









































































































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

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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.

received 10.06.2021

revised 23.08.2021

accepted 23.08.2021

published online 15.12.2021

Bibliography

Pharmacopsychiatry 2022; 55: 73–86

DOI 10.1055/a-1625-6388


ISSN 0176-3679

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 **Supplementary Material** is available under
<https://doi.org/10.1055/a-1625-6388>

ABSTRACT

This international guideline proposes improving clozapine package inserts worldwide by using ancestry-based dosing and titration. Adverse drug reaction (ADR) databases suggest that clozapine is the third most toxic drug in the United States (US), and it produces four times higher worldwide pneumonia mortality than that by 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, the lowest dose; male smokers, the highest dose). Poor metabolizer 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. The Asian population (Pakistan to Japan) or the Americas' original inhabitants have lower CYP1A2 activity and require lower clozapine doses to reach concentrations of 350 ng/mL. In the US, daily doses of 300–600 mg/day are recommended. Slow personalized titration may prevent early ADRs (including syncope, myocarditis, and pneumonia). This guideline defines six personalized titration schedules for inpatients: 1) ancestry from Asia or the original people from the Americas with lower metabolism (obesity or valproate) needing minimum therapeutic dosages of 75–150 mg/day, 2) ancestry from Asia or the original people from the Americas with average metabolism needing 175–300 mg/day, 3) European/Western Asian ancestry with lower metabolism (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 with ancestries other than from Asia or the original people from the Americas with lower clozapine metabolism (obesity or valproate) needing 150–300 mg/day, and 6) in the US with ancestries other than from Asia or the original people from the Americas with average clozapine metabolism needing 300–600 mg/day. Baseline and weekly CRP monitoring for at least four weeks is required to identify any inflammation, including inflammation secondary to clozapine rapid titration.

The History of Clozapine

Clozapine was marketed in some European countries in the early 1970s and in 1975, cases of clozapine-induced agranulocytosis were described in Finland. The association of clozapine with a po-

tentially lethal adverse drug reaction (ADR), agranulocytosis, left clozapine's reputation severely damaged. Clozapine was then 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 a significantly higher efficacy of clozapine than that of 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]. However, in 1996 a drug-drug interaction (DDI) with an antihistamine, terfenadine, was the cause of multiple deaths in the US. This led the FDA to ask for DDI study reports. 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 worldwide to the growing knowledge of clozapine pharmacokinetics has made clozapine package inserts 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 discuss the issues of ancestry or titration speed.

Clozapine Safety

Clozapine may be associated with lower mortality in treatment-refractory schizophrenia

TRS accounts for approximately one-third of people with schizophrenia [5]. While definitions of TRS vary [5], clozapine has been found to be 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 research group published a network meta-analysis [7] that did not find the superiority of clozapine 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 greater effectiveness of clozapine 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** 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 [1, 11–16].

Clozapine pharmacokinetics may explain its adverse drug reactions

Many clinicians are reluctant to use clozapine in patients 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, because clozapine: 1) is the only antipsychotic with FDA approval for reducing suicidal behavior [18], and 2) may reduce hostility and aggressive behaviors independent of its effects on other symptoms [19].

To reduce clozapine ADRs, an expert consensus guideline [20] strongly recommends monitoring 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 amount of drugs (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. According to **Supplementary Table S1**, 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].

Clozapine toxicity

Unfortunately, the data from the FDA in the period from 1998–2005 [24] also suggested that, with its current use in the US, clozapine can be associated with toxicity. Clozapine was associated with 3277 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 focused on severe neutropenia.

The FDA's focus on clozapine-induced agranulocytosis as a major cause of clozapine mortality may be misguided. VigiBase, the pharmacovigilance database of the World Health Organization, has received worldwide reports on ADRs since 1968 from 134 drug agencies. A search on July 15, 2019, [25] indicated that agranulocytosis, including the initial 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 (2077 deaths) [26–29], 2) cardiac arrests (1449 deaths) [30, 31], 3) agranulocytosis (550 deaths) [32, 33], 4) myocarditis (539 deaths) [34–36], 5) constipation (326 deaths) [37–39], 6) arrhythmia (319 deaths) [40, 41], 7) seizures (308 deaths) [40, 42–44], and 8) syncope (299 deaths) [45–47]. These deaths in patients using clozapine can be possibly explained as the combined effects of TRS and clozapine. For each clozapine ADR, the possible contribution of TRS and clozapine has been described in **Supplementary Table S2**.

