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Reflections on the Lack of Consideration of Ethnic Ancestry to Stratify Clozapine Dosing

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This review article argues against trusting standard clozapine references, including the US package insert, because they do not include advances in the sciences of pharmacokinetics and pharmacovigilance and ignore the effects of ethnic ancestry on therapeutic dosing. The minimum therapeutic dose leading to the minimum therapeutic concentration of 350 ng/mL in serum/plasma can be used to compare individuals/groups with treatment-resistant schizophrenia. The US clozapine package insert recommends targeting doses of 300–450 mg/day and, subsequently, increments of up to 100 mg with a maximum dose of 900 mg/day. Ethnic ancestry is defined by DNA ancestry group. Asians (people with ancestry ranging from Pakistan to Japan) and Indigenous Americans are similar in clozapine dosing; their average clozapine minimum therapeutic dose ranged from 166 mg/day (female non-smokers) to 270 mg/day (male smokers). For those with European ancestry, average clozapine minimum therapeutic doses ranged from 236 mg/day (female non-smokers) to 368 mg/day (male smokers). Based on limited studies, Black (African sub-Saharan ancestry) patients may be treated with typical US doses (300–600 mg/day), assuming no poor metabolism (PM) status. Ancestry's impact on clozapine lethality in four countries is discussed (two countries with highly homogenous populations, Denmark and Japan, and two countries with increasingly heterogenous populations due to immigration, Australia and the UK). An international guideline with 104 authors from 50 countries/regions was recently published, providing 6 personalized clozapine titration schedules for adult inpatients (3 ancestry groups and PM/non-PM schedules) and recommending c-reactive protein monitoring at baseline and weekly for 4 weeks. **Psychiatry Investig 2023;20(3):183-195**

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INTRODUCTION

This reflection challenges the reader not to trust standard clozapine references including package inserts since they do not include advances in the sciences of pharmacokinetics and pharmacovigilance.

A paradoxical hypothesis: major standard clozapine references should not be trusted

In this first quarter of the 21st century, most psychiatrists worldwide refer to US psychiatry and psychopharmacology to provide guidance. This author cannot deny that there are strong historical reasons to acknowledge the contributions of US psychiatry in the late 20th century,[1] but he proposes that following US recommendations for clozapine dosing around the world is a mistake. Similarly, most national drug agencies would probably acknowledge that the US drug agency, the Food and Drug Administration (FDA) plays a leading role for orienting their package inserts,[2] but following the US clozapine package insert in all countries is a huge mistake.

The author cannot deny that a reasonable argument in favor of trusting the US recommendations for clozapine use is that the US is responsible for the resurrection of clozapine. Clozapine was introduced in German-speaking countries[3] and was almost "killed" by a letter to the editor[4] from Finland describing 8 patients who died from clozapine-induced agranulocytosis. Then, clozapine was resuscitated for a restricted use in treatment-resistant schizophrenia (TRS) by a US multicenter randomized clinical trial (RCT) published in 1988[5] that led to approval by the FDA in 1989 and the generalized worldwide use of clozapine for TRS. Moreover, the birth of the concept of TRS[5] can be traced back to that US study. That US RCT re-

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cruited 309 patients including 208 (65%) of European ancestry and 111 (35%) of other ancestries. There were 74 (23%) patients of African ancestry, 31 (10%) of Hispanic ethnicity which may include patients with Indigenous American ancestry, 2 (1%) patients of East Asian ancestry and 4 (1%) others.[5] There was no attempt to consider the effects of ancestry on clozapine dosing or response.

In summary, the author acknowledges the leading role of the US in 1) psychiatry, 2) psychopharmacology, 3) drug approval, and 4) resurrection of clozapine use for TRS, but in spite of this he is going to try to convince the skeptical reader that the information provided by the FDA in the US clozapine package insert,[6] US chapters on clozapine psychopharmacology,[7] US textbooks on clozapine,[8] and US clozapine review articles[9] cannot be trusted. He dares to propose that trusting these sources may have deleterious effects in the use of clozapine around the world. If the reader is profoundly shocked by this statement and wants to stop reading, he/she needs to read Supplementary Table 1 (in the online-only Data Supplement)[6-15] that explains that for understanding these or any new ideas the reader needs to be open-minded. As most psychiatrists are not well versed in pharmacokinetics, there is another Supplementary Table 2 (in the online-only Data Supplement)[14,16-21] explaining some basic pharmacokinetic concepts such as poor metabolizers (PMs), who tend to have adverse drug reactions (ADRs) with average doses, while ultrarapid metabolizers (UMs) need high doses for efficacy. These concepts were originally developed for genetic cases but Supplementary Table 3 (in the online-only Data Supplement)[22-54] explains how there are genetic and nongenetic PMs and UMs in terms of clozapine dosing. Clozapine PMs and UMs are defined based on the key idea that for comparing clozapine dosing across individuals or groups it is important to know the minimum therapeutic dose which leads to the minimum therapeutic concentration in serum/plasma of 350 ng/mL for TRS. Standard US sources reviewing clozapine use and dosing[6-9] do not mention these concepts.

Clozapine and development of pharmacokinetic science

In 1989 when clozapine was approved by the FDA, we did not know how clozapine was metabolized. Then in 1994, Karolinska researchers proposed that clozapine is mainly metabolized by a pharmacokinetic protein, a liver enzyme, called cytochrome P450 (CYP) 1A2.[55] Moreover, these researchers also figured out that inducers such as carbamazepine and powerful inhibitors such as fluvoxamine modified the relationship between clozapine dose and serum concentrations.[56] Based on that study one can propose that in the average clozapine patient, once carbamazepine is added and has acquired its maximum inductive effects, there is need to multiply the dose approximately by 2 to maintain its efficacy. Once fluvoxamine is added, there is need to reduce the dose to 1/10 or 1/5 to maintain its safety, which is a very risky proposition unless blood levels are available. This is why 27 years later the author continues to provide similar recommendations on clozapine dosing.[27,28] Currently, it is evident that co-medications influence clozapine personalized dosing from high to low: 1) potent inducers, such as rifampicin; 2) potent to moderate inducers, such as carbamazepine or phenytoin; 3) mild inducers, such as omeprazole; 4) moderate inhibitors, such oral contraceptives or high intake of caffeine; and 5) potent inhibitors, such as fluvoxamine, amiodarone and ciprofloxacin.[27,28] As tobacco smoking is a mild inducer of CYP1A2 and estrogens are moderate CYP1A2 inhibitors, in the absence of other inducers/inhibitors, clozapine personalized dosing goes from high to low in: 1) male smokers, 2) female smokers, 3) male non-smokers, and 4) female non-smokers.[27,28]

Advances in pharmacokinetic science and the FDA

Psychiatrists are not familiar with the fact that in 1996 FDA experts were faced with an earthquake delivered in the form of the drug lethality associated with terfenadine, a second-generation antihistaminic.[57] In 1985 the FDA had approved terfenadine, which behaved very safely in RCTs. In 1996, the FDA realized terfenadine was associated with 125 deaths.[57] Moreover, since its approval, pharmacokinetic science had developed and explained that terfenadine was mainly metabolized by the CYP3A4. The problem was that powerful CYP3A4 inhibitors (e.g., ketoconazole, erythromycin, and grapefruit juice) were frequently used in the US general population at that time. These powerful inhibitors inhibited the metabolism of terfenadine which led to torsades de pointes.[57] Many of the other drugs have also been withdrawn from the US market since their pharmacokinetic properties contributed to their potential lethality.[58] Since 1996, the FDA has progressively increased the requirements of pharmacokinetic studies;[59] thus any new antipsychotic approved in 2022 would have to be thoroughly studied from the pharmacokinetic point of view and it is very unlikely that it would be withdrawn from the market. FDA regulations do not require old drugs to be restudied following current pharmacokinetic requirements.[60] Thus, clozapine has never been well studied. This is not unique for clozapine; other antipsychotics, including haloperidol[61] or risperidone,[62] approved before 1996, have the same problem. Once a drug becomes generic there is no incentive for the pharmaceutical company to economically support the huge effort needed to complete comprehensive studies and update the package insert.[63]

Advances in pharmacokinetic science had little impact on the clozapine package insert

Therefore, the US clozapine package insert has not been updated to reflect our current pharmacokinetic knowledge.[64] The US insert and other package inserts should report that CYP1A2 activity varies across: 1) deoxyribo nucleic acid (DNA) ancestry groups, 2) 4 sex/smoking subgroups, and 3) the presence or absence of PM status. Supplementary Table 3 (in the online-only Data Supplement) explains that clozapine PM status can be explained by genetic cases (<10% of patients) and non-genetic cases associated with coprescription of inhibitors, obesity and/or inflammation.

Clozapine is mainly metabolized by CYP1A2 and there is general agreement that CYP2D6 plays a very small role, so it is not clear why the FDA decided to recommend lower doses of clozapine for CYP2D6 PMs.[6] This mistake has never been removed from the US package insert despite pharmacogenetic experts'[64] agreement that CYP2D6 PM status is not relevant in clozapine dosing.

