


















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

Authors

Jose de Leon^{1, 2, 3, 4} , Georgios Schoretsanitis^{5, 6} , Robert L. Smith⁷ , Espen Molden^{7, 8} , Anssi Solismaa^{9, 10} , Niko Seppälä¹¹ , Miloslav Kopeček^{12, 13} , Patrik Švancer^{12, 13} , Ismael Olmos¹⁴ , Carina Ricciardi¹⁵ , Celso Iglesias-Garcia^{16, 17} , Ana Iglesias-Alonso¹⁸ , Edoardo Spina¹⁹ , Can-Jun Ruan^{20, 21} , Chuan-Yue Wang^{21, 22} , Gang Wang²¹ , Yi-Lang Tang^{23, 24} , Shih-Ku Lin^{25, 26} , Hsien-Yuan Lane^{27, 28, 29} , Yong Sik Kim³⁰ , Se Hyun Kim³¹ , Anto P. Rajkumar^{32, 33} , Dinora F. González-Esquivel³⁴ , Helgi Jung-Cook^{34, 35} , Trino Baptista³⁶ , Christopher Rohde^{37, 38} , Jimmi Nielsen³⁹ , Hélène Verdoux⁴⁰ , Clelia Quiles⁴⁰ , Emilio J. Sanz^{41, 42} , Carlos De las Cuevas⁴³ , Dan Cohen^{44, 45} , Peter F.J. Schulte^{44, 46} , Aygün Ertuğrul⁴⁷ , A.Elif Anıl Yağcıoğlu⁴⁷ , Nitin Chopra^{48, 49} , Betsy McCollum⁵⁰ , Charles Shelton^{2, 50} , Robert O. Cotes²³ , Arun R. Kaithi⁵¹ , John M. Kane^{6, 52} , Saeed Farooq⁵³ , Chee H. Ng⁵⁴ , John Bilbily⁵⁵ , Christoph Hiemke⁵⁶ , Carlos López-Jaramillo^{57, 58} , Ian McGrane⁵⁹ , Fernando Lana^{60, 61} , Chin B. Eap^{62, 63, 64, 65} , Manuel Arrojo-Romero⁶⁶ , Flavian Ş. Rădulescu⁶⁷ , Erich Seifritz⁵ , Susanna Every-Palmer^{68, 69} , Chad A. Bousman⁷⁰ , Emmanuel Bebawi^{71, 72} , Rahul Bhattacharya^{73, 74} , Deanna L. Kelly⁷⁵ , Yuji Otsuka⁷⁶ , Judit Lazary⁷⁷ , Rafael Torres⁷⁸ , Agustín Yecora⁷⁹ , Mariano Motuca⁸⁰ , Sherry K.W. Chan^{81, 82} , Monica Zolezzi⁸³ , Sami Ouanes⁸⁴ , Domenico De Berardis⁸⁵ , Sandeep Grover⁸⁶ , Ric M. Procyshyn⁸⁷ , Richard A. Adebayo⁸⁸ , Oleg O. Kirilochev⁸⁹ , Andrey Soloviev⁹⁰ , Konstantinos N. Fountoulakis⁹¹ , Alina Wilkowska⁹² , Wiesław J. Cubała⁹² , Muhammad Ayub⁹³ , Alzira Silva^{94, 95} , Raphael M. Bonelli⁹⁶ , José M. Villagrán-Moreno⁹⁷ , Benedicto Crespo-Facorro^{98, 99} , Henk Temmingh¹⁰⁰ , Eric Declodt¹⁰¹ , Maria R. Pedro¹⁰² , Hiroyoshi Takeuchi¹⁰³ , Masaru Tsukahara¹⁰⁴ , Gerhard Gründer¹⁰⁵ , Marina Sagud^{106, 107} , Andreja Celofiga¹⁰⁸ , Dragana Ignjatovic Ristic¹⁰⁹ , Bruno B. Ortiz¹¹⁰ , Helio Elkis¹¹¹ , António J. Pacheco Palha^{112, 113} , Adrián Llerena^{114, 115} , Emilio Fernandez-Egea¹¹⁶ , Dan Siskind^{117, 118} , Abraham Weizman^{119, 120} , Rim Masmoudi^{121, 122} , Shamin Mohd Saffian¹²³ , Jonathan G. Leung¹²⁴ , Peter F. Buckley¹²⁵ , Stephen R. Marder^{126, 127} , Leslie Citrome¹²⁸ , Oliver Freudenreich¹²⁹ , Christoph U. Correll^{6, 52, 130} , Daniel J. Müller^{48, 49}

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 Net (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 Biosciences, 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, Satasaairaala, Finland
- 12 National Institute of Mental Health, Klecany, 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

