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

Authors

Affiliations
1. Mental Health Research Center, Eastern State Hospital, Lexington, KY, USA
2. Department of Psychiatry, University of Kentucky, Lexington, KY, USA
3. Psychiatry and Neurosciences Research Group (CTS-549), Institute of Neurosciences, University of Granada, Granada, Spain
4. Biomedical Research Centre in Mental Health (CIBERSAM), Santiago Apostol Hospital, University of the Basque Country, Vitoria, Spain
5. Department of Psychiatry, Psychotherapy and Psychosomatics, Psychiatric Hospital, University of Zürich, Zürich, Switzerland
6. The Zucker Hillside Hospital, Psychiatry Research, Northwell Health, Glen Oaks, New York, USA
7. Center for Psychopharmacology, Diakonhjemmet Hospital, Oslo, Norway
8. Section for Pharmacology and Pharmaceutical Biociences, Department of Pharmacy, University of Oslo, Oslo, Norway
9. Faculty of Medicine and Health Technology, Tampere University, Tampere, Finland
10. Department of Psychiatry, Tampere University Hospital, Tampere, Finland
11. Department of Psychiatry, Satasairaala, Finland
12. National Institute of Mental Health, K clecany, Czech Republic
13. Department of Psychiatry, Charles University, Third Faculty of Medicine, Prague, Czech Republic
14. Clinical Pharmacology Unit and Pharmacy Department, Vilardebó Hospital, Administración de Servicios de Salud, Montevideo, Uruguay
15. Clinical Pharmacology Unit and Outpatient Clinic, Vilardebó Hospital, Administración de Servicios de Salud, Montevideo, Uruguay
16. Universidad de Oviedo. CIBERSAM. INEUROPA. ISPA-FIMBA, Oviedo, Spain
17. Hospital Valle del Nalón, Langreo, Spain
18. Hospital Universitario Central de Asturias, Oviedo, Spain
19. Department of Clinical and Experimental Medicine, University of Messina, Messina, Italy
20. Laboratory of Clinical Psychopharmacology, Beijing Anding Hospital, Capital Medical University, Beijing, China
21. The National Clinical Research Centre for Mental Disorders & Beijing Key Lab of Mental Disorders, Beijing Anding Hospital, Capital Medical University, Beijing, China
22. Department of Psychiatry, Beijing Anding Hospital, Capital Medical University, Beijing, China
Department of Psychiatry and Behavioral Sciences, Emory University School of Medicine, Atlanta, Georgia, USA
Substance Abuse Treatment Program, Atlanta VA Medical Center, Decatur, Georgia, USA
Department of Psychiatry, Linkou Chang Gung Memorial Hospital, Taoyuan, Taiwan
Department of Psychiatry, School of Medicine, Taipei Medical University, Taipei, Taiwan
Graduate Institute of Biomedical Sciences, China Medical University, Taichung, Taiwan
Department of Psychiatry and Brain Disease Research Center, China Medical University Hospital, Taichung, Taiwan
Department of Psychology, College of Medical and Health Sciences, Asia University, Taichung, Taiwan
Department of Neuropsychiatry, Nowon Eulji Medical Center, Eulji University, School of Medicine, Seoul, Korea
Department of Psychiatry, Seoul National University Hospital, Seoul National University College of Medicine, Seoul, Republic of Korea
Department of Psychiatry, Christian Medical College, Vellore, India
Institute of Mental Health, Jubilee Campus, University of Nottingham, Triumph Road, Nottingham, United Kingdom
Instituto Nacional de Neurología y Neurocirugía, México City, México
Facultad de Química, Universidad Nacional Autónoma de México (UNAM), México City, México
Department of Physiology, Los Andes University Medical School, Mérida, Venezuela
Department of Affective Disorders, Aarhus University Hospital - Psychiatry, Aarhus, Denmark
Department of Clinical Medicine, Aarhus University, Aarhus, Denmark
Mental Health Centre Glostrup, Copenhagen University Hospital, Copenhagen, Denmark
Univ. Bordeaux, Inserm, Bordeaux Population Health Research Center, Team Pharmacoepidemiology, UMR 1219, F-33000 Bordeaux, France
Department of Physical Medicine and Pharmacology, School of Medicine, Universidad de La Laguna, Canary Islands, Spain
Hospital Universitario de Canarias, Tenerife, Spain
Department of Internal Medicine, Dermatology and Psychiatry, School of Medicine, and Instituto Universitario de Neurociencia (IUNNE), University of La Laguna, Canary Islands, Spain
Dutch Clozapine Collaboration Group, Castricum, The Netherlands
FACT-team in Heerhugowaard, Department of Severe Mental Illness, Mental Health Services North-Holland North, The Netherlands
Mental Health Team Alkmaar, Mental Health Services Noord-Holland-Noord, Alkmaar, The Netherlands
Department of Psychiatry, Hacettepe University Faculty of Medicine, Ankara, Turkey
Addictions Division, Centre for Addiction and Mental Health, Toronto, Canada