Advances in pharmacovigilance science very slowly impacted the US clozapine package insert

After-marketing reports of ADRs during the period called post-marketing surveillance[65] led to the development of a new science called pharmacoepidemiology, which includes the concept of pharmacovigilance.[66] Supplementary Table 4 (in the online-only Data Supplement)[66-68] explains that pharmacovigilance considers the published reports of ADRs and the reports of the national drug agencies which are sent to the World Health Organization's pharmacovigilance database called VigiBase.[67]

The first pharmacovigilance finding of clozapine-induced agranulocytosis[4] led to the cessation of US clozapine studies that had been started in 1974.[69] Other pharmacovigilance data led the FDA to modify the US clozapine package insert to include warnings for myocarditis in 2002, and severe clozapine-induced gastrointestinal hypomotility (CIGH) in 2020.[70]

The FDA has been "obsessed" with clozapine-induced agranulocytosis since its marketing.[70] In a review of the FDA data from 1998−2005, Moore et al.[71] found that clozapine was associated with 3,277 deaths or serious nonfatal outcomes, making it the third most toxic US drug. That article[71] did not explain how clozapine patients died, but the FDA continued to focus on clozapine-induced agranulocytosis. By studying the deaths of clozapine patients from 2000 to 2019 found in VigiBase,[72] it is obvious that prescribers worldwide know about clozapine-induced agranulocytosis since they reported 29,586 cases of potential agranulocytosis. These cases led to 433 deaths with a relative lethality of 1%. In the same period of 2000 to 2019, pneumonia and myocarditis caused more deaths. There were 1,922 deaths due to pneumonia (30% relative lethality; 1,922/6,506) and 484 deaths due to myocarditis (11% relative lethality; 484/4,536).[72]

Most clozapine-induced pneumonia does not occur during agranulocytosis and its pathophysiology is complex.[73] TRS may explain 2/3 of the risk of pneumonia.[74] Clozapine can contribute to community-acquired pneumonia by decreasing antibodies and to aspiration pneumonia by causing swallowing disturbances, sedation, hypersalivation and/or other possible ADRs, such as CIGH. Once pneumonia develops, the systemic inflammation releases cytokines that inhibit CYP1A2 and other CYPs can cause clozapine intoxication.[73] The combination of severe pneumonia and clozapine intoxication appears to be particularly lethal when compared with other antipsychotics.[75]

Lack of attention to the concept of clozapine-induced inflammation

The literature does not properly reflect the concept that "clozapine-induced inflammation" can happen during rapid titrations. A PubMed search on May 1, 2022, provided no article with "clozapine-induced inflammation" in the title or the abstract.[76] In 2012, Røge et al.[77] describe clozapine "pro-inflammatory" activity during early titration bud did not comment on the role of rapid clozapine titration.

On the other hand, the concept of "clozapine-induced inflammation" included two concepts described in the literature: clozapine-induced fever reviewed in Supplementary Table 5 (in the online-only Data Supplement)[78-84] and clozapine-induced myocarditis reviewed in Supplementary Table 6 (in the online-only Data Supplement).[85-102] Both of them have been proposed to be a hypersensitivity reaction probably explained by rapid clozapine titrations. Supplementary Table 7 (in the online-only Data Supplement)[27,28,76,103,104] summarizes the model of clozapine-induced inflammation.

THE MAIN OVERSIGHT: CLOZAPINE DOSING SHOULD CONSIDER ETHNIC ANCESTRY

The main oversight of worldwide clozapine package inserts is that they do not consider the effects of ethnic ancestry on clozapine dosing. Ethnic ancestry is defined as one's DNA ancestry group.

DNA ancestry

The model of human evolutionary history[105] suggests that there are 5 ancestry groups (each group progressively branched out and separated from the original African population): 1) Blacks with ancestry from Sub-Saharan Africa, 2) Europeans (and Western Asians), 3) Asians, 4) Oceanians, and 5) the origi-

nal inhabitants of the Americas or Indigenous Americans. Different CYPs have different profiles for PMs and UMs, probably based on the complex interactions between human migrations and exposure to a diet containing variable compositions of harmful xenobiotics.[106] These 6 ancestry groups are not particularly relevant for understanding CYP2D6 activity but may be for CYP1A2 activity. Unfortunately, these 6 DNA ancestry groups are not geographic groups. The FDA defines the Asian phenotype[107] as including those people with ancestry ranging from Pakistan to Japan. The Indigenous Americans are descendants of East Asians, so it is not surprising that for clozapine dosing, they behave as Asians.[108]

Clozapine dosing in the US

The US clozapine package insert[6] recommends targeting doses of 300 to 450 mg/day; subsequently, the dose can be increased once weekly or twice weekly, in increments of up to 100 mg with a maximum dose of 900 mg/day. US textbooks and articles[7-9] follow these recommendations.

The long and complicated history of the need for lower clozapine doses for Asians

Since 1997[109,110] indirect and circumstantial evidence suggests Asians should be treated with lower clozapine doses than US-recommended doses; this has never led to a modification of the US package insert or received attention from US clozapine experts. Supplementary Table 8 (in the online-only Data Supplement) reviews this limited evidence, which includes studies on clozapine concentrations[109-111] and the experience of clinicians in Asian countries regarding clozapine dosing.[112-121] Supplementary Table 8 (in the online-only Data Supplement) also describes a 2007 study, in which Ghotbi et al.[122] demonstrated that, in effect, Koreans (with Asian ancestry) have lower CYP1A2 activity than Swedes (with European ancestry) after controlling for smoking, oral contraceptives and known CYP1A2 alleles.

This group of studies led to a systematic review where the average clozapine minimum therapeutic dose was 223 mg/day in 876 East Asians versus 327 mg/day in 1,147 Western patients, mostly of European ancestry.[29] This comparison between East Asian and Western patients is limited by the lack of control for sex and smoking and the exclusion of an Indian sample.[123] After accessing 4 additional Asian samples and stratifying by sex-smoking subgroups, it was clear Indians have a clozapine metabolism similar to East Asians.[33] Furthermore, after accessing a Mexican study,[124] Indigenous Americans were found to be similar to Asians.[125] Thus, when combining all of these Asian and Indigenous American samples, the average clozapine minimum therapeutic dose ranged from 166 mg/day (in 252 female non-smokers) to 270 mg/day (in 137 male smokers).[29]

The clinical relevance of overdosing patients of Asian ancestry by using doses recommended for patients of European ancestry is finally reaching the literature. Recently in India, Chichra et al.[126] completed a retrospective review of a cohort of 288 patients initiated on clozapine of which 38 (17%) had new-onset seizures during clozapine treatment. These patients had significantly higher mean clozapine doses at 1 year of follow-up (373±120 vs. 319±120 mg/day) and this remained significant after adjusting for age and sex. This article suggest that the traditional practice of Indian psychiatrists trained in India of not going above 300 mg/day[115] may be a good idea, particularly when clozapine serum concentrations are not available.

Clozapine dose and European ancestry

In 6 samples of patients of European ancestry, the average clozapine minimum therapeutic dose ranged from 236 mg/day (in 218 female non-smokers) to 368 mg/day (in 546 male smokers).[127] This range for a clozapine minimum therapeutic dose of 236 to 368 mg/day appears higher than the Asian range of 166 to 270 mg/day, but lower than the typical doses of 300 to 600 mg/day recommended in the US package insert. Since early times, Europeans[128,129] have been aware that US psychiatrists prescribed 1.5 to 2-fold higher clozapine doses than in Europe.

A hypothesis for explaining the high doses of clozapine in the US

When developing an international titration schedule,[29] for political reasons, the author initially decided to keep the highest US dose. In the end, the US dosage appeared to be the right one for African-Americans in the absence of risk factors for PM status based on a US clozapine RCT[130] and olanzapine data. Olanzapine is mainly metabolized by CYP1A2 and behaves pharmacokinetically in a way similar to clozapine[131] and, based on a US population pharmacokinetic model,[132] it can be estimated that average olanzapine doses should be 1.25 times higher in African-Americans than in patients of European ancestry.

More recently, Flanagan et al.[133] explored the plasma clozapine concentrations of patients from the UK and Ireland with ethnicity data (763 Afro-Caribbean, 536 Asian, and 7,940 Caucasian patients). After adjusting for confounders, the predicted dose to reach 350 ng/mL was 33% higher in Afro-Caribbean and 20% lower in Asian patients when compared with Caucasians.

CLOZAPINE LETHALITY AND DOSING ACROSS VARIOUS COUNTRIES

This section proposes the controversial hypothesis that ancestry may impact clozapine lethality in various countries around

the world. This relationship is very complex since it impacts clozapine clinical practice in each country. The discussion focuses on four countries: two countries with highly homogenous populations, Denmark and Japan, and two countries with increasingly heterogenous populations due to immigration, Australia and the UK.

