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An international guideline with six personalised titration schedules for preventing myocarditis and pneumonia associated with clozapine

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ABSTRACT

White blood cell (WBC) monitoring has reduced clozapine-treated patient deaths associated with agranulocytosis to a rarity. However, clozapine protocols and package inserts worldwide provide no instructions for preventing myocarditis or pneumonia during clozapine titrations. Prescribers worldwide are largely unaware of that. Meanwhile, as they worry about agranulocytosis, their clozapine-treated patients are at risk of dying from pneumonia or myocarditis. Consequently, an international guideline with 104 authors from 50 countries/regions was recently published to provide personalised clozapine titration schedules for adult inpatients. This forum article reviews pneumonia and myocarditis occurring during clozapine titration, as well as the three most innovative aspects of this new guideline: (1) personalised titration, (2) C reactive protein (CRP) measures, and (3) dose predictions based on blood levels. Clozapine metabolism is influenced by 3 levels of complexity: (1) ancestry groups, (2) sex-smoking subgroups, and (3) presence/absence of poor metabolizer status. These 3 groups of variables should determine the maintenance dose and speed of clozapine titration; they are summarised in a table in the full-text. The international clozapine titration guideline recommends measuring CRP levels simultaneously with WBC, at baseline and weekly at least for the first 4 weeks of titration, the highest risk period for clozapine-induced myocarditis.

INTRODUCTION

Clozapine prescribers worldwide, along with the national drug agencies, are concerned with clozapine toxicity and lethality, which they associate with agranulocytosis. Nowadays, this preferential concern may be mistaken. According to a 2019 search of the World Health Organization (WHO) database¹ for adverse drug reactions (ADRs), the number of deaths reported in clozapine-treated patients was 550 for agranulocytosis, 2077 for pneumonia, and 539 for myocarditis. The 550 deaths from agranulocytosis occurred in 34931 reports (including neutropenia) since the discovery of agranulocytosis as an adverse reaction in 1975² and before countries implemented monitoring of white

blood cells (WBCs). More recently, the same data were reanalyzed to consider the implementation of WBC monitoring. From 2000 to 2019, prescribers around the world reported 29586 cases of potential agranulocytosis to the ADR database of WHO. These cases led to 433 deaths with a relative lethality of 1%, leading to fewer deaths than myocarditis. In the same period, there were 1922 deaths due to pneumonia (30% relative lethality; 1922/6506) and 484 deaths due to myocarditis (11% relative lethality; 484/4536).³ Clozapine protocols and package inserts worldwide provide no instructions for preventing myocarditis or pneumonia during clozapine titrations. Prescribers worldwide are largely unaware of that. Meanwhile, as they worry about agranulocytosis, their clozapine-treated patients are at risk of dying from pneumonia or myocarditis. Consequently, an international guideline with 104 authors from 50 countries/regions was recently published to provide personalised clozapine titration schedules for adult inpatients.⁴

This forum article briefly reviews pneumonia and myocarditis occurring during clozapine titration, as well as the three most innovative aspects of this new guideline.⁴

PNEUMONIA OCCURRING DURING CLOZAPINE TITRATION

The lethality of infections in general and of pneumonia in particular in clozapine-treated patient had been overlooked for more than 15 years.⁵ Then, in 2018, a Danish national registry study verified the significance of pneumonia during clozapine titration.⁶ Danish psychiatrists had already been familiar with clozapine-induced myocarditis (the first case report worldwide was published in that country in 1980).⁷ Because of the very slow outpatient



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titration of clozapine in Denmark, clozapine-induced myocarditis has been extremely rare in that country. Thus in the Danish registry study, Rohde *et al*⁶ found an extremely low number of myocarditis cases during 3262 outpatient titrations (0.03%) but unexpectedly identified 7 deaths associated with pneumonia (among the 26 deaths in the first 2 months).

