An International Adult Guideline for Making Clozapine Titration Safer by Using 6 Ancestry-Based Personalized Dosing Titrations, CRP and Clozapine Levels

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Abstract: This international guideline proposes improving clozapine package inserts worldwide by using ancestry-based: 1) dosing and 2) titration. Adverse drug reaction (ADR) databases suggest clozapine: 1) is the third most toxic drug in the United States (US), and 2) produces worldwide pneumonia mortality four times greater than that of agranulocytosis or myocarditis. For trough steady-state clozapine serum concentrations, the therapeutic reference range is narrow, from 350 to 600 ng/mL with the potential for toxicity and ADRs as concentrations increase. Clozapine is mainly metabolized by CYP1A2. Poor metabolizer (PM) status through phenotypic conversion is associated with co-prescription of inhibitors (including oral contraceptives and valproate), obesity or inflammation with C-reactive protein (CRP) elevations. People with ancestry from Asia (Pakistan to Japan) or the Americas' original inhabitants have lower CYP1A2 activity and require lower clozapine doses to reach concentrations of 350 ng/ml. Daily doses of 300-600 mg/day are recommended in the US. Slow personalized titration may prevent early ADRs (including syncope, myocarditis and pneumonia). The core of this guideline consists of six personalized titration schedules for inpatients. : 1) Asian/Amerindian ancestry with lower metabolism, 2) Asian/Amerindian ancestry with average metabolism, 3) European/Western Asian ancestry with lower metabolism, 4) European/Western Asian ancestry with average metabolism, 5) in the US of non-Asian/Amerindian ancestry with lower clozapine metabolism, and 6) in the US of non-Asian/Amerindian ancestry with average clozapine metabolism. Baseline and weekly CRP monitoring for at least 4 weeks is required to identify any inflammation, including inflammation secondary to clozapine rapid titration.

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Running head: Guideline for Making Clozapine Titration Safer

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Abstract

This international guideline proposes improving clozapine package inserts worldwide by using ancestry-based: 1) dosing and 2) titration. Adverse drug reaction (ADR) databases suggest clozapine: 1) is the third most toxic drug in the United States (US), and 2) produces worldwide pneumonia mortality four times greater than that of agranulocytosis or myocarditis. For trough steady-state clozapine serum concentrations, the therapeutic reference range is narrow, from 350 to 600 ng/mL with the potential for toxicity and ADRs as concentrations increase. Clozapine is mainly metabolized by CYP1A2 (female non-smokers require the lowest dose and male smokers the highest dose). Poor metabolizer (PM) status through phenotypic conversion is associated with co-prescription of inhibitors (including oral contraceptives and valproate), obesity or inflammation with C-reactive protein (CRP) elevations. People with ancestry from Asia (Pakistan to Japan) or the Americas' original inhabitants have lower CYP1A2 activity and require lower clozapine doses to reach concentrations of 350 ng/ml. Daily doses of 300-600 mg/day are recommended in the US. Slow personalized titration may prevent early ADRs (including syncope, myocarditis and pneumonia). The core of this guideline consists of six personalized titration schedules for inpatients: 1) Asian/Amerindian ancestry with lower metabolism (in cases of obesity or valproate) needing minimum therapeutic dosages of 75-150 mg/day, 2) Asian/Amerindian ancestry with average metabolism needing 175-300 mg/day, 3) European/Western Asian ancestry with lower metabolism (in cases of obesity or valproate) needing 100-200 mg/day, 4) European/Western Asian ancestry with average metabolism needing 250-400 mg/day, 5) in the US of non-Asian/Amerindian ancestry with lower clozapine metabolism (in cases of obesity or valproate) needing 150-300 mg/day, and 6) in the US of non-Asian/Amerindian ancestry with average clozapine metabolism needing 300-600 mg/day. Baseline and weekly CRP monitoring for at least 4 weeks is required to identify any inflammation, including inflammation secondary to clozapine rapid titration.

Key words: Native American continental ancestry group; Asian continental ancestry group; clozapine/adverse effects; clozapine/blood; clozapine/metabolism; clozapine/therapeutic use;

clozapine/toxicity; CYP1A2; drug labeling; European continental ancestry group; infection; inflammation; mortality/drug effects; sex; smoking.

1. Clozapine's history

Clozapine was marketed in some European countries in the early 1970s but in 1975 cases of clozapine-induced agranulocytosis were described in Finland. The association of clozapine with a potentially lethal adverse drug reaction (ADR), agranulocytosis, left clozapine's reputation severely damaged. Moreover, clozapine was withdrawn from some European continental countries and the studies in North America were stopped [1]. Everything changed in 1988, when Kane et al. [2] published a randomized clinical trial (RCT) that demonstrated that clozapine was significantly more efficacious than chlorpromazine for treatment-refractory schizophrenia (TRS). In the year following this RCT, the Food & Drug Administration (FDA) approved clozapine in the United States (US) for TRS with a centralized monitoring system called the Clozaril Patient Management System (CPMS). CPMS required weekly white blood counts (WBC) to prevent agranulocytosis. The approval by the FDA was followed by the resurrection of the use of clozapine in Continental Europe and the successive approval in other countries including the United Kingdom (in 1989), Canada (in 1991), Australia (in 1994) and Japan (in 2009).

In 1989, the FDA required almost no clozapine pharmacokinetic studies [1]. In 1996 a drug-drug interaction (DDI) with an antihistamine, terfenadine, became responsible for multiple US deaths. This DDI led the FDA to start requiring DDI studies. As pharmacokinetic science evolved, pharmacokinetic studies became a cornerstone in the FDA's approval of new drugs, but clozapine became generic with no company supporting the required pharmacokinetic studies. As the FDA plays an important role in influencing drug agencies worldwide, the FDA's lack of attention to the growing knowledge of clozapine pharmacokinetics has made clozapine package inserts worldwide unsatisfactory. These package inserts require important changes, particularly the need to describe 1) dosing according to ancestry and 2) ancestry-based titrations [3]. Nielsen et al. [4] completed an excellent comprehensive worldwide comparison of clozapine package inserts which, following the FDA clozapine package insert, focused mainly on agranulocytosis but did not mention the issues of ancestry or titration speed.

2. Clozapine safety

2.1. Clozapine may be associated with lower mortality in TRS

TRS accounts for approximately one-third of people with schizophrenia [5]. While definitions of TRS vary from study to study [5], the literature agrees that clozapine is the most efficacious antipsychotic for TRS in RCTs and the most effective in naturalistic cohorts. Most meta-analyses of RCTs support clozapine as the most efficacious antipsychotic in TRS [6]. A researcher group published a network meta-analysis [7] that did not find superiority in TRS, but also published a meta-analysis describing clozapine as the most efficacious for the acute treatment of multiple-episode schizophrenia in general [8]. Two systematic reviews of naturalistic cohort studies [9,10] demonstrated clozapine had greater effectiveness than other antipsychotics because it was associated with fewer drug discontinuations and hospitalizations. Clozapine may have a particularly positive profile for well-being and some TRS patients are willing to remain on clozapine therapy for many years [1]. Supplementary Box S1 [1,11-16] reviews the complex issue that clozapine may decrease the mortality of patients with TRS who are willing to remain on clozapine for many years and increase their life expectancy when compared with those who are non-adherent.

2.2. Clozapine pharmacokinetics may explain its ADRs

Many clinicians are reluctant to use clozapine in people with TRS due to systemic barriers and in part because of its toxicity, leading to its underuse in many countries [17]. This is not beneficial for people with schizophrenia or schizoaffective disorder, since clozapine: 1) is the only antipsychotic with FDA approval for reducing suicidal behavior [18], and 2) may reduce hostility and aggressive behaviors independently of its effects on other symptoms [19].

To reduce clozapine ADRs, an expert consensus guideline [20] strongly recommends using serum/plasmatic levels, which is called therapeutic drug monitoring (TDM). The consensus guideline proposed a clozapine therapeutic reference range of 350-600 ng/mL for trough steady-state clozapine concentrations. This value is for clozapine concentrations and does not include the major metabolite, norclozapine, nor the total (clozapine plus norclozapine). This range provides a therapeutic index of 1.7

(600/350=1.7), calculated by dividing the upper reference range by the lower reference. Supplementary Table S1 shows that clozapine has the narrowest therapeutic index among second-generation antipsychotics [20-22]; therefore, it may be the most prone to toxicity and to causing dose-dependent ADRs that are really concentration-dependent ADRs within each patient [23].

2.3. Clozapine toxicity

Unfortunately, the data from the FDA from 1998-2005 [24] also suggested that, as currently used in the US, clozapine can be associated with toxicity. Clozapine was associated with 3,277 deaths or serious non-fatal outcomes, making it the third most toxic drug in the US, second only to oxycodone and fentanyl [24]. To address this potential for toxicity, the FDA has focused on decreasing clozapine mortality by raising awareness of myocarditis and severe neutropenia. In 2002, the US clozapine package insert included a warning about myocarditis and in 2015 the FDA required a new program called the Risk Evaluation and Mitigation Strategy (REMS) focused on severe neutropenia.

The FDA's focus on clozapine-induced agranulocytosis as a major cause of clozapine mortality may be misguided. The pharmacovigilance database of the World Health Organization (WHO), VigiBase, has received worldwide reports on ADRs since 1968 from 134 drug agencies. A search on July 15, 2019, [25] indicated that agranulocytosis, including the first cases in 1975, accounted for only 550 clozapine deaths (third in order) and had a low relative lethality of 2%. According to this VigiBase search (Supplementary Table S2), the eight major causes of death in clozapine patients were, in descending order: 1) pneumonia [26-29] (2,077 deaths), 2) cardiac arrests [30,31] (1,449 deaths), 3) agranulocytosis [32,33] (550 deaths), 4) myocarditis [34-36] (539 deaths), 5) constipation [37-39] (326 deaths), 6) arrhythmia [40,41] (319 deaths), 7) seizures [40,42-44] (308 deaths) and 8) syncope [45-47] (299 deaths). These deaths in clozapine patients are probably explained by the combination of the effects of TRS and clozapine. Supplementary Table S2 describes for each clozapine ADR the possible contribution of TRS and clozapine.

3. Advances in clozapine pharmacokinetics not included in the US package insert

After the development of the US clozapine package insert [48], in 1996 Bertilsson et al. [49] reported clozapine as mainly metabolized by the cytochrome P450 1A2 (CYP1A2). Tobacco (and cannabis) smoking is a CYP1A2 inducer while estrogens are inhibitors. As with caffeine [50] and other CYP1A2 substrates, dosing varies based on stratification by sex and smoking into 4 groups. Female non-smokers need the lowest clozapine doses while male smokers need the highest [51]. Supplementary Box S2 provides a detailed review of clozapine metabolism [49-62].

3.1. Clinically relevant variables that may influence clozapine dosing

Supplementary Box S3 provides a detailed review of the pharmacokinetic variables that may influence clozapine metabolism including DDIs, obesity, inflammation, geriatric age and pregnancy [1,21,29,40,56, 63-79].

Clozapine inhibitors include fluvoxamine, ciprofloxacin, and oral contraceptives. High intake of caffeine can also behave as an inhibitor but tends to be more problematic in outpatients than for inpatients in which caffeine intake is easier to control (footnote f of Supplementary Box S3). Clozapine inducers include carbamazepine and phenytoin. Valproate [69] may be both an inhibitor and inducer. However, to optimize a safer clozapine titration, valproate may be considered a potential inhibitor. Clozapine is lipophilic and deposits in the adipose tissue; this appears to explain why obesity is associated with a decrease in clozapine metabolism [75], as with other CYP1A2 substrates [78]. Systemic inflammations, including infections, release cytokines which inhibit CYP1A2 and increased clozapine levels have been described in 40 cases of infection [79]. In a clozapine cohort [65], in the 18 episodes of inflammation/infection the effects ranged from mild TDM changes requiring no dose changes in patients with no leukocytosis and no abnormal C-reactive protein (CRP) to requiring cutting the dosage to one-third to compensate for the three-fold serum concentration levels. Moreover, by inducing inflammation during fast titration, clozapine can decrease its own metabolism to create a positive feedback mechanism.

Supplementary Box S4 [50, 62,68, 80-87] provides a detailed review of the limited available data on the influence of genetics and ancestry on clozapine metabolism and CYP1A2 activity. There are 5 major DNA ancestry groups [80]: African, European (and Western Asian), Asian (defined by the FDA as people whose ancestry ranges geographically from Pakistan to Japan), Oceanian and Amerindian. Asians and their descendants, the Amerindians [83], have lower CYP1A2 activity for unknown reasons (Section 3 of Supplementary Box S4) and need lower clozapine minimum therapeutic doses than the Europeans to reach 350 ng/ml. People from Oceania split from Asians before the separation of East Asians. Based on a limited study [84] and clinical experience, and until more studies are available, it appears reasonable to think that people from Oceania may require doses and titrations similar to patients of European ancestry (Section 4 in Supplementary Box S4). There are no good clozapine TDM studies [62] in patients of African descent. Although in the US clinicians are not aware of clozapine dose differences for African-Americans, olanzapine is a CYP1A2 substrate and a population pharmacokinetic study suggested people of African ancestry may need higher olanzapine doses (Section 5 in Supplementary Box S4).

Supplementary Box S5 [48,88-90] indicates that current genotyping of CYP1A2, CYP2D6 or other genes is not useful for clozapine dosing.

3.2. Establishing minimum therapeutic doses

TDM should be measured under standard conditions, requiring both steady-state and trough conditions which are defined in detail in Supplementary Box S6 [1,20,48,91]. Using trough steady-state TDM is the cornerstone for the rational use [1] of clozapine personalized dosing, if one assumes that a minimum serum level of 350 ng/ml is needed for clozapine response in a majority of patients. Clozapine follows linear kinetics (i.e., the relationship between dose and concentration is linear) when two conditions are met: 1) in therapeutic dosages and 2) in the absence of inducers/inhibitors). The concentration-to-dose (C/D) ratio is relatively stable in each individual unless personal or environmental variables are changed. Higher clozapine C/D ratios indicate lower metabolism and are associated with females, non-smokers, Asian/Amerindian ancestry, co-prescription of inhibitors, obesity, and inflammation. Lower clozapine C/D ratios indicate lack of adherence or higher metabolism associated with males, smokers, European/Western Asian ancestry, and co-prescription of clozapine inducers [40]. The clozapine dose needed to reach a serum concentration of 350 ng/ml can be used to personalize clozapine dosing according to the pharmacokinetic characteristics of each individual and to compare average doses in subgroups after stratification by ancestry, sex and smoking status.