Denmark: a country of homogenous ancestry with extremely low lethality associated with clozapine

Denmark has less than 6 million people of European ancestry and only recently has immigration increased, but they tend to be immigrants with European or Western Asian ancestry that may be similar regarding clozapine dosing. Danish physicians should be considered the leaders in the identification of clozapine-induced myocarditis (Supplementary Table 9 [in the online-only Data Supplement], first panel[67,77,85-87,134-136]). Approximately 40% of the Danish clozapine titrations are given in an outpatient setting[99] and are very gradual; the others are started as inpatients but coordinated with outpatient psychiatrists. Thus, it is not surprising that clozapine-induced myocarditis is rare, according to the Danish registry (Supplementary Table 9 [in the online-only Data Supplement], second panel[99]) or VigiBase reports (Supplementary Table 9 [in the online-only Data Supplement], third panel[67]). The last panel of Supplementary Table 9 (in the online-only Data Supplement)[74,99,137] propose that paying attention to pneumonia may decrease clozapine mortality in Denmark, particularly during the first year.

Japan: probable high lethality in clozapine patients in a country with homogenous ancestry

Japan has around 126 million people, a very homogenous population of Asian ancestry. Japan has a large system of hospitals for long-term psychiatric inpatients, many with TRS.[138] The Japanese national drug agency has complicated bureaucratic procedures highly influenced by university professors working as advisors in their spare time,[139] which led to the delay in clozapine approval (first panel of Supplementary Table 10 [in the online-only Data Supplement][140,141]). Clozapine was therefore approved without studies based in Japan, but rather on US data and recommending US dosing. The Japanese drug agency was quite fearful of agranulocytosis[142] and developed a Clozapine Patient Monitoring Service following the US example. Moreover, clozapine was restricted so that it can only be started in some hospitals and prescribed by some physicians. The official Japanese titrations have led to approximately 1/3 of the patients developing clozapine-induced fever (second panel of Supplementary Table 10 [in the online-only Data Supplement][142,143]) due to intolerance of the titration. Other forms of clozapine-induced inflammation are also frequent in Japan (third panel of Supplementary Table 10 [in the online-only Data Supplement][67,104,142-145]). Therefore, Japanese psychiatrists had no experience with slower titration and were not aware that their titration is too rapid for their patients until a 2022 article identified[146] much slower titration during rechallenge as a method for avoiding a clozapine-induced eosinophilic pneumonia (fourth panel of Supplementary Table 10 [in the online-only Data Supplement]).

High lethality in Australian clozapine patients associated with myocarditis

Australia may be the mirror-image of Denmark.[76] Danish psychiatrists have no expertise in clozapine-induced myocarditis because they have been pioneers in identifying it and use very slow clozapine titration. Australian psychiatrists have extensive experience with clozapine-induced myocarditis. According to VigiBase, until 2021[67] Australia, a country with less than 26 million people, accounted for half of the worldwide clozapine-induced myocarditis (50%, 1,621/3,274) cases and 1/3 of the mortality (32%, 50/158).

Many of the articles on clozapine-induced myocarditis have been published by Australian authors and this may have some negative consequences. First, the author's clozapine articles are frequently rejected by Australian clozapine experts, who think they are being unfairly attacked, so an editorial[63] written in 2019 was rejected by 9 journals before being published in 2020. Second, in an Australian review article, Ronaldson et al.[98] proposed that an incidence rate of 3% for clozapine-induced myocarditis is normal, which led authors in several countries to use this reference and justify as normal this incidence rate of 3% in their settings. Rates around 3% have been described in some hospitals in Canada,[147] the US,[148] and New Zealand.[149]

Supplementary Table 11 (in the online-only Data Supplement) provides a summary of the very important contribution of Australian authors, which has led this author to understand the crucial role of rapid titration in the development of clozapine-induced myocarditis.[46,67,90,96,150-157] Supplementary Table 12 (in the online-only Data Supplement)[28,96,158] details the problem with the official Australian clozapine titration schedules.

High lethality in UK clozapine patients is puzzling

The first 4 panels of Supplementary Table 13 (in the online-only Data Supplement) provide information that the author has gathered on the use of clozapine in the UK; the emphases are on guidelines,[39,127,159,160] the contribution of clozapine-induced agranulocytosis,[70,161-163] what is known of UK fatal outcomes of clozapine-induced myocarditis,[67,104,164] clozapine-induced CIGH,[165] and clozapine-associated pneumonia.[166]

Two months ago, the author's understanding of clozapine use in the UK was completely shaken by discovering a VigiBase

pharmacovigilance study focused on ADRs with fatal outcomes reported by physicians. Over a 10-year period (2010-2019), Montastruc et al.[167] found 1,761 fatal outcomes associated with clozapine. Clozapine was the third most lethal drug in the world overall, but was the most lethal drug among nongeriatric adults worldwide. The distribution was uneven since UK physicians reported 968 fatal outcomes versus 892 in the rest of the world (a country with 67 million people had more fatal outcomes in clozapine patients than the entire rest of the world), including only 105 fatal outcomes reported by physicians in the other European countries[68] The major ADRs associated with worldwide fatal outcomes in VigiBase until 2019 have been described[168] and necessarily include these 986 fatal outcomes reported by UK physicians. After the generalized use of weekly hematological monitoring and during 2000–2019,[72] the four major causes of worldwide fatal outcomes in order were: pneumonia with 1,922 (29.5%, 1,922/6,506), sudden deaths/cardiac arrest with 1,221 (90.5%, 1,221/1,349), myocarditis with 484 (11.1%, 484/4,356) and agranulocytosis with 433 (1.5%, 433/29,586).[168] UK clozapine experts need to explore how these 4 major causes may explain that UK physicians reported 968 UK fatal outcomes in clozapine patients over 10 years, around 97 patients/year. Based on what we know from VigiBase and UK studies (Supplementary Table 13 in the online-only Data Supplement), it is possible to speculate that pneumonia and sudden death may be the major causes of death among clozapine patients in the UK.[68]

The extremely high number of fatal outcomes reported by UK physicians to their drug agency and then to VigiBase appeared hard to believe to the author; unfortunately, a later independent verification indicates the problem is even worse. In an article focused on CIGH, Handley et al.[165] found 4,547 UK fatal outcomes from reports of physicians and nonphysicians from 1992 to 2017. If the last 10 years are selected, this provides 3,828 deaths, 383 deaths/year and a range from 209 deaths in 2008 and 629 deaths in 2011. Thus, it is possible that since 2017, every year 383 clozapine patients may have died due to ADRs in the UK. To compare this number, one needs to remember that 8 deaths associated with agranulocytosis in Finland led to the cessation of US clozapine studies, as well as clozapine restrictions around the world.

If we assume that the data from Handley et al.[165] and Montastruc et al.[167] are correct, this may indicate that of 383 deaths in the UK annually on average, approximately 97 are reported by physicians and another 286 (383-97=286) are reported by nonphysicians. One can argue that the UK system led the pharmaceutical company which controls the hematological database to overreport all deaths in clozapine patients even if they are not really explained by clozapine, which may contribute to 286 deaths annually on average, but this overreport by the drug company could not justify the 97 deaths reported annually by physicians who appear to believe they were possibly caused by clozapine.

The high number of fatal outcomes in clozapine patients in the UK cannot be explained away as a very high number of patients taking clozapine in the UK compared with other countries (see the fifth panel of Supplementary Table 13 [in the online-only Data Supplement][169]), since UK clozapine prescription is intermediate among European countries.

UK clozapine patients include those of African, European and Asian ancestries (see the sixth panel of Supplementary Table 13 [in the online-only Data Supplement][170-172]). There is urgent need to explore whether or not patients of Asian ancestry, who need lower clozapine doses, have greater fatal outcomes in the UK.

FOR SAFER CLOZAPINE USE ALL OVER THE WORLD

A new international titration guideline

An international guideline with 104 authors from 50 countries/regions was recently published to provide personalized clozapine titration schedules for adult inpatients.[28] The two most innovative aspects of this new guideline are: 1) 6 different titration schedules proposed for stratified dosing and 2) c-reactive protein (CRP) monitoring at baseline and weekly for 4 weeks at the same time as the white blood cell count. CRP offers protection for identifying clozapine genetic PMs. If the genetic PM cannot tolerate the prescribed titration, CRP would become abnormal. Thus, CRP is a form of personalized titration, as is using clozapine levels to determine minimum therapeutic dosing.