Pneumonia in clozapine-treated patients can be community-acquired pneumonia or aspiration pneumonia that can occur during titration or maintenance. During rapid titration, the combination of sedation, hypersalivation, and swallowing impairment can lead to aspiration pneumonia.⁸ Once pneumonia has developed, the inflammation releases cytokines which interfere with clozapine metabolism by inhibiting several cytochrome P450 (CYPs), including 1A2 (CYP1A2), the main clozapine metabolic pathway leading to norclozapine. This process creates positive feedback, with pneumonia and clozapine intoxication feeding each other.⁸ A study proposing fast clozapine titration produced 1 pneumonia case among 44 (2.3%) inpatients within the short period of the first 2 weeks of titration.⁹

CLOZAPINE-INDUCED MYOCARDITIS OCCURRING DURING TITRATION

Model of clozapine-induced myocarditis

Clozapine-induced myocarditis is a part of the syndrome of clozapine-induced inflammation.^{10 11} When clozapine is titrated too fast for the metabolism of a specific patient, clozapine can cause inflammation by releasing cytokines that further complicate titration, and unless the process is stopped, can lead to an auto-immune phenomenon. During this progression, auto-antibodies develop a local inflammation, most commonly myocarditis and rarely in other organs.¹¹

Clozapine was marketed in central Europe in the 1970s. Soon it became obvious that fever can occur during titration,² requiring titration to be paused; sometimes clozapine had to be stopped and restarted very slowly. Then, in 1980, the first myocarditis case was published in Denmark of a patient who died after 10 days of taking 300 mg/day of clozapine without titration.⁶ Please change reference to 7 Later, clozapine-induced myocarditis was described as eosinophilic myocarditis, compatible with a hypersensitivity reaction.² In 2012, an Australian case-control study¹² identified rapid titration and valproate co-treatment as risk factors for clozapine-induced myocarditis. During clozapine maintenance, valproate tends to be a mild inducer of norclozapine metabolism, reducing norclozapine concentration. Sometimes clozapine and valproate are titrated at the same time in aggressive/agitated patients. Early in a clozapine and/or valproate titration, insufficient time has elapsed to develop norclozapine induction; thus, valproate can behave as an inhibitor of clozapine metabolism and increase clozapine levels,¹³ increasing the risk of myocarditis.^{14 15} Other inhibitors of clozapine metabolism, including oral contraceptives and high use of caffeinated beverages, can increase the risk of myocarditis. Undiagnosed inflammation and obesity,

which also can impair clozapine metabolism, are additional neglected myocarditis risk factors.^{14 15} Clozapine is lipophilic, and it deposits in fat tissue contributing to decreased clearance. Thus, clozapine-induced inflammation typically manifests early with C reactive protein (CRP) elevations and sometimes fever, and only when the titration is continued does myocarditis develop.¹⁰ A risk factor for the severity of myocarditis is adding clozapine to quetiapine or olanzapine; significantly, a quetiapine co-prescription may also contribute to the lethality of myocarditis.^{16 17}

Prevalence of clozapine-induced myocarditis worldwide

After an extensive review of the literature and the WHO database,¹⁶ the prevalence of myocarditis in various countries manifests in three different patterns: (1) unknown frequency, (2) extremely low frequency, and (3) a frequency of around 3%.

Clozapine is very frequently used in Russia¹⁸ and China,¹⁹ but the WHO database¹⁶ has no clozapine-induced myocarditis cases from these two countries, which rarely send any ADRs to the WHO database. We think that clozapine-induced myocarditis is greatly underdiagnosed in Russia and China, two countries with large numbers of patients on clozapine.