- 23 Department of Psychiatry and Behavioral Sciences, Emory University School of Medicine, Atlanta, Georgia, USA
- 24 Substance Abuse Treatment Program, Atlanta VA Medical Center, Decatur, Georgia, USA
- 25 Department of Psychiatry, Linkou Chang Gung Memorial Hospital, Taoyuan, Taiwan
- 26 Department of Psychiatry, School of Medicine, Taipei Medical University, Taipei, Taiwan
- 27 Graduate Institute of Biomedical Sciences, China Medical University, Taichung, Taiwan
- 28 Department of Psychiatry and Brain Disease Research Center, China Medical University Hospital, Taichung, Taiwan
- 29 Department of Psychology, College of Medical and Health Sciences, Asia University, Taichung, Taiwan
- 30 Department of Neuropsychiatry, Nowon Eulji Medical Center, Eulji University, School of Medicine, Seoul, Korea
- 31 Department of Psychiatry, Seoul National University Hospital, Seoul National University College of Medicine, Seoul, Republic of Korea
- 32 Department of Psychiatry, Christian Medical College, Vellore, India
- 33 Institute of Mental Health, Jubilee Campus, University of Nottingham, Triumph Road, Nottingham, United Kingdom
- 34 Instituto Nacional de Neurología y Neurocirugía, México City, México
- 35 Facultad de Química, Universidad Nacional Autónoma de México (UNAM), México City, México
- 36 Department of Physiology, Los Andes University Medical School, Mérida, Venezuela
- 37 Department of Affective Disorders, Aarhus University Hospital - Psychiatry, Aarhus, Denmark
- 38 Department of Clinical Medicine, Aarhus University, Aarhus, Denmark
- 39 Mental Health Centre Glostrup, Copenhagen University Hospital, Copenhagen, Denmark
- 40 Univ. Bordeaux, Inserm, Bordeaux Population Health Research Center, Team Pharmacoepidemiology, UMR 1219, F-33000 Bordeaux, France
- 41 Department of Physical Medicine and Pharmacology, School of Medicine, Universidad de La Laguna, Canary Islands, Spain
- 42 Hospital Universitario de Canarias, Tenerife, Spain
- 43 Department of Internal Medicine, Dermatology and Psychiatry, School of Medicine, and Instituto Universitario de Neurociencia (IUNE), University of La Laguna, Canary Islands, Spain
- 44 Dutch Clozapine Collaboration Group, Castricum, The Netherlands
- 45 FACT-team in Heerhugowaard, Department of Severe Mental Illness, Mental Health Services North-Holland North, The Netherlands
- 46 Mental Health Team Alkmaar, Mental Health Services Noord-Holland-Noord, Alkmaar, The Netherlands
- 47 Department of Psychiatry, Hacettepe University Faculty of Medicine, Ankara, Turkey
- 48 Addictions Division, Centre for Addiction and Mental Health, Toronto, Canada
- 49 Department of Psychiatry, University of Toronto, Toronto, Ontario, Canada
- 50 Eastern State Hospital, Lexington, Kentucky, USA
- 51 Hazelwood Center, Louisville, Kentucky, USA
- 52 Department of Psychiatry and Molecular Medicine, Donald and Barbara Zucker School of Medicine at Hofstra/Northwell Hempstead, New York, USA
- 53 School of Medicine, Keele University, Staffordshire, and Midlands Partnership NHS Foundation Trust, Staffordshire, United Kingdom
- 54 Department of Psychiatry, The University of Melbourne, Melbourne, Victoria, Australia
- 55 Department of Psychiatry, Washington University in St. Louis, St. Louis, Missouri, USA
- 56 Department of Psychiatry and Psychotherapy, University Medical Center of Mainz, Germany
- 57 Grupo de Investigación en Psiquiatría GIPSI, Departamento de Psiquiatría, Facultad de Medicina, Universidad de Antioquia, Medellín, Colombia
- 58 Programa Trastornos del Ánimo, Hospital Universitario San Vicente Fundación, Medellín, Colombia
- 59 Department of Pharmacy Practice, University of Montana, Missoula, USA
- 60 Institute of Neuropsychiatry and Addictions (INAD), Parc de Salut Mar, Barcelona, Spain
- 61 Department of Psychiatry, Autonomous University of Barcelona, Spain
- 62 Unit of Pharmacogenetics and Clinical Psychopharmacology, Center for Psychiatric Neurosciences, Lausanne University Hospital and University of Lausanne, Switzerland
- 63 Center for Research and Innovation in Clinical Pharmaceutical Sciences, Lausanne University Hospital and University of Lausanne, Switzerland
- 64 School of Pharmaceutical Sciences, University of Geneva, Switzerland
- 65 Institute of Pharmaceutical Sciences of Western Switzerland, University of Geneva, University of Lausanne, Switzerland
- 66 Department of Psychiatry, Complejo Hospitalario Universitario de Santiago, Santiago de Compostela, Spain
- 67 Center for Drug Sciences, Faculty of Pharmacy, University of Medicine and Pharmacy Carol Davila, Bucharest, Romania
- 68 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 Cadiz, 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 Salidedo 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