Update of the international titration guideline

The clozapine titration guideline[28] is based on pharmacokinetic predictions and limited data, so it is a document in progress. Even before it was published, it required 2 major modifications.[173] Writing the first draft and recruiting co-authors worldwide took one year to complete; the modifications could not be included in the published version. The first modification is that the recommended dosage of 300 to 600 mg/day for average patients in the US (who are not Asians or Indigenous Americans) has become the recommended titration for Black patients with ancestry from sub-Saharan Africa. Second, the titrations for PM patients within each ancestry group should be used for patients in whom clozapine is added to olanzapine or quetiapine. The co-prescription of these two antipsychotics may increase the risk of clozapine-induced myocarditis.[67,157] The author is used to adding clozapine to other antipsychotics and does not stop the others until a possible clozapine ther-

apeutic dose has been reached. Clarifications for patients of mixed ancestry have also been suggested.[31]

The international guideline is being translated into Chinese, Croatian, Korean, Japanese, Russian, and Spanish and being disseminated in summary articles in psychiatric journals of national distribution across multiple countries/regions.[3,21,31,70,76,100,141,173-175]

Limitations of the international titration guideline

Clozapine is a generic drug so no company will support new prospective studies of the 6 proposed titration schedules and the author does not know how to obtain funding for such ambitious studies. The proposal of the international guideline that CRP elevations are better and earlier markers than troponin for clozapine-induced myocarditis is supported by an old Australian abstract[176] reanalyzing data from the Ronaldson et al.[96] study. In 105 cases of clozapine-induced myocarditis, CRP could rise up to 5 days before troponin.[176]

A philosopher of science named Karl Popper[177,178] proposed that science advances by falsifying a hypothesis, so the author recommends that the reader try to demonstrate that the author's theory is wrong by using the titration guideline in the care of his/her patients. However, by using the international clozapine titration guideline, the author thinks that readers may find out on their own that diagnosing all types of inflammation[76] may be relevant in decreasing clozapine-related lethality during titration.

FURTHER REFLECTIONS ON ETHNOPSYCHOPHARMACOLOGY RELEVANT FOR EAST ASIANS

Ethnopsychopharmacology refers to the need to consider both cultural and biological diversity and tailor treatment to individual characteristics rather than relying on global guidelines.[179] Thus, this article stresses that the biological diversity seen around the world has not been correctly considered when dosing clozapine. Unfortunately, biological diversity has not received enough attention in psychopharmacology practice, in general, and in patients of East Asian ancestry, specifically. Supplementary Table 14 (in the online-only Data Supplement) uses as examples four other psychiatric drugs (diazepam,[52,180-184] carbamazepine,[185-187] olanzapine,[21,25,131,157,188] and haloperidol[24,61,64,189-191]) in which paying attention to East Asian ancestry may be important. The literature provides reasonable information concerning lower diazepam dosing in East Asians and for genotyping human leukocyte antigen-B*15:02 before starting carbamazepine in East Asian countries, except Japan.[185,186] On the other hand, it is likely that patients of East Asian ancestry may need lower doses of olanzapine[131] and haloperidol[191] and this appears to have been ignored by Western textbooks and articles.

CONCLUSION

Regarding clozapine, there is need for studies of 1) clozapine blood levels in patients with sub-Saharan African, Western Asian, and Oceanian ancestries; 2) the influence of clozapine titration on clozapine-induced inflammations in various countries; and 3) clozapine-induced myocarditis including blood levels[192] in countries such as China[44,67] or Russia,[193] with frequent clozapine use, but limited awareness of this diagnosis. Concerning ethnopsychopharmacology, more attention is needed to personalize antipsychotic dosing and more definitive studies are required for patients of East Asian ancestry, who may need lower doses not only of clozapine, but of olanzapine and haloperidol than those of European ancestry.

Albert Magnus (1200−1280 AD) was known during his lifetime as "Doctor universalis" and "Doctor expertus" because of his encyclopedic knowledge. His knowledge not only included philosophy and theology, but he wrote on different sciences, such as botany, geography, astronomy, mineralogy, alchemy, zoology, and physiology.[194] One of his most important quotes in the development of the scientific method is "The aim of natural science is not simply to accept the statements of others, but to investigate the causes that are at work in nature." To conclude, the author wants to pay tribute to the Asian clozapine prescribers and researchers who did not accept the clozapine doses promoted in the US, but observed that Asians may need lower doses. Among clozapine prescribers, he wants to emphasize 1) Farooq, a Pakistani psychiatrist who in 1998[112] proposed in the *British Journal of Psychiatry* that Pakistani patients may need lower clozapine doses similar to Chinese patients; 2) the Indian psychiatrists trained in India who have figured out that most Indian patients can be treated with up to 300 mg/day of clozapine;[115] and 3) Kikuchi et al.[146] the first Japanese psychiatrists who dared to describe how the titrations proposed by the Japanese package inserts may cause clozapine-induced inflammations in some patients. Two groups of clozapine researchers, in Taiwan Chang et al.[109] and in Singapore Chong et al.,[110] in 1997 published serum clozapine concentrations definitively indicative that patients of Chinese ancestry need approximately half the clozapine dosage used in the US. After 25 years, the clozapine package inserts from the US and other Western countries do not reflect the need for lower doses in Asians and their descendants, the Indigenous peoples of the Americas. It is not known how many lives could have been saved in these 25 years if lower doses had been used, but cases of patients of Asian ancestry who developed clozapine-induced inflammation and tolerate much slower titrations keep getting published.[146,195]

Supplementary Materials

The online-only Data Supplement is available with this article at https://doi.org/10.30773/pi.2022.0293.

Availability of Data and Material

Data sharing not applicable to this article as no datasets were generated or analyzed during the study.

Conflicts of Interest

The author has no potential conflicts of interest to disclose.

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Supplementary Table 1. The need for an open-minded reader

All humans are biased
• There is no doubt that cognitive scientists agree that human beings are biased and go through life verifying their own beliefs.[10] Thus, if the reader is a psychiatrist who thinks of himself/herself as a sophisticated scientist and that the leading psychiatrists in the US are sophisticated scientists, there is not much point in continuing to read an article which defends ideas ignored by US clozapine references.[6-9]
Psychiatrists are practitioners and not scientists
• In a prior article in this journal,[11] the author has defended the idea that psychiatrists are practitioners and not scientists and there are major problems with current psychiatric nosology. If, in effect, psychiatrists are fundamentally practitioners, their role as practitioners should be to use clozapine safely and effectively and any clozapine science should target that main goal. Unfortunately, this is not true; psychiatric science focuses on the unrealized fantasy that psychiatry is a clinical neuroscience, similar to neurology.[12]
Limitations of psychopharmacology as science
• The humbling reality is that the discovery of most important psychiatric drugs, including clozapine, is better described as serendipitous.[13] • Problems occur when psychiatrists tried to focus on advances in scientific knowledge in general or focus on brain mechanisms, which pharmacologists call pharmacodynamic mechanisms.[14] Unfortunately, all the arguments proposed in this article are based on the development of the science of pharmacokinetics. • Pharmacokinetics, usually defined in a simplified way as what the body does to the drug, is almost completely ignored by psychiatric textbooks and most leading psychiatric journals.[14]
Limitations of clozapine science in typical psychiatric articles
• Thus, scientific discussion in psychiatry tends to focus on brain mechanisms. A recent comprehensive review of clozapine cellular mechanisms for the last 50 years has 755 references[15] but ignores most of the pharmacokinetic advances proposed in this article.

Supplementary Table 2. Basic concepts in pharmacokinetics

Concepts
• The term pharmacokinetics was first introduced in 1953.[16]
• The idea that different people may need different drug doses led to the development of a new science called pharmacogenetics.[17] Pharmacogenetic differences in pharmacokinetic genes are crucial in understanding differences in drug dosing.[14]
Genetic PMs and UMs
• Psychiatrists may not be aware that studies in the Karolinska Institute in Sweden on the TCAs have a major role in developing pharmacogenetics as a science.[17] First, some Swedish patients were found to have very high serum concentrations when given average doses and will respond to much lower doses; they were called PMs and this difference appeared to have a genetic basis.[18] Later on, these genetic PMs were found not to have the main metabolic enzyme for TCAs. These TCA PMs had two CYP2D6 alleles with no activity associated with CYP2D6 in their bodies. Third, in a couple of Swedish families, they found patients who had undetectable concentrations and were called UMs. TCA UMs had three or more active CYP2D6 alleles and synthesized too much CYP2D6.[19]
Non-genetic PMs and UMs
• Non-genetic PM/UM status can be caused by personal or environmental factors,[14] as long as they are present. Pharmacologists call this phenoconversion.[20] PM/UM causes, genetic vs non-genetic (phenoconversion), vary according to the metabolic pathways of the drugs, thus, across antipsychotics.[21]

CYP2D6, cytochrome P450 2D6; PM, poor metabolizer; TCAs, tricyclic antidepressants; UM, ultrarapid metabolizer

