased odds of having minor neutropenia or serious unrelated neutropenia, but not a serious neutropenia leading to cessation.

Table 17: Risk of neutropenia according to baseline characteristics for patients with no previous exposure to clozapine

[redacted]

Competing risks analysis showed that cumulative rates of serious neutropenia leading to cessation slowed markedly after 18 weeks, with a cumulative incidence of 0.9% at 18 weeks and 1.4% at 104 weeks. In contrast, isolated minor neutropenic events continued to occur steadily throughout the follow up period, with a cumulative incidence of 1.7% at 18 weeks and 3.5% at 104 weeks. This difference was significant (HR=1.86, 95% CI 1.54 – 1.96, p=0.012) (Figure 15).

Figure 15: Competing risks survival analysis of neutropenic events in patients with no previous clozapine exposure (n=15,973)

[redacted]

A total of 44 (18.9%) patients with serious neutropenia leading to a cessation previously had a minor neutropenic event. Competing risks sub-distribution hazards showed that this did not modify the likelihood of these patients developing serious neutropenia at either 18 weeks (HR 0.67, 95% CI 0.45 – 0.72, p=0.08) or 104 weeks (HR 0.88, 95% CI 0.65 – 1.01, p=0.51).

The weekly incidence rate for serious neutropenia leading to cessation peaked at 9 weeks (0.128%) and reduced to a rolling average weekly incidence of 0.001% at 104 weeks. In contrast, the weekly incidence rate for minor neutropenia peaked at 0.218% at 9 weeks before falling to a stable rolling average of 0.01% maintained thereafter for the duration of monitoring (Figure 16).

Figure 16: Rolling weekly incidence rate of neutropenic events, averaged over 9 weeks, in patients with no previous clozapine exposure (n=15,973)

Competing risks regression for events according to previous clozapine exposure showed that for patients re-trialling clozapine who had not previously had a serious neutropenic event, the incidence of any neutropenic event was much lower than in patients with no previous clozapine exposure, particularly for serious neutropenic events with cessation (HR 0.53, 95% CI 0.22 – 0.68, p< 0.0001) (Figure 17).

Figure 17: Competing risks analysis showing cumulative incidence of neutropenic event by previous clozapine use (n=20,544)

The authors highlight how continued haematological monitoring after 2 years is highly likely to lead to unnecessary cessation of clozapine due to either minor neutropenic events or non-causally related severe neutropenic events.

The authors indicate that their data supports several aspects of haematological monitoring for clozapine. Firstly, cumulative rates of mild neutropenia occurred in 4.1% of patients with no previous clozapine exposure, of which 1.5% had a serious neutropenia and clozapine discontinued. This indicates that more than 60% of

observed neutropenia did not progress to a more severe neutropenia. Based on clozapine monitoring guidelines, these patients would be required to stop clozapine.

Secondly, the risk of neutropenia requiring clozapine cessation occurred predominantly within 18 weeks of commencing treatment, while a marked reduction in risk was seen beyond 104 weeks. However, the cumulative incidence of minor or less clinically relevant neutropenia remained linear from 18 weeks. It is probable that the observed risk of mild neutropenia is driven by causally related factors or observation bias, which calls into question the rationale of sustained haematological monitoring for long-term treatment.

Rates of serious neutropenia leading to clozapine cessation were found to be highest in the first 18 weeks and become negligible after 2 years of clozapine exposure. The results also showed previous clozapine exposure to be protective for future serious neutropenic event.

Overall, the authors conclude that the data supports less stringent ANC threshold for clozapine interruption and a reduction in monitoring frequency following 18 weeks of treatment, with consideration of cessation of regular monitoring after 2 years in patients who has not had a serious neutropenic event unless clinically indicated. The authors also suggested the haematological monitoring might not need to recommence after a treatment interruption after 2 years of monitoring.

Comments

In this study, a total of 93.7% ANC results did not represent a neutropenia. This may show how this event with clozapine is not common. People with previous neutropenia are usually removed from CPMS as clozapine is stopped which would be impactful on the data.

The method of this study used ANC threshold cut-offs different to current monitoring requirements, which were based on clinical relevance. A higher number of mild neutropenic events were identified compared to serious neutropenia both in those with and without prior exposure to clozapine. These results may suggest that not all neutropenic events occurring with clozapine is of clinical relevance. The authors did not specify the management of clozapine in these cases.

The data from this study also suggests that people who experience a mild neutropenia not necessarily also experience a serious neutropenia. It is not known what circumstances a neutropenia would or would not progress to a severe neutropenia. The onset time of the neutropenia could be an important aspect to consider, in addition to possible other causes of neutropenia.

Results of this study highlights how in NZ and Australian clinical practice, for some people who take clozapine and experience a serious neutropenic event (ANC < $1x10^9$/L), clozapine may be continued or restarted as the neutropenia is considered unrelated. As per current data sheet requirements, this group of people would be considered an 'off label rechallenge' if the red result was confirmed by an additional red result.

On further review of the time-to-event (weeks) (cohort without previous exposure), the mean time to onset for a serious neutropenia event leading to cessation was 17 weeks, similar to previous studies where most cases of CIA have been reported within the first 18 weeks. It appears that cases of serious neutropenia events considered unrelated to clozapine had a later time to onset and a wider confidence interval, 184.9 weeks (28.1 – 360.7). The median follow-up time was 107 weeks (approximately 2 years).

The incidence of isolated minor neutropenic event continued to increase over a 2-year period, whereas the incidence of any serious neutropenic event did not show the same trend.

It is noted that a very small percentage of the cohort had BEN, highlighting how people with BEN currently are taking clozapine in NZ and Australia. With immigration, these numbers may change.

Limitations of use of CPMS for data analysis are acknowledged, including lack of information about neutropenia cases. Unfortunately, there was also missing information relating to the NZ cohort in this study.

5.2.7 Clinical impact of reducing the frequency of clozapine monitoring: controlled mirror-image cohort study – Oloyede et al, 2023 [55]

Full article available in **Annex 5.**

The aim of this study was to investigate the impact of policy changes to clozapine haematological monitoring frequency on clinical and safety outcomes in people taking clozapine. During the COVID-19 pandemic, the monitoring intervals had been extended from 4-weekly to 12-weekly intervals for low-risk patients.

This study took place in the UK and included all patients in 2 large London National Health Service trusts who were registered in the clozapine monitoring service data base Zaponex Treatment Access System (ZTAS) for extended monitoring between April 2020 to July 2021. Participants did not have to remain on clozapine treatment throughout to be included in the study.

Haematological data was collected from ZTAS. Demographic and clinical data was collected from electronic medical records. Pharmacy dispensing records were used to collect medicine data. Patients accessed haematological monitoring in a community-based clozapine clinic, where venous samples were analysed using a point of care device.

Eligibility criteria for extended monitoring agreed by expert consensus included an ANC ≥2.0 $x10^9$/L (or ≥1.5 $x10^9$/L if a history of BEN) and demonstrated adherence to clozapine for a least 12 months. All participants were based in the community setting at baseline. Individuals in forensic mental health services were excluded.

The comparison group comprised of patients from the trust who were registered for extended monitoring but received routine monitoring.

Figure 18 outlines the study design. The primary outcome of the study was to compare the proportion of participants with mild to severe neutropenia (ANC between 0.5 and 1.5$x10^9$/L) and the proportion of participants who attended emergency departments for clozapine-induced severe neutropenia (ANC <0.5$x10^9$/L) during the follow up period compared between the two groups.

For the mirror-image analysis, psychiatric hospital admission rate, change in clozapine dose, and concomitant psychotropic medication were compared 1 year before and after the index date. The index date or mirror point was defined as the last blood test date before haematological monitoring was changed from 4-weekly to 12-weekly.

Participants were followed up for 1 year after index date and all-cause treatment discontinuation was recorded. Infection with COVID-19 during the follow up period was also examined.

Figure 18: The mirror-image design

Background risks of mild to moderate neutropenia and of agranulocytosis after 1 year with clozapine treatment were taken from a previous study which reported 0.7% and 0.07% respectively. The number of participants required in the intervention group to provide 95% power was 429 to detect one case of neutropenia and 4286 to detect one case of agranulocytosis.

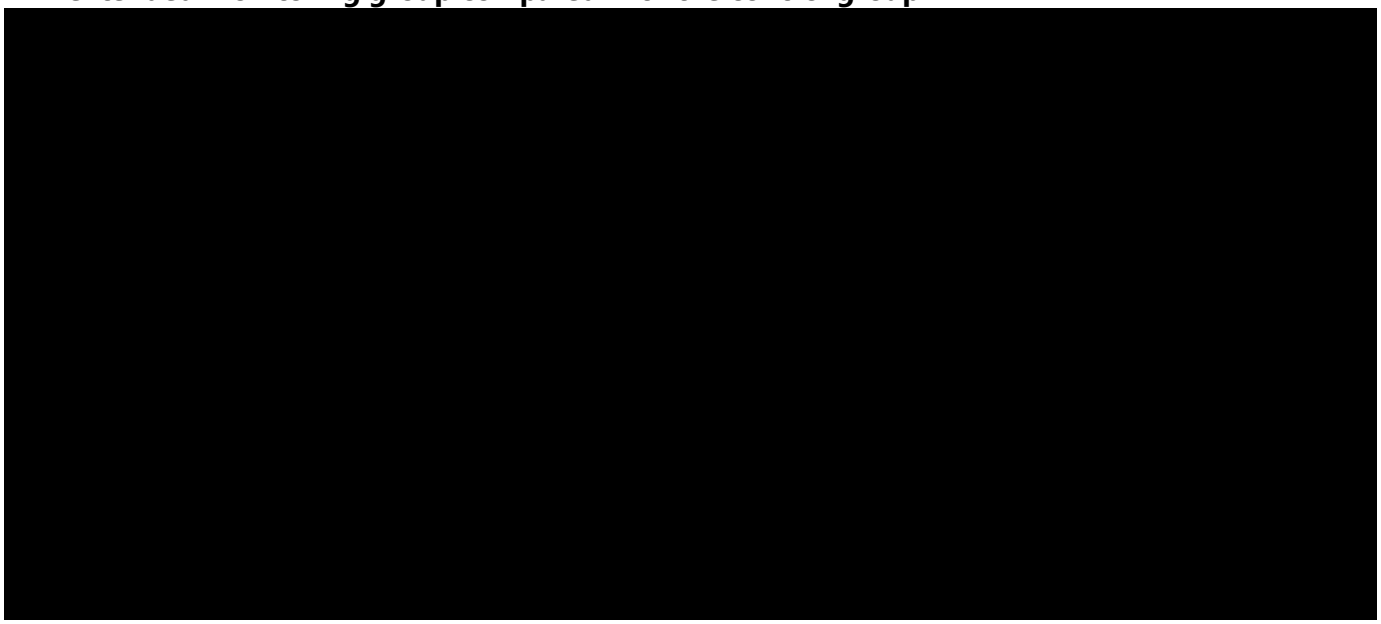
Incidence rates were calculated for the intervention group and comparison groups as the number of cases divided by the number of person-years. Person years was defined as the years contributed by each participant from index date to the first haematological event, treatment discontinuation or end of follow up.

Results

A total of 569 patients were included in this study of which 459 were receiving clozapine treatment with extended monitoring and 110 were on routine monitoring. The total person-years for the intervention group were 458 and the median follow-up time was 1 year. The total person-years for the comparison group was 109 and the median follow-up time was 1 year.

Clinical and demographic data of the study population are outlined in the Table 18 below.

Table 18: Baseline sociodemographic and clinical characteristics of participants in the extended monitoring group compared with the control group



In the extended monitoring groups, 2/459 (0.4%) had a total of 10 episodes of mild to moderate neutropenia during the post-mirror period. All cases occurred during infection with COVID-19. There were no cases of severe neutropenia or acute admissions for treatment of clozapine-induced severe neutropenia.