- 118 Queensland Centre for Mental Health Research and School of Clinical Medicine, University of Queensland, Brisbane, Australia
- 119 Research Unit, Geha Mental Health Center and Molecular Psychiatry Laboratory, Felsenstein Medical Research Center, Tel Aviv, Israel
- 120 Department of Psychiatry Sackler Faculty of Medicine and Sagol School of Neuroscience, Tel Aviv University, Tel Aviv, Israel
- 121 Psychiatry "A" Department, Hedi Chaker University Hospital, Sfax, Tunisia
- 122 Faculty of Medicine, University of Sfax, Sfax, Tunisia
- 123 Centre for Quality Management of Medicines, Faculty of Pharmacy, Universiti Kebangsaan Malaysia, Kuala Lumpur, Malaysia
- 124 Department of Pharmacy, Mayo Clinic, Rochester, MN, USA
- 125 School of Medicine, Virginia Commonwealth University, Richmond, VA, USA
- 126 Semel Institute for Neuroscience at UCLA, Los Angeles, CA, USA
- 127 VA Desert Pacific Mental Illness Research, Education, and Clinical Center, Los Angeles, CA, USA
- 128 New York Medical College, Department of Psychiatry and Behavioral Sciences, Valhalla, NY, USA
- 129 Department of Psychiatry, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA
- 130 Charité Universitätsmedizin Berlin, Department of Child and Adolescent Psychiatry, Berlin, Germany

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

© 2021. Thieme. All rights reserved.

Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany

Correspondence

Jose de Leon, M.D.,
Mental Health Research Center at Eastern State Hospital,
1350 Bull Lea Road,
Lexington, KY 40511,
USA
jdeleon@uky.edu

 **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 Grunbionics, 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).

References

- [1] de Leon J, Ruan C, Schoretsanitis G et al. A rational use of clozapine based on adverse drug reactions, pharmacokinetics, and clinical pharmacopsychology. *Psychother Psychosom* 2020; 89: 200–204
- [2] Kane J, Honigfeld G, Singer J et al. Clozapine for the treatment-resistant schizophrenic: A double-blind comparison with chlorpromazine. *Arch Gen Psychiatry* 1988; 45: 789–796