Supplementary Table 3. Basic concepts in pharmacokinetics applied to clozapine

Clozapine as a narrow therapeutic index drug and its minimum therapeutic dose
• A TDM guideline[22-24] proposed a therapeutic range from 350 to 600 ng/mL.[24]
• Clozapine has a narrow therapeutic index of 1.7[a] (600/350=1.7).[25]
• The literature[26] agrees that a plasma clozapine concentration of 350 ng/mL is the minimum therapeutic concentration in serum/plasma required for therapeutic response.
• Individuals or groups can be compared using their minimum clozapine therapeutic dose.[27,28]
Definition of clozapine PM
• A clozapine PM needs approximately half of the minimum therapeutic dose compared with their ancestry group and sex-smoking subgroup, the doses range from:[29-31] - 75 (♀ non-smokers) to 150 mg/day (♂ smokers) in patients of Asian ancestry, and - 75 (♀ non-smokers) to 200 mg/day (♂ smokers) in patients of European ancestry.[31]
Limited[a] knowledge[30] of clozapine genetic and non-genetic PMs
• Clozapine genetic PMs account for approximately <10% patients.[29,30,33] The mutations associated with total or partial loss of CYP1A2 activity vary according to ancestry:[30] - Asian ancestry. Based on Japanese data,[34,35] in East Asians 4 alleles can result in lower metabolic activity (CYP1A2*8, CYP1A2*11, CYP1A2*15 and CYP1A2*16). In Japanese (and East Asians) clozapine patients <1% may have each of these alleles. - European ancestry. In 2003, a French woman was described with CYP1A2*7;[36] her minimum therapeutic dose was 81 mg/day.[30] This allele has not been described again, but 1% of Europeans have CYP1A2*6, with no or little activity.[37]
• Clozapine non-genetic PMs. In clinical samples, clozapine non-genetic PMs may be more prevalent[29,30,33] than genetic PMs and be explained by: - Inhibitors: potent (including amiodarone, fluvoxamine, or ciprofloxacin)[27,28] or moderate (including oral contraceptives or high doses of caffeine intake).[27,28] - Obesity. Clozapine deposits in the fat tissue; as the % of fat tissue ↑, clozapine metabolism ↓ within an individual patient.[38] In 586 Asians, <1% were PMs due to obesity.[33] Cross-sectional clozapine TDM studies[39,40] also suggest that metabolism and obesity ↓ clozapine metabolism. Obesity ↓ metabolism of other CYP1A2 drugs.[41] - Inflammation. The cytokines released during systemic inflammation and associated with ↑ CRP elevations ↓ the synthesis and action of CYP1A2 and other CYPs metabolizing clozapine.[42-44] Inflammation ↑ clozapine concentrations in case reports[42,45] and cohort studies of infections,[46] including COVID-19.[47]
Clozapine UM definition
• To establish that a patient is a clozapine UM through TDM, complete adherence is required (1/3 of outpatients with schizophrenia report not taking some of their oral medications).[48]
• The clozapine UM literature started in 1998[49] and focuses on Western patients with minimum therapeutic doses >900 mg/day[c] and includes a few male smokers of European ancestry.[30] An African-American male smoker taking valproate has also been described as UM.[50] These genetic UMs under induction are probably rare; around 1% of patients of European ancestry.
• There are no well documented UM cases in patients of Asian ancestry (in them a minimum therapeutic dose >600 mg/day during complete adherence may suggest an UM).
Limited[b] knowledge[30] of clozapine genetic UMs during induction
• Unknown variants of CYP1A2 may explain clozapine UMs, according to published articles.
• Unknown variants of the nuclear receptors[51] which control induction may be a possibility: - UMs during induction of CYP3A4[52] and glucuronidation[53] have also been described. - Caffeine UMs[d] have been described under induction by smoking and omeprazole.[54]

[a]The therapeutic index is 1.7 (found by dividing upper range by lower range; 600/350=1.7). This indicates a narrow therapeutic index; clozapine has the narrowest index among SGAPs;[25] [b]Seven years ago,[32] the definitions of clozapine PMs and UMs by the author was much less developed. Even a review article from two years ago[30] does not have a version as comprehensive as the version in this Box. Thus, this information should be considered provisional and needing confirmation, since it is likely than in 2−3 years this information may need to be corrected and updated; [c]When plasma/serum clozapine concentrations are <150 ng/mL they cannot be used to accurately estimate the dose needed to reach 350 ng/mL. When concentrations are >150 ng/mL (and not very high) clozapine follows linear kinetics, which means that the relationship between the dose and the concentration is stable (the ratio between the concentration and the dose is a constant); [d]In a study of 265 long-term psychiatric patients 3 (1% of 265) had extremely high caffeine intake (≥1,499 mg/day). All three patients were under the influence of two inducers since they were smokers taking another mild CYP1A2 inducer, omeprazole.[54] CRP, c-reactive protein; CYP1A2, cytochrome P450 1A2; CYP3A4, cytochrome P450 3A4; PM, poor metabolizer; SGAP, second-generation antipsychotic; TDM, therapeutic drug monitoring; UM, ultrarapid metabolizer; COVID-19, coronavirus disease-2019

Supplementary Table 4. Basic concepts of pharmacovigilance

Limitations of the RCT
RCTs are the cornerstone of drug evaluation but are designed to demonstrate efficacy of drugs and not ADRs, the second element of the risk-benefit balance. These shortcomings have been summarized in the so-called "five too's" of RCTs:[66] • include "too few" patients, no more than 1,500 before drug approval; • are "too simple," not including usually polypathological or polymedicated patients, i.e., the main populations later exposed to drugs; • are "too often" concerned with median ages, excluding very young or old subjects. However, subjects over 65−70 years old and beyond are frequently those primarily receiving both old and new medications; • "too narrow," respecting very restrictive and well-defined indications not followed in daily clinical practice; and • are "too brief," including, for example, patients treated for only a few months for a chronic disease.
VigiBase
VigiBase, the WHO's global pharmacovigilance database:[67] • It is located at the Uppsala Monitoring Centre, Uppsala, Sweden. • It currently has >25 million reports of spontaneously reported ADRs from the drug agencies of 145 countries. New reports arrive daily. • ADRs are sometimes classified by the reporting clinician but normally those who report would enter free text information and pharmacovigilance staff at a regional or national center or pharmaceutical company would do the encoding using the categories provided by the database. Each patient can be classified in 1 or several ADR categories. This is particularly true for clozapine ADRs, in the experience of the author.
Comparison of transnational clozapine fatal outcomes in VigiBase
The comparison of transnational fatal outcomes in VigiBase is limited by lack of knowledge of:[68] • ADRs occurring versus those reported, • reports of fatal versus non-fatal outcomes, and • the number of patients taking clozapine corrected by population size. Thus, only "gross" transnational comparisons can be made.

ADR, adverse drug reaction; RCT, randomized clinical trial; WHO, World Health Organization

Supplementary Table 5. Clozapine-induced fever

First description in German studies
• Clozapine-induced fever in the absence of any concomitant infection was first described by German researchers in a 1972 article in German.[78]
• The next major step was a 1989 monographic number supported by the pharmaceutical company that marketed clozapine which reviewed experience with clozapine in continental Europe and the US in order to support the US marketing of clozapine. In this monographic number, several German clinicians summarize their clinical experience. Two groups proposed that fever in the absence of another cause developed in approximately 5% of the patients.[79,80]
• More importantly, Helmchen[81] described it as a transient phenomenon in which fever occurred between the 5th and 20th treatment days and was frequently associated with an increase in the erythrocyte sedimentation rate. This is the first article associating clozapine-induced fever with inflammation.
Understanding at the time of US clozapine marketing
• When clozapine was introduced in the US, the US clozapine experts called this fever "benign hyperthermia." They considered a prevalence of 5% normal during the first 3 weeks of clozapine titration.[82] They recommended stopping the clozapine titration when high fever develops (38.3°C) and ruling out infections. When a second titration was offered, it should be slower.[82]
Later developments
• Pui-yin Chung et al.[83] compiled a retrospective chart of 227 inpatients started on clozapine in Hong Kong with a fever incidence of 14% (31/227). After comparing 31 cases with fever versus 196 controls, the significant multivariate ORs and their CIs were 18.9 (5.3 to 66.7) for a rate of titration >50 mg/week, 3.6 (CI 1.5 to 8.9) for valproate and 3.2 (1.2 to 8.3) for the presence of physical illness.
• In 2020, a case from a double-blind RCT using 3 different clozapine dosages was published.[84] This was a clozapine PM due to the co-prescription of oral contraceptives. She could not tolerate the standard titration and developed fever in the absence of infection which led to almost doubling her clozapine concentrations corrected by the dose. The inflammation associated with clozapine-induced fever has positive feedback by further increasing clozapine concentrations that further increased clozapine-induced inflammation.

