An expert review of clozapine in Latin American countries: Use, monitoring, and pharmacovigilance

Article *in* Schizophrenia Research · November 2023

DOI: 10.1016/j.schres.2023.10.025

CITATIONS
3

READS
154

14 authors, including:

Trino Baptista
University of the Andes (Venezuela)
179 PUBLICATIONS **4,618** CITATIONS
SEE PROFILE

Mariano Motuca
Hospital del Salud Mental "El Sauce", Mendoza, Argentina
44 PUBLICATIONS **288** CITATIONS
SEE PROFILE

Alberto Fernandez Arana
Instituto de Neurociencias Aplicadas
9 PUBLICATIONS **22** CITATIONS
SEE PROFILE

Ismael Olmos
Hospital Vilardebó
59 PUBLICATIONS **395** CITATIONS
SEE PROFILE

This is the first submitted version to the journal (prepint) that was finally published as Baptista, T., Motuca, M., Serrano, A., Perez Lo Presti, A., Fernandez-Arana, A., Olmos, I., Pabon, A., Yepez, J. G. A., Alejo Galarza, G. J., Rivera Ramirez, N. M., Elkis, H., Sanz, E. J., Cuevas, C. L., & de Leon, J. (2023). An expert review of clozapine in Latin American countries: Use, monitoring, and pharmacovigilance. Schizophrenia research, S0920-9964(23)00386-9. Advance online publication.https://doi.org/10.1016/j.schres.2023.10.025. The final published version is available in the journal webpage 10.1016/j.schres.2023.10.025. or by requesting from the first/last author for private use. The final Word version will be available here after 12 months from initial publication. Please be aware that this version was substantially modified after peer-review the words changed from 2529 to 2679.

Words in text: 2529. Words in abstract:251. Figure: 0. Tables: 2

1 Supplementary Table

Invited manuscript

FULL-LENGHT PAPER

An expert review of clozapine in Latin American countries: use, monitoring, and pharmacovigilance

Trino Baptista [a,b,c], Mariano Motuca[d,e], Ana Serrano[f], Alirio Perez Lo Presti[g], Alberto Fernandez-Arana[h], Ismael Olmos[i,j], Albis Pabon[k], Juan Genaro Ayala Yépez[l,m], Gabriel de Jesus Alejo Galarza[n], Nuria Monserrat Rivera Ramirez[o], Helio Helkis[p] Emilio J. Sanz[q,r], Carlos De las Cuevas[s,t],Jose de Leon[u,v]

Last names in red font

[a]Department of Physiology, Los Andes University Medical School, Mérida, Venezuela

[b]Medical School, Anáhuac University, Querétaro, México

[c]Neuroorigen, Querétaro, México

[d]Department of Psychiatry, School of Medicine at Universidad Nacional de Cuyo, Mendoza, Argentina

[e]Instituto Vilapriño, Centro de Estudios, Asistencia e Investigación en Neurociencias, Mendoza, Argentina

[f]SAMEIN, Salud Mental Integral SAS, Medellin, Colombia

[g]Centro de Salud Mental y Comunitario Dr Germán Greve Schlegel, Santiago, Chile

[h]Instituto de Neurociencias Aplicadas, Lima, Perú

[i] Clinical Pharmacology Unit and Pharmacy Department, Vilardebó Hospital, Administración de Servicios de Salud, Montevideo, Uruguay

[j]Clinical Pharmacology Unit and Outpatient Clinic, Vilardebó Hospital, Administración de Servicios de Salud, Montevideo, Uruguay

[k]Los Andes University Hospital, Psychiatric Unit, Merida, Venezuela

[l]Posgrado de Psiquiatría, Facultad de Ciencias Médicas de la Universidad Central del Ecuador, Quito, Ecuador

[m]Centro Ambulatorio especializado San Lázaro, Ministerio de Salud Pública, Quito, Ecuador

[n]Instituto Regional de Psiquiatría e Investigación. San Luis Potosi, Mexico

[o]Instituto Regional de Psiquiatría e Investigación. San Luis Potosi, Mexico

[p] Department and Institute of Psychiatry, University of São Paulo Medical School, São Paulo-Brazil

[q]Department of Physical Medicine and Pharmacology, School of Medicine, Universidad de La Laguna, Canary Islands, Spain

[r]Hospital Universitario de Canarias, Tenerife, Spain

[s,]Department of Internal Medicine, Dermatology and Psychiatry, School of Medicine, University of La Laguna, Canary Islands, Spain

[t]Instituto Universitario de Neurociencia (IUNE), Universidad de La Laguna, San Cristóbal de La Laguna, Spain

[u]Mental Health Research Center at Eastern State Hospital, Lexington, KY, US

[v]Biomedical Research Centre in Mental Health Net (CIBERSAM), Santiago Apostol Hospital, University of the Basque Country, Vitoria, Spain

Corresponding author: Trino Baptista, Department of Physiology, Los Andes University Medical School, Av. Urdaneta, Mérida, 5101-A, Venezuela.