In the comparison group, 1/110 (0.9%) had 1 episode of mild to moderate neutropenia. There were no cases of severe neutropenia or acute admissions for treatment of clozapine-induced severe neutropenia.

In the intervention group, there was an incidence of 4 haematological events per 1000 person-years, compared with 9 haematological events per 1000 person-years in the comparison group. The incidence ratio rate (IRR) was 0.48 (95% CI 0.02 – 28.15, p=0.29).

At 1 year follow up, 457 (99.6%) of participants in the extended monitoring group and 109 (99.1%) participants in the comparison group remained on clozapine. The risk ratio (RR) for treatment discontinuation with extended monitoring compared with routine monitoring was 0.48 (95% CI 0.04 – 5.23, p=0.54).

Reason for discontinuation in the extended monitoring group was patient request (2) and death secondary to COVID-19 (1) in the comparison group.

A total of 2 participants in the extended monitoring group, changed to routine monitoring due to clozapine interruption because of COVID-19 infection and missed blood test.

Of the 459 patients in the intervention group, 23 (5%) were admitted to psychiatric hospital during the pre-mirror period and 10 (2%) during the post mirror period. There was no change in the median number of psychiatric admissions in the year after extended monitoring compared with the year before in the

intervention group. A total of 12/23 admissions in the pre-mirror period and 6/10 admissions in the post-mirror period were due to non-adherence to clozapine.

Of the 110 patients in the comparison group, 9 (8%) were admitted to psychiatric hospital during the pre-mirror period and 5 (5%) in the post mirror period. The median number of admissions per patients during the pre and post mirror remained unchanged. A total of 5/9 admissions in the pre-mirror period and 3/5 admissions in the post-mirror period were due to non-adherence to clozapine.

The RR for hospital admission during follow up period with extended monitoring compared with routine monitoring) was 0.5 (95% CI 0.17 – 1.37, p=0.17).

The median clozapine dose was unchanged from the pre- to post-mirror period in both groups.

In the extended monitoring group, the proportion of participants prescribed concomitant antipsychotics increased from 126 to 133, mood stabilises increased from 146 to 151 and antidepressants reduced from 135 to 130. In the comparison group, the proportion of participants prescribed concomitant antipsychotics increased from 34 to 35, mood stabilises increased from 23 to 27 and antidepressants reduced from 26 to 22.

Among the 459 participants on extended monitoring, 25 (5.5%) tested positive for COVID-19 during the follow up period. A total of 7 (6.4%) tested positive in the comparison group. The RR for infection with COVID-19 during follow up period with extended monitoring compared with routine monitoring was 0.86 (95% CI 0.38 – 1.93, p=0.7).

The authors state that the findings of the study indicate that extending the haematological monitoring interval from 4 to 12-weekly did not increase the incidence of agranulocytosis.

There was no increase in people admitted with life-threatening haematological adverse events related to clozapine use in the group who received extended monitoring. The incidence rates of mild to moderate neutropenia were higher than in other studies, however, all cases in this study in the intervention group were likely related to COVID-19 infection.

In the study, there was no difference in psychiatric hospital admissions between the two groups. In addition, clozapine doses and concomitant medications remained unchanged during the observation period, suggesting relative stability of mental state despite reduced face-to-face contact. There was no substantial difference between clozapine non-adherence between the two groups.

The authors comment how the stringency of current practice relating to haematological monitoring of clozapine is a result of isolated cases early in clozapine's development. The impact of these early cases has distorted the perception of clozapine's relative risk. A more pragmatic strategy of intensive haematological monitoring in the first year followed by selective haematological monitoring in case of febrile illness or pharyngitis needs to be explored. Stringent monitoring of people receiving clozapine treatment imposes an unnecessarily burden. Such monitoring also has important economic implications and inequalities in access.

The authors note action taken by the Netherlands Clozapine Collaboration Group, who recommended lowering the frequency of monitoring to 4 times a year (off-label use) for mentally competent and adequately informed patients who request it.

The authors are of the opinion that the relaxation of clozapine blood monitoring requirements prompted by the pandemic provides an opportunity for revising the protocols.

Limitations discussed included that patients selected in the intervention group were selected based on absence of prior haematological events and demonstrated adherence to clozapine. These people generally were well established on clozapine before changing to extended monitoring. This limits the generalisability of the results because participants were selected who were deemed at low risk of complications with extended monitoring.

The study also has a limited follow up period and a small sample size. The study was underpowered to identify potential differences in haematological events.

The sample size of 459 participants in the extended monitoring group provides a power of 96% to detect 1 case of neutropenia and 27% to detect agranulocytosis. Despite insufficient power to detect agranulocytosis, the authors were able to estimate the upper limit of the 95% CI for agranulocytosis risk to be 0 – 0.6%.

It is unknown whether a reduction in the amount of physical contact patients had with clinicians was compensated by increased contact by telephones or other means.

Comment

This study is the first and largest study to investigate the clinical impact of extended monitoring in the UK during the COVID-19 pandemic.

No differences in the incidence of haematological events, including agranulocytosis were identified between those who were on extended monitoring versus those on routine monitoring. However, results of this study should be reviewed in caution noting that the study population in the extended monitoring group included people who resided in the community, who did not have any prior haematological events and had demonstrated good adherence to clozapine. While the eligible criteria for extended monitoring was from after 1 year, it appeared the majority of participants had been on clozapine for long treatment durations. In addition, this study took place within a pandemic.

The study did not have enough people to power the primary outcome for agranulocytosis and differences in haematological events. The IRR of haematological events between the 2 groups has a very wide CI. Previous studies have highlighted how the risk of agranulocytosis is reduced overtime, and therefore it would be hard to detect this event in such a small sample group. This study also had a short follow up (1 year).

Interestingly, the cases of neutropenia in the intervention group coincided with COVID-19 infection and not deemed to be due to clozapine. This is an important aspect as there are many causes of neutropenia. Of note, a higher number of people with BEN were in the intervention group.

While the study did comment in relation to reduced contact time with patients, it is not known if the extending monitoring had any impacts to the patient's health and wellbeing including other side effects of clozapine.

The study showed that in a selected group of people taking clozapine (i.e. people who are established on treatment for a number of years, have not experienced an abnormal haematological result, are adherent to treatment and reside in the community) changing to 12-weekly extended monitoring did not lead to an increase in haematological events or acute admissions for treatment of clozapine-induced severe neutropenia.

Further studies are needed in larger population groups and after shorter durations of clozapine treatment.

There are currently no studies that have assessed patient safety after any changes to monitoring requirements of clozapine that might have occurred during the COVID-19 pandemic in NZ following the consensus statement recommendations[1].

[1]Siskind D, Honer WG, Clark S, et al. 2020. Consensus statement on the use of clozapine during the COVID-19 pandemic. *J Psychiatry Neurosci* 45(3): 222-223. DOI: 10.1503/jpn.200061.

5.3 Monitoring thresholds

5.3.1 Relaxation of the criteria for entry to the UK Clozapine Central Non-Rechallenge Database: a modelling study – Oloyede et al, 2022 [56]

This was a modelling study of all patients registered on the UK Central Non-Rechallenge Database (CNRD).

The aim of the study was to investigate implementation of the USA FDA guidelines to clozapine users in the UK.

The study population included any patient registered on the UK CNRD on 1 March 2021. Under the recommendations this included patients who had 2 consecutive 'red' results (ANC < $1.5x10^9$/L and/or WBC <$3x10^9$/L). The FDA monitoring parameters were applied to these patients. The FDA criteria for clozapine interruption or discontinuation are defined as moderate neutropenia (ANC <$1x10^9$/L) or severe neutropenia (<$0.5x10^9$/L). If the patient in the CNRD had BEN, then the FDA BEN criteria was applied.

The study also looked at patients who had been rechallenged with clozapine after CNRD registration. The number of patients who had a further neutropenia meeting the database criteria following rechallenge was also documented. The FDA parameters were applied for these patients to determine if clozapine would have been discontinued under FDA guidelines. Successful rechallenge was defined as no recurrence of CNRD registration. Success rates between individuals who did meet the database criteria under the FDA monitoring criteria on first exposure and those who did not were compared.

Between 2 May 2002 and 1 March 2021, 3731 unique patients had been registered on the CNRD and were included in the study. Figure 19 outlines the study flow chart of cases in the CNRD.

Figure 19: Study outline flowchart

Information on demographics of the study population is outlined in Table 19. The mean age of the cohort was 47 years and 62% were male. The median WBC at CNRD registration was $2.9x10^9$/L (IQR 2.5 – 3.6) and ANC $1.4x10^9$/L (IQR 1.1- 1.5). A total of 9% (341) of patients on the CNRD had an episode of severe neutropenia at registration. The median time to CNRD registration for these patients was 3.4 months (IQR 2.0 – 35.7) from clozapine initiation compared with 23.5 months (IQR 3.6 – 65.6) for individuals with mild to moderate neutropenia. The median time to CNRD registration from clozapine initiation for all participants was 1.6 years (IQR 0.2 – 4.9).

Table 19: Sociodemographic and clinical characteristics of patients registered on the CNRD

Of the 3731 patients who had haematological events that qualified for CNRD registration and treatment discontinuation under the current MHRA guidelines, 566 (15%) of patients would have qualified for clozapine discontinuation under the FDA guidelines. A total of 470 (13%) of patients would have been able to continue clozapine with routine monitoring, 2096 (56%) patients would have been able to continue clozapine but would have required haematological monitoring 3 times a week and 599 (16%) patients would have required clozapine interruption with daily haematological monitoring.

Of the 519 patients who were rechallenged on clozapine after CNRD registration, 100 (19%) were placed back on the database following a rechallenge. Table 20 outlines the sociodemographic and clinical characteristics of patients who were rechallenged on clozapine.

Table 20: Sociodemographic and clinical characteristics of patients who were rechallenged on clozapine

In the study, 438/3731 patients were registered onto the CNRD solely because of low WBC, even when the ANC values were above the threshold to continue treatment. Under the revised FDA guidelines, these patients would not have discontinued clozapine because WBC is not assessed as neutrophils typically constitute about 50 – 70% of WBC and function as the first line defence against bacteria and other foreign organisms.

A total of 112/3731 patients were placed on the CNRD after recording at least 1 baseline red result. A red result at baseline cannot have been caused by clozapine treatment.

This study identified 519 patients who were rechallenged on clozapine following CRND registration. A total of 473 patients would have not previously had CNRD registration with the FDA monitoring criteria. An unknown proportion of these patients might have gone on to meet the FDA criteria, had they continued clozapine. Of the 519 patients rechallenged, 100 patients had to stop clozapine treatment due to recurrence of neutropenia. The success rates were broadly similar in patients who did not meet FDA monitoring criteria versus those who did (81% vs 78%). The authors assumed that patients with true CIN will progress to severe neutropenia and thus meet FDA criteria. In that case these results suggest that discontinuing clozapine treatment in an earlier stage would not have a substantial effect on the success rate of rechallenge but would lead to more patients discontinuing clozapine.

Patient selection for rechallenge might be influenced by clinical and demographic factors. In this study, patients who were rechallenged on clozapine were younger, less likely to be black, and had experienced CNRD registration later than those who were not rechallenged.

The authors comment how patients are typically only rechallenged after a comprehensive risk-benefit assessment in close liaison with a haematologist in an inpatient setting in which any potential deterioration in physical health can be promptly detected. This multidisciplinary approach could limit the generalisability of the rechallenge because patients deemed at high risk of developing neutropenia and potential neutropenia were not rechallenged.

Limitations of this study included insufficient data to whether clozapine-induced severe neutropenia was associated with any fatalities. The accurate recognition and diagnosis of clozapine-induced severe neutropenia might be complicated by other causative factors for neutropenia such as concomitant medication or viral infections. It is not known if patients had pre-existing conditions increasing the probability of neutropenia, including patients who were rechallenged. The data did not include information on concomitant medication use during rechallenge, so the effects of concomitant treatments, a known differential for suspected clozapine-induced neutropenia, cannot be determined.

