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ORIGINAL ARTICLE

Clozapine-associated myocarditis in the World Health Organization's pharmacovigilance database: Focus on reports from various countries

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Abstract
Introduction: The incidence of clozapine-associated myocarditis varies by country. These variations were explored in VigiBase, the World Health Organization's global database which has >25 million spontaneously reported adverse drug reaction (ADR) reports from 145 national drug agencies.
Methods: On January 15, 2021, a search of VigiBase since inception focused on myocarditis in clozapine patients. The 3572 individual reports were studied using the standard VigiBase logarithmic measure of disproportionality called information component (IC). The IC measures the disproportionality between the expected and the reported rates. After duplicates were eliminated there were 3274 different patients with myocarditis studied in logistic regression models.
Results: The first case was published in 1980 but since 1993 the VigiBase clozapine-myocarditis IC has been significant; moreover, currently it is very strong (IC = 6.0, IC_{005}–IC_{995} = 5.9–6.1) and statistically significantly different from other antipsychotics. Of the 3274 different patients

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with myocarditis, 43.4% were non-serious cases, 51.8% were serious but non-fatal, and 4.8% were fatal. More than half (1621/3274) of the reports came from Australia, of which 69.2% were non-serious, 27.7% serious but non-fatal, and 3.1% fatal. Asian countries contributed only 41 cases.
Conclusions: In pharmacovigilance studies, confounding factors may explain statistical associations, but the strength and robustness of these results are compatible with the hypothesis that myocarditis is definitively associated with early clozapine treatment (84% [1309/1560] and 5% [82/1560] in the first and second months). Myocarditis reports from Australia are overrepresented to a major degree. Asian countries may be underreporting myocarditis to their drug agencies.
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PALABRAS CLAVE
Clozapina/efectos adversos;
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Miocarditis/inducida químicamente

Miocarditis asociada a la clozapina en la base de datos de farmacovigilancia de la Organización Mundial de la Salud: atención a los reportes de los diferentes países

Resumen
Introducción: La incidencia de la miocarditis asociada a clozapina varía en cada país, y esta variación se exploró en VigiBase™, la base de datos de la Organización Mundial de la Salud con más de 25 millones de reportes de reacciones adversas a medicamentos de 145 agencias nacionales de medicamentos.
Métodos: El 15 de enero del 2021, se llevó a cabo una búsqueda en VigiBase™ de las miocarditis y clozapina. El componente de información (CI) que es una medida logarítmica de desproporción se usó para estudiar los 3.752 reportes. Con modelos de regresión logística se estudió 3.274 pacientes diferentes después de eliminar los duplicados.
Resultados: El primer caso fue publicado en 1980, pero desde 1993 el CI ha sido significativo; ahora es muy alto (CI = 6,0; CI_{005}-CI_{995} = 5,9-6,1), y estadísticamente significativo de otros antipsicóticos. En los 3.274 pacientes: el 43,4% de los casos fueron no graves, el 51,4% fueron casos graves, pero no letales y el 4,8% fueron casos letales. Australia contribuyó a más de la mitad de los casos (1.621/3.274): con un 69,2% de casos no graves, un 27,7% de casos graves, pero no letales y un 3,1% de casos letales. Cuarenta y un casos fueron de países de Asia.
Conclusiones: Los factores de confusión pueden explicar asociaciones estadísticas pero el tamaño y la consistencia de estos resultados son compatibles con que la miocarditis está definitivamente asociada con el tratamiento inicial de la clozapina (el 84% [1.309/1.560] fueron durante el primer mes y otro 5% [82/1.560] durante el segundo). Australia está excesivamente representada, mientras que los países de Asia parecen reportar pocos casos a sus agencias de medicamentos.
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Introduction

According to Ioannidis adverse drug reactions (ADRs) in randomized clinical trials (RCTs) are neglected, restricted, distorted, and silenced.[1] If this is correct, that is bad news for clinicians who may underestimate the risk of ADRs from new drugs. Once the drugs are marketed, previously unidentified ADRs are recognized using what is called pharmacovigilance during postmarketing surveillance.[2] These pharmacological terms refer to the case reports and studies of ADRs published in medical journals and the ADR reports to the Food and Drug Administration (FDA) and other drug agencies. Since 1996,[3] the FDA has paid more attention to unexpected ADRs[4] and has progressively increased the requirements of pharmacokinetic studies in order to try to potentially prevent ADRs and avoid lethality. Drugs marketed before 1996 with very limited RCTs and before pharmacokinetic studies were required are heavily dependent on postmarketing surveillance to identify potentially lethal ADRs.