- [3] de Leon J, Ruan CJ, Schoretsanitis G et al. Dose and safety concerns of clozapine: worldwide package inserts need revisions. *Schizophr Res* 2020; 216: 2–4
- [4] Nielsen J, Young C, Ifteni P et al. Worldwide differences in regulations of clozapine use. *CNS Drugs* 2016; 30: 149–161
- [5] Howes OD, McCutcheon R, Agid O et al. Treatment-resistant schizophrenia: Treatment Response and Resistance in Psychosis (TRRIP) Working Group Consensus Guidelines on diagnosis and terminology. *Am J Psychiatry* 2017; 174: 216–229
- [6] Siskind D, McCartney L, Goldschlager R et al. Clozapine v. first- and second-generation antipsychotics in treatment-refractory schizophrenia: systematic review and meta-analysis. *Br J Psychiatry* 2016; 209: 385–392
- [7] Samara MT, Dold M, Gianatsi M et al. Efficacy, acceptability, and tolerability of antipsychotics in treatment-resistant schizophrenia: A network meta-analysis. *JAMA Psychiatry* 2016; 73: 199–210
- [8] Huhn M, Nikolakopoulou A, Schneider-Thoma J et al. Comparative efficacy and tolerability of 32 oral antipsychotics for the acute treatment of adults with multi-episode schizophrenia: A systematic review and network meta-analysis. *Lancet* 2019; 394: 939–951
- [9] Land R, Siskind D, McArdle P et al. The impact of clozapine on hospital use: a systematic review and meta-analysis. *Acta Psychiatr Scand* 2017; 135: 296–309
- [10] Masuda T, Misawa F, Takase M et al. Association with hospitalization and all-cause discontinuation among patients with schizophrenia on clozapine vs other oral second-generation antipsychotics: A systematic review and meta-analysis of cohort studies. *JAMA Psychiatry* 2019; 76: 1052–1062
- [11] Hjorthøj C, Stürup AE, McGrath JJ et al. Years of potential life lost and life expectancy in schizophrenia: a systematic review and meta-analysis. *Lancet Psychiatry* 2017; 4: 295–301
- [12] Vermeulen JM, van Rooijen G, van de Kerkhof MPJ et al. Clozapine and long-term mortality risk in patients with schizophrenia: a systematic review and meta-analysis of studies lasting 1.1–12.5 years. *Schizophr Bull* 2019; 45: 315–329
- [13] Cho J, Hayes RD, Jewell A et al. Clozapine and all-cause mortality in treatment-resistant schizophrenia: a historical cohort study. *Acta Psychiatr Scand* 2019; 139: 237–247
- [14] van der Zalm Y, Foldager L, Termorshuizen F et al. Clozapine and mortality: A comparison with other antipsychotics in a nationwide Danish cohort study. *Acta Psychiatr Scand* 2021; 143: 216–226
- [15] Taipale H, Tanskanen A, Mehtälä J et al. 20-year follow-up study of physical morbidity and mortality in relationship to antipsychotic treatment in a nationwide cohort of 62,250 patients with schizophrenia (FIN20). *World Psychiatry* 2020; 19: 61–68
- [16] Tiihonen J, Lönnqvist J, Wahlbeck K et al. 11-year follow-up of mortality in patients with schizophrenia: a population-based cohort study (FIN11 study). *Lancet* 2009; 374: 620–627
- [17] Bachmann CJ, Aagaard L, Bernardo M et al. International trends in clozapine use: a study in 17 countries. *Acta Psychiatr Scand* 2017; 136: 37–51
- [18] Meltzer HY, Alphas L, Green AI et al. Clozapine treatment for suicidality in schizophrenia: International Suicide Prevention Trial (InterSePT). *Arch Gen Psychiatry* 2003; 60: 82–91
- [19] Citrome L, Volavka J. Specific anti-hostility effects of atypical antipsychotics in persons with schizophrenia: from clozapine to cariprazine. *Harv Rev Psychiatry* 2021; 29: 20–34
- [20] Hiemke C, Bergemann N, Clement HW et al. Consensus guidelines for therapeutic drug monitoring in neuropsychopharmacology: update 2017. *Pharmacopsychiatry* 2018; 51: 9–62
- [21] Schoretsanitis G, Kane JM, Correll CU et al. Blood levels to optimize antipsychotic treatment in clinical practice: a joint consensus statement of the American Society of Clinical Psychopharmacology and the Therapeutic Drug Monitoring Task Force of the Arbeitsgemeinschaft für Neuropsychopharmakologie und Pharmakopsychiatrie. *J Clin Psychiatry* 2020; 81: 19cs13169
- [22] Williams RL. FDA position on product selection for “narrow therapeutic index” drugs. *Am J Health Syst Pharm* 1997; 54: 1630–1632
- [23] Spina E, Hiemke C, de Leon J. Assessing drug-drug interactions through therapeutic drug monitoring when administering oral second-generation antipsychotics. *Expert Opin Drug Metab Toxicol* 2016; 12: 407–422
- [24] Moore TJ, Cohen MR, Furberg CD. Serious adverse drug events reported to the Food and Drug Administration, 1998–2005. *Arch Intern Med* 2007; 167: 1752–1759
- [25] de Leon J, Sanz EJ, De Las Cuevas C. Data from the World Health Organization's pharmacovigilance database supports the prominent role of pneumonia in mortality associated with clozapine adverse drug reactions. *Schizophr Bull* 2020; 46: 1–3
- [26] de Leon J, Sanz EJ, Norén GN et al. Pneumonia may be more frequent and have more fatal outcomes with clozapine than with other second-generation antipsychotics. *World Psychiatry* 2020; 19: 120–121
- [27] Rohde C, Siskind D, de Leon J et al. Antipsychotic medication exposure, clozapine, and pneumonia: results from a self-controlled study. *Acta Psychiatr Scand* 2020; 142: 78–86
- [28] Villasante-Tezanos AG, Rohde C, Nielsen J et al. Pneumonia risk: approximately one-third is due to clozapine and two-thirds is due to treatment-resistant schizophrenia. *Acta Psychiatr Scand* 2020; 142: 66–67
- [29] Schoretsanitis G, Ruan CJ, Rohde C et al. An update on the complex relationship between clozapine and pneumonia. *Expert Rev Clin Pharmacol* 2021; 24: 1–5
- [30] Vohra J. Sudden cardiac death in schizophrenia: a review. *Heart Lung Circ* 2020; 29: 1427–1432
- [31] Papola D, Ostuzzi G, Gastaldon C et al. Antipsychotic use and risk of life-threatening medical events: umbrella review of observational studies. *Acta Psychiatr Scand* 2019; 140: 227–243
- [32] Myles N, Myles H, Xia S et al. A meta-analysis of controlled studies comparing the association between clozapine and other antipsychotic medications and the development of neutropenia. *Aust N Z J Psychiatry* 2019; 53: 403–412
- [33] Wiciński M, Węclewicz MM. Clozapine-induced agranulocytosis/granulocytopenia: mechanisms and monitoring. *Curr Opin Hematol* 2018; 25: 22–28
- [34] Winckel K, Siskind D, Hollingworth S et al. Clozapine-induced myocarditis: separating the wheat from the chaff. *Aust N Z J Psychiatry* 2015; 49: 188
- [35] Ronaldson KJ, Fitzgerald PB, Taylor AJ et al. A new monitoring protocol for clozapine-induced myocarditis based on an analysis of 75 cases and 94 controls. *Aust NZ J Psychiatry* 2011; 45: 458–465
- [36] Ronaldson KJ, Fitzgerald PB, Taylor AJ et al. Rapid clozapine dose titration and concomitant sodium valproate increase the risk of myocarditis with clozapine: a case-control study. *Schizophr Res* 2012; 141: 173–178
- [37] Shirazi A, Stubbs B, Gomez L et al. Prevalence and predictors of clozapine-associated constipation: a systematic review and meta-analysis. *Int J Mol Sci* 2016; 17: 863
- [38] West S, Rowbotham D, Xiong G et al. Clozapine induced gastrointestinal hypomotility: a potentially life threatening adverse event. A review of the literature. *Gen Hosp Psychiatry* 2017; 46: 32–37
- [39] Cohen D. Clozapine and gastrointestinal hypomotility. *CNS Drugs* 2017; 31: 1083–1091