Comments

This study similarly highlights how people experience different severities of neutropenia on clozapine. Interestingly, only 9% of patients who were in the CNRD had an episode of severe neutropenia at registration. The median time to CNRD registration for these patients was 3.4 months, a similar time to onset as noted for other reports of agranulocytosis with clozapine.

The authors highlight how clozapine is underused despite being a treatment of choice for TRS. Application of the FDA criteria to patients in the CNRD identified only 15% patients who would have stopped clozapine. They comment how the study shows the potential effect that revisions of clozapine haematological regulations can have on improving treatment access.

This study found that the median years of clozapine treatment to CNRD registration was 1.6 years. This contrasts with the reports that the risk of clozapine-induced neutropenia being highest at 6 – 18 weeks of treatment. Although, rare cases of late onset severe neutropenia are reported, the authors comment how it is highly likely that many cases of CNRD registration in the cohort were unrelated to clozapine use. This study did find that median time to CNRD registration for individuals with severe neutropenia at registration to be 3.4 months.

This study also highlighted how people who have low baseline WBC and/or ANC were registered with the CNRD, however, this could not have been related to clozapine treatment.

There does not appear to be any specific studies available reviewing the effects of the changes to the FDA clozapine monitoring requirements since 2015.

5.3.2 Benign ethnic neutropenia: an analysis of prevalence, timing and identification accuracy in two large inner-city NHS hospital – Oloyede et al, 2021 [13]

This was an observational, retrospective analysis of patients registered with CPMS in 2 large mental health trusts in the UK.

The objectives of the study were to establish certified BEN prevalence in current users of clozapine and explore the stage of treatment at which BEN was identified. An additional objective was to evaluate the extent of unrecognised BEN in the CNRD database.

The study sample was identified on 1 October 2020. A total of 2020 patients had been registered with the CPMS, of which 574 were black patients. There were 100 black patients who were currently monitored under the BEN criteria. From the 1446 non-black patients, 11 were monitored under the BEN criteria.

Table 21 includes the socio-demographic and clinical characteristics of patients registered with BEN.

Table 21: Socio-demographic and clinical characteristics of patents registered with BEN

Table 22 outlines and compares the treatment stage where BEN was identified for those currently under BEN criteria. A total of 52% of patients were identified with BEN only after a haematological abnormality was recorded and another 16% after CNRD registration. The median time to BEN registration from clozapine initiation was 1.0 (IQR 3.0) years.

Table 22: Treatment stage of BEN diagnosis

[redacted]

The CNRD database was screened for black patients who had not been monitored under BEN criteria prior to CNRD registration. Potential BEN were identified by haematologists. For those who were then classified as BEN, the BEN monitoring parameters were applied to previous haematological results to determine whether CNRD registration would have occurred, had they been certified as BEN initially.

A total of 84 patients were registered on the CNRD at data collection. Of these, 7 were monitored under BEN criteria. A total of 18/26 black patients had available haematological data for retrospective BEN classification, of which 8 cases were identified as BEN and 1 case was undetermined. For the 8 cases that were classified as BEN, none would have met the CNRD criteria if monitored under BEN criteria at clozapine initiation.

Figure 20 shows the distribution of mean ANC and WBC prior to clozapine initiating for patients categorised as BEN (n=8) and BEN excluded (n=9).

Figure 20: Histogram of mean baseline WBC and mean ANC for those categorised as BEN (n=8) and not BEN (n=9)

The authors discuss how despite BEN often being an incidental finding in routine clinical care, the findings from this study highlight the need for more definite and precise guidelines for screening of BEN in potential clozapine candidates. This is especially important considering that BEN identification can be complicated in some individuals by periods of ANC readings within the widely accepted reference range. In addition, the psychological impact of uncertainty experienced with clozapine interruption, continual monitoring and possible relapse cannot be overstated.

In the UK there are no consensus guidelines for when BEN should be investigated in potential clozapine candidates. The authors suggest that assessments should be initiated at first contact with mental health services to reduce the risk of premature treatment discontinuation if clozapine was later indicated.

Comments

UK clozapine monitoring protocols include a separate algorithm for monitoring patients with and without BEN.

It has been recognised that individuals from certain ethnic populations, who are otherwise healthy and not prone to repeated or severe infections, commonly demonstrate low ANC.

Timely identification of BEN could prevent avoidable clozapine discontinuation and improve clinical outcomes. This study found that some patients were prevented from using clozapine due to abnormal blood test results, which may have been related to unidentified BEN.

In New Zealand, monitoring recommendations do not provide separate BEN protocols. It is recommended that patients with BEN may be started on clozapine after the agreement of a haematologist. This may impact accessibility of clozapine for patients with BEN.

New Zealand is a multicultural society and further information related to a patients' ethnicity when starting clozapine and management of 'red' blood test results may need to be considered as part of the monitoring requirements.

5.4 Neutrophil patterns

Several authors have reviewed the pattern of neutrophils in CIA and CIN.

Figure 21 outlines a Kaplan-Meir curve from Mena et al (2019) analysis of clozapine users in Chile. The data suggests differences between the risk of different types of neutropenia across time. During this time in Chile the frequency of heamatological monitoring was weekly for 18-weeks then monthly [57].

The authors discuss how unlike moderate to severe neutropenia, mild neutropenia events did not cluster in the first year of exposure to clozapine. Mild neutropenia could not be established as a clear risk factor for a more severe level of neutropenia. The authors comment that these findings should encourage prescribers to restart clozapine in patients who have previously experienced mild neutropenia or allow new patients to be maintained on clozapine despite a mild lowering in the neutrophil count. In addition, the value of blood monitoring intervals of 4 weeks should be reconsidered because of the low probability of detecting true CIA, which develops over a period of 2 weeks or less [57].

Figure 21: Kaplan-Meier for the time of appear of different levels of neutropenia in clozapine users in Chile between 2003 and 2016

Source: Mena CI, Nachar RA, Crossley NA, et al. 2019. Clozapine-associated neutropenia in Latin America: incidence report of 5380 Chilean users. *Int Clin Psychopharmacol* 34(5): 257-263. DOI: 10.1097/yic.0000000000000270 (accessed 13 August 2024)

Taylor et al (2022) reviewed 9 events of life-threatening CIA. The authors highlight how the cases show that CIA is an all-or-nothing event, which is a rapidly emerging absence or near absence of circulating neutrophils. The authors argue that single episodes of reductions in neutrophil counts, even to ≤ $0.5x10^9$/L and officially registered as agranulocytosis are highly unlikely to be clozapine related or life-threatening. It does not seem likely that clozapine causes benign, non-progressive neutropenia. These episodes can be seen as a result of the intensive blood monitoring, which exposes naturally occurring low neutrophils which are likely seen in any population [16].

The authors discuss how it is highly likely that standard monitoring thresholds overestimate the proportion of patients who have true CIA. Many people are unnecessarily precluded from receiving clozapine because of an assumed clozapine-related blood toxicity. They conclude that clozapine-related blood toxicity should be identified on the basis of the temporal pattern of change of neutrophil counts and not arbitrary threshold neutrophil counts. [16].

Comments

It has been suggested that cases of neutropenia and agranulocytosis associated with clozapine are 2 different events. True CIA develops over a period of 2 weeks or less and is considered an all-or-nothing event.

Cases of mild neutropenia identified in people taking clozapine may be a result of frequent monitoring, rather than caused by clozapine.

Taylor et al (2024)[2] recently published a follow-up study, which examined additional cases of CIA. In the original study, 9/23 cases met the criteria for clozapine-induced, life-threatening agranulocytosis. Of the 13 remaining cases where data was available, 5 were probably caused by clozapine but were not life-threatening, 3 cases were the result of concomitant cancer therapy, 3 were anomalous results probably related to measurement error and in 2 cases the cause was not identified.

The authors comment how not all cases of agranulocytosis occurring in people taking clozapine are caused by clozapine. True clozapine-related agranulocytosis is best identified by pattern-based criteria. This includes a rapid fall in neutrophil counts over around 2 weeks to below $0.5x10^9$/L for 2 consecutive days where other possible causes can be ruled out.

5.4.1 Identifying clinically relevant agranulocytosis in people registered on the UK Clozapine Central Non-rechallenge Database: retrospective cohort study – Oloyede et al, 2024 [58]

This recently published retrospective cohort study in the UK aimed to examine the prevalence and timing of CIA using different diagnostic criteria and to explore demographic differences of CIA in patients registered in the UK CNRD.

Data used in this study was from the Clozaril Patient Monitoring Service CNRD (Viatris).

Individuals were diagnosed with CIA using 2 different methods:

1. At least 1 ANC < $0.5x10^9$/L (threshold-based agranulocytosis).
2. 2 consecutive ANC (over 2 or more days) < $0.5x10^9$/L (pattern-based agranulocytosis).

The number of people who were determined to have transient agranulocytosis was also recorded. Transient agranulocytosis was defined as a single ANC <$0.5x10^9$/L followed by subsequent ANC ≥$0.5x10^9$/L.

[2] Taylor D, Vallianatou K, Gandhi S, et al. 2024. Severe neutropenia unrelated to clozapine in patients receiving clozapine. *J Psychopharmacol* 38(7): 624-635. DOI: 10.1177/02698811241262767

Results

A total of 3029 individuals were registered on the CNRD. Table 23 outlines these individuals. There were 593 individuals determined to have threshold-based agranulocytosis, of these 348 had pattern-based agranulocytosis and 245 were determined to have transient agranulocytosis. A total of 2436 had mild to moderate neutropenia (neutropenia criteria).

Table 23: Sociodemographic and clinical characteristics of people registered on the CNRD

The prevalence of threshold-based agranulocytosis in the CNRD was 19.5% compared with 11.4% if using the pattern-based criterion (Table 24).

Table 24: Prevalence of agranulocytosis (threshold-based versus pattern based) in the CNRD sample

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

Most people transitioned from a normal ANC count to agranulocytosis with threshold based (73%) and pattern-based criteria (Table 25).

Table 25: Proportion of individuals that transitioned from neutropenia or a normal absolute neutrophil count to clozapine-induced agranulocytosis (threshold-based versus pattern-based) in the CRND sample

[redacted]

The median time to pattern-based agranulocytosis was 0.28 (IQR 3.25) years and 0.62 (IQR 3.52) years for threshold-based agranulocytosis. Overall, 43% of people recorded threshold-based agranulocytosis in the first 18 weeks of treatment and 53.16% of people recorded pattern-based agranulocytosis in the same time period. For threshold-based criteria, 55% of individuals recorded agranulocytosis at 1 year and 76% by 4 years. For pattern-based criteria, 58% of individuals recorded agranulocytosis at 1 year and 80% by 4 years.

Figure 22 displays the cumulative frequency of neutropenia and agranulocytosis stratified by threshold and pattern-based criteria for the whole cohort.

Figure 22: Cumulative frequency of haematological events (neutropenia, threshold-based and pattern-based agranulocytosis) in people registered on the CNRD

The heatmaps in Figure 23 present the prevalence of haematological events and median time in days to haematological event, stratified by ethnicity, gender and age quantiles.

Figure 23: Heatmaps (a) prevalence and (b) median time of different haematological events (neutropenia, threshold-based and pattern-based agranulocytosis) for different demographic groups

The authors discuss how this is the first study to evaluate how diagnostic criteria for agranulocytosis affect estimated prevalence rates of CIA. The authors found a difference in the prevalence when a pattern-based criterion for CIA was applied suggesting that the current haematological threshold model overestimates the incidence of CIA.

Consistent with previous studies, this study observed that a large proportion of agranulocytosis cases occurs within the first year, which was more pronounced using a pattern-based criterion. An unexpected finding in the study was the large proportion of people who recorded agranulocytosis after 2 years. However, the authors comment that they were unable to determine non-clozapine causes for these cases.

The authors also discuss how in this study 70% of people transitioned from a normal ANC to agranulocytosis without passing through neutropenia. This may highlight the utility of fortnightly and monthly monitoring to be able to identify agranulocytosis. The authors comment it could be possible that the remaining 30% of people were identified by weekly monitoring.