Supplementary Table S2 [40,68,83,92] summarizes the TDM studies focused on ancestry. Average people of Asian/Amerindian ancestry need a minimum therapeutic dose between 175 mg/day for female non-smokers and 300 mg/day for male smokers [68,83]. In 2021, in 6 samples of average people of European ancestry [92], the minimum therapeutic doses ranged between 275 mg/day for female non-smokers and 400 mg/day for male smokers. On the other hand, the nomogram of a British naturalistic TDM study [93] recommended doses ranging from 265 mg/day in female non-smokers to 525 mg/day in male smokers. Thus, several European textbooks follow that recommendation [94-96].

Pharmacologists use the term *phenoconversion* when a patient who metabolizes a drug normally becomes a poor metabolizer (PM) when compared with the control group of average metabolizers [88]. For clozapine, it can happen temporarily by taking an inhibitor (e.g., an oral contraceptive or sometimes valproate) or by developing inflammation or obesity. Clozapine PM status that is due to inhibitors, inflammation or obesity requires approximately half the clozapine dose needed for their sex and smoking group within their ancestry group. As fluvoxamine is a very powerful clozapine inhibitor with unpredictable effects (the clozapine dose may require reduction to 1/5 or 1/10 in some patients) [23,63], this guideline does not provide titrations for patients on fluvoxamine.

3.3. The US package insert does not comment on individualized doses or ethnicity

The US clozapine package insert [48] provides no recommendation regarding daily dose adjustments for sex, smoking, or ancestry. Moreover, the dosing recommendations in the US package insert were developed before any knowledge of clozapine metabolism was available and without any well-controlled dosing studies. It recommends targeting doses of 300 mg to 450 mg/day; subsequently, the dose can be increased once weekly or twice weekly, in increments of up to 100 mg with a maximum dose of 900 mg/day [48].

Supplementary Box S7 describes all published information on US clozapine dosing including: 1) dose recommendations from textbooks and review articles [97-102], 2) a nomogram from a chart review study [51], 3) a dose recommendation obtained by using clozapine C/D ratios from the literature [103], 4) a re-analysis [92] of a systematic review [62] comparing US and European patients, and 5) a US RCT with 3 doses [104]. The combination of 6 TDM studies in European patients suggests doses up to 400 mg/day for male smokers [92], however, the limited US clozapine data available suggest that up to 600 mg/day is recommended for US male smokers (Supplementary Box S7).

4. Clozapine titration

4.1. Myocarditis and rapid titration

Many Continental European countries typically use slow clozapine titrations and have extremely low incidences of myocarditis [105]. The best example is the Netherlands, which has up to 10% of their schizophrenia patients on clozapine and has developed a guideline [95] that encourages very slow outpatient titration. On the other hand, for many years it has been known that Australia has a much higher incidence of clozapine-induced myocarditis [105]. Supplementary Table S1 describes 3,048 clozapine-induced myocarditis cases reported to worldwide drug agencies; more than half came from Australia [25], a country with only 26 million people. A 2020 meta-analysis [106] of clozapine-induced myocarditis found a seven-fold difference between Australia and other countries with an event rate of 2% in 9 Australian samples and of 0.3% in 15 non-Australian samples.

High rates of clozapine-induced myocarditis in some countries may be due to rapid titration. Slower titration was accompanied by a substantial reduction in the incidence of lamotrigine-induced Stevens-Johnson syndrome, which is believed to be a hypersensitivity reaction associated with rapid titration. This decrease occurred after the company slowed the recommended lamotrigine titration in average patients with further slowing by half in patients taking an inhibitor, valproate, who end up receiving having half the lamotrigine maintenance dose of non-inhibited patients [107]. Clozapine-induced myocarditis may be a similar hypersensitivity reaction associated with rapid titration [108,109].

Supplementary Table S3 [36,68,110-119] provides a comprehensive review of published data supporting the role of rapid titration in clozapine-induced myocarditis.

Supplementary Box S8 describes a hypothetical model for hypersensitivity in clozapine-induced myocarditis which can be outlined in three phases [1]. In this model, the initial symptom is CRP elevation, then frequently fever develops and in the late stage local signs of inflammation become obvious, most frequently myocarditis; but other local inflammations including serositis, pneumonitis, hepatitis, pancreatitis, nephritis or colitis can occur in the first two months of clozapine treatment during too-rapid titration [120].

4.2. Pneumonia may also be increased during titration

No published study has focused on the incidence of pneumonia during clozapine titration but two articles, one on myocarditis in Denmark [121] and the other describing a rapid titration in Romania [113], suggest that pneumonia may be increased during clozapine titration. Aggressive titration may lead to sedation, hypersalivation and swallowing disturbances, increasing the risk of aspiration pneumonia [29]. In Denmark, clozapine-induced myocarditis is extremely rare. In 3,262 outpatient initiations of clozapine in the Danish registry, Rohde et al. [121] found only 0.03% of myocarditis in the first two months. There were no deaths in the first 2 months explained by myocarditis. Surprisingly, seven of 26 deaths in the first two months were due to pneumonia. Another analysis from the Danish registry established an annual pneumonia incidence in clozapine patients of 2.1% [28]. A Romanian study [113] promoting rapid titration had an incidence of pneumonia of 2.3% (1/44=0.23) in only the first two weeks.

4.3. Proposal for six personalized clozapine titrations for inpatients

As slow personalized titration considering DNA ancestry may be important for clozapine safety, this article proposes 6 titration schedules for these inpatient groups: 1) Asian/Amerindian ancestry with lower clozapine metabolism (Supplementary Box S9), 2) Asian/Amerindian ancestry with average clozapine metabolism (Supplementary Box S10), 3) European/Western Asian ancestry with lower clozapine metabolism (Supplementary Box S11), 4) European/Western Asian ancestry with average clozapine metabolism (Supplementary Box S12), 5) in the US with non-Asian/Amerindian ancestry with lower clozapine metabolism (Supplementary Box S13), and 6) in the US with non-Asian/Amerindian ancestry with average clozapine metabolism (Supplementary Box S14).

4.4. Baseline considerations for all 6 titrations

Supplementary Box S15 describes considerations at baseline that are in common for the titrations of all 6 inpatients including: 1) indications for choosing slower titration in each ancestry group (use of oral contraceptives, use of valproate, or obesity), 2) avoiding potent inducers (rifampicin, phenytoin or phenobarbital), 3) avoiding fluvoxamine, 3) stopping benzodiazepines when possible [47], 4) ruling out baseline inflammation, and 5) avoiding smoking cessation during titration. In most countries, clozapine is started in hospitalized patients so our guidelines focus on inpatient titrations. The Dutch guideline [95] provides recommendations for outpatient titration which are even slower than its inpatient titration.

4.5. Role of CRP during titration

Supplementary Box S16 [65,118-120] provides the rationale for measuring the CRP at the same time as the WBC [108] for the first 4 weeks. Troponin is a sensitive and specific marker of myocardial damage. Thus, in countries with enough resources, adding weekly troponin during the first weeks appears reasonable until better studies are available. The limited data available suggest that CRP elevations precede troponin elevations by several days.

When the CRP becomes abnormal for the first time during the titration, clinicians need to rule out a co-occurring inflammation, particularly an upper respiratory infection, and also to consider a clozapine-induced inflammation explained by a titration which has been too fast for that specific patient. After CRP becomes abnormal during the clozapine titration: 1) clinicians should not increase the dose and the titration should be held and 2) when possible, consider daily monitoring of CRP and troponin. If the CRP and troponin do not normalize, clinicians need to decrease the clozapine dose or even stop it.

4.6. Role of clozapine TDM during titration

4.6.1. TDM use when available

Many clinicians around the world have no access to TDM. For those clinicians who want to use TDM during titration, schedules (Supplementary Box S9 to S14) provide rough estimations for which non-steady-state TDMs may look worrisome during the first morning of Weeks 2, 3 and 4. In most settings, clozapine TDM results are not available for several days and may not help in the immediate management of patients based on symptoms and CRP, but they may help in retrospectively interpreting complex cases.

4.6.2. Use of a single TDM in predicting the clozapine maintenance dose

Once the patient has reached the target dose in the fourth week, it is important to remain at the same dose for at least 5 days and measure trough TDM. In therapeutic concentrations (or near therapeutic concentrations) clozapine follows linear kinetics and the clozapine C/D ratio is relatively stable [40] as long as it is not contaminated by inflammation or changes in relevant environmental factors (inhibitors or inducers including smoking). Therefore, a single TDM in the fourth week which is likely to follow linear kinetics can be used to estimate the minimum therapeutic dose, providing a serum concentration of at least 350 ng/ml. Supplementary Table S4 provides multiple examples of TDMs at different clozapine doses and explains how to estimate minimum therapeutic doses.

4.6.3. The mean of multiple TDMs is a better predictor of the final clozapine maintenance dose

Clozapine metabolism in an individual varies substantially and a single trough steady-state TDM provides only a rough approximation of clozapine C/D ratio as long as confounding factors (e.g., co-medication, lack of inflammation, smoking behavior, caffeine intake) remain stable. On the other hand, having at least five trough steady-state TDMs and calculating the mean clozapine C/D ratio provides a more accurate determination of the patient's clozapine C/D ratio, as long as confounding factors do not change.

Supplementary Figures S1 [62] and S2 [122] illustrate this variability in both clozapine and total C/D ratios in two cases with extreme metabolism explained in Supplementary Box S16 [62,122]. Supplementary Figure S1 [62] describes a clozapine PM with a mean minimum therapeutic dose of 90 mg/day based on 17 TDMs but, using individual TDMs, the minimum therapeutic dose ranged from 66 mg/day to 121 mg/day. Supplementary Figure S2 [122] describes an obese US smoker with a mean minimum therapeutic dose of 443 mg/day based on 17 TDMs but, using individual TDMs, the minimum therapeutic dose ranged from 353 mg/day to 565 mg/day.

4.7. Unresolved issues

These guidelines do not try to cover all aspects of clozapine treatment but focus only on making titration safer around the world, hopefully encouraging all drug agencies to consider ancestry-based titration. The neglected issues briefly discussed below are: 1) the problem of current approaches focused on an average dose for an average patient, 2) some titration areas needing development and 3) the need for guidelines to personalize dosing for maintenance treatment.

4.6.1. The need for personalized approaches

Those researchers interested in an approach which focuses on the best average dose for clozapine [123] ignore the need for clozapine personalized dosing based on pharmacokinetic principles. As current approaches have not worked with clozapine, the current guidelines propose that there are at least 6 best personalized dosages and these 6 titrations do not consider that some genetic or ancestry groups may require additional personalized approaches. Future studies will need to verify whether or not using these 6 titrations will help to decrease clozapine toxicity. The current data on clozapine toxicity from the FDA [24] or VigiBase [25] appear concerning. Lower doses during titration and the maintenance phase may decrease clozapine toxicity.

4.6.2. Areas on clozapine titration needing development

Supplementary Box S18 lists as areas of clozapine titration needing development: 1) adjustment of these ancestry-based clozapine guidelines for children and adolescents; 2) study of CYP1A2 mutations and epigenetic mechanisms that may help identify genetic clozapine PMs [62,68,88,118,124-127]; 3) clarification of the existence or non-existence of very rare genetic clozapine ultrarapid metabolizers (UMs) [88,122,128]; 4) consideration of personalized titration for other ancestry groups (e.g., people of Oceanian or African ancestry) and testing, as a strategy, the selection of the ancestry associated with the lowest doses in people with mixed ancestry; 5) US TDM studies with stratification by sex, smoking and ancestry to establish minimum therapeutic doses; 6) concentrations lower or higher than 350 ng/ml may be appropriate for some patients [129,130]; 7) studies on minimum therapeutic doses and concentrations for indications other than TRS; and 8) more flexible clozapine formulations, including those allowing lower dose administration [81].

4.6.3. Future guidelines for personalized dosing during maintenance treatment

These guidelines only focus on clozapine titration in order to prevent myocarditis, orthostatic hypotension, sedation and risk of early pneumonia. Supplementary Box S18 explains the need for future guidelines focused on personalized dosing during the maintenance phase, including a review of 3 major topics: the prevention of concentration-related ADRs [23], the use of adjunctive treatments such as fluvoxamine, and the use of new point-of-care devices to quickly measure WBC and TDM [1].

5. Conclusion

In conclusion, these six sets of personalized titration schedules based on ancestry, sex, smoking, co-medication, obesity, inflammation, and potential for the existence of genetic PMs are intended to make clozapine titration safer. We hope that drug agencies worldwide start considering placing in the clozapine package inserts [3] the role of ancestry in clozapine dosing and considering slow personalized titration as perhaps an inexpensive and easy way to increase clozapine safety around the world. Future studies will need to verify whether these ancestry-based titrations are helpful or not. Readers are encouraged to provide feedback to improve these titrations.

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SUPPLEMENTARY MATERIAL

An International Adult Guideline for Making Clozapine Titration Safer by Using 6 Ancestry-Based Personalized Dosing Titrations, CRP and Clozapine Levels

Table of Contents

Supplementary Table S1. Therapeutic index of second-generation antipsychotics[a]

	Therapeutic index	Range (ng/ml)		Narrow
		lower	upper	(<2)[b]
Clozapine	1.7 (600/350=1.7)	350	600	Yes
Sertindole	2 (100/50=2)	50	100	No
Risperidone[c] (paliperidone)[d]	3 (60/20=3)	20	60	No
Amisulpiride	3.2 (320/100=3.2)	100	320	No
Aripiprazole	3.5 (350/100=3.3)	100	350	No
Olanzapine	4 (80/20=4)	20	80	No
Ziprasadone	4 (200/50=4)	50	200	No
Quetiapine	5 (500/100=5)	100	500	No

AGNP, Arbeitsgemeinschaft für Neuropsychopharmakologie und Pharmakopsychiatrie; FDA, Food and Drug Administration; TDM, therapeutic drug monitoring.

[a]The most updated version [21] of the expert consensus guideline by AGNP [20] was used. Only second-generation antipsychotics with TDM at level 1 (strongly recommended) or level 2 (recommended) were included since it is likely that their therapeutic indexes will be stable in future updates of this guideline.

[b]Although it is not a formal definition, the FDA considers <2 a narrow therapeutic index [22].

[c]It includes risperidone and 9-hydroxyrisperidone.

[d]The therapeutic range of paliperidone is based mainly on data from risperidone studies.