- [40] de Leon J, Schoretsanitis G, Kane JM et al. Using therapeutic drug monitoring to personalize clozapine dosing in Asians. *Asia Pac Psychiatry* 2020; 12: e12384
- [41] Spina E, de Leon J. Clinically relevant interactions between newer antidepressants and second-generation antipsychotics. *Expert Opin Drug Metab Toxicol* 2014; 10: 721–746
- [42] Pacia SV, Devinsky O. Clozapine-related seizures: experience with 5,629 patients. *Neurology* 1994; 44: 2247–2249
- [43] Clancy MJ, Clarke MC, Connor DJ et al. The prevalence of psychosis in epilepsy; a systematic review and meta-analysis. *BMC Psychiatry* 2014; 14: 75
- [44] Asenjo Lobos C, Komossa K, Rummel-Kluge C et al. Clozapine versus other atypical antipsychotics for schizophrenia. *Cochrane Database Syst Rev* 2010; CD006633
- [45] Trifirò G, Spina E. Age-related changes in pharmacodynamics: focus on drugs acting on central nervous and cardiovascular systems. *Curr Drug Metab* 2011; 12: 611–620
- [46] Nielsen J, Correll CU, Manu P et al. Termination of clozapine treatment due to medical reasons: when is it warranted and how can it be avoided? *J Clin Psychiatry* 2013; 74: 603–613
- [47] Sabaawi M, Singh NN, de Leon J. Guidelines for the use of clozapine in individuals with developmental disabilities. *Res Dev Disabil* 2006; 27: 309–336
- [48] Sandoz, Inc. CLOZAPINE tablet [Package insert]. Sandoz Inc. Princeton, NJ. Available from: <https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=e503b3cd-574e-ed6a-c7ed-3368115f7f72>
- [49] Bertilsson L, Carrillo JA, Dahl ML et al. Clozapine disposition covaries with CYP1A2 activity determined by a caffeine test. *Br J Clin Pharmacol* 1994; 38: 471–473
- [50] Ghotbi R, Christensen M, Roh HK et al. Comparisons of CYP1A2 genetic polymorphisms, enzyme activity and the genotype-phenotype relationship in Swedes and Koreans. *Eur J Clin Pharmacol* 2007; 63: 537–546
- [51] Perry PJ, Bever KA, Arndt S et al. Relationship between patient variables and plasma clozapine concentrations: a dosing nomogram. *Biol Psychiatry* 1998; 44: 733–738
- [52] Haslemo T, Eikeseth PH, Tanum L et al. The effect of variable cigarette consumption on the interaction with clozapine and olanzapine. *Eur J Clin Pharmacol* 2006; 62: 1049–1053
- [53] Dobrinias M, Cornuz J, Oneda B et al. Impact of smoking, smoking cessation, and genetic polymorphisms on CYP1A2 activity and inducibility. *Clin Pharmacol Ther* 2011; 90: 117–125
- [54] Wagner E, McMahon L, Falkai P et al. Impact of smoking behavior on clozapine blood levels - a systematic review and meta-analysis. *Acta Psychiatr Scand* 2020; 142: 456–466
- [55] Olesen OV, Linnet K. Contributions of five human cytochrome P450 isoforms to the N-demethylation of clozapine in vitro at low and high concentrations. *J Clin Pharmacol* 2001; 41: 823–832
- [56] Schoretsanitis G, Kane JM, Ruan CJ et al. Comprehensive review of the clinical utility of and a combined analysis of the clozapine/norclozapine ratio in therapeutic drug monitoring for adult patients. *Expert Rev Clin Pharmacol* 2019; 12: 603–621
- [57] Chang WH, Lin SK, Lane HY et al. Reversible metabolism of clozapine and clozapine N-oxide in schizophrenic patients. *Prog Neuropsychopharmacol Biol Psychiatry* 1998; 22: 723–739
- [58] de Leon J. Glucuronidation enzymes, genes and psychiatry. *Int J Neuropsychopharmacol* 2003; 6: 57–72
- [59] Loi CM, Smith DA, Dalvie D. Which metabolites circulate? *Drug Metab Dispos* 2013; 41: 933–951
- [60] Schaber G, Stevens I, Gaertner HJ et al. Pharmacokinetics of clozapine and its metabolites in psychiatric patients: Plasma protein binding and renal clearance. *Br J Clin Pharmacol* 1998; 46: 453–459
- [61] Kuoppamäki M, Syvälahti E, Hietala J. Clozapine and N-desmethylozapine are potent 5-HT1C receptor antagonists. *Eur J Pharmacol* 1993; 245: 179–182
- [62] Ruan CJ, Zang YN, Wang CY et al. Clozapine metabolism in East Asians and Caucasians: a pilot exploration of the prevalence of poor metabolizers and a systematic review. *J Clin Psychopharmacol* 2019; 39: 135–144
- [63] Jerling M, Lindström L, Bondesson U et al. Fluvoxamine inhibition and carbamazepine induction of the metabolism of clozapine: evidence from therapeutic drug monitoring service. *Ther Drug Monit* 1994; 16: 368–374
- [64] Spina E, Barbieri MA, Cicala G et al. Clinically relevant interactions between atypical antipsychotics and anti-infective agents. *Pharmaceuticals (Basel)* 2020; 13: 439
- [65] Ruan CJ, Zang YN, Cheng YH et al. Around 3% of 1,300 levels were elevated during infections in a retrospective review of 131 Beijing hospital in-patients with more than 24,000 days of clozapine treatment. *Psychother Psychosom* 2020; 89: 255–257
- [66] de Leon J. Atypical antipsychotic dosing: the effect of smoking and caffeine. *Psychiatr Serv* 2004; 55: 491–493
- [67] Faber MS, Fuhr U. Time response of cytochrome P450 1A2 activity on cessation of heavy smoking. *Clin Pharmacol Ther* 2004; 76: 178–184
- [68] Ruan CJ, Wang CY, Tang YL et al. Exploring the prevalence of clozapine phenotypic poor metabolizers in 4 Asian samples: they ranged between 2% and 13%. *J Clin Psychopharmacol* 2019; 39: 644–648
- [69] de Leon J. Future studies on the interaction between clozapine and valproic acid should aspire to include longitudinal designs and free valproate concentrations, and should consider that inducer and/or inhibitory effects may vary with time, the individual, and the auto-induction of valproic acid. *Ther Drug Monit* 2020; 42: 159–161
- [70] Facciola G, Avenoso A, Scordo MG et al. Small effects of valproic acid on the plasma concentrations of clozapine and its major metabolites in patients with schizophrenic or affective disorders. *Ther Drug Monit* 1999; 21: 341–345
- [71] Wong JO, Leung SP, Mak T et al. Plasma clozapine levels and clinical response in treatment-refractory Chinese schizophrenic patients. *Prog Neuropsychopharmacol Biol Psychiatry* 2006; 30: 251–264
- [72] Diaz FJ, Santoro V, Spina E et al. Estimating the size of the effects of co-medications on plasma clozapine concentrations using a model that controls for clozapine doses and confounding variables. *Pharmacopsychiatry* 2008; 41: 81–91
- [73] Rajkumar AP, Poonkuzhali B, Kuruvilla A et al. Clinical predictors of serum clozapine levels in patients with treatment-resistant schizophrenia. *Int Clin Psychopharmacol* 2013; 28: 50–56
- [74] Spina E, D'Arrigo C, Santoro V et al. Effect of valproate on olanzapine plasma concentrations in patients with bipolar or schizoaffective disorder. *Ther Drug Monit* 2009; 31: 758–763
- [75] Diaz FJ, Josiassen RC, de Leon J. The effect of body weight changes on total plasma clozapine concentrations determined by applying a statistical model to the data from a double-blind trial. *J Clin Psychopharmacol* 2018; 38: 442–446
- [76] Kuzin M, Haen E, Hiemke C et al. Body mass index as a determinant of clozapine plasma concentrations: A pharmacokinetic-based hypothesis. *J Psychopharmacol* 2021; 35: 273–278
- [77] Zarezaheh M, Saedisomeolia A, Shekarabi M et al. The effect of obesity, macronutrients, fasting and nutritional status on drug-metabolizing cytochrome P450s: a systematic review of current evidence on human studies. *Eur J Nutr* 2021; 60: 2905–2921