The authors also note how from the data, 1 in 10 people registered on the CNRD, there was a single event of an ANC count $<0.5x10^9$/L which is then following by prompt normalisation of the ANC.

Limitations of this study include that no data on the outcomes of the individuals with agranulocytosis was available and that information on comorbidities or other medicines was lacking. In addition, individuals who

recorded threshold and pattern-based agranulocytosis ceased clozapine at the initial instance of neutropenia. It was unable to be determined if clozapine cessation prevented some people from transitioning from threshold to pattern-based criteria.

Comments

This study highlighted how pattern-based definition of agranulocytosis may be more accurate that using threshold-based criteria and may lead to better outcomes through lower clozapine discontinuation rates.

The study also showed the prevalence of neutropenia in the CNRD to be higher than those with agranulocytosis (threshold and pattern-based criteria met).

An interesting finding in this study was that white ethnicity had the highest prevalence of agranulocytosis.

This study identified cases of agranulocytosis after 1 year. The authors note that they could not confirm if the agranulocytosis was caused by clozapine in these cases.

The study also showed how individuals who experience agranulocytosis may have normal ANC counts which then fall. This may emphasise that using monitoring of neutropenia as a warning system for agranulocytosis is important. However, monthly monitoring may not pick up cases of agranulocytosis because the time to onset is likely shorter than this.

5.5 Other medicine-induced agranulocytosis

5.5.1 Risk mitigation with the use of clozapine – Quo vadimus – Suhas et al, 2021 [59]

This paper discussed antithyroid medicines and clozapine in relation to agranulocytosis.

Antithyroid medicines are prescribed long term, and the mechanism of drug-induced agranulocytosis is considered similar, involving direct toxicity and immune-mediated destruction of neutrophils.

The prevalence of agranulocytosis associated with carbimazole has been estimated to be between 0.1% to 0.35%. Studies have documented the risk of agranulocytosis as highest during the first 90 days of treatment and decreasing after 1 year.

Clinical practice guidelines for the use of antithyroid medicines differ significantly to that of clozapine. The American and European Thyroid Association guidelines recommend educating the patient about warning signs of agranulocytosis, such as fever and pharyngitis, and stopping the medicine and seeking urgent medical advice in such cases. These guidelines do not recommend regular haematological monitoring but recommend a complete blood count in febrile illness or pharyngitis.

The authors comment that the rationale for these recommendations is that routine haematological monitoring is unlikely to identify early pre-symptomatic agranulocytosis because of the low incidence of the condition. In one study, 21% of patients who developed agranulocytosis on antithyroid medicines had a normal granulocyte count one week before onset and 53% had a normal granulocyte two weeks before starting treatment. Therefore, measuring the WBC count in patients developing febrile illness is considered a better approach.

The authors highlight that weekly monitoring for at least 18 weeks then fortnightly or monthly monitoring up to 1 year for clozapine treatment is still justified based on a significantly increased risk of haematological adverse events through this period.

Guidelines in oncology have developed risk stratification tools to manage patients with neutropenia which consider a patient's age, presence of co-morbidities and other factors. There is no evidence available to formulate a similar risk stratification system that would allow for a differential and flexible haematological monitoring for people on clozapine.

The authors conclude that a possible option is to have intensive haematological monitoring for the first year and then checking WBC and ANC in case of febrile illness or pharyngitis. This strategy may retain the existing monitoring regimen and improve the use of clozapine.

Comment

Other medicines in addition to clozapine are associated with agranulocytosis, however, are not subject to the same mandatory monitoring requirements.

Guidelines for antithyroid medicines include to perform a blood test if symptoms suggestive of agranulocytosis occur.

The population of people who take clozapine may have varying abilities to recognise symptoms of neutropenia or infection. An individualised approach to monitoring relative to symptom recognition may then be needed.

5.5.2 Long-term persistence of the risk of agranulocytosis with clozapine compared with other antipsychotics: a nationwide cohort and case–control study in Finland – Rubio et al 2024 [60]

Full article available in **Annex 6.**

This study investigated the risk of agranulocytosis associated with long-term treatment with clozapine and non-clozapine antipsychotics.

The primary outcome was the first diagnosis of agranulocytosis, from inpatient and outpatient specialised settings, as well as post-mortem, during the observation period from 1 January 1996 to 31 December 2017.

Secondary outcomes were fatal agranulocytosis (deaths within 30 days of agranulocytosis diagnosis) and recurrent agranulocytosis upon clozapine rechallenge.

The study population came from the Finnish Care Register for Health Care and the Prescription Register. The study included all individuals residing in Finland who were diagnosed with schizophrenia or schizoaffective disorder between 1 January 1972 and 31 December 2014 (n=61,850 (n=14,037 clozapine and n=50,283 non-clozapine antipsychotics). People who had experienced agranulocytosis before cohort entry were excluded (n=81).

Individuals whose first diagnosis of schizophrenia or schizoaffective disorder occurred during the observation period and who did not use antipsychotics during a year preceding the diagnosis were additionally classified as an incident cohort (n=8322).

Antipsychotic medicines were classified as clozapine and non-clozapine antipsychotics. Each exposure was treated as independent. Time was reset to 0 each time there was a change between non-clozapine and clozapine antipsychotic, there was an inpatient hospitalisation, or treatment was interrupted for more than 30 days. Switches between non-clozapine antipsychotics were treated as the same treatment episode. Each exposure was classified by its duration into categories.

Cases were defined as individuals with a diagnosis of agranulocytosis. Controls were drawn from the same base population matched by sex, age, years since diagnosis and belonging to the incident cohort with 5 controls per case.

Results

In the study population of 61,769 individuals who had not experienced agranulocytosis prior to being diagnosed with schizophrenia or schizoaffective disorder, the mean age was 46.67 years (IQR 34.44 – 57.61), and 49.7% were female. The median duration of uninterrupted antipsychotic treatment episodes was 398 days (IQR 95 – 1193) for clozapine and 579 days (IQR 151-1607) for non-clozapine. Across 22 years of follow-up,

398 cases of agranulocytosis were registered, this included 231 with clozapine treatment and 167 with non-clozapine antipsychotics.

The incidence of agranulocytosis was 17.33 events per 10,000 person years of clozapine treatment amongst 14,037 individuals using clozapine and 2.10 events per 10,000 person years of non-clozapine treatment among 47,732 individuals using non-clozapine antipsychotics.

The absolute cumulative incidence of agranulocytosis across the 22 years of observation was 1.37% (95% CI 0.58 – 3.16) on clozapine treatment and 0.13% (95% CI 0.04 – 0.23) on non-clozapine treatment (Figure 24).

Figure 24: Cumulative risk of agranulocytosis over time on treatment

In the nested-case control of 398 cases and 1987 controls, the risk of agranulocytosis with clozapine decreased over time (Table 26). The risk was persistently greater than for the reference condition (i.e., non-clozapine antipsychotic use for 12 – 23 months). For non-clozapine antipsychotic use, the first 6 months of treatment had greater risk of agranulocytosis than the reference condition.

Table 26: Nested case-control model and association between duration of treatment episode with clozapine and non-clozapine antipsychotics and agranulocytosis risk in individuals with schizophrenia

In addition to antipsychotic type and duration of treatment, other factors that were associated with greater risk of developing agranulocytosis were higher-than-standard antipsychotic dose, clozapine combined with a non-clozapine antipsychotic, co-treatment with a mood stabiliser, co-treatment with benzodiazepines, and co-morbid cardiovascular disease and cancer (Table 27).

Table 27: Association between treatment characteristics and the risk of agranulocytosis in individuals with schizophrenia

Of the 231 individuals who developed agranulocytosis with clozapine, 76 (33%) were rechallenged with a second trial of clozapine. Of those, 11 (14%) developed another agranulocytosis event.

From the 398 cases of agranulocytosis, 7 (2%) were fatal within 30 days of diagnosis (4 for clozapine and 3 for non-clozapine antipsychotics). The agranulocytosis fatality rate was 1.13 per 10,000 individuals exposed to antipsychotics, 2.81 per 10,000 individuals exposed to clozapine and 0.63 per 10,000 individuals exposed to non-clozapine antipsychotics.

In the sensitivity analysis for agranulocytosis that required hospitalisation (283 (71%) of 398 cases) the results were similar to in the main case-control model. For clozapine the aOR was 54.76 (95% CI 20.86 – 143.73) and for the non-clozapine group the aOR was 3.76 (95% CI 1.47 – 9.59). There was an elevated risk of agranulocytosis within the initial 6 months of treatment and while the risk decreased for the clozapine group, it remained persistently elevated throughout follow up (aOR 5.22 95% CI 1.78 – 15.25) for treatment duration 54 or more months, while for non-clozapine antipsychotics it became non-significant over follow up (0.68, 0.21 – 2.18).

The authors discuss that the results from this study can contribute to informing monitoring schedules for people on clozapine. More than half the agranulocytosis events in patients treated with clozapine occurred during the initial 6 months and the rest over the remaining 22 years. Notable risk decrements were observed when moving past the first year of treatment and then again moving past the third year. Following this risk trajectory, and being consistent in monitoring recommendations across various countries, the authors make the general recommendation of weekly monitoring for the first 6 months, followed by every other week between 6 -12 months, then monthly between years 1 – 3. After this time, the risk reduction might justify lifting the mandate on the monitoring.

This study showed that after 3 years, the risk is comparable to that of non-clozapine antipsychotics over the initial 6 months of treatment, which do not require mandatory monitoring.

Limitations of this study include that individuals on clozapine were systematically surveyed for agranulocytosis whereas those on other antipsychotics were not, which could have induced surveillance bias, overestimating the risk for clozapine. This possibility was thought to be unlikely since data suggest that less than 10% of agranulocytosis cases are asymptomatic.

Another limitation is that the association between risk factors and agranulocytosis might not be causal. The lower risk of agranulocytosis in individuals using neutropenia-inducing medicines most likely represents selection to avoid drug-induced agranulocytosis. For agranulocytosis events occurring immediately after antipsychotic initiation and before psychiatrist discharge, the antipsychotic exposure could not be determined. However, given the focus of the analyses on long-term risk this would have had minor effects on the implications of the results.

Comments:

This study found cases of agranulocytosis with people taking antipsychotics, particularly in the first 6 months of treatment. The prevalence of agranulocytosis with clozapine was higher than for non-clozapine antipsychotics. Results from this study suggest that other antipsychotics also can cause agranulocytosis. However, the risk may be higher with clozapine, particularly at the initial stages of treatment, and then be reduced but persist over time.

Rates of agranulocytosis in clozapine users versus people taking other antipsychotics should be interpreted cautiously noting regular haematological monitoring is required only for clozapine treatment. There may be underreporting of agranulocytosis in people taking other antipsychotics. If agranulocytosis were to occur though, it is likely that this may be symptomatic and require hospitalisation. The authors note how the sub analysis of cases needing medical hospitalisation were consistent with the main results.

Similar to other studies, most cases of agranulocytosis with clozapine occurred within 6 months of treatment. However, late onset agranulocytosis was identified. The confidence intervals for the risk of developing agranulocytosis with clozapine over time since initiation were noted to be wide.

This study focused on agranulocytosis. There may be a subgroup of patients on clozapine who experience neutropenia and stop clozapine, who would not have been included in this study. A limitation of this study is that no information was provided about ANC.

5.6 Point of care testing

Atkins et al (2023) investigated the utility of a POCT finger prick method for clozapine patients. In this study, 226 patients who were under treatment with clozapine, and having venous blood samples, also provided a finger prick capillary blood sample. The PixCell HemoScreen POCT analyser was used to test both the capillary and venous samples, and the venous sample was also tested using a standard laboratory method [61].

The study found strong correlations between the result from the standard venous methods and the PCOT capillary and venous assays for WBC and neutrophils and eosinophils [60].