E-mails and ORCID

Trino Baptista trinobaptista@gmail.com; https://orcid.org/0000-0001-6839-4614

Mariano Motuca memotuca@gmail.com; https://orcid.org/0000-0001-5910-8575

Ana Serrano aserrano.Ve@gmail.com; https://orcid.org/0000-0001-5677-3342

Alirio Perez Lo Presti aperezlopresti@gmail.com; https://orcid.org/0009-0000-7760-8987

Alberto Fernandez-Arana a.fernandez@neurocienciasaplicadas; https://orcid.org/0000-0003-1737-2233

Ismael Olmos ismael.olmos@asse.com.uy; https://orcid.org/0000-0002-3074-7637

Albis Pabon aypb06@hotmail.com; https://orcid.org/0000-0002-1898-6125

Juan Genaro Ayala Yépez jayalayepez58@hotmail.com; https://orcid.org/0009-0004-3383-8384

Gabriel de Jesus Alejo Galarza gabrielalejo@irpmexico.com; https://orcid.org/0009-0006-0784-3424

Nuria Monserrat Rivera Ramirez nuriarivera@irpmexico.com; https://orcid.org/0009-0008-8510-0102

Helio Helkis helkis@usp.br; https://orcid.org/0000.0003.0156.7511

Emilio J. Sanz ejsanz@gmail.com; https://orcid.org/0000-0001-6788-4435

Carlos De las Cuevas cdelascuevas@gmail.com; https://orcid.org/0000-0001-5742-905X

Jose de Leon jdeleon@uky.edu; http://orcid.org/0000-0002-7756-2314

Funding

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

Authorship contribution statement

JdL developed the idea for this study. The first draft of the country questionnaire was developed MS and JdL, but then MS reviewed the literature and wrote the first version of the questionnaire. Several authors (TB, MM, AS, ALP, AF, IO, AP, JA, GA, NM, HH) completed the questionnaire using data for their respective countries. Regarding the VigiBase search, CDlC and JdL proposed the design for the analysis to EJS. EJS and CDlC downloaded the files. CDlC worked on cleaning the files. TB wrote the first draft of this manuscript and JdL added the sections on pharmacovigilance. All the co-authors reviewed, provided modifications and approved the final version of this manuscript.

Declaration of competing interest

In the last 3 years, the other authors report no conflicts of interest.

Acknowledgments

The authors are indebted to the national centers which make up the World Health Organization (WHO) Program for International Drug Monitoring and contribute reports to VigiBase at the Uppsala Monitoring Centre. The information comes from a variety of sources, and the probability that the suspected adverse effect is drug-related is not the same in all cases. However, the opinions and conclusions of this study are not necessarily those of the various centers nor of the WHO. The authors are grateful to Marina Sagud, M.D. who helped Jose de Leon, MD to develop the first version of the country questionnaire for a similar study in Eastern Europe.

Abstract

There is a growing interest all around the world in clozapine clinical use, monitoring, and research, particularly adverse drug reactions (ADRs) other that agranulocytosis. In this study we focused on clozapine pharmacovigilance. Hence, we contacted clinicians and researchers in Latin America and requested information about local psychiatric services, clozapine availability, clinical use, and ADR monitoring with the VigiBase system. Only two countries have the minimal advisable psychiatric beds (15 per 100.000 habitants): Uruguay (N= 34.9) and Argentine (N= 17). Bolivia is the only country where clozapine is unavailable. Nine out of twenty countries (45%) reported ADRs to VigiBase. Brazil, Chile, Colombia, and Mexico published national guidelines for schizophrenia treatment. Chile is the sole country with clozapine clinics with drug serum monitoring. Ethnicity-related drug titration in not described in package inserts in any country. We examined in detail the 9 most frequent and important clozapine ADRs in the worldwide database (pneumonia, sudden death, cardiac arrest, agranulocytosis, myocarditis, constipation, arrhythmia, seizure, and syncope). These 9 ADRs led to 294 reports with fatal outcomes in Argentine (N=3), Brazil (N=3), Chile (N=2), and Peru (N=1).

Agranulocytosis was reported from 7 countries, constipation, or seizures from 8 countries. Only two countries reported pneumonia and one country reported myocarditis. The number of clozapine reports on VigiBase has no relation with the country population. All Latin American countries underreport clozapine associated ADRs. Latin American governments along with clinicians, researchers, and educators should optimize clozapine use and monitoring for the benefit people with severe mental and some neurological disorders.

Key words:

Adverse effects, antipsychotic agents, clozapine, hospitals, pharmacovigilance, risk assessment,

Running tittle: clozapine pharmacovigilance in Latin American

1. Introduction

We are witnessing an increased interest in clozapine research and clinical use not only in treatment resistant schizophrenia but also in off-label indications such as bipolar disorder, treatment emergent tardive dyskinesia, aggressive behavior in patients with schizophrenia, refractory aggressive or self-injurious behavior in patients with intellectual disability and dementia, Parkinson-related psychosis, polydipsia associated with severe mental illness, borderline personality disorder and suicidality in a wide range of mental disorders (Leung et al., 2022; Masdrakis and Baldwin, 2023; Teodorescu et al., 2018).