Department of Psychiatry, University of Toronto, Toronto, Ontario, Canada
Eastern State Hospital, Lexington, Kentucky, USA
Hazelwood Center, Louisville, Kentucky, USA
Department of Psychiatry and Molecular Medicine, Donald and Barbara Zucker School of Medicine at Hofstra/Northwell Hempstead, New York, USA
School of Medicine, Keele University, Staffordshire, and Midlands Partnership NHS Foundation Trust, Staffordshire, United Kingdom
Department of Psychiatry, The University of Melbourne, Melbourne, Victoria, Australia
Department of Psychiatry, Washington University in St. Louis, St. Louis, Missouri, USA
Department of Psychiatry and Psychotherapy, University Medical Center of Mainz, Germany
Grupo de Investigación en Psiquiatría GIPSI, Departamento de Psiquiatría, Facultad de Medicina, Universidad de Antioquia, Medellín, Colombia
Programa Trastornos del Ánimo, Hospital Universitario San Vicente Fundación, Medellín, Colombia
Department of Pharmacy Practice, University of Montana, Missoula, USA
Institute of Neuropsychiatry and Addictions (INAD), Parc de Salut Mar, Barcelona, Spain
Department of Psychiatry, Autonomous University of Barcelona, Spain
Unit of Pharmacogenetics and Clinical Psychopharmacology, Center for Psychiatric Neurosciences, Lausanne University Hospital and University of Lausanne, Switzerland
Center for Research and Innovation in Clinical Pharmaceutical Sciences, Lausanne University Hospital and University of Lausanne, Switzerland
School of Pharmaceutical Sciences, University of Geneva, Switzerland
Institute of Pharmaceutical Sciences of Western Switzerland, University of Geneva, University of Lausanne, Switzerland
Department of Psychiatry, Complejo Hospitalario Universitario de Santiago, Santiago de Compostela, Spain
Center for Drug Sciences, Faculty of Pharmacy, University of Medicine and Pharmacy Carol Davila, Bucharest, Romania
Te Korowai Whāriki Central Regional Forensic Service, Capital and Coast District Health Board, Wellington, New Zealand
| 69 | Department of Psychological Medicine, University of Otago, Wellington, New Zealand |
| 70 | Departments of Medical Genetics, Psychiatry, Physiology & Pharmacology, and Community Health Sciences University of Calgary, Alberta, Canada |
| 71 | Faculty of Medicine, University of Montreal, Montreal, Canada |
| 72 | Department of Pharmacy, Hôpital du Sacré-Cœur de Montréal, Montreal, Canada |
| 73 | East London NHS Foundation Trust, London, United Kingdom |
| 74 | Honorary Clinical Senior Lecturer, Barts and the London School of Medicine, Queen Mary University of London, United Kingdom |
| 75 | Department of Psychiatry, School of Medicine, Maryland Psychiatric Research Center, University of Maryland School of Medicine, Baltimore, Maryland, USA |
| 76 | Department of Psychiatry, Asahi General Hospital, Chiba, Japan |
| 77 | National Institute of Mental Health, Neurology and Neurosurgery, Budapest, Hungary |
| 78 | Department of Psychiatry, School of Medicine, Pontificia Universidad Católica de Chile, Santiago, Chile |
| 79 | Secretaría de Salud Mental y Adicciones, Ministerio de Salud de la Provincia de Jujuy, San Salvador de Jujuy, Argentina |
| 80 | Instituto Vilapriño, Center for Studies, Assistance and Research in Neurosciences, Mendoza, Argentina |
| 81 | Department of Psychiatry, LSK Faculty of Medicine, The University of Hong Kong, Hong Kong SAR |
| 82 | State Key Laboratory of Brain and Cognitive Sciences, The University of Hong Kong, Hong Kong SAR |
| 83 | College of Pharmacy, QU Health, Qatar University, Doha, Qatar |
| 84 | Department of Psychiatry, Hamad Medical Corporation, Doha, Qatar |
| 85 | NHS, Department of Mental Health, “G. Mazzini” Hospital, Teramo, Italy |
| 86 | Department of Psychiatry, Post Graduate Institute of Medical Education and Research, Chandigarh, India |
| 87 | British Columbia Mental Health and Substance Use Research Institute, Department of Psychiatry, University of British Columbia, Vancouver, BC, Canada |
| 88 | Federal Neuropsychiatric Hospital Yaba, Lagos, Nigeria |
| 89 | Department of Clinical Pharmacology, Astrakhan State Medical University, Astrakhan, Russian Federation |
| 90 | Department of Psychiatry and Clinical Psychology, Northern State Medical University, Arkhangelsk, Russia |
| 91 | 3rd Department of Psychiatry, Division of Neurosciences, School of Medicine, Faculty of Health Sciences, Aristotle University of Thessaloniki, Greece |
| 92 | Department of Psychiatry, Medical University of Gdańsk, Gdańsk, Poland |
| 93 | Department of Psychiatry, Queens University, Kingston, Canada |
| 94 | Psychiatry Department, Centro Hospitalar Universitário de S. João, Porto, Portugal |