Supplementary Table S2. Eight major causes of fatal outcomes for clozapine ADRs in VigiBase [23]

Order	Deaths[a]	ADRs[b]	Relative lethality	TRS (other risk factors besides clozapine)	Clozapine
First	2,077	Broad pneumonia (pneumonia [c] [26], lower respiratory infection and aspiration)	30% (2,077/6,983)	70% risk (0.45/0.64) in Danish registry [27,28] Smoking, obesity, medical comorbidities, co-medications, lack of adherence [29]	30% risk (0.19/0.64) in Danish registry [27-28] Associated[c] with community-acquired and aspiration pneumonia [29] Pneumonia causes a clozapine intoxication[d]
Second	1,449	Cardiac arrests and sudden deaths	90% (1,449/1,614)	↑ cardiovascular deaths in S[e] (4 times more sudden deaths than in the population) [30]	Unclear [31] (weak association with antipsychotics[f]; approximately 10% of sudden deaths in S may be due to arrhythmias[e] [30]
Third	550	Broad agranulocytosis (agranulocytosis, WBC decrease, neutropenia, leukopenia, neutrophil count decrease and granulocytopenia)	2% (550/34,931)	Some mild cases of neutropenia may be explained by co-occurrent illness (viral infections) [32]	Agranulocytosis is an idiosyncratic ADR. Probably immunologically related and associated with some HLAs [33].
Fourth	539	Broad myocarditis (cardiac failure, myocarditis,[g] and cardiomyopathy)	12% (539/4,586)	Australia[h] (> half world cases): possible overdiagnosis [34,35] and valproate (inhibitor)	Rapid clozapine titrations are definitively important in Australia [36]
Fifth	326	Broad constipation (constipation, toxic megacolon and paralytic ileus)	12% (326/2,814)	Inpatient setting [37], and anticholinergic co-medication [38,39]	3 times as much as other SGAPs [37]. Probably concentration[i]-related [40]
Sixth	319	Broad arrhythmia (tachycardia and arrhythmia)	5% (319/6,927)	TdP risks:[j] females >65 yo, prior heart problems, some co-medications and electrolyte disturbances [41]	Probably concentration[i]-related [40]
Seventh	308	Broad seizures (seizures and generalized tonic-clonic seizures)	5% (308/6,231)	History[k] of epilepsy [42] (possible ↑ risk in S[l]) [43]	Worst SGAP for seizures [44] Probably concentration[i]-related [40]
Eighth	299	Broad syncope (hypotension, syncope and orthostatic hypotension)	7% (299/4,058)	Geriatric age [45]	Probably[m] rapid titrations [46,47]

ADRs, adverse drug reactions; HLA, human leukocyte antigen; S, Schizophrenia; TdP, Torsades de Pointes; TRS, treatment-resistant schizophrenia.

[a]When the same patient was reported as having different ADRs (e.g., pneumonia and aspiration), only 1 death was counted.

[b]ADRs are grouped into major overlapping categories. For example, broad pneumonia includes any patient who had any of the following diagnoses: pneumonia, lower respiratory infection or aspiration. A patient with two overlapping diagnoses (e.g., pneumonia and aspiration) is only counted once.
[c]Pneumonia had 1,654 deaths with a relative lethality of 33% (1,654/4,951) in Vigibase and higher than other frequently used antipsychotics [26].
[d]The association between clozapine and community-acquired pneumonia may be explained by ↓ of immunoglobulins and ↑ in interleukin-1 receptor antagonism. The association between clozapine and aspiration pneumonia may be explained by ↓ swallowing and ↑ sedation and hypersalivation. Pneumonia is associated with releases of cytokines which ↑ clozapine serum concentration and create positive feedback, increasing these ADRs and even contributing to arrhythmia [29].
[e]In his recent review Vohra [30] reported that patients with S cardiovascular disease account for nearly 50% of deaths and decreased life expectancy, and the incidence of sudden cardiac death is about four times higher than in the background population. While the majority of sudden deaths are due to ischemic heart disease and its recognized risk factors, about 10% of sudden deaths are unexplained and are thought to be due to cardiac arrhythmias.
[f]According to a meta-analysis by Papola et al. [31], the strength of associations of antipsychotics with stroke, sudden cardiac death and myocardial infarction was weak.
[g]Myocarditis had 170 deaths with a relative lethality of 3% (170/3,048) in Vigibase [25].
[h]Australia accounts for >1/2 of the diagnoses in the world. In an Australian sample, Winckle et al. [34] found that many cases of myocarditis, 65% (13/20), did not meet criteria for myocarditis [35]; 25% (5/20) had upper respiratory infections that may explain the myocarditis.
[i]These ADRs are usually described as dose-related, but it is probably more accurate to call them concentration-related since they appear to be explained by the total serum concentration levels obtained by adding clozapine and norclozapine [40].
[j]TdP cases in patients on antipsychotics are usually explained by the combination of multiple risk factors. It is expected that clozapine TdP cases probably also occur in patients with several other risk factors [41].
[k]In 5,629 US patients from the centralized clozapine database, Pacia and Devinsky [42] found prevalences of 1.3% (71/5,629) of generalized tonic-clonic seizures, with two types of seizures happening during: 1) the titration phase: at low Ds (< 300 mg/day) in those with history of seizures or epilepsy, and 2) the maintenance phase: at high doses ≥ 600 mg/day.
[l]Epilepsy is more frequent in patients with psychosis. Some forms of epilepsy (particularly temporal lobe epilepsy) are associated with psychosis. It is possible that patients with S (or at least some of them) may have increased risk of epilepsy, but this issue is controversial [43].
[m]The best way of avoiding syncope and/or orthostatic hypotension is monitoring orthostatic changes during titration [46,47].

Supplementary Table S3. Estimating minimum therapeutic doses in ancestry groups

	Asian/Amerindians[a] [68,83]			Europeans [92]		
	Clozapine	D for C=350 ng/ml		Clozapine	D for C=350 ng/ml	
	C/D ratio (ng/ml per mg/day)	Calculated	Rounded[b] (mg/day)	C/D ratio (ng/ml per mg/day)	Calculated	Rounded[b] (mg/day)
♀ non-smokers	2.12	166 (350/2.12)	175	1.48	236 (350/1.48)	250
♂ non-smokers	1.67	210 (350/1.67)	225	1.18	256 (350/1.18)	275
♀ smokers	1.30	270 (350/1.30	300	0.99	357 (350/0.99)	375
♂ smokers	1.30	270 (350/1.30)	300	0.95	368 (350/0.95)	400[c]

C, concentration; C/D, concentration-to-dose; D, dose; PM, poor metabolizer; US, United States. The lowest and highest values for the four stratified groups are in red text.

[a]In 586 people of Asian ancestry from 5 samples [38 ,68], 4 clozapine PMs (0.7% of 586) were found to have a body mass index ≥ 29 mg/m, (very close to the traditional obesity cut score of body mass index ≥ 30 kg/m). These clozapine PMs, which were explained by obesity, when compared with their sex and smoking group, required much lower minimum therapeutic clozapine Ds ranging from 67 to 121 mg/day. They appear to need less than half of the minimum therapeutic clozapine D when compared with the average patient of the same sex and smoking group. In summary, obesity in these patients appears to be enough to decrease clozapine metabolism by approximately half [68].

[b]It is not easy to administer clozapine in D increments lower than 25 mg, so the calculated D was rounded to get the closest higher clozapine D that could easily be administered.

[c]Smokers tend to show greater variability in their C than non-smokers, so it may be safer to consider 400 mg/day as the minimum therapeutic D rather than 375 mg/day in male smokers. Moreover, 400 mg/day is easier to remember for clinicians.

Supplementary Table S3. Articles relevant to the issue of clozapine rapid titration

Author	Location	Titration	Patients	ADRs
Bandelow et al., 1995 [110]	Germany	Started at 25 mg 500 mg/day on day 8	1 S	First published myocarditis case in English not due to voluntary overdose
Pui-yin Chung et al., 2008 [111]	Hong-Kong	OR=18.9 rate of titration >50 mg/week OR=3.6 VPA OR=3.2 presence of physical illness	31 clozapine-induced fever cases[a]	Selected for fever after eliminating other causes
Ronaldson et al., 2012 [36]	Australia	OR=1.26 each additional 250 mg in first 9 days OR=2.59 VPA	105 myocarditis cases[b]	Selected for myocarditis
Ifteni et al., 2014 [112]	Romania	25 mg followed by 25–100 mg every 6 h (maximum of 100 mg) on day 1. Followed by ↑ of 25–100 mg/day	38 S with rapid titration	0 seizures 0 symptomatic hypotension 0 NMS
Ifteni et al., 2014 [113]	Romania	25 mg followed by 25–50 mg every 6 h (maximum 100 mg/day) on day 1. Followed by ↑ of 25–100 mg/day	44 TR BPD with mixed or manic episode	1 discontinuation due to pneumonia 1 discontinuation due to hypotension 1 discontinuation due to sedation
Aksoy Poyraz et al., 2015 [114]	Turkey	Varied in each patient	4 BPD with mania	1 excessive sedation 1 hypersalivation (sedation was considered therapeutic)
Lockhead et al., 2016 [115]	USA	25 mg started 175 mg/day & VPA added on day 8 300 mg/day on day 10	1 S (AA)	1 NMS on day 10 Transferred to medical hospital where he recovered
Chopra and de Leon, 2016 [116]	USA	On VPA. Started on 25 mg/day, 50 mg/day on day 2, 100 mg/day on day 5, 150 mg/day on day 8, 250 mg/day on day 11, 300 mg/day on day 12	1 S (AA)	Death on day 15 Myocarditis verified by autopsy
Poyraz et al., 2016 [117]	Turkey	25–50 mg followed by 50–100 mg every 6 h (maximum 150 mg/day) on day 1. Followed by increases of 50–100 mg/day	25 S with rapid titration	9 hypotension 3 excessive sedation
de Leon et al., 2020 [118]	USA	A: 175 mg/day on day 7, 300 mg/day on day 14 B: poor tolerance to 25 mg/day (kept for 4 days) C: 175 mg/day on day 7, stopped on day 14 D: 175 mg/day on day 7, 200 mg/day on day 14 E: 100 mg/day on day 7, 250 mg/day on day 14	5 S (4 AA)	5 myocarditis in New York hospital Patients B and D had levels with high clozapine C/D ratios.[c] Patient B appears to be a PM (no data on co-medication or obesity).
Danilewitz et al., 2021 [119]	Canada	Started with abnormal CRP 25 mg started, 50 mg/day on day 7, 75 mg/day on day 9, 100 mg/day on day 11 Stopped on day 16	1 S (Asian) Relative PM[d]	First clozapine trial led to myocarditis. No myocarditis after an extremely slow titration (started on 6.25 mg) in absence of ↑ CRP and very low final therapeutic dose (81.25 mg/day).

AA, African-American; ADRs, adverse drug reactions; BPD, bipolar disorder; C/D, concentration-to-dose; OR, odds ratio; PM, poor metabolizer; S, schizophrenia; TR, treatment-resistant; VPA, valproate. The clozapine dose information is in red text.

[a]Used 196 controls who did not develop fever.

[b]Used 296 controls who took clozapine for ≥45 days and did not develop myocarditis.

[c]Patient B: 34-yo AA male (unknown smoking status) with clozapine C/D ratio of 3.20 (833/260 = 3.20). Patient D: 29-yo White male (unknown smoking status) with clozapine C/D ratio of 3.68 (735/200=3.68).

[d]The patient was a clozapine PM when compared with Canadians of European ancestry: he was a male non-smoker of Asian ancestry and had a ↑ CRP before starting clozapine. After the second titration, on a clozapine dose of 81.25 mg/day of clozapine, the patient's clozapine and norclozapine concentrations were 138.6 ng/ml and 67.6 ng/ml. The clozapine C/D ratio was 1.71 (138.6/81.25=1.71) which provides a minimum therapeutic dose of 205 mg/day; that is normal for an Asian male non-smoker (the average mean clozapine C/D in 209 Asians was 1.67 ng/ml which corresponds to a minimum therapeutic dose of 210 mg/day [68]; see Supplementary Table S2).

Supplementary Table S4. Using a trough steady-state clozapine concentration to estimate final dose

	Steady state[a]		Estimated final D	
Dose	**C**	**C/D ratio**	**350 divided by C/D ratio**	**Clinical D[b]**
100 mg/day	50 ng/ml	0.50	700	700 mg/day
	100 ng/ml	1.00	350	350 mg/day
	200 ng/ml	2.00	175	175 mg/day
	300 ng/ml	3.00	117	125 mg/day
	400 ng/ml	4.00	87.5	100 mg/day
150 mg/day	100 ng/ml	0.67	522	525 mg/day
	200 ng/ml	1.33	263	275 mg/day
	300 ng/ml	2.00	175	175 mg/day
	400 ng/ml	2.67	131	150 mg/day
	500 ng/ml	3.33	105	125 mg/day
200 mg/day	100 ng/ml	0.50	700	700 mg/day
	200 ng/ml	1.00	350	350 mg/day
	300 ng/ml	1.50	233	250 mg/day
	400 ng/ml	2.00	175	175 mg/day
	500 ng/ml	2.50	140	150 mg/day
	600 ng/ml	3.00	117	125 mg/day
	700 ng/ml	3.50	100	100 mg/day
	800 ng/ml	4.00	87.5	100 mg/day
300 mg/day	200 ng/ml	0.67	522	525 mg/day
	300 ng/ml	1.00	350	350 mg/day
	400 ng/ml	1.33	263	275 mg/day
	500 ng/ml	1.67	210	225 mg/day
	600 ng/ml	2.00	175	175 mg/day
	700 ng/ml	2.33	150	150 mg/day
	800 ng/ml	2.67	131	150 mg/day
	900 ng/ml	3.00	117	125 mg/day
	1,000 ng/ml	3.33	105	125 mg/day
	1,100 ng/ml	3.66	96	100 mg/day
	1,200 ng/ml	4.00	87.5	100 mg/day

C, concentration; C/D, concentration-to-dose; D, dose.

[a]Steady state is usually defined as having no changes in clozapine D for at least 5 days.

[b]It is not easy to administer clozapine in D increments lower than 25 mg; therefore, the calculated D (350 divided by C/D ratio) was rounded to get the closest higher clozapine D that could easily be administered.