The authors comment how the PixCell HemoScreen POCT analyser provided results that were comparable with those from a standard venous blood laboratory method for WBC, neutrophil and eosinophil counts. The availability of an accurate capillary monitoring method may result in increased clozapine uptake and better adherence [61].

Comments

Overseas, point of care testing devices have been used for blood tests relating to clozapine haematological monitoring. It appears that such devices are used in parts of the UK and in Canada.

Use of a point of care device could help improve tolerability and ease of blood testing for clozapine, as well as reporting of faster blood test results. Testing could be done in pharmacies similar to point of care testing with warfarin monitoring.

5.7 Other clozapine side effects

In addition to CIA, clozapine is associated with other serious side effects including cardiac, metabolic, gastro-intestinal, and neurological events, which can also be life-threatening [62].

Clozapine is associated with increase in weight, total cholesterol, triglycerides, and glucose levels. Patients can expect to gain >10% of their body weight in the first year of treatment. Almost half of people on clozapine develop diabetes [62].

Myocarditis is an early onset adverse event, with most events occurring in the first 6 weeks. Myocarditis can be fatal and early detection is key to its management. Cardiomyopathy, in contrast to myocarditis, develops less acutely [62].

Clozapine-induced constipation is the leading cause of clozapine-related death. Colonic transit times may slow to over four-times longer than the general population and lead to paralytic ileus, ischemia, breakdown of bowel mucosa and sepsis [62].

Clozapine is associated with an increased risk of pneumonia. Sedation, aspiration due to sialorrhea, and confounding factors such as severe psychiatric illness, higher rates of smoking and obesity, low rates of vaccination, and high rates of viral illness may contribute [62].

An observational, retrospective, pharmacovigilance study using VigiBase (World Health Organisation global database of individual case safety reports) reviewed clozapine adverse drug reactions (ADRs) and their fatal outcomes. On 15 January 2023, there were a total of 191,557 clozapine ADRs with 22,956 fatal outcomes [63].

Table 28 shows the most frequently reported potential clozapine ADRs and their fatal outcomes [63].

Table 28: Most frequent VigiAccess-reported potential ADRs associated with clozapine use (n=191,557 as of 15 January 2023) and reported fata outcomes (22,956 as of 15 January 2023)

[redacted]

:

Comparing the top four reporting countries (US, UK, Canada and Australia). *Schizophrenia Research* 268: 165-174. DOI: https://doi.org/10.1016/j.schres.2023.05.004 (accessed 13 August 2024)

Comments

Whilst haematological adverse reactions are commonly associated with clozapine treatment, there are a number of other serious adverse reactions that may be caused by clozapine. Compared with other side effects of clozapine, CIA monitoring is mandatory. The number of reports of neutropenia and leukopenia is higher than other ADRs in Vigibase likely due to these ADRs being identified through routine monitoring.

It is important that all side effects of clozapine are closely monitored, diagnosed and treated. A high number of fatal cases relating to pneumonia and myocardial infarction was identified by spontaneous reporting. Clozapine can also cause severe gastrointestinal side effects such as a bowel obstruction. This side effect may be prevented through monitoring and treating constipation. It has been proposed that regular interaction of health services as a result of the mandatory haematological monitoring requirements of clozapine users may aid in the monitoring of all clozapine side effects and early intervention for management.

5.8 Clozapine experiences relating to haematological monitoring

Risk of CIA and associated haematological monitoring requirements of clozapine is often cited as a barrier for clozapine use [64].

A survey by Oloyede et al (2023), found that out of 123 clinicians, 38% responded that clozapine was 'adequately prescribed', 37% of clinicians responded that clozapine was 'under prescribed', 2.3% felt that it is 'over prescribed' and a further 23% of respondents were 'unclear'. The most important perceived barrier was

'patient concerns with side effects', followed by 'monitoring requirements' and 'clinician concerns with side effects' [64].

There were 3 major themes identified regarding perceived barriers to clozapine use. The most frequently mentioned theme was administrative barriers (41%), with the sub themes of blood monitoring, clozapine initiation, patient information, resources and treatment plans. The second most common theme was patient related barriers (39%), with the subthemes of adherence, blood monitoring, family and carer attitudes, side effects and stigmas. For clinician related barriers (20%), the subthemes were clinician attitudes, formulation, prescriber confidence, side effects, treatment pathway and treatment resistant psychosis identification [64].

Taylor et al (2000) undertook a survey for clozapine users in the UK. A total of 570 people took part in the survey. Respondents were mostly men (63.3%) and Caucasian (89.5%). The age of respondents ranged between 18- 65 years of age, with the majority between 25 – 44 years of age. Most respondents had been taking clozapine for 2 years or more [65].

A total of 202/570 respondents cited 'feeling better' as something they liked about clozapine. A similar question asked what they did not like about clozapine. Blood tests were most often cited (24.2%), followed by drowsiness (13.0%) and increased salivation (9.8%). A total of 87% of participants felt that the advantages of clozapine outweighed the disadvantages [65].

Participants were asked for their views on regular blood testing. A total of 64% claimed to feel that 'they're okay – a necessary part of treatment, and a further 4.7% claimed to 'look forward' to blood tests. There were 28.2% of participants that claimed they 'did not like blood tests much' or 'at all/ and a further 1.6% said that blood tests made them want to stop taking clozapine [65].

Another study by Oloyede et al (2023), reviewed experiences of 4 patients and 4 related carers who previously experienced a 'red' result while being treated with clozapine [66].

Abnormal haematological reactions with clozapine were associated with feelings of worry, uncertainty, anxiety and service abandonment. For carers, the sense of being neglected by services and being left in the dark about what was likely to occur in their relative's health and about any mitigation plan and/or solutions were particularly highlighted [66].

Patients and carers experienced elevated levels of distress and adjustment difficulties and described the process that followed neutropenia notification as traumatic. They felt unsupported and not adequately informed about the potential consequences of recording neutropenia with clozapine treatment. Patients and caregivers expressed a lack of contingency and prevention planning, despite the potential prognostic impact of clozapine discontinuation and the role that information was likely to have in reducing levels of anxiety and uncertainty [66].

Analysis of responses suggested that CPMS prioritises physical health over mental health. The impact of sudden cessation of clozapine should be considered when stopping clozapine. Providing psychosocial support for patients and carers is crucial. The authors discuss how clozapine discontinuation after a suspected abnormal haematological blood test results should not be automatic but rather should prompt clinicians to investigate differential causes of neutropenia such as viral infections, concomitant medicines or BEN [66].

Comments

Clozapine side effects and monitoring requirements, particularly haematological monitoring, have been cited as barriers for clozapine use.

Some patients who take clozapine may not like having blood tests, which may impact their adherence to treatment.

A study highlighted patients and caregiver's concerns and experiences relating to having a red blood test result and processes around this, including the impact of sudden cessation of clozapine.

5.9 Changes to monitoring requirements

5.9.1 Time for a change to clozapine haematological monitoring – Cheng et al, 2024 [67]

Table 29 below summaries comments discussed in a recently published opinion article about clozapine and haematological monitoring requirements in Australia as well as possible changes.

Table 29: Summary of opinions relating to clozapine and haematological monitoring requirements

Topic	Comments about current clozapine haematological monitoring requirements
Possible changes to monitoring requirements	
White blood cell (WBC) counts	Remove requirement for monitoring of WBC (similar to FDA clozapine monitoring requirements)
Absolute neutrophil count (ANC)	Reduction in the ANC threshold for cessation of clozapine (similar to FDA clozapine monitoring requirements)
Frequency of monitoring	Reduce frequency of monitoring or remove mandatory monitoring after 2 years
Clozapine rechallenge	Allow patients with severe neutropenia to undergo clozapine rechallenge (similar to FDA clozapine monitoring requirements)
Benign Ethnic Neutropenia (BEN)	New eligibility criteria for BEN (similar to FDA clozapine monitoring requirements)

The authors suggest that changes to Australian clozapine monitoring requirements should occur in stages overtime. Firstly, modification of current guidelines to introduce lower ANC threshold for cessation of clozapine for patients with BEN. Secondly, either reduce the frequency of monitoring or remove mandatory haematological monitoring after 2 years.

The authors suggest non-mandatory annual blood test monitoring which is recommended for all antipsychotic medicines by RANZCP guidelines.

Comments

There has been recent literature calling for change with clozapine monitoring requirements around the world, including consistency across different countries that reflects updated evidence available.

A common theme among authors who propose changes include reducing the frequency of monitoring and changing thresholds for clozapine cessation.

5.9.2 Pros and cons of changes to monitoring requirements

Information from articles which have discussed changes to clozapine monitoring requirements in terms of pros and cons are summarised in Table 30.

Table 30: Pros and cons of intensive versus relaxed monitoring of clozapine

	Intensive monitoring of clozapine	Relaxed monitoring of clozapine
Pros	• Early detection of agranulocytosis and prompt investigations • Detect other clozapine adverse effects more frequently if monitoring is associated with a consultation • Regular interaction with services may improve the patient's quality of life through familiar social interactions • Early detection of non-adherence during assessments from routine visits • May lead to the identification of those who are at more risk of developing agranulocytosis	• May reduce the fear of clozapine in both doctors, caregivers and patients • More cost-effective from both patients and health care providers perspectives • May improve compliance due to cost-effectiveness • Allow increased resources in mental health • Increase in clozapine use • Safety evidence points towards the feasibility of relaxed monitoring and that almost all cases of CIA occur within the first year • The characteristic rapid and catastrophic decrease in neutrophil count during CIA makes it unlikely that twice or monthly monitoring would be sufficient to identify such reactions • Haematological monitoring for clozapine varies in different countries
Cons	• Financial, logistical burden increases (directly and indirectly) for the patients family and healthcare providers • Adverse effects related fears in the patients, their caregivers and the doctors lead to underutilisation of clozapine • Withholding clozapine for TRS and using other antipsychotics lead to increased morbidity/mortality. This includes ethical dilemmas • Clozapine may be the only treatment option compared with other antipsychotics • Regular blood tests can still not differentiate between benign neutropenia and fatal agranulocytosis	• Potentially overlooks severe and fatal adverse effects and reduce the treatment window to intervene in agranulocytosis • Decreased need for monitoring may reduce compliance • Self-monitoring of symptoms may not be feasible by the patient or the caregivers • Neutropenia will not become clinically obvious since symptomatic infections usually only occur with low ANC counts • Who chooses whether to be monitored intensively or not (patients still be given an option to be monitored intensively) • Ethical and legal issues if guidelines support intensive monitoring

Source: Adapted from the following articles:

- Cheng A, Buten S and Large M. Time for a change to clozapine haematological monitoring. *Australasian Psychiatry* 0(0): 10398562241258764. DOI: 10.1177/10398562241258764 (accessed 13 August 2024).
- Oloyede E, Blackman G, Whiskey E, et al. 2022. Clozapine haematological monitoring for neutropenia: a global perspective. *Epidemiol Psychiatr Sci* 31: e83. DOI: 10.1017/s204579602200066x (accessed 7 August 2024)
- Suhas S, Jolly AJ, Nayok SB, et al. 2021. Risk mitigation with the use of clozapine - Quo vadimus. *Asian J Psychiatr* 61: 102693. DOI: 10.1016/j.ajp.2021.102693 (accessed 13 August 2024)

6 OTHER SOURCES OF INFORMATION

6.1 Clozapine Consultation 2023

6.1.1 Background

From 7 August 2023 to 6 October 2023, Medsafe welcomed participants to take part in an online voluntary survey/consultation about clozapine.

This was carried out to gather information and understanding about people's real-life experiences with clozapine in NZ to inform the MARC's review of clozapine safety and monitoring requirements.

The responses to the consultation have been summarised in the Clozapine Consultation 2023 report, which is provided in **Annex 7**. The report is also published on the Medsafe website.

1.1.2 Summary

Comments
Medsafe received a small number of responses from people who take clozapine compared to healthcare professional responses.
Not all people taking clozapine and healthcare professionals took part in the consultation. Therefore, information about the experiences of clozapine represents those that took part only.
This section focuses on haematological monitoring only.
The Clozapine Consultation 2023 asked questions about clozapine use and side effects, and participants also provided more information and feedback. Please refer to the full report for more information.