While clozapine's efficacy in the above-mentioned psychiatric and neurological disorder is repeatedly demonstrated and it's an open field for innovation (Gammon et al., 2021), concern about its safety profile has increased as well. Specifically, agranulocytosis contribution to clozapine-associated lethality is relatively low (Goldani et al., 2022; De las Cuevas et al., 2023; de Leon et al., 2023) compared to the risk of pneumonia and myocarditis early in treatment (de Leon et al., 2023), metabolic syndrome and gastrointestinal hypomotility after more prolonged treatment (Baptista et., 2015; de Leon et al., 2023; Every-Palmer and Ellis, 2017; Quek et al., 2022). A recent review also points to a risk of hematological cancer after prolonged clozapine administration (Tiihonen et al., 2022). Numerous clozapine-associated adverse drug reactions (ADRs) effects such as sialorrhea, syncope, hepatitis, pancreatitis, orthostatic hypotension, bradycardia, syncope, cardiomyopathies, and mitral valve incompetence are of clinical relevance as well (Correll et al., 2022).

The growing understanding of clozapine's pharmacokinetics points to relevant interindividual differences in drug metabolism related to ethnicity, gender, obesity, tobacco use

and drugs that stimulate or inhibit clozapine metabolism mainly thorough the hepatic cytochrome P450 1A2 (de Leon et al., 2022a; Reeves et al., 2023). Clozapine-related inflammation probably underlies many potentially ADRs in a dose-related way, which may be significantly minimized by slow and individualized titration according to the above/mentioned factors at all the states of clozapine treatment (de Leon et al., 2022ab; Correll et al., 2022).

As a whole, the fast-growing knowledge on clozapine efficacy and toxicity warrants for optimal education of contemporary psychiatrists and neurologists, and the availability of technical support such as serum clozapine, C-reactive protein (CRP) and troponin I level measurement, and basic electrocardiography. In countries with more resources therapeutic drug monitoring (TDM) can help to personalize dosing (de Leon et al., 2020).

This led to developing “clozapine clinics” as a subsection of the general psychiatric institutions. This does not happen with any other psychiatric drug and may explain clozapine underutilization and the strong reluctance for its clinical use.

Marked differences in the quality and quantity research and monitoring exist among the countries, even within the same continent. A particular subject of this special supplement on clozapine is to show those relevant differences in clozapine research and monitoring in the diverse world regions. A prior article has reviewed the published clozapine articles from South America to improve clozapine research in the region (Baptista et al., 2024). Here, we focused here on clozapine use and pharmacovigilance in selected continental countries from Mexico to Chile, in the hope of improving clozapine practice.

2. Methods

2.1. Country survey

The authors reported general information about their countries and psychiatric services, use of antipsychotics and schizophrenia guidelines. Regarding clozapine they provided data from 1) year of marketing, 2) dose and formulations, and 3) existence of clozapine clinics.

We made multiple attempts to include at least one author from all the countries from Latin America but were only able to recruit authors from Mexico from North America, El Salvador, and Costa Rica from Central America, Argentine, Brazil, Chile, Colombia, Ecuador, Peru, Paraguay, Uruguay, and Venezuela from South America. Clozapine is no available in Bolivia and we could not find authors from small continental countries such as Belice, Guyana, Suriname, and French Guyana. As far as we know, clozapine is fully available in all Central America countries as 25 and 100 mg oral tables, but no author and little additional information could be retrieved from Honduras, Panama, and Nicaragua. Hence, these countries could not be included in Table 1. No attempt was made to contact the island countries due to their small size and limited resources.

2.2. Pharmacovigilance database search

The World Health Organization (WHO) pharmacovigilance program was launched in 1968. Nowadays, over 170 countries and territories are part of the WHO program as full (153) or associate members (22) representing close to 99% of the world's population (Uppsala Monitoring Centre, 2022). The members submit reports of ADRs associated with medicinal products to the WHO global database. ADRs are reported by health

professionals, pharmaceutical companies, and consumers to national pharmacovigilance authorities (Lindquist, 2008).

This is an observational, retrospective, pharmacovigilance study using VigiBase that was carried out on January 15, 2023. The extracted information for each clozapine ADR report was: a unique report identification, date of entrance into VigiBase, country of origin, and type and seriousness of reported ADRs. VigiBase classifies a case as serious based on the following criteria: an ADR that requires hospitalization or extension of hospital stay, results in persistent or significant disability or incapacity, or is life-threatening. If the case did not meet the criteria for seriousness, it was considered non-serious. VigiBase also reports fatal outcomes (De Las Cuevas et al., 2024). In this article, we report data from countries in Latin America that has never been published before.

The study follows the principles of the Helsinki Declaration. The questionnaire for each country was filed by the author from that country. The VigiBase data was presented as a retrospective review of deidentified worldwide patient data and does not require the signed consent of the individual patient, according to the ethics of the institutional review board of the second to last author's (CDlC) university who reviewed in detail the deidentified data for cleaning and analysis.

3. Results

3.1. Country survey

Table 1 describes the country surveys from 10 countries of which we were able to recruit at least 1 author, but Ecuador does not have pharmacovigilance data. The number of beds ranged from 34.9 per 100,000 in Uruguay to 2.8 in Ecuador. The number of

psychiatrists ranged from 22.9 per 100,000 in Uruguay to 1.9 in Ecuador. Brazil, Chile, Colombia, and Mexico reported national guidelines for schizophrenia treatment.

Regarding the year of clozapine marketing, it varied widely. Argentina had access to clozapine from 1974 to 1977 and then was reintroduced in 1996. In the other 10 countries where was available it ranged from 1993 to 2000. Only 25 and/or 100 mg oral tablets were available in all 10 countries.