Supplementary Box S1. Mortality: Treatment-resistant schizophrenia and clozapine

1. Mortality and schizophrenia
• Schizophrenia is associated with a weighted average of 14.5 years of potential life lost [11].
2. Mortality and treatment-resistant schizophrenia
• Prior literature has not explored potential for life lost due to treatment-resistant schizophrenia [1].
3. Mortality and clozapine in patients with treatment-resistant schizophrenia
• In a meta-analysis of 24 studies with long-term follow-up treatment, Vermeulen et al. [12] found long-term, crude mortality rate ratios were significantly lower in patients continuously treated with clozapine compared to patients treated with other antipsychotics (mortality rate ratio = 0.56, 95% confidence interval = 0.36–0.85, p-value =0.007). • After this meta-analysis, a British cohort study [13] of treatment-resistant schizophrenia has also supported lower mortality in clozapine. • The recent data from the Danish registry [14], which excluded deaths after 14 days of hospitalization, found cumulative use of other antipsychotics for up to 1 year was associated with a lower all-cause mortality and suicide risk than a similar period of clozapine use (all-cause: adjusted hazard ratios = 0.73; 95% confidence interval, 0.63–0.85, suicide-adjusted hazard ratios = 0.65; 95% confidence interval, 0.46–0.91). They found that clozapine was not associated with increased cardiovascular mortality but found a lower risk of suicide. Moreover, clozapine cessation was associated with a possible increase in suicide deaths. • A re-analysis of the data of the Finnish registry (FIN20) [15] no longer found significantly lower mortality with clozapine compared to all other categories of antipsychotics, as was previously found in the first analysis (FIN11) [16].

Supplementary Box S2. Pharmacokinetics of clozapine metabolism: enzymes and metabolites

1. CYP1A2 is the main metabolic enzyme

- CYP1A2 is the most important metabolic enzyme for clozapine (>70%) [49] and leads to N-demethylation to norclozapine (or N-desmethylclozapine).
- Soon it became obvious that this contributes to metabolism differences in dosing based on sex and smoking [51]. In the clinical environment, clozapine behaves as a CYP1A2 drug with the lowest activity in female non-smokers (estrogens are CYP1A2 inhibitors) and the highest in male smokers (PAHs in tobacco smoke are inducers of CYP1A2). This is similar to another CYP1A2 drug: caffeine [50].
- Smoking inductive effects are complex and may vary per individual. On average [52-54], increased smoking increases clozapine metabolism, but at some point maximum induction may be reached.[a]

2. Other minor metabolic pathways

- Other minor metabolic enzymes that can also produce N-demethylation are [55]:
  - CYP2C19
  - CYP2D6
  - CYP3A4
- The second most important pathway may be oxidation to clozapine-N-oxide [56]. The N-oxidation may be reversible and is mainly thought to be produced [57]:
  - mainly by CYP3A4
  - secondarily by FMO3 (which is the main FMO in the liver).
- Clozapine metabolites[b] can also be conjugated by UGTs, which facilitates urinary elimination [58].

3. Norclozapine

- Norclozapine has no antipsychotic activity but may contribute to several ADRs [56].
- It is not known how well norclozapine crosses the BBB [56] but many of the receptors important for hypersalivation, constipation and cardiac ADRs are located in the periphery.
- Norclozapine is the most important metabolite in serum. In a combined analysis of 2,317 adult patients from 19 studies, the weighted mean serum clozapine/norclozapine ratio was 1.73 but the range in the studies varied widely [56]. Using this mean the serum norclozapine is estimated to be 37%[c] (1/2.73=0.37) of the total serum concentration in the average patient if the small contribution of the clozapine-N-oxide is ignored.
- Norclozapine[d] is mainly (5/6) [59] excreted through the kidney [60]. An unknown renal transporter (that can be blocked by gemfibrozil) may contribute to its excretion [56].

4. Clozapine-N-oxide

- Clozapine-N-oxide does not appear to have relevant activity at the dopamine or serotonin receptors [61].
- Clozapine-N-oxide is the second most prevalent metabolite in serum; most of the time the concentrations are low. In a systematic review that included 23 TDM studies [62], only 3 included clozapine-N-oxide concentrations. After adding the three concentrations (clozapine, norclozapine and clozapine-N-oxide), the range for the clozapine-N-oxide was between 8-10%.
- Clozapine-N-oxide [60] is the most important urinary metabolite[e] (and is probably eliminated by a renal transporter).[f]

ADRs, adverse drug reactions; BBB, blood-brain barrier; CYP, cytochrome P450; FMO, flavin-containing monooxygenase; PAH, polycyclic aromatic hydrocarbon; TDM, therapeutic drug monitoring; US, United States; UGT, UDP-glucuronosyltransferase

[a]Haslemo et al. [52] proposed that 7–12 cigarettes/day is probably sufficient for maximum induction of clozapine metabolism. Dobrina et al. [53] estimated that on average the CYP1A2 inducibility varied per

number of cigarettes. The inducibility was 1.44 for 10-19 cigarettes/day, 1.67 for 20-19 cigarettes/day, 1.54 for 30-39 cigarettes/day and 2.12 for 40-70 cigarettes/day. In a meta-analysis, Wagner et al. [54] proposed an average 30% reduction of dose after smoking cessation but wide individual variability.

[b]For a more precise estimation of the relative percentage, the concentration should be compared using µmol/L instead of ng/ml which is typically used by commercial laboratories and psychiatric articles.

[c]UGT1A4 conjugates glucuronide to produce clozapine-5-N-glucuronide and norclozapine-5-N-glucuronide while UGT1A3 conjugates glucuronide to produce clozapine-5-N-glucuronide. These glucuronides explain 1-3% of clozapine elimination in urine [58].

[d]In a study of 15 patients in long-term clozapine treatment, Schaber et al. [60] proposed that clozapine is mainly metabolized while norclozapine's renal elimination is 3 times higher than the creatinine clearance, which is an index of glomerular filtration, meaning that norclozapine is eliminated by net tubular secretion. In fact, they estimate that 71% of free norclozapine was eliminated by tubular secretion.

[e]Using isotopes to study renal clearance, Schaber et al. [60] found that the mean ratios in urine for clozapine:norclozapine:clozapine-N-oxide were 1:43:85 in the patients with an even distribution of doses.

[f]In a study of 15 patients on long-term clozapine treatment, Schaber et al. [60] proposed that clozapine-N-oxide is 6 times higher than creatinine clearance, which is an index of glomerular filtration, meaning that clozapine-N-oxide is eliminated by net tubular secretion. In fact, the authors estimated that 86% of free clozapine-N-oxide was eliminated by tubular secretion.

Supplementary Box S3. Variables that are clinically relevant in clozapine metabolism[a]

1. Drug-drug interactions
• CYP1A2 activity is ↓ by inhibitors. Inhibitors can be classified based on impact: o Strong [1,63,64]: amiodarone,[b] fluvoxamine,[c] and ciprofloxacin[d] (do not start clozapine) o Moderate (↓ to 1/2 of D): oral contraceptives.[e] Use slower titration. o Possibly moderate: caffeine in high doses.[f] Avoid use or consider slower titration. o Possibly mild/moderate: flupenthixol, TCAs and high Ds of sertraline or perphenazine [1,65]. It may depend on the patient and be an inhibitor only in high doses. o Clinically irrelevant: paroxetine and fluoxetine can be ignored in most patients. • Remember smoking cessation or removal of an inducer also ↓ CYP1A2 activity [66,67].[g] • CYP1A2 activity is ↑ by inducers. Inducers can be classified according to their impact: o Strong: rifampicin (do not combine) [64] o Moderate (↑ D by 1.5-2 times) [21]: carbamazepine,[h] phenobarbital and phenytoin. Consider stopping them before starting clozapine and waiting 2 weeks (titration may take a very long time with our guideline recommendations). o Mild: only evident in non-smokers [1]: omeprazole.[i] o Possibly mild inducers but not well studied: modafinil, levopromazine,[j] high intake of coffee in South Asia [68],[k] oxcarbazepine (≥1200 mg/day) and topiramate (≥400 mg/day) [21]. • Valproate (as with olanzapine) has a complex profile and can be an inhibitor/inducer and vary over time and from individual to individual [69]: o Induction: predominates after several weeks and is clearer for norclozapine o Inhibition: appears to happen with clozapine and predominates in first 1-2 weeks; thus, during titration it is safer to consider valproate as a potential inhibitor [70-74].[l]
2. Obesity
• Clozapine is lipophilic and deposits in the fat tissue. In a longitudinal study, the ↑ % of fat tissue was associated with a ↓ clozapine metabolism within an individual patient [75]. As far as we can tell, BMI ≥ 29 may be associated with a decrease in clozapine metabolism by approximately half and explains 4 cases (0.7%) of clozapine PMs in 586 Asians from 5 samples [40,68]. • Cross-sectional TDM studies [68,77] suggest that increased weight is associated with greater clozapine concentrations and that obesity decreases the metabolism of other CYP1A2 drugs [78].
3. Inflammation
• Inflammation releases cytokines which inhibit CYP1A2 and other CYPs. The US package insert for theophylline (CYP1A2 drug) warns that its levels increase during any fever [1]. • CRP elevations are associated with increases in serum clozapine concentrations [78].[m] • ↑ in serum clozapine concentrations during infections were described in 40 cases [79]. • In a large clozapine cohort [65] of 131 Chinese inpatients, inflammation/infection was present during 2% of days (482/24,789) including 18 different episodes in 16 patients. The episodes were associated with: o no clinically relevant effects in 11% of infection episodes (no leukocytosis or ↑ CRP), o ↓ clozapine D to 1/2 would be advisable in 61% of the infection episodes, and o ↓ clozapine D to 1/3 would be advisable in 28% of infection episodes [65] • Clozapine, by inducing inflammation during fast titrations, can decrease its own metabolism [1].
4. Geriatric age
• Geriatric age is associated with ↓ in elimination of urinary clozapine metabolites [56].
5. Pregnancy
• ↑ Estrogens in the 2nd & 3rd trimesters: ↓ CYP1A2 activity and ↑ serum clozapine concentration.

CRP, C-reactive protein; CYP, cytochrome P450; BMI, body mass index; D, dose; TCA, tricyclic antidepressant; TDM, therapeutic drug monitoring.

[a]These recommendations will need to be updated as new information becomes available.

[b]Amiodarone is a potent inhibitor of CYP3A4, while its metabolite inhibits CYP1A2, CYP2B6, and CYP2D6 so it can increase clozapine levels. It is a drug with high potential for toxicity used to prevent severe arrhythmias including recurrent ventricular tachycardia and should not be combined with clozapine.

[c]Fluvoxamine is a strong inhibitor, although several randomized clinical trials have used fluvoxamine as a potential adjuvant therapy, particularly for metabolic ADRs. Since 1994 [63] it is clear it is a very potent inhibitor of clozapine metabolism that may require ↓ D to 1/5 to 1/10 to keep the same C [23] As it is not easy to predict the effects in each individual, it does not appear safe to try to titrate clozapine in patients on fluvoxamine or add fluvoxamine to a maintenance D without a sophisticated understanding of TDM [23].

[d]Ciprofloxacin is a powerful CYP1A2 inhibitor, a moderate CYP3A4 inhibitor and ↑ QTc by inhibiting the heart potassium channels. There are cases of death due to the combination of clozapine and ciprofloxacin; therefore, patients should not be started on clozapine when they are taking ciprofloxacin [64]. Enoxacin and norfloxacin are also relevant CYP1A2 inhibitors and ↑ QTc by inhibiting the heart potassium channels. Thus, it is also very risky to start clozapine in patients taking enoxacin and norfloxacin. Levofloxacin is not believed to be a CYP1A2 inhibitor [65] but we also recommend avoiding it as much as possible and starting clozapine when the trial of levofloxacin has been completed.

[e]The estrogens in oral contraceptives are moderate CYP1A2 inhibitors.

[f]Caffeine is present in coffee, tea and caffeinated beverages. A detailed list of estimated caffeine content in US beverages is provided on a webpage https://www.caffeineinformer.com/the-caffeine-database

No study provides clear instructions to clinicians on what quantity of caffeine could be clinically relevant. Until prospective studies are available, we recommend caution with increases or decreases of daily caffeine intake of > 1 cup of coffee (or 2 cans of caffeinated soda) in non-smokers and > 3 cups of coffee (or 6 cans of caffeinated soda) in smokers. For example, when a smoker taking clozapine increases caffeine intake by 3 cups of coffee (e.g., from 2 to 5 cups per day), clinicians should watch for increased side effects due to ↑ clozapine C.

[g]In smokers, smoking cessation can lead to increases in the serum clozapine concentrations; studies suggest that it may take 2-4 weeks to reach maximum increases in serum clozapine concentrations [66]. A study on smoking cessation [67] provided a CYP1A2 half-life of 38.6 hours (27.4 to 54.4 hours). In days, the value is 1.6 days (1.1 to 2.3 days). If we assume that 5 half-lives of CYP1A2 are required for eliminating almost all (95%) of the extra CYP1A2 synthesized under induction. This provides on average 8 days (5 x 1.6 days=8). The lower range is 5.5 days (5 x 1.1 days=5.5) and the upper range is 11.5 days (5 x 2.3 days=8). Once CYP1A2 induction has completely disappeared, 5 clozapine half-lives are needed for reaching 95% of the maximum clozapine concentrations; if we assume a clozapine half-life of 1 day, this provides 5 extra days. Adding these two figures (CYP1A2 half-life and clozapine half-life) provides a mean of 13 days (8+5=13), but the range is 10.5 days (5.5+5=10.5) to 16.5 days (11.5+5=16.5). If instead of 5 half-lives, a stricter limit of 7 half-lives (99% of steady state concentration) is used, the time for reaching maximum clozapine serum concentrations is 18 days (range of 15 to 23 days).

[h]Carbamazepine can cause agranulocytosis; in many countries, its combination with clozapine is contraindicated.

[i]Omeprazole, esomeprazole and lansoprazole appear to be mild CYP1A2 inducers. Pantoprazole does not appear to be an inducer of clozapine metabolism.

[j]Two cases of possible clozapine induction by high doses of levomepromazine (>100 mg/day) have been described.

[k]Roasted coffee beans in the coffee of India and Sri Lanka appear to have a high quantity of polycyclic aromatic hydrocarbons (such as those in tobacco smoke) and when consumed in great quantities may induce clozapine metabolism [68].