Advances in Clozapine Pharmacokinetics not Included in the US Package Insert

After the development of the clozapine package insert in the US [48], in 1996 Bertilsson et al. [49] reported clozapine as mainly metabolized by 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 four 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].

Clinically relevant variables that may influence clozapine dosing

The pharmacokinetic variables that may influence clozapine metabolism including DDIs, obesity, inflammation, geriatric age, and pregnancy have been reviewed in **Supplementary Box S3** [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 inpatients for whom it is easier to control caffeine intake (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 may explain the association between obesity and a decrease in clozapine metabolism [75], as with other CYP1A2 substrates [78]. Systemic inflammations, including infections, release cytokines that inhibit CYP1A2; increased clozapine level was described in 40 cases of infection [79]. In one 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 the need for reducing 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 five main 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 the original people from the Americas. Asians and their descendants, the original people from the Americas [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 significant 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 that 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.

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 personalized clozapine 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., linear relationship between dose and concentration when two conditions, including 1) in therapeutic dosages and 2) in the absence of inducers/inhibitors are met). 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, ancestries from Asia or the original people from the Americas, 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 S3 [40, 68, 83, 92] summarizes the TDM studies focused on ancestry. Average people of ancestries from Asia or the original people from the Americas 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 a sample size of six average people of European ancestry [92], the minimum therapeutic doses were in the range of 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 due to inhibitors, inflammation, or obesity requires approximately half the dose needed for their sex and smoking group within their ancestry group. As fluvoxamine is a very powerful clozapine inhibitor with unpredictable effects (a reduction of the clozapine dose to 1/5 or 1/10 may be required in some patients) [23, 63], this guideline does not provide titrations for patients on fluvoxamine.

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 300–450 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 in studies published earlier [103], 4) a re-analysis [92] of a systematic review [62] comparing US and European patients, and 5) a US RCT with three doses [104]. The finding of six TDM studies in European patients suggests doses up to 400 mg/day for male smokers [92], although, according to the limited US clozapine data available, up to 600 mg/day is recommended for US male smokers (**Supplementary Box S7**).

Clozapine Titration

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, where up to 10% of schizophrenia patients are on clozapine and it has developed a guideline [95] that encourages very slow outpatient titration. On the other hand, for many years Australia has been known to have a much higher incidence of clozapine-induced myocarditis [105]. **Supplementary Table S2** describes 3048 clozapine-induced myocarditis cases reported to drug agencies worldwide, with more than half the number of cases from Australia [25], a country of 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 nine Australian samples and of 0.3% in 15 non-Australian samples.

High rates of clozapine-induced myocarditis reported 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 manufacturer slowed the recommended lamotrigine titration in average patients and further slowed by half in patients taking an inhibitor, valproate, who end up receiving 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 S4** [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 and frequent fever, then in the late-stage local signs of inflammation, most frequently myocarditis, become obvious; 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].

Pneumonia may also be more severe during titration

Only two published studies have focused on the incidence of pneumonia during clozapine titration, including one on myocarditis in Denmark [121] and the other describing a rapid titration in Romania [113], suggesting that the severity of pneumonia may increase 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 3262 outpatient initiations of clozapine in the Danish registry, Rohde et al. [121] found only 0.03% of myocarditis and no associated deaths in the first two months. 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 of 2.1% in patients on clozapine [28]. A Romanian study [113] promoting rapid titration had an incidence of 2.3% of pneumonia ($1/44 = 0.23$) in only the first two weeks.