Only Chile has "clozapine clinics" which provide TDM. No country has formally incorporated ethnicity-related clozapine titration early in treatment.

Table 1 provide a brief summary on the package inserts but in these countries the package inserts have limited influence in clinical practice.

3.2. Pharmacovigilance database search

Based on prior experience (De Las Cuevas et al., 2024), we examined in detail the 9 most frequent and important clozapine ADRs (pneumonia, sudden death, cardiac arrest, agranulocytosis, myocarditis, constipation, arrhythmia, seizure, and syncope). The search included all countries from Latin America but only 9 had at least 1 ADR. Other countries are not listed because they sent no clozapine reports to VigiBase.

Table 2 describes a total of 294 of any of those 9 clozapine ADRs. The countries including ADRs with fatal outcomes are: Argentine (N=3), Brazil (N=3), Chile (N=2), and Peru (N=1). These ADR reports and sometimes the same fatal outcome can be reported in several ADRs. A patient can be reported as presenting with pneumonia and myocarditis. When the reports of any of these ADRs were combined Chile had the maximum number with 125 and Uruguay the minimum number with 2.

Supplementary Table S1 lists the details of these 9 clozapine ADRs and reports the totals of all the clozapine ADRs and in all drugs in VigiBase. The last column indicated that

the number of reports of all drugs ranged from a maximum of 230,851 in Brazil to a minimum of 12,771 in Venezuela. The column second to last indicated that the number of clozapine ADRs ranged from a maximum of 3,206 in Argentine to a minimum of 8 in Uruguay.

Table 2 describes agranulocytosis reports that were sent by Argentine (N=15), Brazil (N=3), Chile (N=116), Colombia (N=5), Costa Rica (N=2), Mexico (N=1), and Venezuela (N=21). Constipation reports were sent by Argentine (N=1), Brazil (N=5), Colombia (N=9), Costa Rica (N=25), Mexico (N=15), Peru (N=21), Uruguay (N=1) and Venezuela (N=1). Pneumonia reports were sent by Argentine (N=10), and Brazil (N=1). Seizure reports were sent by Argentine (N=7), Brazil (N=5), Chile (N=2), Colombia (N=2), Costa Rica (N=4), Mexico (N=2), Peru (N=2) and Venezuela (N=21). Only one case of myocarditis was reported from Venezuela.

4. Discussion

4.1. Number of psychiatric beds and psychiatrists

Mundt et al., (2022) proposed that 60 psychiatric beds x 100.000 habitants was the optimal number and 15 or less as a severe shortage. Only two countries have values higher than 15, Uruguay (34.9 per 100,000) and Argentine (17 per 100,000).

If we assume, that 10 psychiatrists x l00.000 habitants are the minimal acceptable in mental health management (Burbill et al., 1992), only Uruguay (22.9 per 100,000), Argentine (12.5 per 100,000) and Brazil (12.5 per 100,000) reached that value.

4.2. Lack of clozapine guidelines and of clozapine clinics

As indicated only 4 countries had national guidelines for schizophrenia. Latin America is a continent with patients of multiple ancestries which vary in each country. An

international guideline has proposed lower doses for Indigenous Americans, Intermediate for those of European ancestry and highest for those of African Ancestry (de Leon et al, 2022a) and recommend clozapine TDM when available. There are no recommendations for dose according to ancestry in the schizophrenia guidelines or package inserts. Clozapine clinics are only available in Chile. Thus, there is major need to disseminate these new ideas to promote safer clozapine use in Latin America (de Leon et al., 2023b).

4.3. The number reports on VigiBase have no relation with the country population

Table 1 indicates that Chile has only around 18 million people but Table 2 and 3 indicated that Chile provided 125 reports from 9 the selected ADRs provided and 2,059 total clozapine ADRs. Costa Rica only has around 5 million people (Table 1) but had 33 reports from selected 9 clozapine ADRs and 135 clozapine reports.

The largest countries appear to report much less. Mexico has 126 million people and 156,219 reports from all drugs but only 201 clozapine reports and 19 reports from 9 most important ADRs we selected. Brazil has 110 million people and the largest number of reports of all drugs (N=230,851) but only 73 clozapine reports and 15 reports from 9 most important ADRs we selected. Colombia has 52 million people and 96,798 reports from all drugs but only 189 clozapine reports and 16 reports from 9 most important ADRs we selected. Argentine has 40 million people, 105,830 reports of all drugs and the largest number of clozapine reports with 3,206. On the other hand, there were only 34 reports from 9 most important ADRs we selected.

4.4. VigiBase Clozapine reports from Latin America

Among the 9 most important ADRs we selected, agranulocytosis was reported from 7 countries, constipation or seizures from 8 countries. Only two countries reported pneumonia. Myocarditis was reported only by Venezuela which was is not surprising since

it is the only country with published studies in international journals (Serrano et al., 2014; Baptista et al., 2015a;2016). A Colombian myocarditis published in Spanish (Castañeda Ramírez et al., 2011) was not reported to VigiBase. There is a published Venezuelan fatal case of constipation-related colitis (Baptista, 2014). The person who reported this case to the Venezuelan pharmacovigilance database did not report the final fatal outcome, so the report of this case is reflected in VigiBase as non-fatal. This is not unusual many ADR report are done early and before the final outcome is available.