[l]All the studies on valproate's effects on clozapine metabolism have been cross-sectional and there are no longitudinal studies. Although in several of them the inductive effects predominate some of them suggested that inhibition of clozapine, the main compound may predominate. In 1999, Facciola et al. using a design of off-on in 6 Italian patients found variable inhibitory effects [70]. In 2006, Wong in 51 Chinese patients found than on average the inhibitory effects corresponded to a dose-correction factor of 0.85 [71]. In 2008, Diaz et al. studied 37 patients on VPA (with 45 Cs) and 255 patients without VPA (415 Cs) and found that in a statistical model VPA had an inhibitory effect in non-smokers, significantly increasing clozapine levels by 16%. The effect was much smaller in the total concentration, only a 6% increase, and no longer significant. This is compatible with VPA having a competitive inhibitory effect in non-smokers, probably restricted to clozapine and not influencing norclozapine [72]. In 2013, Rajkumar et al. studied 101 consecutive Indian patients (33% smokers) using a single clozapine concentration; 9 patients were co-prescribed VPA. VPA behaved as an inhibitor of clozapine (norclozapine was not measured) [73]. Olanzapine is also mainly metabolized by CYP1A2, as clozapine is, and in a longitudinal study of 18 patients when valproate was added inhibitory and inductive effects of valproate were found that depend on the VPA concentration and time. In non-smokers with low VPA concentrations inhibition predominated in the second week, while in the fourth week the inhibitory effects were overruled by the inductive effects which predominated [74].

[m]During the infections some patients develop intoxication symptoms with relatively low concentrations (clozapine <1000 ng/ml) and others do not develop even with very high concentrations (>1000 ng/ml). Some have proposed that the explanation may be that personal, environmental and genetic influences may explain differences in pharmacodynamic response [65]. Other have proposed that during infections there is an increase of serum clozapine concentrations, but also increases in orosomucoid/alpha1-acid glycoprotein which reduce the free clozapine concentration [78]. It is also possible that norclozapine concentrations may contribute to signs of clozapine intoxication in some patients [56].

Supplementary Box S4. CYP1A2 gene and DNA ancestry

1. DNA ancestry

- The model of human evolutionary history [80] suggests that there are 5 ancestry groups (each group progressively branched out and separated from the original African population):
  - African
  - European (and Western Asians[b])
  - Asian (the FDA [81] definition: ancestry ranging from Pakistan to Japan)
  - Oceania
  - Original inhabitants of the Americas or Amerindians (split from East Asians[a]).

2. CYP1A2 activity and Asian ancestry

- According to a very well-controlled study using caffeine as a CYP1A2 probe after stratifying by sex, smoking and CYP1A2 alleles, Swedes always had higher CYP1A2 activity than Koreans [50].
- Since 1997, studies [68,81,82] have reported that Asians have the same serum clozapine concentrations with half the clozapine dosage prescribed in Western countries. Doses > 300 mg/day are infrequently used in Asian countries [81]. According to a systematic review [62], Asians have lower clozapine metabolism than patients in the US and Europe.
- The original inhabitants of the Americas (Amerindians) are descendants of Asians and metabolize clozapine similarly to people of Asian ancestry [83].

3. Explanation for lower CYP1A2 activity in people of Asian (and Amerindian) ancestry

- There are two major explanations [62] for lower CYP1A2 activity in Asians (and Amerindians) when compared with those of European (and Western Asian[b]) ancestry, Asians have:
  - a change in a CYP1A2 gene that ↓ its activity, or
  - a change in other gene/genes that may control CYP1A2 activity.

4. People of Oceanian ancestry

- No recommendation is provided in this article for patients of Oceanian ancestry due to a lack of published TDM data on repeated dosing. A study funded by a commercial company [84] proposed that Māoris (the indigenous people of New Zealand) may have similar clozapine clearance to people of Caucasian ancestry, but this study used a complex pharmacokinetic model to compare a single dose in 12 Māori (8 smokers) and 16 European (6 smokers) patients from New Zealand and did not adjust for smoking, sex or co-medications. Based on this study and the clinical experience of one of the authors, it appears reasonable, until more studies are available, to consider people from Oceania as a group who require doses similar to the doses of people of European ancestry.

5. People of African ancestry and their data on olanzapine

- There are no good TDM studies [62] in patients of African descent. In the US, clinicians are not aware of clozapine dose differences for African-Americans.
- The literature does not give enough attention to the fact that olanzapine, another drug mainly metabolized by CYP1A2, can also be induced by valproate, and can be inhibited by inflammation [85]. This is a pattern similar to clozapine. Moreover, a single-dose study in males [86], completed by the company which marketed olanzapine, suggests that Asians need lower olanzapine doses, approximately 20% lower [85]. The company completed a population pharmacokinetic study using the olanzapine RCTs. After controlling for sex and smoking, olanzapine metabolism was lower in Asians than Whites and higher in African-Americans [87]. Based on this study, it can be estimated that average olanzapine Ds should be 1.25 times higher in African-Americans [85].
- If the olanzapine analogy is correct, it is likely that African-Americans may need higher clozapine Ds than those of European ancestry.

CYP, cytochrome P450; TDM, therapeutic drug monitoring; US, United States.

[a]East Asians include people from China, Korea, Japan, and Mongolia, who are closely related from the genetic point of view.
[b]Western Asians [80] are those Asians whose ancestry is from countries west of Pakistan. This definition will need more clarification as new genetic studies are completed.

Supplementary Box S5. Clozapine and genotyping

1. CYP1A2 genotyping is not ready for clinical use
• Multiple alleles have been described in CYP1A2. • Commercial tests in the US and Europe describe some frequent CYP1A2 variants (particularly CYP1A2*1F and CYP1A2*1K) that have no clinical relevance [88].
2. CYP2D6 genotyping is irrelevant for clozapine metabolism
• In the US clozapine package insert [48] the FDA recommends lower clozapine doses in CYP2D6 PMs, but there is general agreement in the literature that this is not correct [88]. • The DPWG guideline recommends paying no attention to CYP2D6 genotyping for clozapine dosing [89].
3. Nuclear receptor genotyping is not ready for clinical use
• CYP1A2 inducers are believed to act through the aryl hydrocarbon and/or nuclear receptors. Thus, the nuclear receptor gene variants [90] are likely candidates to explain variations in CYP1A2 activity but are not ready for clinical practice.
4. Genotyping to classify ancestry
• Multiple commercial companies provide ancestry classification based on DNA markers. Currently it is not known how these tests can be used to help classify patients according to ancestry and therefore select among our clozapine titrations. Once our knowledge of CYP1A2 genotyping and/or epigenetics develops (see Section 2, Supplementary Box S15), our ancestry classification may no longer be needed and more precise titration will be based on genotyping of CYP1A2 or other genes, or identification of epigenetic markers on CYP1A2 or other genes.

CYP, cytochrome P450; DPWG, Dutch Pharmacogenetics Working Group; FDA, Food & Drug Administration; PM, poor metabolizer.

Supplementary Box S6. Measuring serum/plasma clozapine concentrations

1. Elimination half-life
• The package insert [46] states the mean elimination half-life of clozapine after a single 75-mg dose was 8 hours (range: 4 to 12 hours), compared to a mean elimination half-life of 12 hours (range: 4 to 66 hours), after achieving steady-state with 100 mg twice daily dosing. There is no description of how this half-life was calculated. • Single-dose studies provide short half-lives and suggest dosing twice a day. As clozapine is lipophilic, in repeated dosing, clozapine deposits in fat tissue providing longer half-lives (e.g., 17-34 hours in 3 US patients). This may explain why clozapine can be administered once a day. As people from Asian and Amerindian ancestry have lower clearance and longer half-life, it is very likely that once-a-day dosing should be appropriate for them.
2. Steady-state conditions
• Steady state is usually described as needing at least 5 drug half-lives [1]. Steady state refers to the equilibrium between absorption and elimination that occurs in serum/plasma concentrations after changing a drug dose. • In average patients, at least 5 days are required to achieve clozapine steady-state conditions (if we assume clozapine half-life under repeated dosing is approximately 24 hours; thus 5 times 24 hours is 5 days).
3. Trough conditions
• Trough refers to the lowest point of the serum concentration during the day. • In patients taking two doses (one during the day and one at night) trough drawing will be done before taking the daytime dose [20]. • For practical reasons, in patients taking only a nighttime dose, some authors recommend drawing 12 hours after the last clozapine dose [91]. A careful TDM study [91] suggested that there are small variations in collecting samples between 10 to 14 hours after the last dose, but it is important to standardize the timing of collection after the last dose in each patient to better compare all his/her TDMs.
4. Using prior TDM to predict target dose
• As the text described, clozapine follows linear kinetics (i.e., the relationship between dose and concentration is linear) when two conditions are met: 1) therapeutic dosages and 2) the absence of inducers/inhibitors). • Although it has not been systematically studied, when serum concentrations are very low (<150 ng/ml) or very high (>1000 ng/ml) clozapine may not follow linear kinetics. Moreover, in low serum concentrations (≤ 150 ng/ml) clozapine TDM has substantial variations in the same patient taking the same clozapine dose and does not follow linear kinetics.
5. Analytical techniques
• A prior TDM review [20] has briefly addressed the advances in this area.

TDM, therapeutic drug monitoring.

Supplementary Box S7. Limited US information suggesting need for higher clozapine daily doses

1. Clozapine doses recommended in US textbooks and review articles
• Lieberman et al., 1989 [97]: 450-600 mg/day • Baldessarini and Frankenburg, 1991 [98]: 250-450 mg/day (maximum 900 mg/day) • Citrome, 2009 [99]: 300-450 mg/day • Meltzer, 2012 [100]: 300-600 mg/day (maximum 900 mg/day) • Marder and Yang, 2017 [101]: typical doses 300-400 mg/day (associated with TDM 200-400 ng/mL) • Meyer and Stahl, 2020 [102]: It recommends TDM to establish doses
2. Retrospective chart review of 71[a] patients in a US hospital providing a nomogram [51]

• The graphic representation of the nomogram[b] indicates that minimal therapeutic doses were:
  ○ male smokers: around 450 mg/day,
  ○ female smokers: 300 mg/day, and
  ○ male non-smokers: 200 mg/day.

3. Minimum therapeutic dose calculated using clozapine C/D ratios from literature [103]

• In 2005, US clozapine C/D ratios were proposed to range from 0.6 to 1.2 ng/ml per mg/day:
  ○ male smokers: may need 600 mg/day (C/D ratio = 0.6 ng/ml per mg/day)
  ○ female non-smokers: may need 300 mg/day (C/D ratio = 1.2 ng/ml per mg/day)

4. Systematic review TDM studies:[c] US patients needed higher clozapine doses than Europeans[a]

• Weighted average mean clozapine C/D ratios were used to calculate minimum clozapine therapeutic doses [92]:
  ○ 312 mg/day in 790 European patients from 6 studies (probably all of European ancestry)
  ○ 368 mg/day in 357 US patients (3%, 9/357, described as African-Americans) in 6 studies
• These samples provided no data stratified by sex and smoking status so it cannot be controlled by these two confounders. Moreover, most included studies ignored co-medication [62].

5. US RCT with 3 clozapine doses [104]
• Unpublished data[d] from a RCT of 50 patients [104] suggested that the average minimum therapeutic dose for male smokers (many smoking 1-2 packs/day) was around 515 mg/day (35%, 6/17 needed minimum therapeutic doses >600 mg/day) with no obvious difference in African vs. European ancestry.

C/D, concentration-to-dose; CYP, cytochrome P450; D, dose; RCT, randomized clinical trial; TDM, therapeutic drug monitoring; UM, ultrarapid metabolizer; US, United States.

[a]The chart review included 71 patients, 96% (68/71) of European ancestry and 4% (3/71) of African ancestry, 73% (52/71) smokers and 27% (19/71) non-smokers, 62% (44/77) males and 38% (27/71) females [51].

[b]The nomogram was represented in a figure published in the article [51]. The serum clozapine concentration of 350 ng/ml on the y axis was used to estimate the clozapine dose on the x-axis. The line representing female non-smokers started above 350 ng/ml; thus, a minimum therapeutic dose could not be estimated.

[c]In the original meta-analysis [62] the European and US patients were combined together. In a rank re-analysis [92] of the 13 samples, 6 of the 7 European samples had the highest clozapine C/D ratios. This difference in rank was significant according to an independent-sample Mann-Whitney U test ($p = 0.035$).

[d]The first author supervised an RCT funded by the US National Institute of Mental Health to compare 3 doses under double-blind conditions in 50 patients (only 10% response). A dose of 100 mg/day was not effective in any patient while the doses of 300 mg/day and 600 mg/day were effective in some patients but the study did not have enough statistical power to establish anything else [104].

Supplementary Box S8. Hypothetical model for hypersensitivity in clozapine-induced myocarditis[4]

1. First phase

• The titration is too fast for that specific patient, due to:
  ○ the psychiatrist's over-aggressive prescribing and/or
  ○ the patient's clozapine PM status
• This leads to a clozapine-induced inflammation which releases cytokines and ↑ CRP.
• Fever or eosinophilia can also be present.

2. Second phase
• A positive feedback loop develops, the cytokines inhibit CYP1A2 and other CYPs; thus, further increasing the serum clozapine concentrations.
3. Third phase

• If the titration continues, the inflammation becomes complicated by the development of a hypersensitivity reaction (presumably with auto-antibodies) which leads to:
  ○ myocarditis, or
  ○ other local inflammations including serositis, pneumonitis, hepatitis, pancreatitis, nephritis or colitis, which can also occur in the first two months of treatment during too-rapid titration [141].

CRP, C-reactive protein; CYP, cytochrome P450; PM, poor metabolizer.