- [78] Moschyn N, Hefner G, Grohmann R et al. Therapeutic drug monitoring of second- and third-generation antipsychotic drugs- influence of smoking behavior and inflammation on pharmacokinetics. *Pharmaceuticals (Basel)* 2021; 14: 514
- [79] Clark SR, Warren NS, Kim G et al. Elevated clozapine levels associated with infection: A systematic review. *Schizophr Res* 2018; 192: 50–56
- [80] Nielsen R, Akey JM, Jakobsson M et al. Tracing the peopling of the world through genomics. *Nature* 2017; 541: 302–310
- [81] de Leon J, Rajkumar AP, Kaithi AR et al. Do Asian patients require only half of the clozapine dose prescribed for Caucasians? A critical overview. *Indian J Psychol Med* 2020; 42: 4–10
- [82] Suhas S, Kumar V, Damodharan D et al. Do Indian patients with schizophrenia need half the recommended clozapine dose to achieve therapeutic serum level? An exploratory study. *Schizophr Res* 2020; 222: 195–201
- [83] González-Esquivel DF, Jung-Cook H, Baptista T et al. Amerindians may need clozapine dosing similar to that of Asians. *Rev Psiquiatr Salud Ment* 2021; 14: 177–179
- [84] Menkes DB, Glue P, Gale C et al. Steady-state clozapine and norclozapine pharmacokinetics in Maori and European patients. *EBioMedicine* 2018; 27: 134–137
- [85] Zang YN, Dong F, Li AN et al. The impact of smoking, sex, infection, and comedication administration on oral olanzapine: a population pharmacokinetic model in Chinese psychiatric patients. *Eur J Drug Metab Pharmacokinet* 2021; 46: 353–37
- [86] Sathirakul K, Chan C, Teng L et al. Olanzapine pharmacokinetics are similar in Chinese and Caucasian subjects. *Br J Clin Pharmacol* 2003; 56: 184–187
- [87] Bigos KL, Pollock BG, Coley KC et al. Sex, race, and smoking impact olanzapine exposure. *J Clin Pharmacol* 2008; 48: 157–165
- [88] Ruan CJ, de Leon J. Is there a future for CYP1A2 pharmacogenetics in the optimal dosing of clozapine? *Pharmacogenomics* 2020; 21: 369–373
- [89] The Dutch Pharmacogenomic Working Group. Pharmacogenomic recommendations, farmacogenetica-update. 2020; Available at www.knmp.nl/
- [90] Dobrinas M, Cornuz J, Eap CB. Pharmacogenetics of CYP1A2 activity and inducibility in smokers and exsmokers. *Pharmacogenet Genomics* 2013; 23: 286–292
- [91] Jakobsen MI, Larsen JR, Svensson CK et al. The significance of sampling time in therapeutic drug monitoring of clozapine. *Acta Psychiatr Scand* 2017; 135: 159–169
- [92] Schoretsanitis G, Smith RL, Molden E et al. European Caucasians may need lower minimum therapeutic clozapine doses than those customarily proposed. *J Clin Psychopharmacol* 2021; 41: 140–147
- [93] Rostami-Hodjegan A, Amin AM, Spencer EP et al. Influence of dose, cigarette smoking, age, sex, and metabolic activity on plasma clozapine concentrations: a predictive model and nomograms to aid clozapine dose adjustment and to assess compliance in individual patients. *J Clin Psychopharmacol* 2004; 24: 70–78
- [94] Quiles C, Verdoux H. La clozapine. *Encyclopédie Médico-chirurgicale*. Paris: Elsevier Masson SAS; 2020
- [95] Netherlands clozapine collaboration group [Internet]. Guideline for the use of clozapine <http://www.clozapinepluswerkgroep.nl/wp-content/uploads/2013/07/Guideline-for-the-use-of-Clozapine-2013.pdf>
- [96] Taylor DM, Barnes TRE, Young AH. *Maudsley Prescribing Guidelines in Psychiatry*. 13th edition. Hoesboken, NJ: Wiley-Blackwell; 2018
- [97] Lieberman JA, Kane JM, Johns CA. Clozapine: guidelines for clinical management. *J Clin Psychiatry* 1989; 50: 329–338
- [98] Baldessarini RJ, Frankenburg FR. Clozapine. A novel antipsychotic agent. *N Engl J Med* 1991; 324: 746–754