History of clozapine-induced myocarditis

Clozapine was one of these old drugs that has heavily relied on postmarketing surveillance to decrease potentially lethal ADRs. Clozapine was marketed in some European countries in the early 1970s[5] but postmarketing surveillance was first used to identify clozapine-induced agranulocytosis. In 1975, agranulocytosis cases were described in Finland[6] leading to its withdrawal from some European countries and the cessation of North America studies.[5] In 1989, the study by Kane et al.[7] led to its approval by the FDA and its marketing in the

US with a system requiring weekly white blood cell counts (WBCs). Then clozapine was first introduced or reintroduced in many other countries.

Clozapine-associated myocarditis was also identified by postmarketing surveillance (Supplementary table* S1[8–23]). In 1980, Danish authors[8] published in Danish the first case of clozapine-associated myocarditis as an overdose, which can be described as ''rapid titration by a patient''. The first overdose case written in English was published in 1992 by US authors.[9] The first ''rapid titration by a doctor'' was described in a German patient in 1995.[11] The doctor started with 25 mg but increased the dosage very fast, reaching 500 mg/day on the 8th day. In 1999 an important article by Killian et al.[12] reviewed 23 cases from the Australian drug registry and placed clozapine-associated myocarditis on the radar of the drug agencies. It is unfortunate that the drug agencies did not pay attention to a comment on Killian's cases by Canadian authors: Dejeveran et al.[13] stated that ''in all cases, daily clozapine doses were increased rapidly'' and that the Australian titrations were much faster than their Canadian titrations.

Controversies surrounding clozapine-associated myocarditis

In 2012, two crucial articles defending two extreme positions on clozapine-associated myocarditis were published by Continental Europeans[24] and Australians.[25] The Continental European position was exemplified by the Dutch group Cohen et al.,[24] who brought attention to an incidence rate of 0.7–1.12% in Australia versus 0.07% worldwide. In the Netherlands, they found almost no cases of clozapine-associated myocarditis in spite of extremely wide use of clozapine (approximately 10% of schizophrenia outpatients)[26]; it is important, however, to emphasize that the Dutch guideline[27] proposes very slow clozapine titration, particularly for outpatients.

In a case-control study, Ronaldson et al.[25] found that clozapine-associated 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 odds ratio (OR) of 1.26, while valproate co-administration was associated with an OR of 2.59. Since 2012 these two positions may have become further apart. In their 2015 review of the literature, Ronaldson et al.[28] 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''. The Continental Europeans responded with a study from the Danish registry; Rohde et al.[29] studied all 3262 outpatient starts of clozapine and found 0.03% developed myocarditis in the first 2 months and, more importantly, that none of the 26 deaths in the first 2 months was explained by myocarditis. If the Danish psychiatrists do not identify clozapine-associated myocarditis as Ronaldson et al.[28] proposed and continue with clozapine titration in patients with early myocarditis, one should think that many of these patients would die. If one proposes an incidence of 3% of myocarditis in 3262 clozapine initiations, one should expect 97 undiagnosed clozapine-associated myocarditis cases with high risk of death due to lack of identification by their Danish psychiatrists.

In 2020, a meta-analysis[30] of clozapine-associated myocarditis found an event rate of 2% in 9 Australian samples and of 0.3% in 15 non-Australian samples. This meta-analysis did not explain this roughly seven-fold difference between Australia and other countries.