Supplementary Box S9. Inpatients of Asian/Amerindian ancestry: titration for lower metabolism[a]

Baseline (check general instructions)
-Expected therapeutic Ds: 75-150 mg/day (expected range for clozapine C/D ratios: 4.7 to 2.3) -This is required for patients taking oral contraceptives or valproate or who are obese. -Remember, when giving the next clozapine D, tolerance is measured by sedation and orthostatic hypotension. Moreover, when you are titrating there are 2 additional reasons to stop up-titration and hold the dose: 1) If CRP becomes abnormal,[b] hold dose escalation until CRP normalizes. Add troponin monitoring. 2) If clozapine C is higher than the value provided for that week.
First week
-Administer the first dose of 6.25 mg at night to avoid sedation and orthostatic hypotension.[c] -If tolerated,[c] ↑ daily dose by 6.25 mg, keeping all[d] or approximately 2/3 at night (avoid ↑ during a weekend).[e] -Target 25 mg/day at the end of the first week.
Second week
-With WBC, order CRP and, when possible, clozapine C (should be <118 ng/ml). -If tolerated,[c] ↑ twice at 12.5 mg/day each time, keeping all[d] or approximately 2/3 at night (avoid ↑ during a weekend).[e] -Target 50 mg/day at the end of the second week.
Third week
-With WBC, order CRP and, when possible, clozapine C (should be <235 ng/ml). -If tolerated,[c] ↑ twice at 12.5 mg/day each time, keeping all[d] or approximately 2/3 at night (avoid ↑ during a weekend).[e] -Target 75 mg/day at the end of the third week.
Fourth and following weeks
-With WBC, order CRP and, when possible, clozapine C (should be <353 ng/ml). -The recommended target efficacious D is between 75 mg/day for a ♀ non-smoker and 150 mg/day for a ♂ smoker. -If the patient is a ♀ non-smoker and C is available, measure it 1 week after reaching 75 mg/day to decide target D. -For ↑ dose in others: ↑ 25 mg/day each time with a target ↑ not >50 mg/week and 1 week after reaching a target D not >150 mg/day. Once the target D is reached, measure C 1 week later to decide final D.

C, concentration; C/D, concentration-to-dose; CRP, C-reactive protein; D, dose; TDM, therapeutic drug monitoring; WBC, white blood cells. The Ds and C/D ratios to remember are in red text.

[a]These recommendations will need to be updated as new information becomes available.

[b]If the CRP becomes abnormal after having a normal baseline, the clinician should consider the possibility that an infection or a clozapine-induced inflammation is present. Both can be associated with ↓ clozapine metabolism; it is better to hold clozapine D increases until CRP becomes normal.

[c]When possible during titration, orthostatic changes in blood pressure and pulse need to be measured (see the scale in the Appendix). Orthostatic abnormalities or other ADRs should signal the need for a slower titration. Fever should prompt stopping titration and drawing CRP (and troponin when available).

[d]Giving 1/3 of the dose during the daytime (morning or noon) allows for observation during the daytime, while giving the whole dose at night makes it less likely that ADRs will be detected. However, if orthostatic changes happen during the night they will have little clinical relevance unless the patient gets up in the middle of the night. Asian patients have lower clozapine clearance and higher clozapine half-life; thus, once-a-day administration at night is a very reasonable option.

[e]Avoid major ↑ in dose during weekends or times with less nursing supervision.

Supplementary Box S10. Inpatients of Asian/Amerindian ancestry: titration for average metabolism[a]

Baseline (check general instructions)
-Expected therapeutic Ds: 175-300 mg/day (expected range for clozapine C/D ratios: 2.1 to 1.3) -Remember, when giving the next clozapine D, tolerance is measured by sedation and orthostatic hypotension. Moreover, when you are titrating there are 2 additional reasons to stop up-titration and hold the dose: 1) If CRP becomes abnormal,[b] hold D escalation until CRP normalizes. Add troponin monitoring. 2) If Clozapine C is higher than the value provided for that week.
First week
-Administer the first D of 12.5 mg at night to avoid sedation and orthostatic hypotension.[c] -If tolerated,[c] ↑ daily D by 12.5 mg, keeping all[d] or approximately 2/3 at night (avoid ↑ during a weekend).[e] -Target 50 mg/day at the end of the first week.
Second week
-With WBC, order CRP and, when possible, clozapine C (should be <105 ng/ml). -If tolerated,[c] ↑ twice at 12.5 mg/day each time, keeping all[e] or approximately 2/3 at night (avoid ↑ during a weekend).[e] -Target 100 mg/day at the end of the second week.
Third week
-With WBC, order CRP and, when possible, clozapine C (should be <210 ng/ml). -If tolerated,[c] ↑ twice at 25 mg/day each time, keeping all[d] or approximately 2/3 at night (avoid ↑ during a weekend).[e] -Target 150 mg/day at the end of the third week.
Fourth and following weeks
-With WBC, order CRP and, when possible, clozapine C (should be <315 ng/ml). -The recommended target efficacious D is between 175 mg/day for a ♀ non-smoker and 300 mg/day for a ♂ smoker. -If the patient is a ♀ non-smoker and C is available, measure it 1 week after reaching 175 mg/day to decide target D. -For ↑ D in others: ↑ 25 mg/day each time with a target ↑ not >50 mg/week and 1 week after reaching a target D not >300 mg/day. Once target D is reached, measure C 1 week later to decide final D.

C, concentration; C/D, concentration-to-dose; CRP, C-reactive protein; D, dose; TDM, therapeutic drug monitoring; WBC, white blood cells. The Ds and C/D ratios to remember are in red text.

[a]These recommendations will need to be updated as new information becomes available.

[b]If the CRP becomes abnormal after having a normal baseline, the clinician should consider the possibility that an infection or a clozapine-induced inflammation is present. Both can be associated with ↓ clozapine metabolism; it is better to hold clozapine dose increases until CRP becomes normal.

[c]When possible during titration, orthostatic changes in blood pressure and pulse need to be measured (see the scale in the Appendix). Orthostatic abnormalities or other ADRs should signal the need for a slower titration. Fever should prompt stopping titration and drawing CRP (and troponin when available).

[d]Giving 1/3 of the dose during the daytime (morning or noon) allows for observation during the daytime, while giving the whole dose at night makes it less likely that ADRs will be detected. However, if orthostatic changes happen during the night they will have little clinical relevance unless the patient gets up in the middle of the night. Asian patients have lower clozapine clearance and higher clozapine half-life; thus, once-a-day administration at night is a very reasonable option.

[e]Avoid major ↑ dose during weekends or times with less nursing supervision.

Supplementary Box S11. Inpatients of European/Western Asian[a] ancestry: titration for lower metabolism[b]

Baseline (check general instructions)
-Expected therapeutic Ds: 100-200 mg/day (expected range for clozapine C/D ratios: 3.5 to 1.75) -This is required for patients taking oral contraceptives or valproate or who are obese. -Remember, when giving the next clozapine D, tolerance is measured by sedation and orthostatic hypotension. Moreover, when you are titrating there are 2 additional reasons to stop up-titration and hold the dose: 1) If CRP becomes abnormal,[c] hold D escalation until CRP normalizes. Add troponin monitoring. 2) If Clozapine C is higher than the value provided for that week.
First week
-Administer the first D of 12.5 mg at night to avoid sedation and orthostatic hypotension.[c] -If tolerated,[d] ↑ the daily D by 12.5 mg, keeping approximately 2/3 at night (avoid ↑ during a weekend).[e] -Target 50 mg/day at the end of the first week.
Second week
-With WBC, order CRP and, when possible, clozapine C (should be <175 ng/ml). -If tolerated,[d] ↑ twice at 25 mg/day each time, keeping approximately 2/3 at night (avoid ↑ during a weekend).[e] -Target 75 mg/day at the end of the second week.
Third week
-With WBC, order CRP and, when possible, clozapine C (should be <263 ng/ml). -If tolerated,[d] ↑ twice at 25 mg/day each time, keeping approximately 2/3 at night (avoid ↑ during a weekend).[e] -Target 100 mg/day for ♀ non-smokers and 150 mg/day for others at the end of the third week.
Fourth and following weeks
-With WBC, order CRP and, when possible, clozapine C (should be <350 ng/ml). -The recommended target efficacious D is between 100 mg/day for a ♀ non-smoker and 200 mg/day for a ♂ smoker. -If the patient is a ♀ non-smoker and C is available, measure it 1 week after reaching 100 mg/day to decide target D. -For ↑ D in others: ↑ 25 mg/day each time with a target ↑ not >50 mg/week and 1 week after reaching a target D not >200 mg/day. Once the target D is reached, measure C 1 week later to decide final D.

C, concentration; C/D, concentration-to-dose; CRP, C-reactive protein; D, dose; TDM, therapeutic drug monitoring; WBC, white blood cells. The Ds and C/D ratios to remember are in red text.

[a]Western Asians are those whose ancestry is from Asian countries west of Pakistan. This definition will need more clarification as new genetic studies are completed.

[b]These recommendations will need to be updated as new information becomes available.

[c]If the CRP becomes abnormal after having a normal baseline, the clinician should consider the possibility that an infection or a clozapine-induced inflammation is present. Both can be associated with ↓ clozapine metabolism; it is better to hold clozapine dose increases until CRP becomes normal.

[d]When possible during titration, orthostatic changes in blood pressure and pulse need to be measured (see the scale in the Appendix). Giving 1/3 of the dose in the early morning allows for observation during the morning while giving the whole dose at night makes it less likely that ADRs will be detected. However, if orthostatic changes happen they will have no relevance unless the patient gets up in the middle of the night. Orthostatic abnormalities or other ADRs should signal the need for a slower titration. Fever should prompt stopping titration and drawing CRP (and troponin when available)

[e]Avoid major ↑ in D during weekends or times with less nursing supervision.

Supplementary Box S12. Inpatients of European/Western Asian[a] ancestry: titration for average metabolism[b]

Baseline (check general instructions)
-Expected therapeutic Ds: 250-400 mg/day (expected range for clozapine C/D ratios: 1.4 to 0.88) -Remember, when giving the next clozapine D, tolerance is measured by sedation and orthostatic hypotension. Moreover, when you are titrating there are 2 additional reasons to stop up-titration and hold the dose: 1) If CRP becomes abnormal,[c] hold dose escalation until CRP normalizes. Add troponin monitoring. 2) If clozapine C is higher than the value provided for that week.
First week
-Administer the first D of 25 mg at night to avoid sedation and orthostatic hypotension.[d] -If tolerated, ↑ the daily D by 25 mg, keeping approximately 2/3 at night (avoid ↑ during a weekend).[e] -Target 100 mg/day at the end of the first week.
Second week
-With WBC, order CRP and, when possible, clozapine C (should be <140 ng/ml). -If tolerated,[d] ↑ twice at 50 mg/day each time, keeping approximately 2/3 at night (avoid ↑ during a weekend).[e] -Target 200 mg/day at the end of the second week.
Third week
-With WBC, order CRP and, when possible, clozapine C (should be <280 ng/ml). -If tolerated,[d] ↑ twice at 25 mg/day each time, keeping approximately 2/3 at night (avoid ↑ during weekend).[e] -Target 250 mg/day for a ♀ non-smoker and 300 mg/day for others at the end of the third week.
Fourth and following weeks
-With WBC, order CRP and, when possible, clozapine C (should be <350 ng/ml). -The recommended target efficacious D is between 250 mg/day for a ♀ non-smoker and 400 mg/day for a ♂ smoker. -If the patient is a ♀ non-smoker and C is available, measure it 1 week after reaching 250 mg/day to decide target D. -For ↑ D in others: ↑ 25 mg/day each time with a target ↑ not >50 mg/week and 1 week after reaching a target D not >400 mg/day. Once target D is reached, measure level 1 week later to decide final D.

C, concentration; C/D, concentration-to-dose; CRP, C-reactive protein; D, dose; TDM, therapeutic drug monitoring; WBC, white blood cells. The Ds and C/D ratios to remember are in red text.

[a]Western Asians are those whose ancestry is from Asian countries west of Pakistan. This definition will need more clarification as new genetic studies are completed.

[b]These recommendations will need to be updated as new information becomes available.

[c]If the CRP becomes abnormal after having a normal baseline, the clinician should consider the possibility that an infection or a clozapine-induced inflammation is present. Both can be associated with ↓ clozapine metabolism; it is better to hold clozapine D increases until CRP becomes normal.

[d]When possible during titration, orthostatic changes in blood pressure and pulse need to be measured (see the scale in the Appendix). Giving 1/3 of the dose in the early morning allows for observation during the morning while giving the whole dose at night makes it less likely that ADRs will be detected. However, if orthostatic changes happen they will have no relevance unless the patient gets up in the middle of the night. Orthostatic abnormalities or other ADRs should signal the need for a slower titration. Fever should prompt stopping titration and drawing CRP (and troponin when available).

[e]Avoid major ↑ D during weekends or times with less nursing supervision.

Supplementary Box S13. US inpatients of Non-Asian/Amerindian ancestry: titration for lower metabolism[a]

Baseline (check general instructions)
-Inpatients of Asian or Amerindian (original inhabitants of the Americas) ancestry should be treated following Supplementary Box S9. This titration is for inpatients of European or African ancestry. -Expected therapeutic Ds: 150-300 mg/day (expected range for clozapine C/D ratios: 2.33 to 1.17) -This is required for patients taking oral contraceptives or valproate or who are obese. -Remember, when giving the next clozapine D, tolerance is measured by sedation and orthostatic hypotension. Moreover, when you are titrating there are 2 additional reasons to stop up-titration and hold the dose: 1) If CRP becomes abnormal,[b] hold D escalation until CRP normalizes. Add troponin monitoring. 2) If Clozapine C is higher than the value provided for that week.
First week
-Administer the first D of 12.5 mg at night to avoid sedation and orthostatic hypotension.[c] -If tolerated,[c] ↑ the daily D by 12.5 mg, keeping approximately 2/3 at night (avoid ↑ during a weekend).[d] -Target 50 mg/day at the end of the first week.
Second week
-With WBC, order CRP and, when possible, clozapine C (should be <117 ng/ml). -If tolerated,[c] ↑ twice at 25 mg/day each time, keeping approximately 2/3 at night (avoid ↑ during a weekend).[d] -Target 100 mg/day at the end of the second week.
Third week
-With WBC, order CRP and, when possible, clozapine C (should be <233 ng/ml). -If tolerated,[c] ↑ twice at 25 mg/day each time, keeping approximately 2/3 at night (avoid ↑ during a weekend).[d] -Target 125 mg/day for a ♀ non-smoker and 150 mg/day for others at the end of the third week.
Fourth and following weeks
-With WBC, order CRP and, when possible, clozapine C (should be <291 ng/ml). -The recommended target efficacious D is between 150 mg/day for a ♀ non-smoker and 300 mg/day for a ♂ smoker. -If the patient is a ♀ non-smoker and C is available, measure it 1 week after reaching 125 mg/day to decide target D. -For ↑ D in others: ↑ 25 mg/day each time with a target ↑ not >50 mg/week and 1 week after reaching a target D not >300 mg/day. Once the target D is reached, measure C 1 week later to decide final D.

C, concentration; C/D, concentration-to-dose; CRP, C-reactive protein; D, dose; TDM, therapeutic drug monitoring; WBC, white blood cells. The Ds and C/D ratios to remember are in red text.