6.1.1.1 Summary of participants

The majority of responses came from healthcare professionals (160/187). A higher number of responses were from medical doctors, followed by nurses, pharmacists and other healthcare professionals. Experiences of healthcare professionals working in diverse roles in both hospital and community care was gathered, including healthcare professionals with expertise within mental health.

Despite only a small number of responses from individuals who take clozapine (11/187), 4/11 reported their ethnicity as Māori.

6.1.1.2 Consumer experiences

Respondents talk to different people about side effects of clozapine.

Whānau, family and/or caregivers may be an important source of information about side effects that the person taking clozapine may experience.

Approximately one third of participants said that they would tell someone about an infection, and around 40% about a high temperature or feeling unwell.

Most respondents had blood tests for clozapine every 4 weeks.

Most respondents said that they have not had to stop or interrupt clozapine treatment due to a blood test result. However, some respondents mentioned that they have had increased monitoring on occasions.

Respondents were asked if they experience any difficulties in getting a regular blood test, of which nearly 20% of respondents answered 'yes'.

Nearly half of respondents said that they would not like to make any changes to the blood testing requirements for clozapine. However, around 35% of respondents answered 'I am not sure' or did not provide an answer.

Several respondents mentioned that they experience difficulties getting a regular blood test.

Transportation was listed as an issue for one respondent, whereas being able to get the test on the right day was difficult for another. Another respondent suggested that it would be helpful to get blood tests at home. Finding veins for the blood test was mentioned by another respondent.

A response discussed issues with blood test request form not being sent to the lab in time. The respondent provided information about experiences of a family member and how stressful and impactful this situation was both for them and the person who takes clozapine.

In contrast, one respondent mentioned that their family member organises their blood test themselves and has a positive experience with getting blood tests. Another response mentioned the security of knowing the blood test results.

There was concern about long term effects of regular blood tests and damage to veins.

From 17 respondents who selected either 'yes' or 'no' when asked would they like to make any changes to the blood testing requirements. A total of 4/17 selected 'yes' and 13/17 selected 'no'.

6.1.1.3 Healthcare professional experiences

More than 50% of healthcare respondents selected Clozapine Patient Monitoring Services provided by pharmaceutical companies as a resource to find out information about clozapine.

How much the healthcare professionals enquired about side effects depended on the stage of clozapine treatment, the individual's clozapine management and the healthcare professional's role.

Clozapine side effects were mostly identified through asking patients directly and routine monitoring.

Less than 10% of healthcare professionals responded that their patients have had to interrupt or discontinue clozapine due to blood test results.

Some respondents commented that agranulocytosis has not happened to patients under their care.

Information provided by responses found that agranulocytosis was more likely to be identified via a routine blood test compared to signs or symptoms that may be indicative of neutropenia resulting in an additional test.

Many respondents provided information on their experience about the benefits and challenges around the mandatory haematological testing.

Benefits included in response were grouped into themes. A summary of the themes relating to the challenges of the mandatory haematological testing is outlined in Table 31.

Table 31: Challenges of mandatory haematological testing of clozapine

Theme identified	Summary of comments
Requirement of ongoing testing	• ongoing haematological monitoring after 1 year with clozapine is a burden for patients and healthcare professionals • discourages clozapine use • recent study reviewed less frequent monitoring • updated thresholds for blood counts have caused unnecessary treatment interruptions and inappropriate cessation of clozapine treatment
Impacts to patients	• regular blood tests are disruptive to people's lives, especially if they live in rural areas or travel • difficulties in accessing lab for blood tests • cost • do not like having blood tests and may refuse a blood test • discontinued clozapine due to difficulties with haematological monitoring
Blood tests	• delays in blood test results, impact to dispensing and follow-up of results (particularly if abnormal) • blood test results not available or not copied to clozapine patient monitoring system and difficulties in finding the results • difficulties in blood test being taken on the correct day or when taken close to weekends • delayed alerts from clozapine patient monitoring systems • issues with collecting suitable blood samples • haematologist input required for abnormal blood test results
Clozapine patient monitoring system	• inflexibility of clozapine patient monitoring systems; clozapine interrupted due to a one off 'red' blood test, timeframes between blood test dates and dispensing dates • communication issues • new user registrations difficulties • slow transfer of patients between systems • use of an overseas based monitoring system
Activities associated with testing requirements	• lack of coordination between services • communication difficulties • increases in workload
Awareness of monitoring requirements	• lack of understanding of the importance of timely blood tests
Nurse practitioners	• restrictions on nurse practitioners being able to commence clozapine is a major barrier
Recognition of other side effects	• importance of other side effects of clozapine such as constipation, cardiac events and seizures

Participants were asked how the current haematological testing requirements for clozapine could be improved. Some people said that they did not feel any changes to the testing requirements for clozapine are needed.

Suggestions for improvements in responses have been summarised and grouped into themes in Table 32 below.

Table 32: Suggested improvements of the current testing requirements for clozapine

Themes identified	Summary of comments
Frequency of haematological testing	• reduce frequency • provide greater flexibility
Thresholds of blood counts	• return to higher white blood cell counts and neutrophils counts post 18 weeks of treatment (pre 2020 requirements)
Testing methods	• point of care testing at pharmacies • home blood tests • access to phlebotomists onsite
Management of blood tests	• guidance to haematologists • access to haematologists specialising in clozapine • use of clinical judgement
Blood test results	• faster reporting including availability in clozapine patient monitoring systems
Follow-up of blood test results	• same day follow-up • faster reporting of overdue blood tests
Reminders about blood test	• text reminders
Responsibility for follow-up of blood tests	• clarification of who is responsible
Blood test date and dispensing	• extend time period between blood test date and dispensing date
Clozapine patient monitoring system	• register patient prior to having a blood test • one monitoring system • New Zealand based system • increased flexibility within system • nurse practitioners as lead clinician in system
Education and awareness	• increased education and awareness • communication between services • alerts on medical records
Extending testing parameters	• myocarditis • metabolic screening

Comments

The Clozapine Consultation 2023 provided insight into people's experiences with clozapine in NZ.

Some of the challenges and improvements relating to haematological monitoring included in some responses were similar to that of information identified in the literature section.

6.2 New Zealand Case Reports

This section provides further information about individual case safety reports (ISCRs) that have been reported to Centre for Adverse Reactions Monitoring (CARM) and Medsafe with clozapine.

6.2.1 Overview of all clozapine reports

Between 1991 and 8 July 2024, CARM and Medsafe have received 2,606 reports where clozapine was reported as a suspect medicine. From these reports, 2,098 were reported as serious.

6.2.1.1 Demographics

From the 2,606 reports, 64.5% were in males, 35.1% in females and 0.42% other.

[redacted]

6.2.2 Clozapine and haematological adverse reaction reports

[redacted]

6.2.2.1 Neutropenia

Neutropenia was the [redacted] reported adverse reaction from SOC 'blood and lymphatic disorders'.

CARM/Medsafe have received 316 reports of neutropenia and clozapine (suspect medicine). From these cases, 242 were serious. Some cases also reported agranulocytosis, in addition to neutropenia. Table 34 outlines a summary of cases reporting 'neutropenia'.

Table 34: Summary of cases of reporting 'neutropenia' and clozapine reported to CARM/Medsafe (as of 8 July 2024)

Sub-group	Number (n=316)
Gender	
Male	201
Female	114
Other	1
[redacted]	

Comments

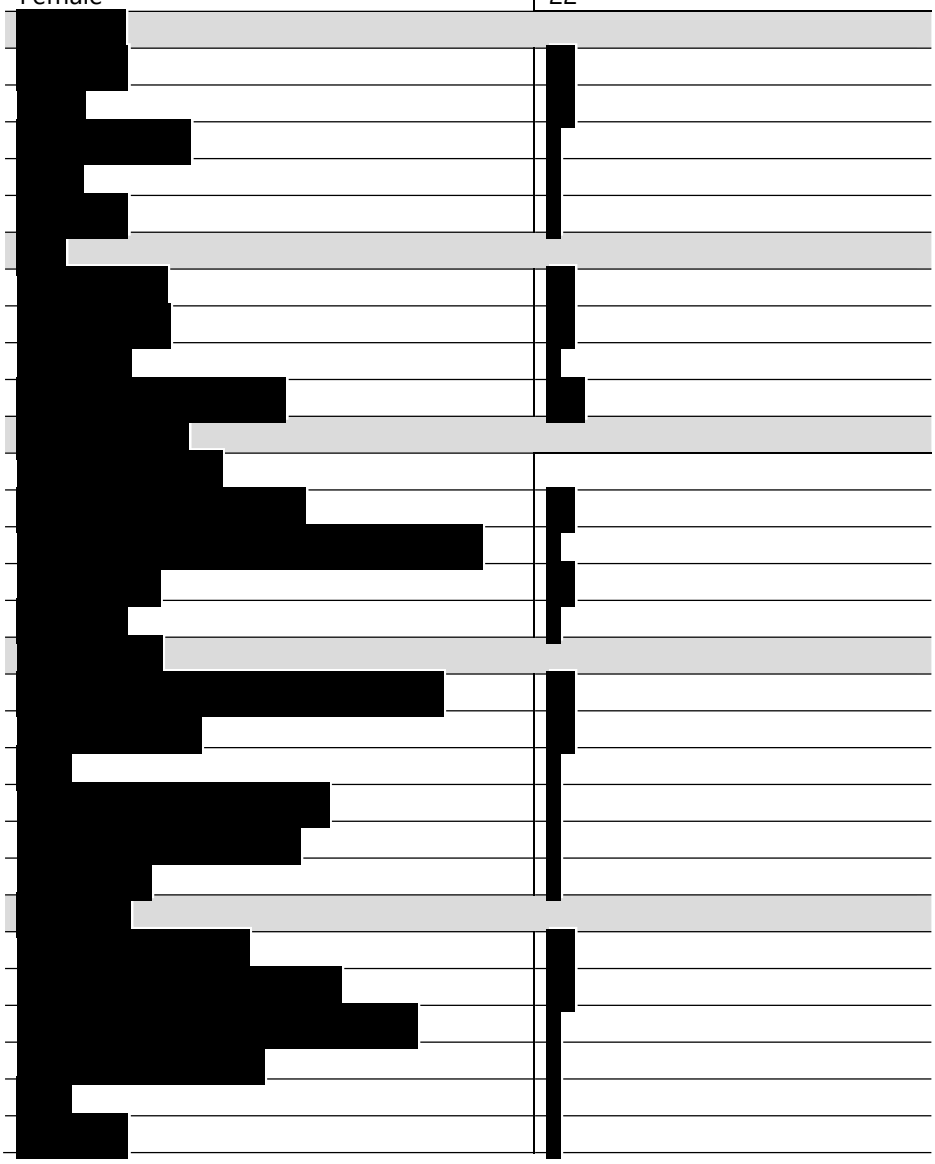
Medsafe and CARM have received a number of cases where neutropenia was reported in association with clozapine. It is noted that there was a wide range of onset times on review of these cases.

6.2.2.2 Agranulocytosis

A total of 46 agranulocytosis cases associated with clozapine have been reported to CARM/Medsafe. **Annex 8** provides a line listing of these cases. Table 35 outlines a summary of information from these cases.

Table 35: Summary of cases of reporting 'agranulocytosis' and clozapine reported to CARM/Medsafe (as of 8 July 2024)

Sub-group	Number (n = 46)
Gender	
Male	24
Female	22



Medicines co-reported that also are associated with agranulocytosis (as per data sheet) included trimethoprim (2), trimethoprim and sulfamethoxazole (1), sodium valproate (5), carbamazepine (1), tranylcypromine (1), amoxicillin and clavulanic acid (1), temazepam (1), quinapril (1), gliclazide (2), pantoprazole (1), haloperidol (1), venlafaxine (1), zuclopenthixol (1), azathioprine (1), tacrolimus (1), allopurinol (1).