4.4. Severe underreporting in Latin America

In the worldwide search (De las Cuevas, et al., 2024), the top ADR category was "blood and lymphatic system disorder" with 53,505 ADRs; the top ADR was neutropenia with 20,976 reports while agranulocytosis had 5,094. Latin America only provided 163 reports of agranulocytosis. There were 28,435 ADRs labeled "nervous system disorders" with 4,273 seizures as the top ADR in this category. Latin America only provided 30 reports of seizures. Among cardiac disorders there were 3,725 worldwide myocarditis ADRs, of which 1 was from Latin America. Among infections there were 5,582 worldwide pneumonia ADRs, of which 11 were from Latin America.

United Kingdom (UK) has less than 68 million people but had sent 62,252 clozapine with 6,567 fatal outcomes at the same date (De las Cuevas, et al., 2024). Therefore, all countries of Latin America had a major underreporting when compared with UK.

4.5. Limitations

4.5.1. Country survey

We made multiple efforts using contacts in multiple countries but were only able be successful in 10 countries. There was no attempt to establish prevalence of clozapine or antipsychotic use since the data is not available. Besides, clozapine availability is an issue

in some countries. For example, Bolivia has no access, it was not marketed in Venezuela from 2014 to 2022, and there has been a severe clozapine shortage in the first semester of 2023 in Mexico.

4.5.2. VigiBase search

VigiBase relies on voluntary reporting of ADRs which can result in underreporting or selective reporting of certain events (Hazell and Shakir, 2006; Lopez-Gonzalez et al., 2009), particularly those that are well-known or frequently reported. The reporting practices and standards can vary across countries which may impact the quality and completeness of the data. Therefore, while VigiBase can be a useful tool for monitoring the safety of medications, including clozapine, it is important to interpret the data with caution and consider these limitations when evaluating the safety of clozapine. Although the UK may be the best reporter of clozapine ADRs and fatal outcomes in the world (De las Cuevas et al., 2024), there is no doubt that countries in Latin America have a major problem with underreporting clozapine ADRs and fatal outcomes to their national drug agencies compared with the UK.

5. Conclusions

Clozapine use and ADRs reports are inconsistent and notably uneven in Latin America. Our initial search comprised 20 continental countries: Mexico from North America, seven from Central America and 12 from South America. As shown in Tables 2 and 3, pharmacovigilance data from VigiBase was only available from 9 countries, which represents almost half of all the countries. The reasons for such a shortage were not explored in this study but they are surely related to reluctance from clinicians to use clozapine, inconsistent drug availability and ADR report, and scarce research (Baptista et

al., 2024). Hence, modernization of clozapine use and monitoring broadcasting is an urgent task for Latin American psychiatrists and neurologists. As an example, the proportion in these countries of Asian descendants and Amerindians who require lower clozapine doses a careful drug titration than other ethnic groups (de Leon et al., 2022b), is significantly high.

We expect to contribute with this article and this Schizophrenia Research Issue focus on clozapine to help improving clozapine use, monitoring, and research, for the benefit of vulnerable psychiatric populations in the Americas.

6. References

Baptista, T., 2014. A fatal case of ischemic colitis during clozapine administration. Rev. Bras. De Psiquiatr. 36: 358. https://doi.org/10.1590/1516-4446-2014-1402

Baptista, T., Rojas, N., Dávila, D.F., 2015a Heterogeneity of clozapine-associated myocarditis: An opportunity for novel preventing strategies. Aust N Z J Psychiatry. 49, 1068. https://doi.org/ 10.1177/0004867415585584

Baptista, T., Carrizo, E., Fernandez, E., Connell, L., Servigna, M., Parra, A., Quintero, J., Pabón, A., Sandia, I., Uzcátegui, E., Serrano, A., Pirela, N., Villarreal, L., 2015b. Colonic transit diagnostic test shows significant gastrointestinal hypomotility in clozapine-treated patients in comparison with subjects treated with other antipsychotics. Schizophr. Res. 166, 207-211. https://doi: 10.1016/j.schres.2015.05.025.

Baptista, T., Rojas, N., Carrizo, E., Fernandez, E., Servigna, M., Serrano, A., Sandia, I., Perez-Lopresti, S., 2016. Clozapine-induced myocarditis in observational cross-sectional and follow-up evaluations: comparison with other antipsychotics in naturalistic settings. Invest. Clin. 57, 352-364. PMID: 29938983.

Burvill PW., 1992. Looking beyond the 1:10,000 ratio of psychiatrists to population. Aust. N. Z. J. Psychiatry. 26, 265-269.PMID: 1642618.

Castañeda Ramírez, J.J., Cardona Deaza, J.L., Miranda Rosero, H., Londoño, J.F., 2011. Miocarditis por clozapina: reporte de caso y revisión de tema, Rev. Colomb. Psiquiatr. 40, 170-182. Available from: <http://www.scielo.org.co/scielo.php?script=sci_arttext&pid=S0034-74502011000100015&lng=en&nrm=iso> ISSN 0034-7450.