CI, confidence interval; OR, odds ratios; RCT, randomized clinical trial; PM, poor metabolizer

Supplementary Table 6. Clozapine-induced myocarditis

First descriptions
• In 1980, Danish authors[85] published in Danish the first case of clozapine-induced myocarditis in a patient started on 300 mg/day (rapid titration by a doctor).
• In 1992, US authors[86] described the "first rapid titration by a patient" (a lethal intentional overdose using 2,000 mg). They found eosinophilic myocarditis.
• Two years later, the same eosinophilic myocarditis was described in Danish by Jensen and Gøtzsche,[87] who first proposed it was an "allergic" myocarditis.
• Eosinophilic myocarditis is the typical presentation of clozapine-induced myoacrditis.[88]
Drug agencies
• In 1993, the British agency first described clozapine as a possible cause of myocarditis.[89]
• In 1999, an article by Kilian et al.[90] reviewed 23 cases from the Australian drug registry and placed clozapine-induced myocarditis on the radar of the drug agencies.
• This article prompted skeptical reviews by investigators from VigiBase[91] and the FDA.[92] In 2002, the FDA included the warning in the US package insert.
• It is unfortunate that the drug agencies did not pay attention to a comment on Killian's cases by Canadians[93] who stated that "in all cases, daily clozapine doses were increased rapidly" and that the Australian titrations were much faster than their Canadian titrations.
• In a review of reports to the Swedish drug agency, Scandinavian investigators[94] related myocarditis to hypersensitivity myocarditis and other clozapine-induced eosinophilic syndromes.
Unusually high incidence of clozapine-induced myocarditis in Australia
• In 2012, two crucial articles defending two extreme positions on clozapine-induced myocarditis were published by Continental Europeans[95] and Australians.[96]
• Authors from the Netherlands[95] brought attention to an incidence rate of 0.7%−1.12% in Australia versus 0.07% worldwide. This difference was replicated in a 2020 meta-analysis (2% in 9 Australian samples vs 0.3% in 15 non-Australian samples).[97]
• In the Australian case-control study, Ronaldson et al.[96] found that clozapine-induced myocarditis in Australia was significantly associated with rapid titration (rapidity was defined on the basis of each additional 250 mg of clozapine administered in the first nine days) with an OR of 1.26 (CI 1.02 to 1.55), while valproate co-administration was associated with an OR of 2.59 (CI 1.51 to 4.42).
• Since 2012 these two positions may have become further apart. In their 2015 review literature, Ronaldson et al.[98] proposed that the Australian experience is the correct one since the real incidence of myocarditis is around 3% and "that a similar incidence would be found in other jurisdictions, if a practice of routine monitoring for myocarditis was adopted."
• Ronaldson's estimates are obviously wrong, according to the Danish registry. Rohde et al.[99] found no deaths in the first 2 months of clozapine treatment. According to the theory of Ronaldson et al.,[98] Danish psychiatrists overlooked approximately 97 (3% of 3,262) cases of clozapine-induced myocarditis but, surprisingly, none of them died.[100]
A hypersensitivity reaction associated with rapid titration
• In 2015 two articles,[101,102] independently commenting on the myocarditis review by Ronaldson et al.,[98] proposed that clozapine-induced myocarditis is a hypersensitivity reaction associated with rapid titration of clozapine and analogous to the lamotrigine-induced Stevens-Johnson syndrome.

CI, confidence interval; FDA, Food and Drug Administration; OR, odds ratios

Supplementary Table 7. Clozapine-induced inflammation

Hypothetical model with 3 phases[27,28,76]
• In the first phase, the titration is too fast for a specific patient, as the psychiatrist was too aggressive with it, and/or due to the patient's clozapine PM status; this leads to a release of cytokines. • In the second phase, a positive feedback loop develops, the cytokines inhibit CYP1A2, which further increase the plasma clozapine concentrations. • In the third phase, if the titration continues, the inflammation becomes complicated by the development of auto-antibodies (or another auto-immune phenomenon) which leads to myocarditis or other inflammations.
Extension of the concept
In a literature review, Verdoux et al.[103] proposed that manifestations of clozapine-induced inflammation due to rapid titration may include a wide variety of presentations including: • systemic inflammatory processes: - fever - fever with isolated CRP elevation - lupus • localized signs of inflammation: - myocarditis, - serositis, - pneumonitis/alveolitis, - hepatitis, - pancreatitis, - nephritis, - colitis, and - dermatological disorders
Overlap among definitions
• The above classification is somewhat arbitrary since these presentations may lie on a continuum with no clear-cut boundary between them, and several conditions may co-occur. • Moreover, it overlaps with manifestations associated with eosinophilia; the typical clozapine-induced myocarditis is associated with eosinophilic infiltrations. A recent review from a European pharmacovigilance database identified 51, of which 47 were new cases of clozapine-related DRESS syndrome which appear to have associated variables similar to clozapine-induced myocarditis.[104]

CRP, c-reactive protein; CYP1A2, cytochrome P450 1A2; DRESS, drug reactions with eosinophilia and systemic symptoms; PM, poor metabolizers

Supplementary Table 8. Clozapine dosing in Asians

Limited TDM studies
• In 1997 in 162 Taiwanese patients, Chang et al.[109] calculated that each their patients had 30%−50% higher plasma clozapine concentrations than in Western studies.[a]
• In 1997, in 12 Chinese Singaporean patients, Chong et al.[110] found much higher mean plasma clozapine concentrations than in the US clozapine RCT. They proposed the higher clozapine concentration was due to: 1) other factors (lower body weight, female preponderance, and absence of smoking and alcohol use), and/or 2) ethnic differences.[b]
• In 2005, Ng et al.[111] compared 20 Asian Singaporean patients (13 Chinese, 4 Indians and 3 Malayans) and 20 Caucasian patients from Australia. Asian patients received a significantly lower mean clozapine dose (176 mg/day) than the Caucasian group (433 mg/day), but plasma clozapine levels were similar. Asian patients had higher clozapine concentration-to-dose ratios. The study was limited, as patients were not matched for sex or smoking status.
Clinician experience with dosing in Asian countries
• In 1998 in the *British Journal of Psychiatry*, Farooq[112] suggested that Pakistani patients may need lower clozapine doses than Western patients and are similar to Chinese patients.
• In a 2000 chart review of stable outpatients from 45 Singaporean patients (43 Chinese, 1 Malay, and 1 Indian) and 42 Canadian patients (36 Caucasians, 2 African-Americans, and 4 of Asian ancestry) Chong et al.[113] found the mean clozapine doses were 169 vs. 408 mg/day.
• In 2008, Tang et al.[114] reported that in China clozapine usual doses ranged from 200 to 400 mg/day.
• In a 2009 survey of 117 Indian psychiatrists, Shrivastava and Shah[115] indicated that most (86%) of their patients were stabilized on clozapine doses lower than 300 mg/day.
• In 2012 Wang and Li,[116] in an editorial in a Chinese psychiatric journal, stated that the mean dose reported in Chinese studies was 216 mg/day, which was much lower than the 431 mg/day reported in the non-Chinese literature, but they acknowledge that in China clozapine was used in the context of antipsychotic polypharmacy. Two US experts[117,118] commented on this editorial but did not appear to be aware that Asians need lower clozapine doses.
• A 2016 survey of 15 Asian sites published in 2020[119] reported mean clozapine doses of 198 mg/day, but clozapine was frequently prescribed with other antipsychotics.
• In a study of the national Japanese database for prescribing clozapine from 2009 to 2020, Toyoda et al.[120] found a mean dose had decreased in the last 4 years to 248 mg/day (4,567 patients) from 309 mg/day (3,696 patients) in the first 6.5 years.
• In a Taiwanese study in 2 hospitals from 2006 to 2017,[121] 2,874 patients on monotherapy (2/3 of total clozapine patients) had a mean dose of 372 mg/day.
Lower CYP1A2 activity in Asians
• Ghotbi et al.[122] used caffeine TDM as a probe for CYP1A2 activity and demonstrated, when compared with 190 Swedes, that 140 Koreans had approximately a 1.54-times higher caffeine index which is inversely related to CYP1A2 activity. Importantly in this study, they demonstrated that Koreans having the same CYP1A2 genotype, smoking habit and oral contraceptive use displayed significantly lower CYP1A2 activity than Swedes.
Cause of lower CYP1A2 activity in Asians
Currently,[29] it is unknown whether differences in CYP1A2 activity between Asians and Europeans may be related to differences at: • the CYP1A2 gene, or • another gene/s controlling CYP1A2 function.

[a]They calculated that each 100 mg/day dose results in 150 ng/mL plasma clozapine concentrations (30%−50% higher than that in Caucasian studies);[109] [b]Chong et al.[110] found a mean daily dosage at week 12 was 373±90 mg/day, which was lower than that reported in a US clozapine RCT (444 mg/day), but produced much higher mean plasma clozapine concentrations (1,078±385 ng/mL). CYP1A2, cytochrome P450 1A2; RCT, randomized clinical trial; TDM, therapeutic drug monitoring