Denmark and the Netherlands appear to have extremely low clozapine-induced myocarditis rates due to the use of very slow clozapine outpatient titration.² Meanwhile, Australian researchers identified a 3% myocarditis prevalence.²⁰ In Japan, there are very high rates of fever during titration (around one-third of the patients), and some hospitals find a 3% rate of myocarditis.²¹ Clozapine was introduced in Japan mainly using studies and experience from the USA. This is unfortunate because since 1997 it has been known that East Asians, using half the clozapine dosage, get the same plasma concentrations as patients of European ancestry.²² More than 60% of the world's population needs lower clozapine doses than those recommended in the USA. The patient groups requiring lower doses include all those of Asian ancestry—defined as those whose ancestry ranges from Pakistan to Japan and includes the original inhabitants of the Americas²² (called Native Americans or Indigenous Americans) who descended from East Asians. Thus, the Japanese titration protocol is not safe for Asians, particularly for those with additional risk factors (eg, valproate, obesity, females on contraceptives), which further impair clozapine clearance. Some hospitals in Canada²³ and the USA²⁴ also report a prevalence of myocarditis around 3%, due to the use of standard titration in Asians, Native Americans, and Europeans with impaired clozapine metabolism.

INTERNATIONAL CLOZAPINE TITRATION GUIDELINE

The international clozapine guideline⁴ was developed for inpatients since, in many countries, clozapine is started during hospitalisation. Its new recommendations include: (1) personalised titration, (2) CRP measures, and (3) dose predictions based on blood levels.

Table 1 Summary of international clozapine titration guideline for adult inpatients according to ancestry groups with updates*

| | Asians/Native Americans | | Europeans/Western Asians | | Blacks (US extrapolation)† | |
|---------------|-------------------------|----------------|--------------------------|----------------|----------------------------|----------------|
| | PMs* | Non-PMs | PMs* | Non-PMs | PMs* | Non-PMs |
| Target | 75–150 mg/day | 175–300 mg/day | 100–200 mg/day | 250–400 mg/day | 150–300 mg/day | 300–600 mg/day |
| Week 1 | | | | | | |
| Day 1 | 6.25 mg/day | 12.5 mg/day | 12.5 mg/day | 25 mg/day | 12.5 mg/day | 25 mg/day |
| ↑ D by | 6.25 mg/day | 12.5 mg/day | 12.5 mg/day | 25 mg/day | 12.5 mg/day | 25 mg/day |
| Day 7 | 25 mg/day | 50 mg/day | 50 mg/day | 100 mg/day | 50 mg/day | 100 mg/day |
| Alert C | <118 ng/mL | <105 ng/mL | <175 ng/mL | <140 ng/mL | <117 ng/mL | <117 ng/mL |
| Week 2 | | | | | | |
| ↑ D by | 12.5 mg | 12.5 mg/day | 12.5 mg/day | 25 mg/day | 25 mg/day | 50 mg/day |
| Day 14 | 50 mg/day | 100 mg/day | 75 mg/day | 200 mg/day | 100 mg/day | 200 mg/day |
| Alert C | <235 ng/mL | <210 ng/mL | <263 ng/mL | <280 ng/mL | <233 ng/mL | <234 ng/mL |
| Week 3 | | | | | | |
| ↑ D by | 12.5 mg | 25 mg/day | 25 mg/day | 25/50 mg/day | 25 mg/day | 50 mg/day |
| Day 21 | 75 mg/day | 150 mg/day | | | 150 mg/day | 300 mg/day |
| NS ♀ | | | 100 mg/day | 250 mg/day | | |
| Other | | | 125 mg/day | 300 mg/day | | |
| Alert C | <353 ng/mL | <315 ng/mL | <350 ng/mL | <350 ng/mL | <291 ng/mL | <351 ng/mL |
| Week 4 | | | | | | |
| NS ♀ | 75 mg/day | 150 mg/day | 100 mg/day | 250 mg/day | 150 mg/day | 300 mg/day |
| C | C 1 week later | C 1 week later | C 1 week later | C 1 week later | C 1 week later | C 1 week later |
| Other | 75–150 mg/day | 175–300 mg/day | 100–200 mg/day | 250–400 mg/day | 150–300 mg/day | 300 mg/day |
| ↑ D by | 25 mg/day | 25/50 mg/day | 25/50 mg/day | 25/50 mg/day | 25/50 mg/day | 25/100 mg/day |
| C | C 1 week later | C 1 week later | C 1 week later | C 1 week later | C 1 week later | C 1 week later |

Interpreting clozapine C

Cs before week 4 are not at a steady state but are used in order not to delay titrations. They are alert signs.‡

Titrations try to reach the target dose for an NS ♀ at day 21 so that 1 week later a steady state C is measured at week 4.