Correll, C.U., Agid, O., Crespo-Facorro, B. · de Bartolomeis, A., Fagiolini, A., Seppälä, N., Howes, O.D., 2022. A guideline and checklist for initiating and managing clozapine treatment in patients with treatment-resistant schizophrenia. CNS Drugs**.** 36, 659–679. https://doi.org/10.1007/s40263-022-00932-2.

De las Cuevas, C., Sanz, E.; de Leon, J., 2023. Adverse drug reactions and their fatal outcomes in clozapine patients in VigiBase: Comparing the top four reporting countries (US, UK, Canada and Australia), Schizophr Res. (in press). https://doi.org/10.1016/j.schres.2023.05.004

De las Cuevas, C., Sanz, E.J., de Leon J., 2024. Adverse drug reactions and their fatal outcomes in clozapine-treated patients in VigiBase: comparing the top four reporting countries (US, UK, Canada and Australia). Schizophr Res. 2023 Jun 8:S0920-9964(23)00184-6. https://doi.org/10.1016/j.schres.2023.05.004.

de Leon, J., Schoretsanitis, G., Kane, J.M., Ruan, C.J. 2020. Using therapeutic drug monitoring to personalize clozapine dosing in Asians. Asia Pac Psychiatry. 12(2):e12384. doi: 10.1111/appy.12384.

de Leon, J., Schoretsanitis, G., Smith, R.L., Molden, E., Solismaa, A., Seppälä, N., Kopeček, M., Švancer, P., Olmos, I., Ricciardi, C., Iglesias-Garcia, C., Iglesias-Alonso, A., Spina, E., Ruan, C.J., Wang, C.Y., Wang, G., Tang, Y.L., Lin, S.K., Lane, H.Y., Kim, Y.S., Kim, S.H., Rajkumar, A.P., González-Esquivel, D.F., Jung-Cook, H., Baptista, T., Rohde, C., Nielsen, J., Verdoux, H., Quiles, C., Sanz, E.J., Las Cuevas, C., Cohen, D., Schulte, P.F.J., Ertuğrul, A., Yağcıoğlu, A.E.A., Chopra, N., McCollum, B., Shelton, C., Cotes, R.O., Kaithi, A.R., Kane, J.M., Farooq, S., Ng, C.H., Bilbily, J., Hiemke, C., López-Jaramillo, C., McGrane, I., Lana, F., Eap, C.B., Arrojo-Romero, M., Rădulescu, F.Ş., Seifritz, E., Every-Palmer, S., Bousman, C.A.,

Bebawi, E., Bhattacharya, R., Kelly, D.L., Otsuka, Y., Lazary, J., Torres, R., Yecora, A., Motuca, M., Chan, S.K.W., Zolezzi, M., Ouanes, S., Berardis, D., Grover, S., Procyshyn, R.M., Adebayo, R.A., Kirilochev, O.O., Soloviev, A., Fountoulakis, K.N., Wilkowska, A., Cubała, W.J., Ayub, M., Silva, A., Bonelli, R.M., Villagrán-Moreno, J.M., Crespo-Facorro, B., Temmingh, H., Decloedt, E., Pedro, M.R., Takeuchi, H., Tsukahara, M., Gründer, G., Sagud, M., Celofiga, A., Ristic D.I., Ortiz, B.B., Elkis, H., Pacheco Palha, A.J., LLerena, A., Fernandez-Egea, E., Siskind, D., Weizman, A., Masmoudi, R., Saffian, S.M., Leung, J.G., Buckley, P.F., Marder, S.R., Citrome, L., Freudenreich, O., Correll, C.U., Müller, D.J., 2022a. An international adult guideline for making clozapine titration safer by using 6 ancestry-based personalized dosing titrations, CRP and clozapine levels. Pharmacopsychiatry. 55, 73-86. http://doi.or/ 10.1055/a-1625-6388.

de Leon, J., 2022b. Reflections on the complex history of the concept of clozapine-induced inflammation during titration. Psychiatr. Danub. 34. 411-421. http://doi.org/ 10.24869/psyd.2022c.411.

de Leon, J., Arrojo-Romero, M., Verdoux,, H., Ruan,, Can-Jun-. Schoretsanitis, G., Rohde, Ch., Cohen, Dan., Schulte, P.F.J., Kim, Se-Hyun., Cotes, R., Leung, J.G., Otsuka,, Y., Kirilochev, O.O., Baptista, T., Grover, S.,Every-Palmer, S., Clark, S.R., McGrane, I.R., Motuca, M., Olmos, I., Wilkowska, A., Sagud, M., Anil Yağcioğlu, A.E., Ristic, D.I., Lazary, J., Sanz, E.J., De Las Cuevas, C., 2023a. Escaping the long shadow cast by agranulocytosis: Reflections on clozapine pharmacovigilance focused on the United Kingdom. J. Clin. Psychopharmacol. 43, 239-245. http:doi.org/ 10.1097/JCP.0000000000001678.

de Leon, J., Baptista, T., Motuca, M., Ruan, C-J., Schoretsanitis, G., De las Cuevas,

C., 2022b. Promoting safer clozapine dosing in the Americas. Braz. J. Psychiatry. 44: 363-365. http:// doi.org/10.47626/1516-4446-2021-0041

Every-Palmer, S., Ellis, P.M., 2017. Clozapine-induced gastrointestinal hypomotility: A 22-year bi-national pharmacovigilance study of serious or fatal 'slow gut' reactions, and comparison with international drug safety advice. CNS Drugs. 31, 699-709. http://doi.org/ 10.1007/s40263-017-0448-6.