Supplementary Table 9. Clozapine in Denmark

Danish physicians: leaders in the identification of clozapine-induced myocarditis
They made several first steps worldwide regarding clozapine-induced myocarditis in: • 1980 with the publication of the 1st case[85] (versus 1986 for the 2nd case[86] from the US), • 1985 with publication of the 1st large sample[134] of clozapine discontinuations including 1 myocarditis case out of 216 patients (versus 1988 for the 2nd sample[135] from Sweden), • 1986 with the 1st case reported to VigiBase (versus 1990 for the 2nd case from Germany),[67] • 1994 with the publication of the 1st description that this was an "allergic"[87] or hypersensitivity reaction (versus 1995 for the 2nd description[136] from Norway), and • 2012 with publication of a review[77] showing that clozapine can have pro-inflammatory activity during early titration.
Clozapine-induced myocarditis is rare in the Danish registry
• Rohde et al.[99] studied 3,262 outpatient starts of clozapine in which 0.03% developed myocarditis in the first 2 months. More importantly, none of the 26 deaths in the first 2 months was explained by myocarditis.
Clozapine-induced myocarditis in Denmark is rare in the VigiBase pharmacovigilance database
• In VigiBase through January 15, 2021,[67] there were 3,572 clozapine-induced myocarditis cases with 178 deaths. Danish cases accounted for only 12 cases or 0.3% of the total cases and 3 deaths or 0.02% of total deaths.
Long-term clozapine safety in the Danish registry
• Within the long-term data in the Danish registry, van der Zalm et al.[137] found that clozapine was not associated with increased cardiovascular mortality but with a lower risk of suicide. Moreover, clozapine cessation was associated with a possible increase in suicide deaths. • The first year of clozapine was more problematic since cumulative use of other antipsychotics for up to 1 year was associated with a lower all-cause mortality and suicide risk than a similar period of clozapine use (all-cause: adjusted hazard ratios=0.73; CI, 0.63−0.85, suicide-adjusted hazard ratios=0.65; CI, 0.46−0.91).[137]
Possible effect on mortality of TRS in the 1st year of clozapine use in Denmark
• Patients with TRS probably have greater risk of mortality than patients with non-TRS. • Patients with TRS have definitively more pneumonia risk. In Denmark, TRS patients had an annual pneumonia incidence of 1.229% versus 0.758% in antipsychotic-naïve schizophrenia patients.[74] This means that in Danish clozapine patients, 2/3 of the pneumonia risk is associated with TRS and 1/3 with clozapine.[74]
Definitive effect on mortality of pneumonia in the 1st month of clozapine use in Denmark
• In the Danish registry, Rohde et al.[99] found, in the first month of clozapine treatment, pneumonia explained 7 of 28 deaths in clozapine patients.
Hypothesis about pneumonia in the first year of clozapine use in Denmark
There are probably two major types of pneumonia during the first month of a clozapine titration: • those associated with aspiration which may be ↓ by slower personalized titrations, and • those not associated with aspiration but explained by an infectious agent, typically a bacterium. This may be more associated with the risk associated with TRS while clozapine may have a lesser contribution (possibly ↓ antibodies in some patients).

CI, confidence interval; TRS, treatment-resistant schizophrenia

Supplementary Table 10. Clozapine in Japan

Delay in clozapine approval
• The first clozapine application in 1975 was retracted due to concern about agranulocytosis.[140]
• During the 1990s several lawsuits against the Japanese drug agency concerning drug-related deaths led to slower approval of new drugs. Thus, many psychiatric drugs which had been approved in Western countries took many years to be approved in Japan.[140]
• The clozapine application took from December 2007 to April 2009 for approval.[140]
• The Japanese package insert states, "Start at 12.5 mg, increasing by 25 mg/day, with a target dose of 200 mg/day in 3 weeks. The maintenance dose is 200−400 mg/day, with a maximum dose of 600 mg." This titration may be too fast for Japanese clozapine PMs.[141]
1/3 of Japanese patients may develop clozapine-induced fever (vs. 5% prevalence in initial German and US studies)
• In 2013, Kishi et al.[142] published the first clozapine trial in Japan including 38 TRS inpatients treated in a 12-week, single-arm clinical trial under real-world conditions using raters masked for the type of antipsychotic. They targeted a dose of 200 mg/day within 3 weeks; the maximum dose was up to 600 mg/day and 34% (13/38) were taking valproate. The 29% (11/38) incidence of fever was described but not commented upon.
• In 152 patients following the standard Japanese titration, Tsukahara et al.[143] found a 38% (57/152) incidence of fever during the first 4 weeks.
Other clozapine-induced inflammations are also frequent with rapid Japanese titration
• In the first Japanese trial with 38 patients, Kishi et al.[142] found no cases of myocarditis, but - 1 case of pneumonia and - 1 case of high fever with eosinophilia.
• In the 152 titrations during the first 4 weeks, Tsukahara et al.[143] also found: - 13% (20/152) incidence of pleuritis, - 5% (7/152) incidence of myocarditis and - 1% (2/152) incidence of interstitial nephritis.
• Japanese cases of myocarditis have been published.[144,145]
• In VigiBase until 2021,[67] Japan accounted for 73% (30/41) of Asian reports of clozapine-induced myocarditis. During clozapine-induced myocarditis and compared with non-Asian countries, Asian countries had the highest risk of: - serious outcomes (adjusted OR=2.39, CI 1.11 to 5.17; p=0.02) and - fatal outcomes (adjusted OR=4.35, CI 1.25 to 15.19; p=0.021).
• A study in a pharmacovigilance database identified 51 clozapine-related DRESS[104] cases of which Japan was first, accounting for 24% (12/51), while UK was second with 18% (9/51).
1st article commenting on the role of rapid Japanese clozapine titrations in 2022
• In 2022, Kikuchi et al.[146] published a 43-yo male non-smoker Japanese patient: - He was started on 12.5 mg/day of clozapine and up-titrated to 150 mg/day on day 15. - A fever on day 17 led to suspicion of pneumonia and antibiotic treatment. - On day 22, they wisely diagnosed clozapine-induced acute eosinophilic pneumonia. - After clozapine discontinuation, they waited until after there were no signs of inflammation including a normal CRP and on day 81, they restarted 12.5 mg/day of clozapine. They only increased the dose by 25 mg/week up to 200 mg/day, which is much slower than the protocol issued by the Japanese package insert.

CRP, c-reactive protein; DRESS, drug reaction with eosinophilia and systemic symptoms; OR, odds ratio; CI, confidence interval; PM, poor metabolizer; TRS, treatment-resistant schizophrenia

Supplementary Table 11. Contribution of Australians to the field of clozapine-induced myocarditis

Putting clozapine-induced myocarditis on the radar of the drug agencies
• In 1999, Kilian et al.[90] placed clozapine-induced myocarditis on the radar of drug agencies.
First Australian comment on the role of rapid titrations in the 2007 guideline
• In 2007, a comment was included in a consensus guide for the safe use of clozapine by Australian experts:[150] "Some groups have found that abnormalities are more likely to be associated with more rapid titration (Pantelis C, unpublished observations). There are, nevertheless, no current data or studies to definitively support this notion."
Bringing attention to the role of rapid titration in 2012 by Ronaldson et al.[96]
• In a case-control study, Ronaldson et al.[96] was the first to describe clozapine-induced myocarditis in Australia as significantly associated with rapid titration. Rapid titration was defined on the basis of each additional 250 mg of clozapine administered in the first nine days with an OR of 1.26 (CI 1.02 to 1.55).
Bringing attention to the role of valproate by Ronaldson et al.[96]
• Ronaldson et al.[96] was also the first who described clozapine-induced myocarditis due to valproate co-administration as associated with an OR of 2.59 (CI 1.51 to 4.42). This is one of the most consistent findings in studies of clozapine-induced myocarditis.[151] • Valproate can behave as an inhibitor during early titration before the inductive effects of valproate on norclozapine predominate.[152] • In 13 patients with clozapine-induced myocarditis from 2 case series with blood levels,[153,154] 8 patients took valproate and behaved as clozapine PMs.
Bringing attention to the confounding role of co-infections
• Regarding the diagnosis of clozapine-induced myocarditis diagnosed in a referral to an Australian hospital, Winckel et al.[155] found: - 65% (13/20) did not meet criteria for myocarditis. - 25% (5/20) had upper respiratory infections, which may explain the myocarditis. They proposed that this diagnosis included cases of inflammation that did not strictly meet the diagnosis of myocarditis and cases with concomitant viral infections. • Meeting or not meeting the criteria for a diagnosis of clozapine-induced myocarditis is not important. Any inflammation during clozapine titration is extremely worrisome. It does not matter whether it is secondary to rapid clozapine titration or has another cause; all inflammation releases cytokines that decrease clozapine metabolism.[46] As a matter of fact, patients with undiagnosed inflammation cannot tolerate normal titrations and can develop additional clozapine-induced inflammation, making titration very risky.[46]
Bringing attention to the role of co-medication with quetiapine
• A small case-control study[156] in Australia found significant increases of quetiapine co-prescription in 29% of the 24 myocarditis cases versus 18% of the 121 controls (This provided an OR=1.79, slightly higher than the valproate OR=1.69). • In VigiBase data on clozapine-induced myocarditis through 2021,[67] quetiapine co-prescription increased the risk for: - seriousness OR 2.83 (95% CI 1.82 to 4.40) and - lethality 2.12 (95% CI 1.03 to 4.35). • Quetiapine, in overdoses or rapid titrations, may cause myocarditis by itself.[157]

CI, confidence interval; OR, odds ratios; PM, poor metabolizer

Supplementary Table 12. Detailed analysis of accumulated clozapine dosage in Australian protocols

Ronaldson et al.[96] defined rapid doses based on accumulated dosage by day 9
• One of the official Australian protocols recommends 612.5 mg. • The other protocol recommends 812.5 mg.
Data from Ronaldson et al.[96] indicate these accumulated dosages are not always followed
• 15% of 401 titrations were more aggressive and reached ≥920 mg/day on day 9.[96]
The official Australian protocols are too aggressive for PMs of European ancestry
• The international guideline[28] proposed for non-PM patients of European ancestry an accumulated dosage on day 9 around 700 mg/day (roughly between both Australian protocols). • On the other hand, for PM patients of European ancestry it proposed an accumulated dosage around 262 mg/day, which is much lower. If the international guideline is correct, Australian patients of European ancestry be at risk of clozapine-induced myocarditis, including patients: - taking valproate, - taking oral contraceptives, - with any systemic inflammation or - perhaps those with obesity.
These Australian dosages are inappropriate for patients of Asian ancestry
• The international guideline[28] recommends much lower accumulated dosages at day 9 for patients of Asian ancestry around: - 287.5 mg for non-PMs and - 187.5 mg for PMs. • The Australian titrations are likely to be very rapid for Asians. • No Australian study of clozapine-induced myocarditis has been published with data on the ancestry of the patients. • In the past, the majority of Australians were of European ancestry but Australia is fast becoming a diverse nation with recent census data estimating that one-third of the population was born outside of Australia. According to a 2019 article, since 2011, the proportion of Australian citizens born in China had increased from 6% to 8.3%.[158]