At week 4, the prescriber needs to decide on a target dose for other patients who are not NS ♀. Ranges include two extremes: NS ♀ and S ♂. The prescriber chooses a target dose and continues it for 1 week to obtain the C, to determine the final dose.

Published information suggests that 5 days on the same clozapine dose may be enough to reach a steady state. We use 1 week.§

In S ♂ who continue to smoke during hospitalisation, an additional 1–3 weeks may be needed to reach the final dosage.

If the patient did not smoke during hospitalisation, further increases may be needed after discharge if smoking is restarted.

*The international clozapine titration guideline⁴ recommended considering those taking oral contraceptives or valproate or who are obese to be clozapine PMs. The update³⁰ added those taking flupentixol, olanzapine, perphenazine or quetiapine to the list of those who should be titrated as clozapine PMs and provided recommendations for how to stop these antipsychotics once the minimum clozapine therapeutic dose has been reached.

†This table provides a one-page summary of six prior titration schedules described in the already published supplemental tables S9–S14 of the international clozapine titration guideline.⁴ The titration schedules for black patients are extrapolated from the US titration schedules. It includes corrections of errors that the guideline had. The table is an update and modification from the table published in the update³⁰ of the guideline.

‡Cs provided at the end of weeks 1, 2 and 3 are alert signs that the titration may be too fast for that patient. These Cs are estimated in each group using clozapine C/D ratios.

§One week for a steady state, which is easier to remember and implement (in many hospitals, Cs cannot be collected during weekends) than 5 days. Some clozapine PMs may need 2 weeks to reach a steady state; thus, allotting 1 week to reach a steady state is a practical compromise. It may be wise in clozapine PMs to get another C 2 weeks after the maintenance dosage has been selected.

C, concentration; C/D, concentration-to-dose; D, dose; NS, non-smoking; PM, poor metabolizer; S, smoking; US, United States.

Personalised titration

Based on a comprehensive review of the clozapine pharmacokinetic literature,⁵ the international guideline⁴ proposes that clozapine clearance can be measured by the dose needed to reach the minimum therapeutic range of the plasma concentration of 350 ng/mL. Clozapine clearance is influenced by three levels of complexity: (1) ancestry groups, (2) sex-smoking subgroups, and (3) absence/presence of poor metabolizer (PM) status.⁴ These three groups of variables should determine the maintenance dose and speed of clozapine titration (table 1).

It is not known why people of Asian or Native American ancestry have lower CYP1A2 activity than those with European ancestry, leading to lower clozapine doses needed to get a therapeutic response.²⁵ Olanzapine is also mainly metabolised by CYP1A2. Asians need lower olanzapine doses.²⁶ On the other hand, people of black ancestry (sub-Saharan Africans) may need higher olanzapine²⁷ and, possibly, clozapine doses. Moreover, higher clozapine dose requirements in African-American patients in the USA versus those of European ancestry may explain why US experts and the US package insert recommend 300–600 mg/day of clozapine,

which is higher than the dosages used in Europe. Extrapolation from US dosages to black patients provides three basic levels of clozapine dose ranges. They are dose ranges because within each ancestry group (Asians/Native Americans, Europeans and blacks), female non-smokers need the lowest doses while male smokers need the highest doses. Oestrogens inhibit CYP1A2, so women need lower clozapine (and olanzapine) doses, while tobacco smoking induces CYP1A2, so smokers need higher clozapine (and olanzapine) doses.