Proposal for six personalized clozapine titrations for inpatients

As slow personalized titration considering DNA ancestry may be important for clozapine safety, this article proposes six titration schedules based on these inpatient groups: 1) ancestries from Asia or the original people from the Americas with lower clozapine metabolism (**Supplementary Box S9**), 2) ancestries from Asia or the original people from the Americas 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 of ancestries other than from Asia or the original people from the Americas with lower clozapine metabolism (**Supplementary Box S13**), and 6) in the US of ancestries other than from Asia or the original people from the Americas with average clozapine metabolism (**Supplementary Box S14**).

Baseline considerations for all six titrations

Supplementary Box S15 describes considerations at baseline that are in common for the titrations of all six inpatient groups 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, therefore, our guidelines focus on inpatient titrations. The Dutch guideline [95] provides recommendations for outpatient titration which are even slower than its inpatient titration.

Role of CRP during titration

Supplementary Box S16 [65, 118–120] provides the rationale for simultaneous measurement of CRP and WBC [108] for the first four

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 studies with better outcomes are available. The limited data available suggest that CRP elevations precede troponin elevations by several days.

In the first incidence of abnormal CRP during the titration, clinicians need to rule out a co-occurring inflammation, particularly an upper respiratory infection, and also consider a clozapine-induced inflammation explained by a titration that has been too fast for that specific patient. In case of abnormal CRP during 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.

Role of clozapine therapeutic drug monitoring during titration

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–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.

Use of a single therapeutic drug monitoring in predicting the clozapine maintenance dose

Once the patient has reached the target dose in the fourth week, it is important to maintain the same dose for at least five 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 affected 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 S5** provides multiple examples of TDMs at different clozapine doses and explains the estimation of minimum therapeutic doses.

The mean of multiple therapeutic drug monitorings 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., comedication, absence of inflammation, smoking behavior, and 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 S17** [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 the case of 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.

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 need development and 3) the need for guidelines to personalize dosing for maintenance treatment.

The need for personalized approaches

Those researchers interested in an approach that 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 at least six best-personalized dosages and these six titrations do not consider that some genetic or ancestry groups may require additional personalized approaches. Future studies are needed to verify whether or not using these six 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 (**Supplementary Box S18**).

Areas of clozapine titration that need development

Supplementary Box S19 lists as areas of clozapine titration that need the following 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].

Future guidelines for personalized dosing during maintenance treatment

These guidelines only focus on clozapine titration to prevent myocarditis, orthostatic hypotension, sedation, and the 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 three 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].

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 the role of ancestry in clozapine dosing and considering slow personalized titration as perhaps an inexpensive and easy way to increase clozapine safety [3]. 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.

Acknowledgments

Lorraine Maw, M.A., at the University of Kentucky Mental Health Research Center, helped with editing.

Contributors

The first version of this guide was developed by Dr. de Leon based on his 30 years of experience with clozapine including five years of research managing a double-blind study of three clozapine dosages used in Philadelphia state hospitals; the study was awarded by the National Institute of Mental Health to George Simpson, M.D., and Richard Josiassen, Ph.D. Dr. de Leon has also spent 25 years in clinical activity in Kentucky state mental health facilities. Other authors contributed with their clinical and/or research experience in clozapine. Many of them have been co-authors in articles regarding clozapine dosing based on ancestry: Drs. Schoretsanitis, Smith, Molden, Solismaa, Seppälä, Kopeček, Švancer, Olmos, Iglesias-Garcia, Iglesias-Alonso, Spina, Ruan, Chun-Yue Wang, Tang, Lin, Rajkumar, González-Esquivel, Jung-Cook, and Baptista; regarding clozapine and infection: Drs. Ruan, Chun-Yue Wang, Rohde, Nielsen, Verdoux, Quiles, Sanz, and De las Cuevas; regarding clozapine and myocarditis: Drs. Cohen, Schulte, Ertuğrul, and Anil Yağcıoğlu; regarding clozapine reviews: Drs. Schoretsanitis, Ruan, Chun-Yue Wang, De las Cuevas, Kaithi, Kane, Farooq, and Ng; regarding antipsychotic pharmacokinetics: Drs. McCollum, Shelton, Hiemke, López-Jaramillo, McGrane, Lana, Eap, Arrojo-Romero, and Rădulescu; and regarding antipsychotic response: Drs. Motuca and Crespo-Facorro. All authors either drafted or critically revised the content and approved the final version.