Published review of clozapine-associated myocarditis

Supplementary table* S2[12,28,31–40] described prior published reviews of clozapine-associated myocarditis found in PubMed. These review articles mainly collected cases from published case reports or ADR reports to drug agencies. The sample size has progressively increased from 23 cases,[12] to 24 cases,[31] 65 cases,[33] 69 cases,[32] 88 cases,[36] 116 cases,[34] 250 cases,[28] or 359 cases.[37]

VigiBase is the World Health Organization's global ADR database. On January 15, 2021, we completed a search focused on more than 3000 myocarditis cases suspected to be associated with clozapine.

Methods

VigiBase search on January 15, 2021

VigiBase, the World Health Organization's global database, 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. Clozapine ADRs are classified some times 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 clozapine ADR categories. Myocarditis is a well-established clozapine ADR in VigiBase.

From the inception of the database until January 15, 2021, all 3752 reports of myocarditis and clozapine that were reported have been scrutinized by the first and second authors. They represent nearly half the VigiBase reports of myocarditis for all drugs. This is a retrospective review of deidentified cases (see Table 1, footnote a).

Statistical analyses using standard VigiBase's disproportionality approach

VigiBase uses as a standard method a logarithmic measure of disproportionality called the information component (IC).[41] The IC measures disproportionality between the expected and the reported rates of myocarditis related to clozapine and is described in detail in footnote e of Table 1. All of these VigiBase standard analyses are con-

Table 1 Reports of myocarditis and lethality (including duplicates).[a]

Countries[b]	First case in VigiBase[c] (approval year)	Frequency %	Myocarditis *N*	Seriousness[d]	Relative lethality[e]	IC[f] (IC_{005}–IC_{995})
Australia	1995 (1994)	50.8	1813	34.0% (617/1813)	2.9% (53/1813)	4.6 (4.5–4.8)
United Kingdom of Great Britain	1993 (1989)	16.5	590	87.6% (517/590)	4.2% (25/590)	4.0 (3.8–4.2)
Canada	1999 (1991)	9.3	331	90.0% (298/331)	4.5% (15/331)	5.0 (4.7–5.2)
United States of America	2000 (1989)	8.3	295	96.6% (285/295)	17.3% (51/295)	4.9 (4.6–5.2)
Germany	1990 (1972)[g]	4.3	155	65.2% (101/155)	5.2% (8/155)	5.2 (4.8–5.6)
New Zealand	2001 (1989)	2.4	85	5.9% (5/85)	5.9% (5/85)	5.3 (4.8–5.6)
18 other European countries <1%	1986[h] (different years)	6.8	244	86.8% (212/244)	6.7% (17/244)	–
6 Asian[i] countries <1%	2008[j] (different years)	1.2	42	76.2% (32/42)	7.1% (3/42)	–
1 Western Asian[k] country (Turkey) <1%	2017 (1993)	0.36	13	53.8% (7/13)	7.7% (1/13)	–
2 African countries <1%	2010[l] (different years)	0.06	2	50% (1/2)	0% (0/2)	–
1 South American country <1%	2016[m] (different years)	0.06	2	100% (2/2)	0% (0/2)	–
Total		100	3572	58.1% (2077/3572)	5.0% (178/3572)	6.0 (5.9–6.1)

ADR: adverse drug reaction; FDA: Food and Drug Administration; CI: confidence interval; IC: information component.

[a] This is a retrospective review of deidentified worldwide patient data that does not require the signed consent of the individual patient according to the ethics of the institutional review board of the first author's university.

[b] Only countries with >50 cases are described with separate numbers of myocarditis reports.

[c] This column briefly summarizes data from Supplementary table* S2.

[d] Seriousness was calculated by dividing serious cases by myocarditis cases. To make it easier for clinicians to understand the results, any fatal outcome was also considered a serious case.

[e] Relative lethality was calculated by dividing fatal outcomes by myocarditis cases.