The tricyclic antidepressants are metabolised by the cytochrome P450 2D6 (CYP2D6). First, some genetic PMs were found who do not have this metabolic enzyme due to the presence of two *CYP2D6* alleles with no activity. Then, those who had three or more active *CYP2D6* alleles and too much of the enzyme were identified and called ultrarapid metabolizers (UMs). This terminology of PMs and UMs was later applied to other CYPs. Finally, it was found that non-genetic PMs or UMs can be caused by personal or environmental factors, as long as they are present (phenoconversion). PMs and UMs can be identified by plasma drug concentrations after considering dosing.

Genetic CYP1A2 PMs exist but are probably rare and cannot be identified by current pharmacogenetic tests.²⁵ Non-genetic CYP1A2 PMs may be more frequent. In 573 Asian patients from 5 samples combined, phenotypic clozapine PMs were defined as those with a clozapine clearance >2 standard deviation (SD) from the mean for their group stratified by sex and smoking. PM prevalence included around 2% due to co-prescription of inhibitors, 2% due to inflammation, 1% due to obesity, and 7% without evident cause or potential genetic explanation.²⁸ In East Asians, the following *CYP1A2* alleles with no/limited function have been described: *CYP1A2**8, *CYP1A2**11, *CYP1A2**15, and *CYP1A2**16. They appear to be rare (<1% in Japanese) and have not yet been studied in clozapine-treated patients.²⁵

In many countries, clozapine is available only in tablets or capsules of 25 or 100 mg. These types of formulations may not be appropriate for clozapine treatment of Asian PMs. Asian countries should consider developing clozapine formulations that allow administrations of only 5 or 10 mg.⁴ These lower formulations would allow developing titrations slower than those proposed in [table 1](#).

CRP levels during clozapine titration

CRP monitoring is an inexpensive laboratory technique which is available around the world. It lacks specificity and is just a signal of the presence of inflammation. The international clozapine titration guideline⁴ recommends measuring CRP levels simultaneously with WBC at baseline and weekly at least for the first 4 weeks of titration, the highest risk period for clozapine-induced myocarditis. In the WHO database, 84% (1309/1560) of clozapine-induced myocarditis cases were diagnosed in the first month and another 5% (82/1560) in the second month.¹⁶

The baseline CRP value helps avoid starting clozapine in someone with an undiagnosed systemic inflammation that could impair clozapine metabolism and contribute to additional inflammation secondary to an overly rapid clozapine

titration due to impaired clozapine metabolism. An abnormal baseline CRP value should lead to the investigation of any undiagnosed infection or systemic inflammations, which should be resolved before starting clozapine. Prescribing clozapine during a chronic inflammatory process, such as rheumatoid arthritis or Crohn's disease, is a complex decision. There is a need to carefully balance co-medications (some associated with neutropenia), low clozapine doses, and repeated clozapine level monitoring to avoid inflammatory exacerbations leading to clozapine intoxications.⁴

If the baseline or prior CRPs were normal and then become abnormal during titration, this indicates: (1) clozapine-induced inflammation associated with too-rapid titration for the clozapine metabolism of that specific patient and/or (2) co-occurrence of an infection, most frequently an upper respiratory infection. As the CRP value becomes abnormal, there is potential for the inhibition of clozapine metabolism by cytokine release. Thus, clozapine titration should be stopped by holding the clozapine dose and not increasing it, or stopping clozapine. If a co-infection exits, it may be better to stop clozapine and only restart it after the infection has disappeared and CRP has normalised. If clozapine-induced inflammation is suspected and troponin levels are available, they should be measured to rule out myocarditis. Close monitoring with daily CRP and troponin, if possible, may be helpful. An Australian case-control²⁹ study suggests that CRP elevations precede troponin elevations by up to 5 days; similarly, in our limited experience,^{15 16} CRP elevations always happened several days before troponin elevations.