PM, poor metabolizers

Supplementary Table 13. Clozapine in the UK

Guidelines for clozapine use
• The NICE guideline for schizophrenia[159] and the internationally recognized Maudsley psychopharmacology textbooks[160] do not mention ancestry in reference to clozapine dosing. • Using TDM data from the UK/Ireland, Rostami-Hodjegan et al.[39] recommended, for reaching a concentration of 350 ng/mL, doses ranging from 265 mg/day in female non-smokers to 525 mg/day in male smokers. This study is contaminated by including 1) concentrations that were not trough or steady-state, 2) multiple measures of the same individual analyzed as independent samples, and 3) ignoring the possibility of non-adherence. • Ignoring non-adherence provides higher recommended doses. In 6 well-controlled samples of patients of European ancestry,[127] the proposed range was 236 to 360 mg/day, lower than the UK recommendation of 265 to 525 mg/day.
Contributions from the UK in the area of clozapine-induced agranulocytosis
• Since 2005 (10 years earlier than the FDA[70]) the UK has considered the role of benign ethnic neutropenia for prescribing clozapine.[161] • Of 23 episodes recorded as agranulocytosis in clozapine patients, Taylor et al.[162] proposed that 14 were not life-threatening and may not even be clozapine-related. • The same group[163] has proposed implementing the revised FDA monitoring criteria in the UK.
Clozapine-induced myocarditis in the UK
• Until 2021, in Vigibase cases[67] of clozapine-induced myocarditis, the UK ranked 2nd after Australia in: - cases: with 590 (16.5% of 3752 myocarditis cases) and - fatal outcomes: with 25 fatal outcomes (providing a relative lethality of 4.2% of 590). • In the 51 clozapine-related DRESS cases for a pharmacovigilance study,[104] the UK ranked second with 18% (9/51), this time after Japan. • Segev et al.[164] proposed that only 11% (29/228) who had myocarditis diagnosed by UK clinicians were confirmed as probable for myocarditis but did not discuss their lethality.
Clozapine-induced CIGH in the UK
• Handley et al.[165] found GI ADRs explained 16% of UK clozapine fatal outcomes (718/4,572). • They reviewed in detail reports of CIGH from 1992 to 2017 in UK:[165] - 169 within the first 4 years of clozapine treatment, of which 3% (n=5) were fatal - 63 at 10−14 years of treatment, of which 25% (n=16) were fatal
Contributions in the area of clozapine-associated pneumonia
• In 2009, Taylor et al.[166] studied discontinuations and found: - 5 pneumonia deaths among 169 discontinuers out of 529 patients receiving clozapine - no pneumonia deaths in 250 controls receiving long-acting risperidone.
Clozapine prescriptions in the UK are average when compared with other European countries
• Whiskey et al.[169] estimated 69.3 clozapine prescriptions per 100,000 adults. This is intermediate among 10 other European countries (189 in Finland to 42 in Italy per 100,000 adults).
Clozapine in the UK is prescribed across all ancestry groups
• Iqbal et al.[170] reviewed the electronic medical records of 2,835 clozapine patients from 3 areas. Black patients accounted for 21% to 40% of the patients in the two London areas and 4% in the Oxford area. Asian patients ranged from 5%−7% in the London areas to 8% in Oxford. • de Freitas et al.[171] reviewed 1,837 clozapine patients in London. Patients considered of Black ancestry were 866 or 47% of 1,837 and those of Asian ancestry 123 or 7% of 1,837. • In a 2002 review of charts at a London hospital,[172] Taylor found 188 patients on clozapine; the mean doses ranged from 487 mg/day in 73 patients of Black ancestry, 473 mg/day in 104 of European ancestry and 391 in 11 of Asian ancestry.

ADRs, adverse drug reactions; CIGH, clozapine-induced gastrointestinal hypomotility; DRESS, drug reaction with eosinophilia and systemic symptoms; FDA, Food and Drug Administration; GI, gastrointestinal; NICE, National Institute for Health and Care Excellence; TDM, therapeutic drug monitoring

Supplementary Table 14. Ethnopsychopharmacology relevant for patients of East Asian ancestry

East Asians need lower doses of diazepam: well described in the literature
• In typical doses, diazepam is mainly metabolized by CYP2C19 but at higher diazepam doses, the relative contribution of CYP3A4 ↑.[52] In CYP2C19 PMs it is metabolized by CYP3A4.[52]
• CYP2C19 PMs are frequent in East Asia with an average prevalence of 13% (versus 2% in Europeans)[180] and they have twice the serum concentrations of normal metabolizers.[181]
• As CYP2C19 PMs appear to have longer diazepam half-life and may have a higher risk of diazepam-induced sedation,[182] physicians from East Asian countries have empirically prescribed lower doses in East Asian populations than those recommended in the West.[183] In a meta-analysis of Japanese diazepam studies for anxiety, the maximum effective doses were 12−18 mg/day,[184] lower than those recommended in Western countries.
Some but not all East Asians may have greater risk for carbamazepine SJS/TEN: well described in the literature
• HLA-B*15:02 is strongly associated with carbamazepine-induced SJS/TEN.[185]
• HLA-B*15:02 throughout South and East Asian populations ranges from 22% in the Philippines to 1.5% in South Korea.[185] Therefore, in these countries genotyping for HLA-B*15:02 in all patients before starting carbamazepine is recommended as cost-effective,[186] since this drug should not be prescribed in patients with this allele.
• Japan is the exception with <0.1% HLA-B*15:02.[185] HLA variants in the Japanese population may differ from other East Asian populations due to differences in the genetic footprints of prehistoric migrations. A mix with some archaic humans (Denisovan) may be absent in the Japanese, but may influence the HLA genes of other East Asians.[187]
East Asians may need lower doses of olanzapine: not well described in the literature
• Olanzapine is also mainly metabolized by CYP1A2. As with clozapine dosing, olanzapine dosing may also be influenced by three levels of complexity: 1) ancestry groups, 2) sex-smoking subgroups and 3) presence/absence of PM status.[21,131] Olanzapine does not appear to be prone to cause inflammation or myocarditis;[157] a personalized olanzapine dosing guideline does not need to include CRP measures or worry about rapid titration causing inflammation.[21]
• Olanzapine has a wide therapeutic index of 4 (80/20=4).[25]
• The abstract of a single-dose study in 12 male Caucasians and 12 male Chinese in Singapore by the marketer,[188] stated that "the pharmacokinetics of olanzapine are similar in both Chinese and Caucasian racial groups." Based on the study data,[a] the author estimates the plasma/serum concentrations are the same for males of East Asian ancestry vs males of European ancestry when taking 1) 8 vs. 10 mg/day, or 2) 24 vs. 30 mg/day.
East Asians may need lower doses of haloperidol: not well described in the literature
• Western articles usually state that haloperidol is metabolized by CYP3A4 and that CYP2D6 PMs may need lower haloperidol doses.[24,64] Japanese articles disagree. In 1999, Kudo and Ishizaki[189] proposed that the greatest proportion of haloperidol metabolism is by UGT enzymes. In 2012, in an in vitro study, Kato et al.[190] reported that haloperidol glucuronidation is explained by several UGTs, but UGT2B7 is the most important.
• In a recent review of haloperidol pharmacokinetics,[61] the author commented that some patients of African-American ancestry may have longer elimination half-lives possibly due to differences in UGTs, but there was little understanding of the functional effects and racial variations of the UGT2B7 allele. Unfortunately, he was not aware of differences for East Asians.
• In a 2022 review of antipsychotics focused on differences for patients of East Asian ancestry, Lin[191] explained that haloperidol is among the antipsychotics that, under similar dosing, provides patients of East Asian ancestry with higher plasma concentrations than in Western studies.

[a]Table 1 from that article[188] indicates that a 10-mg single dose produced a significant difference (using only one dose and not repeated dosing) in a very small sample of only 12 male patients of both ancestries. CYP1A2, cytochrome P450 1A2; CYP2C19, cytochrome P450 2C19; CYP2D6, cytochrome P450 2D6; CYP3A4, cytochrome P450 3A4; CRP, c-reactive protein; HLA, human leukocyte antigen; PM, poor metabolizer; SJS/TEN, Stevens-Johnson syndrome/toxic epidermal necrolysis; UGT, UDP-glucuronosyltransferase enzymes; UGT2B7, UDP-glucuronosyltransferase 2B7