- [99] Citrome L. Schizophrenia life-threatening and life-saving treatment? *Curr Psychiatry* 2009; 8: 57–63
- [100] Meltzer HY. Clozapine: balancing safety with superior antipsychotic efficacy. *Clin Schizophr Relat Psychoses* 2012; 6: 134–144
- [101] Marder SR, Yang YS. Chapter 25. Clozapine. In: Schatzberg AF, Nemeroff CB, Ed. *The American Psychiatric Association Publishing textbook of psychopharmacology*. 5th edition. Washington, DC: American Psychiatric Association Publishing; 2017: 623–648
- [102] Meyer JM, Stahl SM. *The clozapine handbook: Stahl's handbooks (Stahl's essential psychopharmacology handbooks)*. Cambridge: Cambridge University Press; 2020
- [103] de Leon J, Armstrong SC, Cozza KL. The dosing of atypical antipsychotics. *Psychosomatics* 2005; 46: 262–273
- [104] Simpson GM, Josiassen RC, Stanilla JK et al. Double-blind study of clozapine dose response in chronic schizophrenia. *Am J Psychiatry* 1999; 156: 1744–1750
- [105] Cohen D, Bogers JP, van Dijk D et al. Beyond white blood cell monitoring: screening in the initial phase of clozapine therapy. *J Clin Psychiatry* 2012; 73: 1307–1312
- [106] Siskind D, Sidhu A, Cross J et al. Systematic review and meta-analysis of rates of clozapine-associated myocarditis and cardiomyopathy. *Aust N Z J Psychiatry* 2020; 54: 467–481
- [107] Wang XQ, Lv B, Wang HF et al. Lamotrigine-induced severe cutaneous adverse reaction: Update data from 1999–2014. *J Clin Neurosci* 2015; 22: 1005–1011
- [108] Freudenreich O. Clozapine-induced myocarditis: prescribe safely but do not prescribe. *Acta Psychiatr Scand* 2015; 132: 240–241
- [109] de Leon J, Tang YL, Baptista T et al. Titrating clozapine amidst recommendations proposing high myocarditis risk and rapid titrations. *Acta Psychiatr Scand* 2015; 132: 242–243
- [110] Bandelow B, Degner D, Kreusch U et al. Myocarditis under therapy with clozapine. *Schizophr Res* 1995; 17: 293–294
- [111] Pui-yin Chung J, Shiu-yin Chong C, Chung KF et al. The incidence and characteristics of clozapine-induced fever in a local psychiatric unit in Hong Kong. *Can J Psychiatry* 2008; 53: 857–862
- [112] Ifteni P, Nielsen J, Burtse V et al. Effectiveness and safety of rapid clozapine titration in schizophrenia. *Acta Psychiatr Scand* 2014; 130: 25–29
- [113] Ifteni P, Correll CU, Nielsen J et al. Rapid clozapine titration in treatment-refractory bipolar disorder. *J Affect Disord* 2014; 166: 168–172
- [114] Aksoy Poyraz C, Turan Ş, Demirel ÖF et al. Effectiveness of ultra-rapid dose titration of clozapine for treatment-resistant bipolar mania: case series. *Ther Adv Psychopharmacol* 2015; 5: 237–242
- [115] Lochhead JD, Nelson MA, Schneider AL. Risks and benefits of rapid clozapine titration. *Ment Illn* 2016; 8: 6457
- [116] Chopra N, de Leon J. Clozapine-induced myocarditis may be associated with rapid titration: A case report verified with autopsy. *Int J Psychiatry Med* 2016; 51: 104–115
- [117] Poyraz CA, Özdemir A, Sağlam NG et al. Rapid clozapine titration in patients with treatment refractory schizophrenia. *Psychiatr Q* 2016; 87: 315–322
- [118] de Leon J, Rhee DW, Kondracke A et al. Rapid titration and decreased clozapine clearance may help explain five cases of clozapine-induced myocarditis in a New York Hospital. *Psychosomatics* 2020; 61: 102–103
- [119] Danilewitz M, Rafizadeh R, Bousman CA. Successful clozapine rechallenge after suspected clozapine-associated myocarditis: a case report. *J Clin Psychopharmacol* 2021; 41: 218–220
- [120] Verdoux H, Quiles C, de Leon J. Clinical determinants of fever in clozapine users and implications for treatment management: A narrative review. *Schizophr Res* 2019; 211: 1–9