| 95 | Faculdade de Medicina da Universidade do Porto, Porto, Portugal |
| 96 | Sigmund Freud University, Vienna, Austria |
| 97 | Department of Neurosciences, Jerez University Hospital, Andalusian Health Service, University of Cádiz, Jerez, Spain |
| 98 | Department of Psychiatry, School of Medicine, University Hospital Virgen del Rocío-IBIS, Sevilla, Spain |
| 99 | Spanish Network for Research in Mental Health (CIBERSAM), Sevilla, Spain |
| 100 | Department of Psychiatry and Mental Health, University of Cape Town, Valkenberg Hospital, Western Cape, Cape Town, South Africa |
| 101 | Division of Clinical Pharmacology, Department of Medicine, Faculty of Medicine and Health Sciences, Stellenbosch University, Cape Town, South Africa |
| 102 | Hospital Central de Maputo, Maputo, Mozambique |
| 103 | Department of Neuropsychiatry, Keio University School of Medicine, Tokyo, Japan |
| 104 | Department of Psychiatry, Okayama Psychiatric Medical Center, Okayama, Japan |
| 105 | Central Institute of Mental Health, Department of Molecular Neuroimaging, Medical Faculty Mannheim, University of Heidelberg, Mannheim, Germany |
| 106 | Department of Psychiatry, School of Medicine, University of Zagreb, Zagreb, Croatia |
| 107 | Department for Psychiatry and Psychological Medicine, University Hospital Center Zagreb, Croatia |
| 108 | Department of Psychiatry, University Medical Centre Maribor, Maribor, Slovenia |
| 109 | University of Kragujevac, Faculty of Medical Sciences, Department of Psychiatry, Kragujevac, Serbia |
| 110 | Group of Resistant Schizophrenia (GER), Schizophrenia Program (Proesq), Federal University of Sao Paulo, SP, Brazil |
| 111 | Department and Institute of Psychiatry, University of São Paulo Medical School (FMUSP), Sao Paulo, Brazil |
| 112 | Department and Institute of Psychiatry and Mental Health, Oporto Faculty of Medicine, Oporto, Portugal |
| 113 | Casa de Salidello Som Jesus (Psychiatric Hospital), Oporto, Portugal |
| 114 | INUBE Biosanitary Research Institute of Extremadura. Extremadura University Hospital and Medical School, Badajoz, Spain |
| 115 | Spanish Network for Research in Mental Health (CIBERSAM), Instituto de Salud Carlos III, Madrid, Spain |
| 116 | Cambridge Psychosis Centre, Cambridgeshire and Peterborough NHS Foundation Trust & Department of Psychiatry, University of Cambridge, Cambridge, United Kingdom |
| 117 | Metro South Addiction and Mental Health Service, Brisbane, Australia |
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/Asian ancestry with average metabolism needing 250–400 mg/day, 4) European/Western Asian ancestry with lower metabolism (obesity or valproate) needing 150–300 mg/day, and 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 potentially 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.

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Supplementary Material
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 levels 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 TMD 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. Filipinos are 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 the original people from the Americas 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., co-medication, 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 Oceania 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.

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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 Josiasssen, 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, Molen, Solisamoa, Seppalä, Kopeček, Śvancer, Olmos, Iglesias-Garcia, Iglesias-Alonso, Spina, Ruan, Chun-Yue Wang, Tang, Lin, Rajkumar, González-Esquível, Jung-Cook, Baptista, Rohde, Nielsen, Verdoux, Quiles, Sanz, De las Cuevas, Cohen, Schulte, Chopra, McCollum, Shelton, Kaiti, Farooq, McGrane, Lana, Arrojo-Romero, Rădulescu, Every-Palmer, Bebawi, Bhattacharya, Otsuka, Lazary, Torres, Yecora, Motuca, Chan, Zolezzi, Ouanes, De Berardis, Grover, Kiroloche, 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 Viatris 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 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 Ibrahim Otsuka. Dr. Anıl Yağcıoğlu has received speaker’s honoraria and consulting fees from Janssen and Abdi Ibrahim 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 Alpergan, personal fees from Bristol-Myters 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. IMcG 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, Angeli, 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

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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.