[a]These recommendations will need to be updated as new information becomes available.

[b]If the CRP becomes abnormal after having a normal baseline, the clinician should consider the possibility that an infection or a clozapine-induced inflammation is present. Both can be associated with ↓ clozapine metabolism; it is better to hold clozapine dose increases until CRP becomes normal.

[c]When possible during titration, orthostatic changes in blood pressure and pulse need to be measured (see the scale in the Appendix). Giving 1/3 of the dose in the early morning allows for observation during the morning while giving the whole dose at night makes it less likely that ADRs will be detected. However, if orthostatic changes happen they will have no relevance unless the patient gets up in the middle of the night. Orthostatic abnormalities or other ADRs should signal the need for a slower titration. Fever should prompt stopping titration and drawing CRP (and troponin when available).

[d]Avoid major ↑ in D during weekends or times with less nursing supervision.

Supplementary Box S14. US inpatients of Non-Asian/Amerindian ancestry: titration for average metabolism[a]

Baseline (check general instructions)
-Inpatients of Asian or Amerindian (original inhabitants of the Americas) ancestry should be treated following Supplementary Box S10. This titration is for inpatients of European or African ancestry. -Expected therapeutic Ds: 300-600 mg/day (expected range for clozapine C/D ratios: 1.17 to 0.58) -Remember, when giving the next clozapine D, tolerance is measured by sedation and orthostatic hypotension. Moreover, when you are titrating there are 2 additional reasons to stop up-titration and hold the dose: 1) If CRP becomes abnormal,[b] hold dose escalation until CRP normalizes. Add troponin monitoring. 2) If clozapine C is higher than the value provided for that week.
First week
-Administer the first D of 25 mg at night to avoid sedation and orthostatic hypotension.[c] -If tolerated, ↑ the daily D by 25 mg, keeping approximately 2/3 at night (avoid ↑ during a weekend).[d] -Target 100 mg/day at the end of the first week.
Second week
-With WBC, order CRP and, when possible, clozapine C (should be <117 ng/ml). -If tolerated,[c] ↑ twice at 50 mg/day each time, keeping approximately 2/3 at night (avoid ↑ during a weekend).[d] -Target 200 mg/day at the end of the second week.
Third week
-With WBC, order CRP and, when possible, clozapine C (should be <234 ng/ml). -If tolerated,[c] ↑ twice at 25 mg/day each time, keeping approximately 2/3 at night (avoid ↑ during weekend).[d] -Target 300 mg/day at the end of the third week.
Fourth and following weeks
-With WBC, order CRP and, when possible, clozapine C (should be <351 ng/ml). -The recommended target efficacious D is between 300 mg/day for a ♀ non-smoker and up to 600 mg/day for a ♂ smoker. -Measure C 1 week after reaching 300 mg/day to decide target D. -For ↑ D in other than ♀ non-smokers: ↑ 25 mg/day each time with a target ↑ not >50 mg/week and 1 week after reaching a target D not >600 mg/day. Once target D is reached, measure level 1 week later to decide final D.

C, concentration; C/D, concentration-to-dose; CRP, C-reactive protein; D, dose; TDM, therapeutic drug monitoring; WBC, white blood cells. The Ds and C/D ratios to remember are in red text.

[a]These recommendations will need to be updated as new information becomes available.

[b]If the CRP becomes abnormal after having a normal baseline, the clinician should consider the possibility that an infection or a clozapine-induced inflammation is present. Both can be associated with ↓ clozapine metabolism; it is better to hold clozapine D increases until CRP becomes normal.

[c]When possible during titration, orthostatic changes in blood pressure and pulse need to be measured (see the scale in the Appendix). Giving 1/3 of the dose in the early morning allows for observation during the morning while giving the whole dose at night makes it less likely that ADRs will be detected. However, if orthostatic changes happen they will have no relevance unless the patient gets up in the middle of the night. Orthostatic abnormalities or other ADRs should signal the need for a slower titration. Fever should prompt stopping titration and drawing CRP (and troponin when available).

[d]Avoid major ↑ D during weekends or times with less nursing supervision.

Supplementary Box S15. General instructions for baseline variables for all 6 inpatient[a] titrations

1. Indications for choosing slower titration in each ancestry group
-Each of the 3 ancestry groups has slower titration for patients taking oral contraceptives or valproate or who are obese.
2. Avoid potent inducers
-Do not recommend starting clozapine in patients taking a potent inducer: rifampicin, phenytoin or phenobarbital. It is safe, but it will take much longer to get therapeutic levels. Future titration guidelines will need to consider clozapine titration in the context of potent inducers.
3. Avoid fluvoxamine
-Do not start clozapine in patients on fluvoxamine (potent inhibitor). Future titration guidelines will need to consider clozapine titration in the context of fluvoxamine.
4. Benzodiazepines (stop when possible)
-When possible, stop benzodiazepines. If not stopped, be vigilant for the first 2 days, as collapse/respiratory arrest has been described on rare occasions [47].
4. Rule out baseline inflammation
-Monitor CRP with baseline and weekly WBCs. Do not start clozapine if CRP is abnormal. If repeated CRP is abnormal, look for undiagnosed inflammations before starting clozapine. See Supplementary Box S16 for additional information.
5. Avoid smoking cessation during titration
-Recommend that patients avoid trying smoking cessation during titration since this will change the clozapine dose requirements for reaching 350 ng/ml. -If the patient is prevented from smoking at admission by a smoking ban at the hospital, this is not a problem but use the titration for non-smokers, which requires lower doses, to be on the safe side. If the titration is completed at the hospital and the clozapine dose provides at least 350 ng/ml, once the patient is discharged and starts smoking, after 2-4 weeks the patient will need a higher dose (See Supplementary Table S3 footnote g); therefore, outpatient TDM is recommended when available.

CRP, C-reactive protein; TDM, therapeutic drug monitoring; WBC, white blood cells.

[a]For outpatient titration (https://www.clozapinepluswerkgroep.nl/wp-content/uploads/2021/04/clozapine-titration-scheme-for-inand-outpatients.docx) based on a recommendation from the Dutch guideline, it appears reasonable to slow titration in half. Similarly, slower titrations are required in inpatients of geriatric age or who are taking medication that increases clozapine risk due to pharmacodynamic drug interactions.

Supplementary Box S16. Weekly CRP monitoring during the titration

1. Rationale

- 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 which is important since during clozapine titration, a normal CRP that becomes abnormal indicates the need to exclude:
    - clozapine-induced inflammation associated with too-rapid titration for the clozapine clearance of that specific patient, and/or
    - co-occurrence of an infection, most frequently an upper respiratory infection.
- The CRP becoming abnormal suggests that systemic inflammation has the potential of inhibiting clozapine metabolism through the release of cytokines.
- We recommend weekly CRP monitoring (at the same time as the WBC) since the limited data available suggest that CRP elevations are usually the first sign of clozapine-induced inflammation and in early phases can be the only sign [120]. Moreover, genetic clozapine PMs frequently tend to have low minimum therapeutic doses (<100 mg/day) and may be identified by their inability to tolerate the usual titrations even in the first week; they can develop early CRP elevations [118,119].

2. Measurement

- CRP measurement techniques and ranges vary in each laboratory; therefore, we recommend that clinicians use the norms available in their setting.

3. Abnormal baseline CRP

- Baseline CRP helps to avoid starting clozapine in someone with an undiagnosed systemic inflammation that could impair clozapine metabolism and contribute additional inflammation secondary to relatively rapid clozapine titration.
- If the baseline CRP is abnormal [65], the source of the inflammation should be identified and resolved before starting clozapine.
- Prescribing clozapine to someone with a chronic inflammatory process, such as rheumatoid arthritis or Crohn's disease, is a complex decision that needs to be carefully balanced considering co-medications (some associated with neutropenia) and the need for low clozapine doses and repeated TDM.

CRP, C-reactive protein; CYP, cytochrome P450; PM, poor metabolizer; TDM, therapeutic drug monitoring.

Supplementary Box S17. Interpretation of cases described in Supplementary Figures S1 and S2

1. Potential clozapine PM (Supplementary Figure S1)
• Female non-smoker: Han Chinese genetic PM [62] (see Section 1 of Supplementary Box S18 for CYP1A2 alleles with low activity in Asians). • Supplementary Figure S1 describes 17 TDMs during >300 days of admission. The mean clozapine C/D ratio for these 17 values was 3.91 ng/ml per mg/day, which corresponds to a minimum therapeutic clozapine D of 90 mg/day. • The 17 values provide some variability in clozapine C/D ratios ranging from 2.88 to 5.33 ng/ml per mg/day which provide a minimum therapeutic D ranging from 66 to 121 mg/day. All of these D values are compatible with the possibility that she was a clozapine PM. • She was treated with maintenance Ds ranging from 100 to 175 mg/day. • Clozapine half-life in clozapine PMs is likely to be much longer than in the normal patient, so we considered it to be roughly twice (2 days instead of 1 day) as long, which means that steady state for this patient probably required 10 days. As a matter of fact, 2 TDM values that were not steady-state values using the 10-day rule but were steady-state values using the 5-day rule were excluded, since they were the two lowest values, suggesting that they were not steady-state values (footnote c of Supplementary Figure S1).
2. A patient needing higher Ds in spite of obesity (Supplementary Figure S2)
• US male smoker of European ancestry [122]. He was taking valproate and appeared to be very sensitive to induction (footnote b of Supplementary Figure S2). • As he was obese, obesity could contribute to a substantially increased clozapine C/D ratio. • Supplementary Figure S2 describes 15 TDMs he had during a hospitalization of 50 weeks. The mean clozapine C/D ratio for these 15 values was 0.79 ng/ml per mg/day, which corresponds to a minimum therapeutic D of 443 mg/day. • The 15 values provide some variability in clozapine C/D ratios ranging from 0.62 to 0.99 ng/ml per mg/day which provides a minimum therapeutic D ranging from 373 to 565 mg/day. • The patient was prescribed a maintenance D ranging from 400 to 800 mg/day and discharged on 700 mg/day. In a patient with a mean clozapine C/D ratio of 0.79 ng/ml per mg/day, a D of 700 mg/day provides a trough steady-state clozapine C around 886 ng/ml (700/0.79=886), but the patient was only smoking 10 cigarettes/day in the inpatient unit. It was expected that after discharge, he might increase smoking substantially to 20 cigarettes/day or more, and that would have substantially reduced his serum Cs, which was a concern because of his history of very severe violence. The target serum C was not 350 ng/ml; the target Cs were in the 400s or 500s to provide for some room above 350 ng/ml. If he had Cs of 400s or 500s, more smoking or missing a few Ds might keep his Cs above 350 ng/ml.

C, concentration; C/D, concentration-to-dose; CYP, cytochrome P450; D, dose; PM, poor metabolizer; US, United States.

Supplementary Box S18. Future need for an international clozapine maintenance guideline

1. Prevention and treatment of clozapine concentration-related ADRs
• Concentration-related ADRs include hypersalivation, gastro-intestinal hypomotility, arrhythmia and seizures [21]. • The literature provides many adjunctive treatments for these ADRs which rarely have been systematically studied and have very different accessibility in different countries. • It will be a complex task to reach consensus among international experts on the management of specific clozapine ADRs; it will require balancing the published studies versus their clinical experience and the feasibility of worldwide implementation.
2. Adjunctive treatments
• Many adjunctive treatments have been studied to augment clozapine: ○ efficacy and/or ○ safety. • It will be a complex task to reach consensus among international experts on adjunctive treatments; it will require balancing the published studies versus their clinical experience and the feasibility of worldwide implementation. • For example, some experts recommend fluvoxamine to reduce clozapine dosages or to treat clozapine metabolic ADRs. On the other hand, with the unpredictable degree to which fluvoxamine alters clozapine metabolism, it appears safer to consider its use during maintenance treatment rather than during titration. An issue never considered in the published literature is the consideration of the complexities of making fluvoxamine recommendations across ancestry groups when there is very limited data.
3. Point-of-care devices
• New point-of-care devices may facilitate TDM and WBC monitoring [1]. • Different devices are being marketed in different countries [1] but their analytical validity, clinical validity and clinical utility are not yet well established. • An international guideline will need to carefully balance cost and availability across the world.

TDM, therapeutic drug monitoring; WBC, white blood cell count.

Supplementary Box S19. Areas of clozapine titration needing development

1. Adjusting these 6 titrations for children and adolescents[a]
2. Study of CYP1A2 mutations and/or epigenetic mechanisms may help identify clozapine PMs

• Clozapine PMs are defined by considering ancestry, sex and smoking status [88].
• Some PMs (<10-15%) are not explained by phenoconversion and are genetic PMs [62,68]. Lack of tolerance to usual Ds or an unexplained ↑ CRP during titration may signal a genetic PM [118].
• Epigenetic changes may explain CYP1A2 PMs and ancestry differences.
• Europeans: 2 CYP1A2 alleles with no or very limited function have been described [124]:
  o CYP1A2*7 (<0.1% Europeans). A French PM clozapine patient with a heterologous state (1 of 2 chromosomes) [115] had 81 mg/day for minimum therapeutic D [88].
  o CYP1A2*6 (0.9% European). Never described in published clozapine studies.
• East Asians: alleles with no/limited function (CYP1A2*8, CYP1A2*11, CYP1A2*15 and CYP1A2*16) were described in <1% of Japanese [126,127] but not studied in clozapine patients.