Other clozapine-induced inflammation can occur during rapid titration including serositis, pneumonitis/alveolitis, hepatitis, pancreatitis, nephritis, colitis, and skin abnormalities.¹⁰ In the most comprehensive study, which included 152 Japanese clozapine uptitrations, Tsukahara *et al*²¹ found 38% (57/152) with fever during the first 4 weeks, 13% (20/152) with pleuritis, 5% (7/152) with myocarditis, and 1% (2/152) with interstitial nephritis. Although we are not aware of any other comprehensive study of clozapine-induced inflammation conditions, other inflammation conditions in the literature¹¹ are usually considered to be rarer than myocarditis, but they should be considered in the differential diagnosis when CRP elevations or fever develop during clozapine titration.¹⁰

Our limited experience with clozapine-induced myocarditis suggests it is very important to stop inflammation as soon as possible to halt progression to myocarditis. Some patients can develop auto-immune phenomena, possibly auto-antibodies with the risk of relapse once clozapine is restarted. This is described in a published case,¹⁶ which explains the risk of titrating an unknown genetic PM. The reader should not think that the titrations in [table 1](#) are completely safe for all patients; they may not be safe for genetic clozapine PMs.

We hope that using the clozapine titration guideline is particularly helpful for psychiatrists in countries, such as China, with little familiarity regarding the diagnosis of clozapine-induced inflammation conditions, including myocarditis. The use of personalised titration schedules

and CRP monitoring may prevent many cases of clozapine-induced inflammatory complications during up-titration and may help to identify them early when only fever or CRP elevations are present and before the development of other signs including troponin elevations, cardiac symptoms, or echocardiogram abnormalities.

The role of clozapine levels during titration

The international guideline was developed for countries with varying levels of resources. Ideally, in the fourth week after reaching a target dose and waiting for at least 5 days (1 week is better) for a steady-state concentration, the clozapine prescriber can use that concentration to predict the therapeutic dose needed to reach at least 350 ng/mL clozapine concentration. The already published supplemental table S2 of the international guideline³ can help clinicians estimate therapeutic doses for specific patients based on their clozapine concentration in the fourth week. At therapeutic doses and in the absence of inhibitors/inducers or inflammation, clozapine follows linear kinetics. This means that the relationship between the dose and the plasma concentration is a constant (if the patient in the fourth week on 100 mg/day has a clozapine plasma concentration of 175 ng/mL, this patient needs at least 200 mg/day to reach 350 ng/mL).

If the clozapine prescriber cannot access clozapine levels, [table 1](#) provides a rough estimation of the approximated maintenance doses according to the patient's characteristics. Lithium prescribers worldwide routinely use lithium levels to determine safe doses; similarly, clozapine prescribers worldwide should ideally use clozapine levels. In some countries, measuring clozapine levels is easy and relatively affordable, and new point-devices may provide concentrations quickly.³ The guideline titrations mention that obtaining a trough level on the day next to the end of the week (days 8, 15, and 22) may be an additional safety measure for identifying clozapine PMs. The problem with these levels is that if the dosage has not been stable for at least 5 days (or better 1 week), the concentration has not reached a steady state. [Table 1](#) provides alert numbers indicating which non-steady-state concentrations may be a concern for each titration week.

Clozapine does not follow linear kinetics in very low and subtherapeutic doses. This means that when the dose provides low plasma concentrations (below 150 ng/mL), these concentrations cannot be used to estimate the final dose, providing a minimum therapeutic concentration of 350 ng/mL. This is why a trough steady-state concentration at week 4 may be better for predicting maintenance clozapine dosing.

In summary, clozapine prescribers need to know that clozapine toxicity and lethality may no longer be explained only by agranulocytosis, which is widely known, but also by myocarditis and pneumonia and that a new guideline³ was developed to prevent these conditions by using slow, personalised clozapine titrations for adult inpatients. The first update of the guideline suggested using the PM titrations of each ancestry when clozapine is added to olanzapine, quetiapine, perphenazine or

flupenthixol.³⁰ Other updates will be provided as new information becomes available. Future guidelines to be developed for clozapine maintenance treatment should address how to prevent deaths associated with other clozapine ADRs including constipation, seizures, and arrhythmia.

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