Gammon, D., Cheng, C., Volkovinskaia, A., Baker, G.B., Dursun, S.M. 2021. Clozapine: Why is it so uniquely effective in the treatment of a range of neuropsychiatric disorders? Biomolecules. 11, 1030. doi: 10.3390/biom11071030.

Goldani, A.A.S., Rabelo-da-Ponte, FD., Feiten, J.G., Lobato, M.I.R., Belmonte-de-Abreu, P.S., Gama, C.S., 2022. Risk of neutropenia among clozapine users and non-users: results from 5,847 patients. Braz. J. Psychiatry. 44, 21-25. http://dx.doi.org/10.1590/1516-4446-2021-176

Hazell, L., Shakir, S.A., 2006. Under-reporting of adverse drug reactions: systematic review. Drug Saf. 29, 385–396. https://doi.org/10.2165/00002018-200629050-0003.

Lindquist, M., 2008. VigiBase, the WHO Global ICSR database system: basic facts. Drug Inf. J. 42, 409-419. https://doi.org/10.1177/009286150804200501.

Leung, J.G., de Leon, J., Frye, M.A., Singh, B., Cotes, R.O., McElroy, S.L., 2022. The modernization of clozapine: A recapitulation of the past in the United States and the view forward. J. Clin. Psychopharmacol. 42, 565-580. https://doi.org/10.1097/JCP.0000000000001606.

Lopez-Gonzalez, E., Herdeiro, M.T., Figueiras, A., 2009. Determinants of under-reporting of adverse drug reactions: a systematic review. Drug Saf. 32, 19–31. https://doi.org/10.2165/00002018-200932010-00002.

Masdrakis, V.G., Baldwin, D.S. 2023. Prevention of suicide by clozapine in mental disorders: systematic review. Eur. Neuropsychopharmacol. 69, 4-23. doi: 10.1016/j.euroneuro.2022.12.011.

Mundt, A.P., Rozas Serri, E., Irarrázaval, M., O'Reilly, R., Allison, S., Bastiampillai, T., Musisi, S., Kagee, A., Golenkov, A., El-Khoury, J., Park, S.C., Chwastiak, L., Priebe, S. 2022. Minimum and optimal numbers of psychiatric beds: expert consensus using a Delphi process. Mol. Psychiatry. 27, 1873-1879. https://doi: 10.1038/s41380-021-01435-0.

Reeves, S., Bertrand, J., Obee, S.J., Hunter, S., Howard, R., Flanagan, R.J., 2023. A population pharmacokinetic model to guide clozapine dose selection, based on age, sex, ethnicity, body weight and smoking status. Br. J. Clin. Pharmacol. Feb 15. http://doi: 10.1111/bcp.15691.

Serrano, A., Rangel, N., Carrizo, E., Uzcátegui, E., Sandia, I., Zabala, A., Fernández, E., Tálamo, E., Servigna, M., Prieto, D., Connell, L., Baptista, T., 2014. Safety of long-term clozapine administration. Frequency of cardiomyopathy and hyponatraemia: two cross-sectional, naturalistic studies. Aust. N. Z. J. Psychiatry. 48, 183-192. http://doi: 10.1177/0004867413502089.

Teodorescu, A., Dima, L., Ifteni, P., Rogozea, L.M. 2018. Clozapine for treatment-refractory behavioral disturbance in dementia. Am. J. Ther. 25, e320-e325. doi: 10.1097/MJT.0000000000000735.

Tiihonen, J., Tanskanen, A., Bell, J.S., Dawson, J.L., Kataja, V., Taipale, H., 2022. Long-term treatment with clozapine and other antipsychotic drugs and the risk of haematological malignancies in people with schizophrenia: a nationwide case-

control and cohort study in Finland. Lancet Psychiat. 9, 353-362. http://doi.org/10.1016/S2215-0366(22)00044-X.

Uppsala Monitoring Centre, 2022. VigiBase: WHO's global database signalling harm and pointing to safer use. Available from https://who-umc.org/vigibase/vigibase-who-s-global-database/ Accessed December 17, 2022.