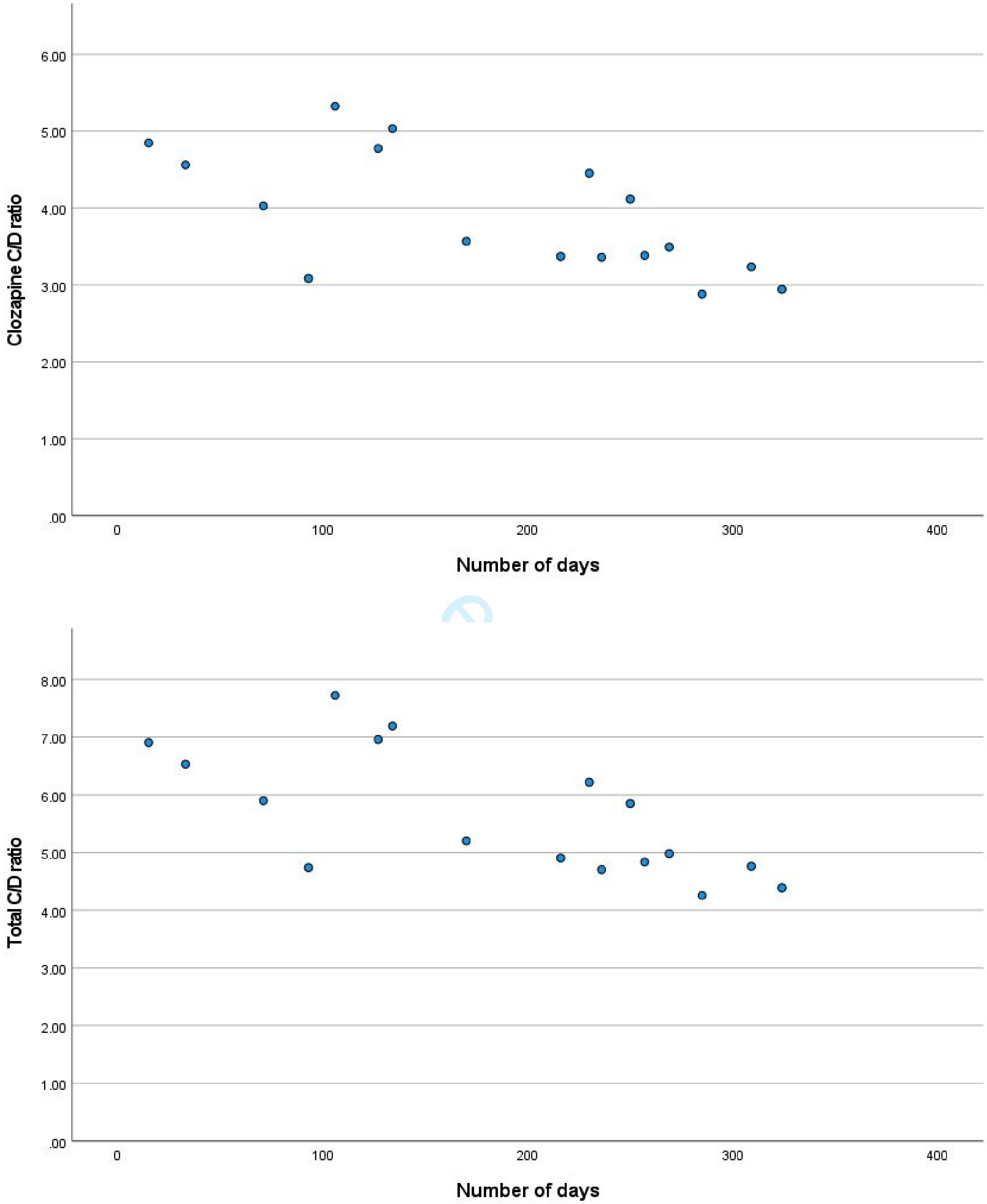
3. Clarification over the existence of very rare genetic clozapine UMs
• In 1998, a rare clozapine UM [128] was recognized, but no gene variant was identified. His clozapine C/D ratio was 0.17 (corresponding to 2058 mg/day as minimum therapeutic D) [88]. • Several clozapine UM cases have been published, but the authors did not consider[a] poor adherence and/or co-prescription of potent inducers [88]. • It is possible that genetic variants in nuclear receptors may explain clozapine UMs [122].
4. Possible need for titrations for other ancestry groups
• African ancestry. Supplementary Box S4 (section 5) suggests that they may need higher clozapine Ds. If future studies support that hypothesis, 2 sets of new titrations may be needed for them. • Oceanian ancestry. We currently suggest using the same titration as for those with European ancestry. Future studies will need to establish whether this is correct or not. It will be very important to monitor CRP extremely closely in them in case our current recommendation is not correct and they need Ds similar to Asians/Amerindians. • Mixed ancestry between European/Western Asians and Asian/Amerindians. It is safer to use the titration for Asian/Amerindians which recommends the lowest Ds.
5. Need for US studies on minimum therapeutic Ds (after stratification by sex, smoking and ancestry)
6. C lower or higher than 350 ng/ml may be more suitable for some patients

• Lower C. Two articles suggest that lower clozapine Cs may be effective:
  o A US inpatient DB RCT [129] (with D divided into 2-3 administrations) compared 3 ranges of Cs (extrapolating to outpatients taking a single D is not easy). The medium C (200-300 ng/ml) had the same efficacy as the high C (350-450 ng/ml) with less sedation.
  o In a review of clozapine TDM studies in TRS, Schulte [130] found in the group with levels below 350 ng/ml, 30% of patients were responders and in the group with levels above that threshold, 73% of patients were responders.[b]
• Higher C. In outpatients whom psychiatrists suspect may miss Ds or increase smoking, it may be safer to target Cs in the high 400s or low 500s to have some room for decreases.

7. Need for studies on minimum therapeutic Ds and Cs for other indications besides TRS
8. Need for more flexible clozapine formulations
• Lowest D administration. In most countries the lowest-dosage tablet available is 25 mg, which usually can be split in two, to allow a starting D of 12.5 mg. In some countries, pharmacists may help by offering Ds of 6.25 mg. In Asian countries [81] there is need for smaller doses (6.25 mg, 5 mg or 10 mg). • Unreliable generic formulations. In some countries there are generic formulations with low availability, but it is not easy to learn about this unless TDM is available.

C, concentration; C/D, concentration-to-dose; CYP, cytochrome P450; D, dose; DB, double-blind; PM, poor metabolizer; TRS, treatment-resistant schizophrenia; UM, ultrarapid metabolizer
[a]The clozapine studies in children and adolescents are limited and scarce.
[b]Schulte [130] also summarized the studies with smaller shortcomings. In them, the percentages of response ranged between 8-38% below the threshold (350 or 400 ng/ml) and between 54-73% in those above the threshold.

Supplementary Figure S1. TDM: Asian clozapine PM[a] (90[b] mg/day of minimum therapeutic dose)[c]



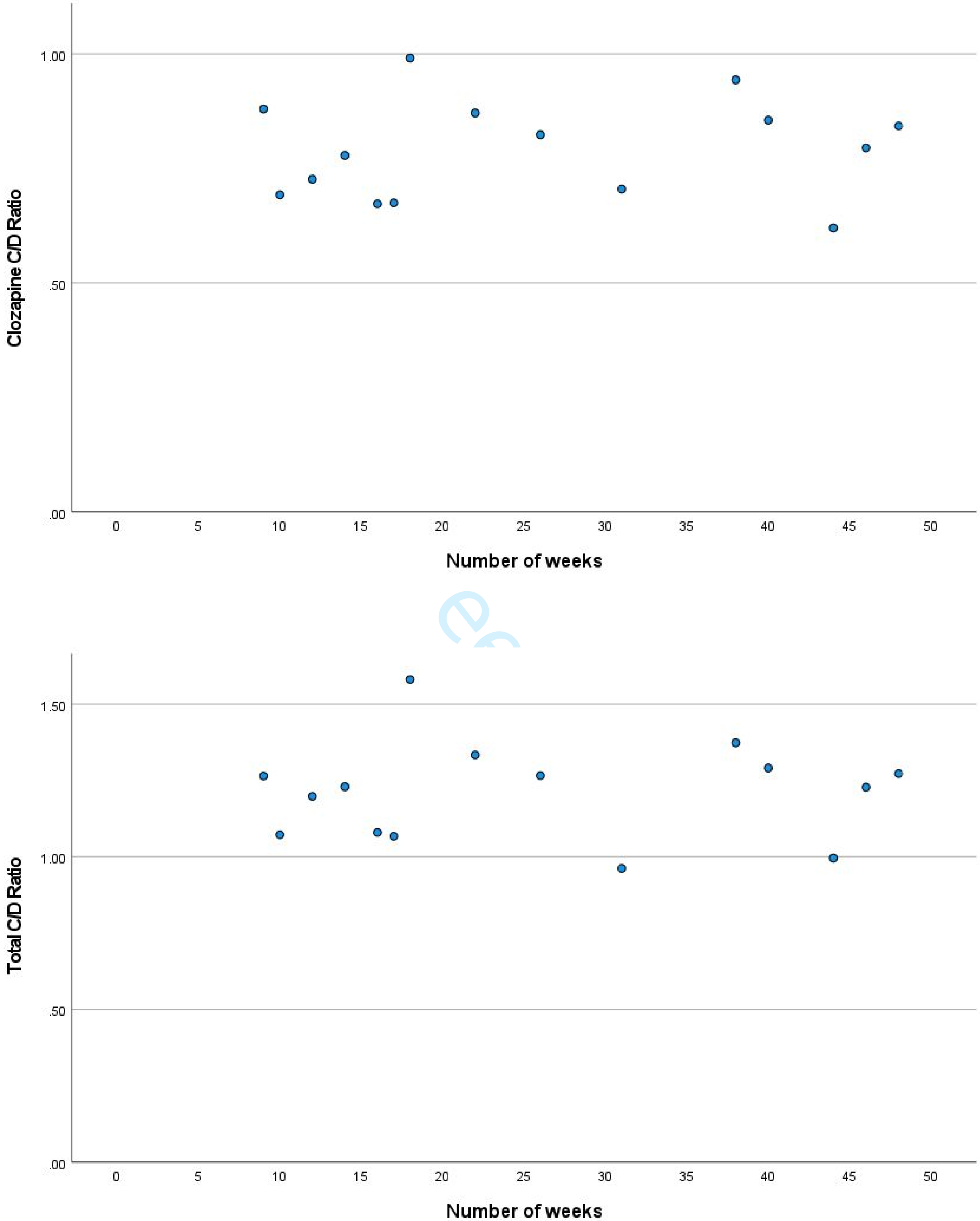
BMI, body mass index; C, concentration; C/D, concentration-to-dose; CYP, cytochrome P450; D, dose, PM, poor metabolizer.

[a]Chinese female non-smoker inpatient at Beijing Anding Hospital. Her age=53, BMI=25.2, no inflammation, no relevant co-medications and no caffeine intake. We suspect she has an unidentified CYP1A2 mutation associated with very low clozapine metabolism [62].

[b]The estimated minimum therapeutic D for 350 ng/ml was 90 mg/day. She was prescribed 100-175 mg/day. From these 17 values with no D changes in 10 days the clozapine C/D ratio had a mean of 3.91 with a range of 2.88 to 5.33 ng/ml per mg/day. This value of 3.91 provides a minimum therapeutic D of 90 mg/day (350/3.91=90), but the minimum therapeutic D range was 66 mg/day (350/5.33=66) to 121 mg/day (350/2.88=121). The mean total C/D ratio, calculated by adding clozapine and norclozapine Cs, was 5.65 with a range of 4.26 to 7.73 ng/ml per mg/day.

[c]She had 2 outlier values not included in this graphic: on day 188 with a clozapine C/D ratio of 2.28 (total clozapine C/D ratio of 2.69) and on day 209 with a C/D ratio of 3.38 (total C/D ratio of 4.00). They were eliminated because they happened a few days after D increases. They were steady-state Cs using a 5-day limit for steady state but were not steady-state Cs according to the longer limit of 10 days for a clozapine PM. We recommend using 10 days for defining steady-state Cs in clozapine PMs.

Supplementary Figure S2. TDM: US White obese male[a] (443 mg/day of minimum therapeutic dose)



C/D, concentration-to-dose; D, dose; US, United States

[a]Male smoker inpatient of European ancestry at a US psychiatric state hospital. He was taking valproate and other medications that were stable. During the clozapine treatment his age was 34 years. He smoked only 10 cigarettes per day controlled by the nursing staff and weighed 102 Kg with a BMI=32.2. His initial weight at admission to the hospital at age 30 was 85 Kg (BMI=26.8) [116].

[b]The estimated minimum therapeutic D for 350 ng/ml was 443 mg/day but he was prescribed 400-800 mg/day. The figure represents 15 TDMs. One episode of infection was excluded from the figure. From

these 15 values the clozapine C/D ratio had a mean of 0.79 with a range of 0.62 to 0.99 ng/ml per mg/day. This value of 0.79 provides a minimum therapeutic D of 443 mg/day (350/0.79=443) but his minimum therapeutic D ranged from 353 (350/0.99=353) to 565 mg/day (350/0.62=565). The mean total C/D ratio was 1.21 with a range of 0.96 to 1.58 ng/ml per mg/day. It is remarkable that this patient had low clozapine and total C/D ratios in spite of being obese. The patient was already obese when started on clozapine but we have assumed that obesity decreased his clozapine metabolism in half; this should correspond to a C/D ratio of 0.40 which provides an estimated dose for 350 ng/ml of 875 mg/day. This patient appeared to be particularly sensitive to induction [116].

[c]The patient had a history of severe violence and his clozapine Ds were estimated to provide Cs in the 400s-500s (mean ± standard deviation of clozapine Cs was 596±146 ng/ml). In that way at the time of discharge, it was felt that even if the patient increased his smoking or missed some Ds, his serum Cs would likely be >350 ng/ml. He was discharged on 700 mg/day.

Appendix. Clozapine Adverse Reactions Scale for Nurses

Patient:_____________________ Date & Time:_____________________

Rater:_____________________ Unit:_____________________

A. Observe and if possible ask patient if s/he has any physical problems or complaints (check present/absent):

	Absent	Present (can write comment)
1. Symptoms/signs of infection (e.g., sore throat or cough, mouth ulcers; chills; rectal soreness/itching; vaginal soreness/itching; urinary frequency/burning)		
2. Hypersalivation		
3. Drowsiness/sedation		
4. Falling		
5. Leg folding or knee buckling		
6. Dizziness		
7. Constipation		
8. Urinary incontinence		
9: Other (Specify):		
B. Record Oral Temperature:	Initial:	Repeat:

*****If vital signs are not within normal parameters, repeat in 15 minutes and fill out section D*****

C. Record pulse and blood pressure:	**Initial BP**	Repeated BP	**Initial Pulse**	Repeated Pulse
After sitting for three minutes:				
After standing for two minutes:				

D. Abnormal values after repetition: 1) Check absent or present. 2) If present, hold dose and call physician.

	Absent	Present (write abnormal value)
1. Temp above 37.7 ^{0}C (99.9^0 F) orally		
2. Systolic BP below 90 mm, or above 150 mm		
3. Diastolic BP below 60 mm or above 100 mm		
4. Greater than a 20 mm drop of systolic or 10 mm drop of diastolic between sitting and standing		
5. Pulse over 120 bpm/min or less than 60 bpm/min		

This is a modified and improved version of a published scale [47] that improves a prior version from a clozapine study [104].