- [121] Rohde C, Polcwiartek C, Kragholm K et al. Adverse cardiac events in out-patients initiating clozapine treatment: a nationwide register-based study. *Acta Psychiatr Scand* 2018; 137: 47–53
- [122] Chopra N, Ruan CJ, McCollum B et al. High doses of drugs extensively metabolized by CYP3A4 were needed to reach therapeutic concentrations in two patients taking inducers. *Rev Colomb Psiquiatr* 2020; 49: 84–95
- [123] Subramanian S, Völlm BA, Huband N. Clozapine dose for schizophrenia. *Cochrane Database Syst Rev* 2017; 6: CD009555
- [124] Zhou Y, Ingelman-Sundberg M, Lauschke VM. Worldwide distribution of Cytochrome P450 Alleles: A meta-analysis of population-scale sequencing projects. *Clin Pharmacol Ther* 2017; 102: 688–700
- [125] Allorge D, Chevalier D, Lo-Guidice JM et al. Identification of a novel splice-site mutation in the CYP1A2 gene. *Br J Clin Pharmacol* 2003; 56: 341–344
- [126] Ito M, Katono Y, Oda A et al. Functional characterization of 20 allelic variants of CYP1A2. *Drug Metab Pharmacokinet* 2015; 30: 247–252
- [127] Soyama A, Saito Y, Hanioka N et al. Single nucleotide polymorphisms and haplotypes of CYP1A2 in a Japanese population. *Drug Metab Pharmacokinet* 2005; 20: 24–33
- [128] Bender S, Eap CB. Very high cytochrome P4501A2 activity and nonresponse to clozapine. *Arch Gen Psychiatry* 1998; 55: 1048–1050
- [129] VanderZwaag C, McGee M, McEvoy JP et al. Response of patients with treatment-refractory schizophrenia to clozapine within three serum level ranges. *Am J Psychiatry* 1996; 153: 1579–1584
- [130] Schulte P. What is an adequate trial with clozapine?: therapeutic drug monitoring and time to response in treatment-refractory schizophrenia. *Clin Pharmacokinet* 2003; 42: 607–618

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.