Funding

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

Conflict of Interest

In the last 3 years, the following authors had no conflict of interest: Drs. de Leon, Schoretsanitis, Molden, Smith, Solismaa, Švancer, Olmos, Ricciardi, Iglesias-Garcia, Iglesias-Alonso, Spina, Ruan, Chuan-Yue Wang, Gang Wang, Tang, Lin, Lane, Rajkumar, González-Esquivel, Jung-Cook, Baptista, Rohde, Nielsen, Verdoux, Quiles, Sanz, De las Cuevas, Cohen, Schulte, Chopra, McCollum, Shelton, Kaithi, Farooq, McGrane, Lana, Arrojo-Romero, Rădulescu, Every-Palmer, Bebawi, Bhattacharya, Otsuka, Lazary, Torres, Yecora, Motuca, Chan, Zolezzi, Ouanes, De Berardis, Grover, Kirilochev, Soloviev, Ayub, Silva, Bonelli, Temmingh, Decloedt, Pedro, Pacheco Palha, LLerena, Fernandez-Egea, Siskind, Masmoudi, Mohd Saffian, Leung and Buckley. In the last 3 years several authors report conflicts of interests. Dr. Seppälä is permanent medical advisor, received lecture fees and is an advisory board member from Viatrix that markets clozapine in Finland and other European countries. Dr. Kopeček participated in speakers/advisory boards and lectured with the support of Angelini, Janssen Pharmaceuticals, Lundbeck and Richter Gedeon. Dr. Yong Sik Kim received grants, research support and honoraria from Janssen, Otsuka, Whan in Pharm and Bukwang Pharm (Sumitomo Dannipon Pharma). Dr. Se Hyun Kim received research grants from and/or served as a lecturer for Janssen, Eli Lilly, and Dongwha. Dr. Ertuğrul has received speaker's honoraria from Abdi İbrahim Otsuka. Dr. Anil Yağcıoğlu has received speaker's honoraria and consulting fees from Janssen and Abdi İbrahim Otsuka. Dr. Cotes has received research funding from Otsuka, Lundbeck, Roche, Alkermes, and is a consultant for Saladax Biomedical. Dr. Kane reports personal fees from Alkermes, personal fees from Allergan, personal fees from Bristol-Myers Squibb, personal fees from IntraCellular Therapies, Janssen, Lundbeck, Minerva, Neurocrine, Otsuka, Pierre Fabre, Reviva, Sunovion, Takeda, Teva, outside-the-submitted work from LB Pharma, MedAvante and The Vanguard Research Group. Dr. Ng had served as consultant for Grunbiotics, Lundbeck, Servier, and Janssen-Cilag, and received research speaker honoraria from Servier, Janssen-Cilag and Pfizer. I.McG received royalties from Hogrefe Publishing Corp. T.L. Dr. Bilbily is supported by the National Institute on Drug Abuse training grant 5T32DA007261-30 (MPI). Dr. Hiemke received speaker's honoraria from Otsuka. Dr. López-Jaramillo reports financial support for research from Financial support from the National Institute of Mental Health, USA, MinCiencias, Colombia and the Universidad de Antioquia, Colombia. Dr. Eap received honoraria for conferences or teaching CME courses from Janssen-Cilag, Lundbeck, Otsuka, Sandoz, Servier, Sunovion, Vifor-Pharma, and Zeller. Dr. Seifritz has received honoraria from Schwabe GmbH for educational lectures. He has further received educational grants and consulting fees from Janssen Cilag, Lundbeck, Angelini, Otsuka, Servier, Recordati, Vifor, Sunovion, and Mepha. Dr. Bousman is a member of the Clinical Pharmacogenetics Implementation Consortium (CPIC) and Pharmacogene Variation Consortium (PharmVar). Dr. Kelly has served as a consultant for Alkermes, Lyndra and Sunovion. Dr. Procyshyn has been on the speaker's bureau and attended advisory board meetings for Janssen, Lundbeck, and Otsuka. Dr. Adebayo was on the advisory board of Janssen for a Long Acting Injectable Paliperidone palmitate in Nigeria. Janssen is not involved in Clozapine in Nigeria. Dr. Fountoulakis has received grants in the past, served as