In addition to reporting agranulocytosis, some cases had co-reported adverse reactions. Several cases reported infection related reactions. A total of 3 cases reported malignancy including [redacted]

In 3 cases, the outcome for agranulocytosis was reported [redacted] Co-concomitant medicines were reported (temazepam and venlafaxine) in [redacted] of those cases.

Comments

CARM/Medsafe have received 46 cases of agranulocytosis associated with clozapine since 1991, [redacted]

Where information on time to onset was available, [redacted]

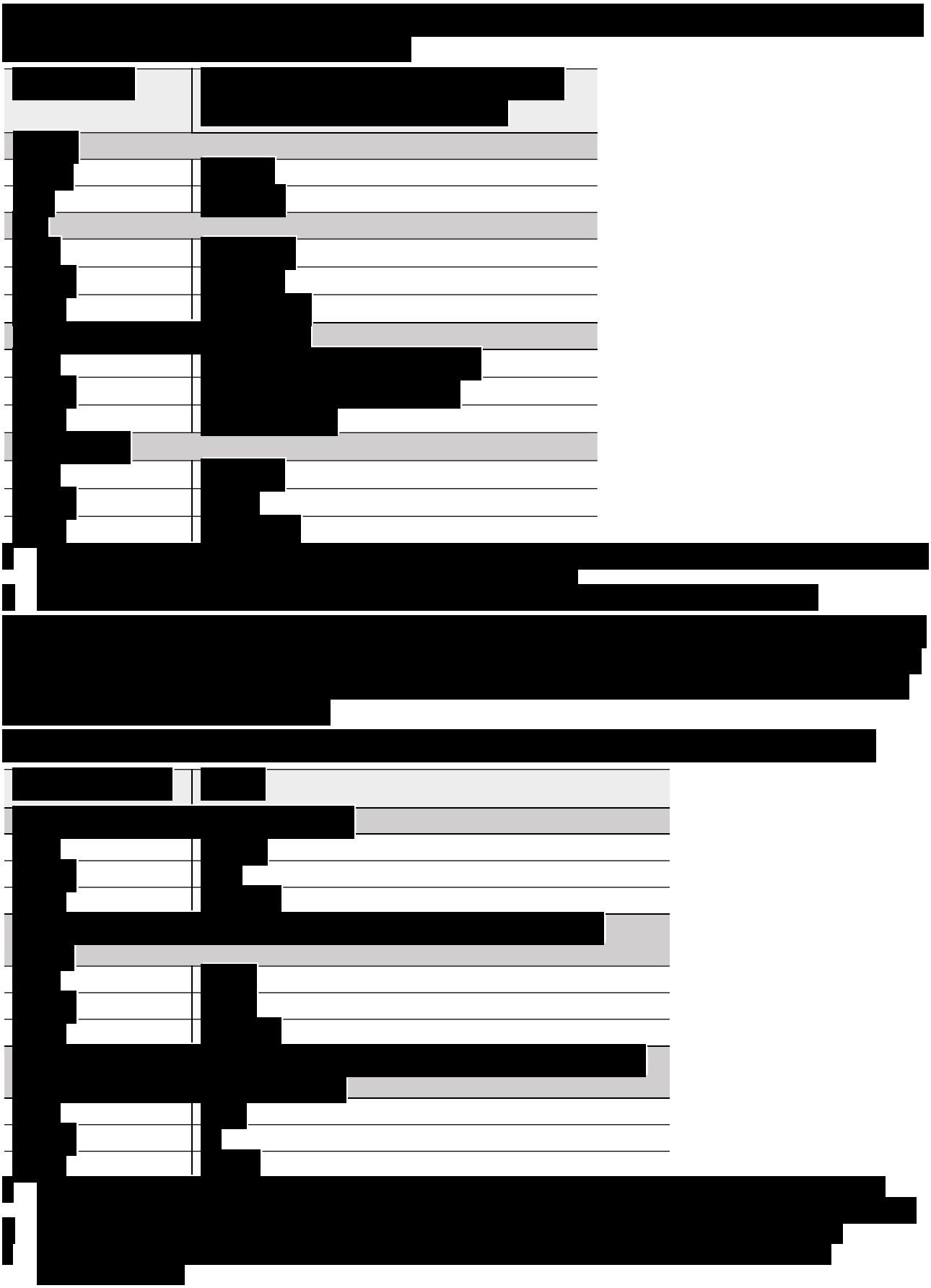
Some reports included co-reported medicines that also are associated with agranulocytosis.

The cases include limited information, which makes it hard to further understand these reports

6.3 Company data

[redacted]

[redacted]



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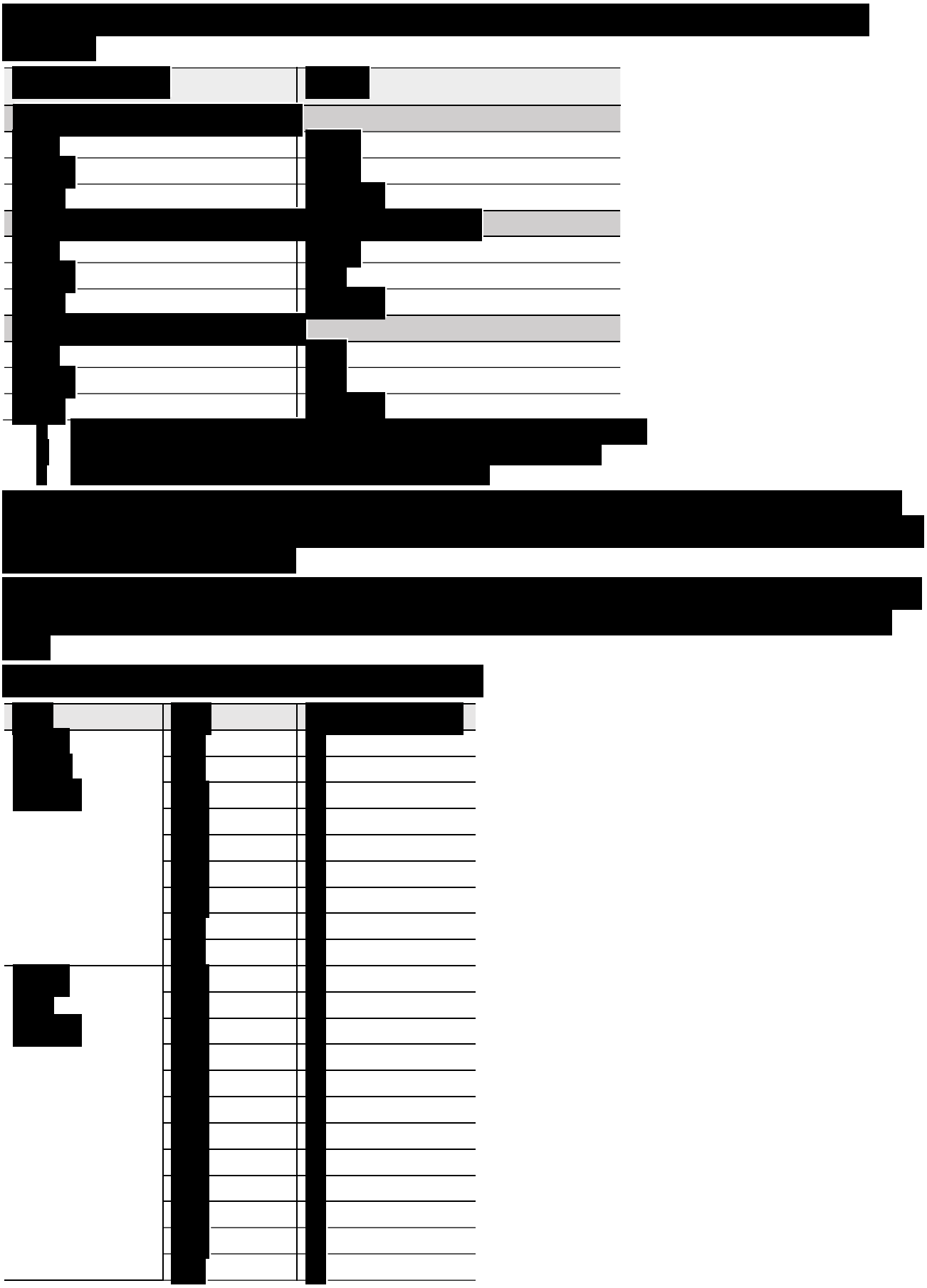

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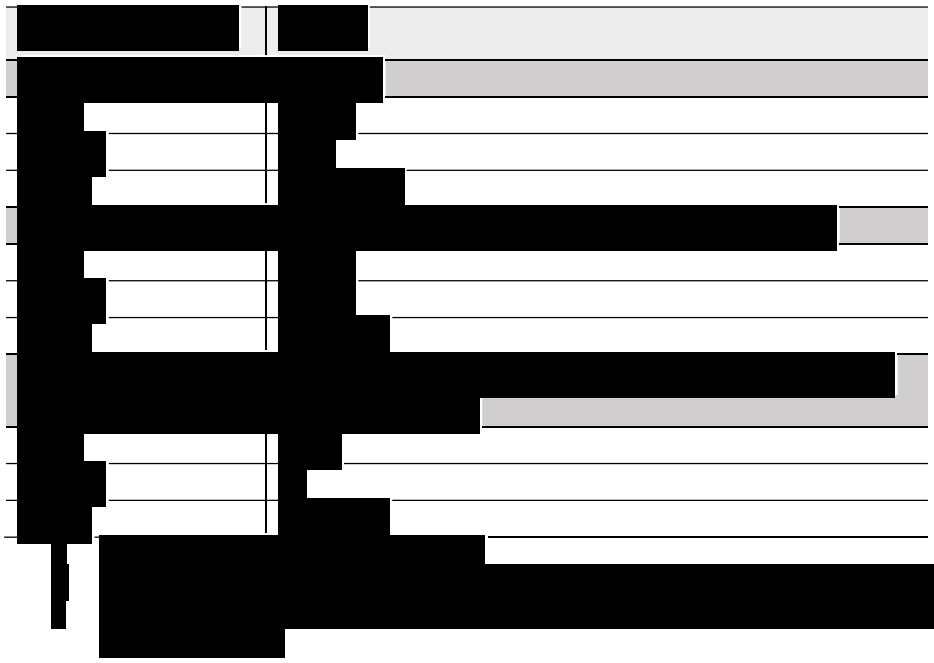