Table 1

Country survey: general psychiatric information and clozapine use

Country	Argentina	Brazil	Chile	Colombia	Costa Rica	Ecuador	Mexico	Peru	Uruguay	Venezuela
Population size[a] (millions)	40	110	18	52	5	18	126	32	4	30
Clozapine year of marketing	1974-77 1996	1990	2000	1993	1997	1993	1994	1993	1995	1993
Clozapine formulations/dosages	Oral tablets 25 & 100 mg	Oral tablets 25 & 100 mg	Oral tablets 25 & 100 mg	Oral tablets 25 & 100 mg	Oral tablets 100 mg	Oral tablets 100 mg	Oral tablets 25 & 100 mg	Oral tablets 25 & 100 mg	Oral tablets 25 & 100 mg	Oral tablets 100 mg
Other antipsychotics	7 FGA, 11 SGA	7 FGA, 9 SGA	8 FGA, 9 SGA	3 FGA, 8 SGA	12 (FGA + SGA)	1 FGA, 4 SGA	5 FGA, 5 SCA	7 FGA, 7 SGA	12 (FGA + SGA)	2 FGA, 4 SGA
National guidelines on schizophrenia treatment	Yes	Yes	Yes	Yes	No	No	Yes	No	No	No
Clozapine package insert warnings and indications	Neutropenia, myocarditis, hypotension, gastrointestinal hypomotility. Weekly hematological control for 18 weeks; then every month. Treatment-resistant schizophrenia (nonresponse is defined as a lack of satisfactory clinical improvement despite the use of adequate doses of at least two marketed antipsychotics for an adequate period of time).									
Clozapine clinics	No	No	Yes	No	No	No	No	No	No	No
Ethnicity-related dose titration	No	No	No	No	No	No	No	No	No	No
Number of psychiatric beds x 100.000 people	17	9.5	12.4	9.5	23	2.8	3.7	4.1	34.9	4.1
Number of psychiatrists x 100.000 people	12.5	12.5	9.6	2.5	3.5	1.9	3.1	2.9	22.9	5.1

FGA: first-generation antipsychotic; SGA: second-generation antipsychotic

[a]By adding these numbers we obtained an estimated population of 435 millions. On October 20, 2023, Wikpedia provided a population of 656 millions of all 20 countries of Latin America.

Table 2
VigiBase pharmacovigilance data in countries in Latin America as of January 15, 2023: number of clozapine reports from 9 ADRs[a]

	Reported serious		Reported serious Total	Not serious		Not serious Total	Grand Total
Country	Not fatal	Fatal outcome		Not fatal	Fatal outcome		
Argentina	31	2	33	-	1	1	34
Brazil	11	1	12	1	2	3	15
Chile	-	-	-	123	2	125	125
Colombia	1	-	1	15	-	15	16
Costa Rica	31	-	31	2	-	2	33
Mexico	15	-	15	4	-	4	19
Peru	25	1	26	-	-	-	26
Uruguay	-	-	-	2	-	2	2
Venezuela	3	-	3	21	-	21	24
Total	117	4	121	168	5	173	294

ADR: adverse drug reaction.
[a]Based on prior experience (De Las Cuevas et al., 2024), we examined in detail the 9 most frequent and important clozapine ADRs (pneumonia, sudden death, cardiac arrest, agranulocytosis, myocarditis, constipation, arrhythmia, seizure, and syncope).

Supplementary Table S1

Nine specific clozapine ADRs[a] in countries in Central and South America (until January 15, 2023) in the context of all drug reports

Country	ADR	Clozapine Reports	Non-serious	Serious non-fatal	Fatal	All clozapine Reports	Reports for all drugs for this ADR	Total number of reports (all drugs and all ADRs)
Argentina	Agranulocytosis	15	-	15	-	3,206	26	105,830
	Cardiac arrest	1	-	-	1	3,206	216	105,830
	Constipation	1	-	1	-	3,206	340	105,830
	Pneumonia	10	-	8	2	3,206	1,736	105,830
	Seizure	7	-	7	-	3,206	415	105,830
Brazil	Agranulocytosis	3	1	2	-	73	26	230,851
	Cardiac arrest	1	-	-	1	73	322	230,851
	Constipation	5	-	5	-	73	1,230	230,851
	Pneumonia	1	-	1	-	73	1,335	230,851
	Seizure	5	-	3	2	73	2,850	230,851
Chile	Agranulocytosis	116	114	-	2	2,059	150	29,898
	Seizure	7	7	-	-	2,059	331	29,898
	Syncope	2	2	-	-	2,059	367	29,898
Colombia	Agranulocytosis	5	5	-	-	189	24	96,798
	Constipation	9	9	-	-	189	159	96,798
	Seizure	2	1	1	-	189	315	96,798
Costa Rica	Agranulocytosis	2	1	1	-	135	6	59,478
	Arrhythmia	1	-	1	-	135	52	59,478
	Constipation	25	1	24	-	135	616	59,478
	Seizure	4	-	4	-	135	102	59,478
	Syncope	1	-	1	-	135	294	59,478
Mexico	Agranulocytosis	1	1	-	-	201	8	156,219
	Constipation	15	2	13	-	201	2,360	156,219
	Seizure	2	1	1	-	201	976	156,219
	Syncope	1	-	1	-	201	668	156,219

Peru	Cardiac arrest	1	-	-	1	118	158	167,234
	Constipation	21	-	21	-	118	2,566	167,234
	Seizure	2	-	2	-	118	458	167,234
	Syncope	2	-	2	-	118	708	167,234
Uruguay	Constipation	1	1	-	-	8	38	16,120
	Syncope	1	1	-	-	8	79	16,120
Venezuela	Agranulocytosis	21	20	1	-	885	26	12,771
	Constipation	1	-	1	-	885	86	12,771
	Myocarditis	1	-	1	-	885	3	12,771
	Seizure	1	1	-	-	885	107	12,771

ADR: adverse drug reaction.

[a]Based on prior experience (De Las Cuevas et al., 2024), we examined in detail the 9 most frequent and important clozapine ADRs (pneumonia, sudden death, cardiac arrest, agranulocytosis, myocarditis, constipation, arrhythmia, seizure, and syncope).