consultant, advisor or CME speaker, or received support to attend congresses by the following entities: AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Ferrer, Gedeon Richter, Janssen, Lundbeck, Otsuka, Pfizer, the Pfizer Foundation, Sanofi-Aventis, Servier, Shire and others. Since January 2020 he has been the director of Cochrane Greece and completely free from any conflict of interest. Dr. Wilkowska has received research support from Angelini, Biogen, Eli Lilly and Company, Janssen-Cilag, Lundbeck, Polpharma, Sanofi and Valeant. Dr. Cubała has received research support from Alkermes, Allergan, Auspex, Biogen, Celon, Ferrier, Forest Laboratories, Janssen, Otsuka, and Sanofi; he has served on speaker bureaus for Angelini, Celon, Janssen, and Sanofi, and he has served as a consultant for GW Pharmaceuticals, Janssen, Celon and Sanofi. Dr. Villagrán-Moreno has received speaker's honoraria from Janssen and have developed lectures and presented clozapine lectures for Adamed, which sells clozapine in Spain; he has participated in advisory boards for Rovi and in research projects for Otsuka. Dr. Crespo-Facorro has received funding unrelated to the present work for research projects and/or honoraria as a consultant or speaker from the following entities: Angelini, Janssen-Cilag, Lundbeck, Otsuka, Mylan, Sanofi-Aventis, ADAMED, Agencia Española de Investigación, Instituto de Salud Carlos III, the EU Seventh Framework Program and Horizon 2020. Dr. Takeuchi has received speaker's fees from EA Pharma, Kyowa, Janssen, Lundbeck, Meiji Seika Pharma, Mochida, Otsuka, Sumitomo Dainippon Pharma, Takeda, and Yoshitomyakuhin. Dr. Tsukahara has received speaker's honoraria from Eisai Inc. Dr. Gründer has served as a consultant for Allergan (Dublin, Ireland), Boehringer Ingelheim (Ingelheim, Germany), Institute for Quality and Efficiency in Health Care (IQWiG, Cologne, Germany), Janssen-Cilag (Neuss, Germany), Lundbeck (Copenhagen, Denmark), Otsuka (Chiyoda, Japan), Recordati (Milan, Italy), Sage (Cambridge, USA), and Takeda (Osaka, Japan). He has served on the speakers' bureau of Gedeon Richter (Budapest, Hungary), Janssen Cilag, Lundbeck, Otsuka, Recordati. He has received grant support from Boehringer Ingelheim, Lundbeck and Saladax (Bethlehem, USA). He is co-founder and/or shareholder of Mind and Brain Institute GmbH (Zornheim, Germany), Brainfoods GmbH (Zornheim, Germany), OVID Health Systems GmbH (Berlin, Germany) and MIND Foundation gGmbH (Berlin, Germany). Dr. Sagud participated in lectures for the following companies: Alkaloid, Belupo, Eli Lilly, Gedeon Richter, Jadran Galenski Laboratorij, Johnson / Johnson, Lundbeck, Makpharm, Pliva, Stada and participated in the clinical trial: Eli Lilly, Krka and Gedeon Richter. Dr. Celofiga received speaker's honoraria from Eli Lilly, Lundbeck, Richter Gedeon, Krka, Lek, Pliva, Angelini Pharma and participated in advisory boards for Janssen Pharmaceuticals and Lundbeck. Dr. Ignjatovic Ristic developed and presented clozapine lectures with the support of Mylan, received speaker's honoraria from Mylan, Teva Serbia, Pharm Swiss, Krka and Janssen. Dr. Ortiz has been a consultant and has received honoraria from Janssen-Cilag. Dr. Elkis received research grants from the São Paulo Research Support Foundation (FAPESP) and honoraria for participation as a member of advisory boards, speaker, or travel support from the following pharmaceutical companies: Aché, Cristalia, Daiichi-Sankyo, Janssen, Mantecorp-Hypera, Sandoz, and Teva. Dr. Weizman received speaker's honoraria from Lundbeck, Lilly, Teva, Trima, Jansen, Medison, Novartis and AstraZeneca. These activities were unrelated to the current study. Dr. Marder