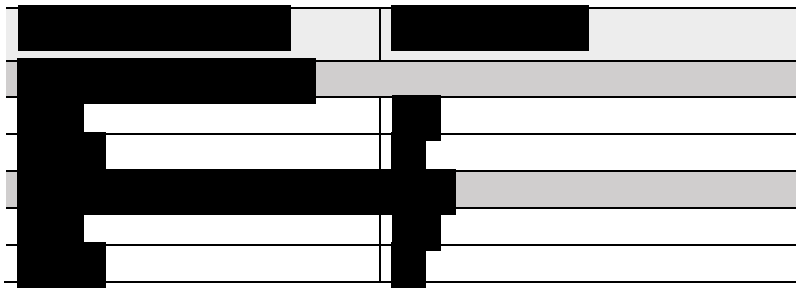

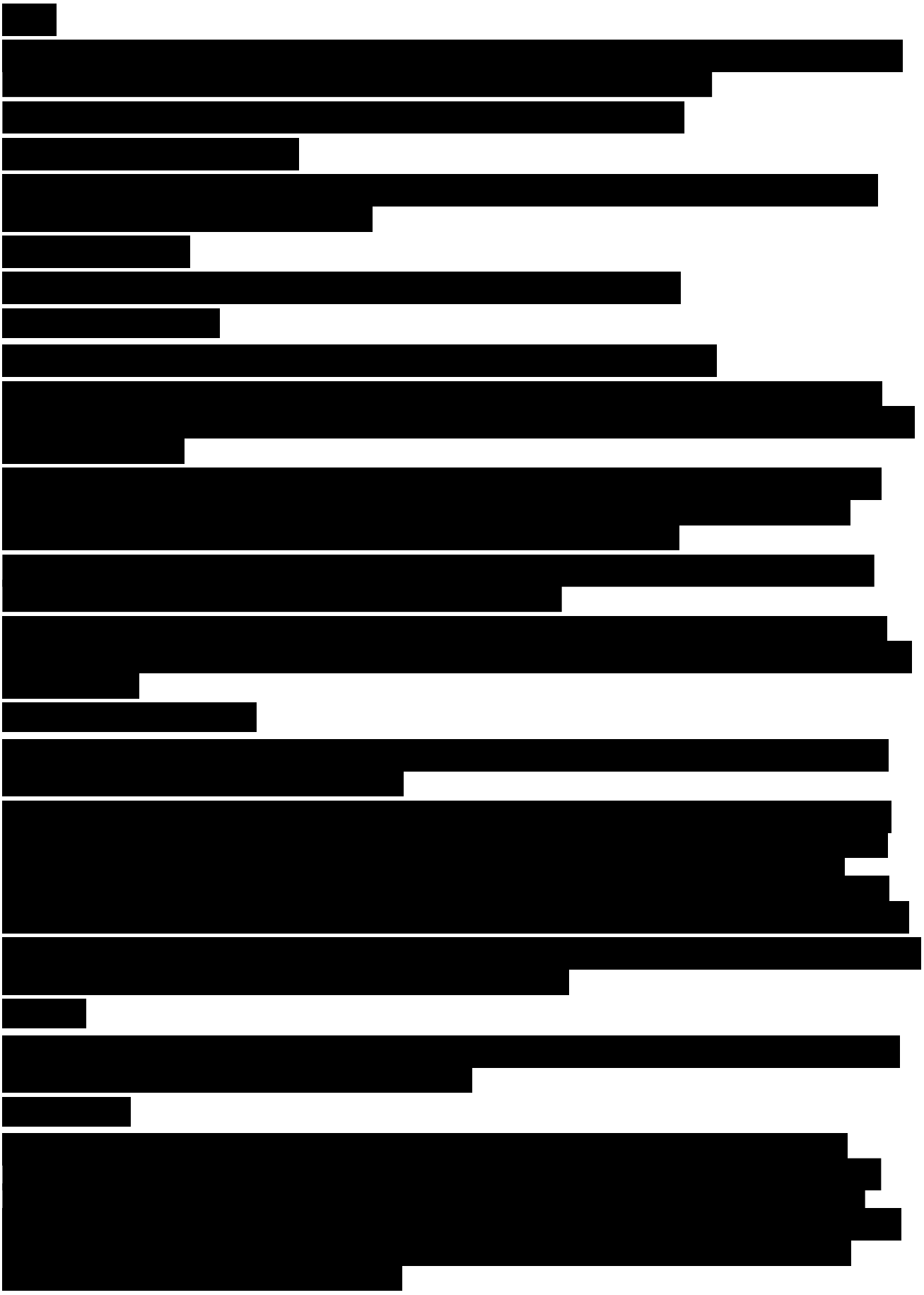

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6.4 Hospitalisation data (agranulocytosis)

Medsafe requested information on hospitalisation data for clozapine and agranulocytosis from the National Minimum Dataset, Te Whatu Ora.

The data was extracted on 17 January 2024. The available data includes the number of people who were dispensed clozapine between 2018 and 2002, had a publicly funded hospitalisation period involving the ICD code for agranulocytosis (D70) and a discharge date between 2018 and 2022.

Table 45 outlines number of people per year of discharge.

[redacted]

Comments

[redacted]

There are many limitations in the data. For example, it is not known if the agranulocytosis was caused by clozapine, other medicines or medical condition present, nor the stage of clozapine treatment.

[redacted]

7 DISCUSSION AND CONCLUSIONS

Clozapine is the treatment of choice for TRS. Unlike other antipsychotics, mandatory haematological monitoring is required throughout treatment in NZ and in many different countries.

Recent literature has questioned current monitoring requirements and whether these align with information available relating to the risk of agranulocytosis with clozapine. Mandatory clozapine haematological monitoring requirements worldwide have been cited as a barrier to clozapine use. Recent literature articles have reviewed possible changes to help both patients and healthcare providers utilise clozapine, an effective medicine for TRS, while minimising the burden relating to haematologic monitoring requirements.

Many aspects of the haematological monitoring requirements for clozapine have been highlighted throughout this report.

A summary of themes that have been identified are outlined below.

Agranulocytosis with clozapine

CIA is an idiosyncratic, dose-independent drug reaction. Reviews of cases of agranulocytosis reported in people taking clozapine have highlighted that the majority of cases occur within the initial stages of treatment.

Cases of agranulocytosis have been reported after 1 year of clozapine, but the prevalence of such cases is reported to be less compared to prevalence in the first 18 weeks. The number of people who experienced agranulocytosis generally decreased over time also in studies that assessed the frequency.

People who experience agranulocytosis (or any neutropenia) with clozapine are removed from CPMS. Many of the studies which review frequency of these events use data from CPMS.

Agranulocytosis is considered to be an all or nothing event with a progressive drop to low ANC counts, which is sustained with accompanying symptoms. Examining the pattern of neutrophil count changes may be an important measure in confirmation of CIA.

In cases of agranulocytosis, neutropenia has been detected, which then progressed to agranulocytosis. It is currently impossible to predict who will experience CIA with clozapine.

Use of CPMS and mandatory haematological requirements has shown a reduction in the risk of mortality associated with CIA compared to before these processes where in place.

People who experience neutropenia during the initial stages of treatment, where there is no other definitive cause, such cases may be more likely attributable to CIA and appropriate action for management should therefore be taken due to the seriousness of the agranulocytosis event.

The causality of late onset agranulocytosis with clozapine may be more uncertain, compared to people who experienced agranulocytosis during the initial stages of treatment.

Neutropenia with clozapine

Mild and moderate neutropenia events were found to be more common on clozapine treatment than agranulocytosis. This was also noted on review of company data, where a large number of individuals experienced a single red blood test result.

Mild neutropenia with clozapine treatment may occur as a slight drop in ANC levels with quick recovery. Cases of mild neutropenia occur throughout clozapine treatment.

Regular monitoring requirements may identify cases of neutropenia that are not related to clozapine. Recent studies have suggested milder forms of neutropenia (as opposed to agranulocytosis) with clozapine treatment may be identified as a result of observation bias.

Not all people who experience a mild or moderate neutropenia event will progress to agranulocytosis. This may suggest that the neutropenia is from another cause. However, it is not known in which patients a neutropenia will progress to agranulocytosis.

While the data sheet specifically states that clozapine should be infinitely stopped after a confirmed red result, in clinical practice, there may be circumstances where clozapine is restarted. It is also noted that in clinical practice, patients may experience a slight fluctuation in WBC/ANC which returns to amber or green results and clozapine is restarted.

The clinical management of a mild neutropenia differs to that of agranulocytosis. Moderate or severe neutropenia (ANC < $1.0x10^9$/L) increases the risk of infection.

Studies which assessed neutropenia cases (excluding agranulocytosis) in people taking clozapine did not identify any associated fatalities, however, clozapine was likely discontinued as a precautionary measure and as per monitoring recommendations.

Clozapine cessation

Repetition of blood tests and communication with different healthcare professionals, company CPMS staff (including haematologist), patients, family and caregivers, are processes that take place when a red blood test occurs.

Monitoring requirements in NZ use both WBC and ANC levels for determining action to take with clozapine treatment. The ANC may be more specific to identification of neutropenia, noting that the WBC includes other white blood cell counts.

Lower ANC thresholds for discontinuation are used by the FDA. Use of FDA criteria on patients in the UK have highlighted a subgroup of patients where clozapine could have been continued. It has also been suggested that the threshold model for clozapine cessation overestimates rates of potential CIA.

Some clozapine patients may have lower WBC/ANC counts identified overtime which is normal reference range for them, and while clozapine is continued, the low WBC/ANC do not become clinically significant. For example, people who have BEN.

Clozapine is an effective treatment for TRS. Some patients may not have any other treatment option. Stopping clozapine abruptly may increase the risk of relapse and cholinergic rebound. Interruption of clozapine while appropriate clinical management is decided may also cause adverse effects on the individual including possible periods of time without antipsychotic treatment.

Current monitoring requirements recommend stopping clozapine for management of red blood tests results at any time during treatment and that clozapine must not be restarted.

The advice to permanently stop clozapine with red blood test results may require greater flexibility. The association between neutropenia (and possible progression to agranulocytosis) or agranulocytosis events and clozapine treatment, might be impacted by several factors such as duration of treatment, history of blood test

results, clinical significance of the WBC/ANC result, neutrophil patterns and other possible causes of neutropenia.

The data sheet does not currently have any information to assist clinicians in understanding risk periods of agranulocytosis during clozapine treatment. Available data could inform clinicians, families and patients about risks and benefits for informed decision making.

Frequency of monitoring

Recent literature has discussed changes to the frequency of monitoring, particularly after 1 or 2 years of treatment and whether treatment-long haematological monitoring of clozapine is needed.

A study in the UK found that in a small sub-group of people taking clozapine for long treatment durations, lengthening the monitoring interval from 4-weekly to 12 -weekly did not increase the incidence of agranulocytosis. However, this study did not have enough people to power the primary outcome (differences in haematological events).

There does not appear to be any other studies that also review use of different frequency of monitoring requirements for clozapine. Most studies assess the prevalence of cases at different time points in CPMS systems or are reviews of agranulocytosis cases, both having associated limitations.

Interaction between patient and healthcare services for clozapine management often follows the frequency of monitoring. Regular interaction with health care professionals is important also for monitoring of other important clozapine side effects and adherence. The population likely to be prescribed clozapine is a vulnerable group of people. Some individuals may not recognise symptoms of infection, which may relate to an underlying neutropenia.

Experiences

People taking clozapine have regular blood tests and interact with multiple services in relation to their clozapine treatment. Individuals are required to visit the lab regularly for their blood test and pharmacy to collect their medicines. The monitoring requirements may become difficult at times such as public holidays, weekends or if the individual would like to go on an overseas holiday, or if live in rural locations.

People taking clozapine may be concerned if changes to the monitoring requirements occur due to possible perceptions about agranulocytosis, a serious side effect, and the requirement of regular monitoring for this.

The Clozapine Consultation 2023 provided important insight into the experiences of those who took part and included benefits and challenges faced relating to the haematological monitoring requirements.

Healthcare professionals who responded to the consultation suggested improvements to the current haematological testing requirements which included changes to frequency, threshold of blood tests, testing methods and management of red blood tests.

8 ADVICE SOUGHT

The Committee is asked to advise:

- Are changes to the haematological monitoring requirements for clozapine needed?
- If yes, what possible changes could be implemented to minimise the impact of the monitoring requirements to patients and healthcare professionals while maintaining the safe use of clozapine and manage the risk of clozapine-induced agranulocytosis.

9 ANNEXES

Annex 1: Clozapine patient monitoring systems New Zealand

Annex 2: Clozapine prescribing information (NZ, UK, Australia)

Annex 3: Clozapine monitoring frequency and duration (MARC March 2021 report).

Annex 4: Evaluating the epidemiology of clozapine-associated neutropenia among people on clozapine across Australia and Aotearoa New Zealand: a retrospective cohort study (Northwood et al, 2024).

Annex 5: Clinical impact of reducing the frequency of clozapine monitoring: controlled mirror-image cohort study (Oloyede et al, 2023).

Annex 6: Long-term persistence of the risk of agranulocytosis with clozapine compared with other antipsychotics: a nationwide cohort and case-control study in Finland (Rubio et al, 2024).

Annex 7: Clozapine Consultation 2023 report.

Annex 8: New Zealand case reports (agranulocytosis).

Annex 9: Company data [redacted]

Annex 10: Company data [redacted]

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