reports consultation fees from Roche, Sunovion, Merck, Boehringer Ingelheim and Otsuka. He reports research support from Boehringer-Ingelheim, and GW Pharma. Dr. Citrome has engaged in collaborative research with, or received consulting or speaking fees, from: AbbVie, Acadia, Alexza, Alkermes, Allergan, Angelini, Astellas, AstraZeneca, Avanir, Axsome, BioXcel, Boehringer Ingelheim, Bristol-Myers Squibb, Cadent Therapeutics, Eisai, Eli Lilly, Forum, Genentech, Impel, Indivior, Intra-Cellular Therapies, Janssen, Jazz, Karuna, Lundbeck, Luye, Lyndra, Medavante-Prophase, Meiji, Merck, Medivation, Mylan, Neurocrine, NeuroRx, Novartis, Noven, Osmotica, Otsuka, Pfizer, Reckitt Benckiser, Relmada, Reviva, Sage, Shire, Sunovion, Takeda, Teva, University of Arizona, Valeant, Vanda, and one-off ad hoc consulting for individuals/entities conducting marketing, commercial, or scientific scoping research. Dr. Freudenreich has the following financial relationship with a commercial interest to disclose (recipient SELF; content area SCHIZOPHRENIA): Alkermes – Research grant (to institution), consultant honoraria (Advisory Board); Avanir – Research grant (to institution); Janssen – Research grant (to institution), consultant honoraria (Advisory Board); Integral - Consultant honoraria; Neurocrine – Consultant honoraria (Advisory Board); Novartis – Consultant honoraria; Otsuka – Research grant (to institution); Roche – Consultant honoraria; Springer Verlag – Royalties (medical writer); Elsevier – Honoraria (medical editing); Global Medical Education – Honoraria (CME speaker and content developer); Medscape – Honoraria (CME speaker); American Psychiatric Association – Consultant honoraria (SMI Adviser); Wolters-Kluwer – Royalties (content developer); UpToDate – Royalties, honoraria (content developer and editor, including for a chapter on clozapine). Dr. Correll has been a consultant and/or advisor to or has received honoraria from: AbbVie, Acadia, Alkermes, Allergan, Angelini, Aristo, Axsome, Damitsa, Gedeon Richter, Hikma, IntraCellular Therapies, Janssen/J&J, Karuna, LB Pharma, Lundbeck, MedAvante-ProPhase, MedinCell, Medscape, Merck, Mitsubishi Tanabe Pharma, Mylan, Neurocrine, Noven, Otsuka, Pfizer, Recordati, Rovi, Servier, Sumitomo Dainippon, Sunovion, Supernus, Takeda, Teva, and Viatrix. He provided expert testimony for Janssen and Otsuka. He served on a Data Safety Monitoring Board for Lundbeck, Rovi, Supernus, and Teva. He has received grant support from Janssen and Takeda. He received royalties from UpToDate and is also a stock option holder of LB Pharma. Dr. Müller reports he has been a co-investigator for two pharmacogenetic studies where genetic test kits were provided as an in-kind contribution by Myriad Neuroscience. He did not receive any payments or any equity, stocks, or options from any pharmacogenetic companies. He is also a co-inventor of two patents assessing risk for antipsychotic-induced weight gain (pending).

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Notice

This article was changed according to the following Erratum on January 20 2022.

Erratum

In the above-mentioned article, the spelling of 5 authors last names has been wrong and these names have been corrected.