[f] An IC value of 0 indicates drug–ADR combinations for which the number of observed cases is the same as that which might be expected from the overall reporting in the dataset. Positive values (IC > 0) represent combinations reported more frequently, and negative values more infrequently, than expected. CIs (confidence intervals) of the IC are calculated to account for sampling variability. An IC_{025} with a positive lower 95% CI indicates a statistically significant disproportionality between the expected and the reported rates for a drug and an ADR. A high IC value in addition to IC_{025} (lower 95% CI) denotes a strong association between clozapine and myocarditis in the database. Although IC_{025} is at the lower end of a 95% confidence interval for the IC and a positive IC_{025} value is the traditional threshold used in statistical signal detection at VigiBase, the lower endpoint of a 99.95% confidence interval for the IC, IC_{0005} is used to support analysis of subgroup-specific associations between substances and effects analogously to how IC_{025} is used for general analysis of substance–effect associations; a positive value for IC_{0005} suggests, but does not prove, a causal relation between the substance and the reaction in the subgroup under consideration. The reason that analysis of subgroup-specific associations requires a wider credibility interval than standard analysis is that many more potential associations are investigated; for each drug–reaction pair, one IC value is computed for each age group, for each sex, for each country, and for other variables. This decreases the risk of detecting spurious positive associations.

[g] Clozapine started being used in West Germany in 1972. It continued to be used in spite of the scare of agranulocytosis in Finland in 1975 but new regulations were introduced in 1979.

[h] The first case of clozapine-associated myocarditis in Europe (and in the world) was reported in 1986 in Denmark. Clozapine had been introduced in Denmark in 1974.

[i] Asian countries are defined by the FDA based on DNA ancestry and include those ranging from Pakistan to Japan.

[j] The first case in Asia was reported in Singapore in 2008. Japan provided the majority of Asian cases. Clozapine was approved in Japan in 2009 and the first Japanese case of clozapine-associated myocarditis was reported in VigiBase in 2013.

[k] People from Western Asia are from the same DNA ancestry group as European Whites and metabolize clozapine in a similar way. All 13 of these cases were from Turkey.

[l] The first case in Africa was reported in South Africa in 2010.

[m] The first case in South America was reported in Venezuela in 2016.

Table 2 Sample analyzed after eliminating duplications ($N = 3274$ patients).

	%	Mean ± SD	P25	Median	P75
Country of primary source					
Australia	50.5% (1653/3274)				
33 other countries	49.5% (1621/3274)				
Age					
Missing	13.5% (442/3274)				
Present	86.5% (2832/3274)	37.7 ± 13.7	26.0	36.0	47.0
Sex					
Missing	4.5% (147/3274)				
Present	95.5% (3127/3274)				
Male	75.5% (2360/3127)				
Female	24.5% (767/3127)				
Seriousness[a]					
Non-serious	43.3% (1419/3274)				
Serious but non-fatal	51.8% (1697/3274)				
Fatal	4.8% (158/3274)				
Dose at time of diagnosis					
Missing	41.8% (1367/3274)				
Present	58.2% (1907-3274)	231 ± 139	150	200	300
Days until myocarditis					
Missing	52.0% (1703/3274)				
Present	48.0% (1571/3274)	166 ± 722[b]	14	18	23
Valproate	9.0% (296/3274)				
Olanzapine	8.7% (284/3274)				
Risperidone	4.8% (157/3274)				
Quetiapine	5.2% (171/3274)				

P25: 25th percentile; P75: 75th percentile; SD: standard deviation.

[a] VigiBase reports fatal outcomes. VigiBase may classify a case as serious (defined as an adverse event or reaction 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 criteria for seriousness, it was considered non-serious.

[b] This variable has a very large SD so it is not well represented by the mean, which is heavily influenced by the small number of patients after 2 months (11% 169/1560). The median provides a better representation of the average.

taminated by the possibility of some level of duplicate reports.

Statistical analyses calculated for this article using non-duplicate reports

All 3572 reports were scrutinized by the first author. He reviewed each case carefully for possible duplicates and for myocarditis unique cases associated with clozapine up through December 31, 2020.

After a careful discussion with the last author, 298 records were eliminated (including 287 duplicate cases, 10 from 2021 and 1 baby) leading to 3274 different patients with myocarditis. They are described in Table 2, which includes the most frequently reported co-medications, fatal outcomes and serious cases. Table 3 described logistic regression models with seriousness (yes/no) or fatal outcomes (yes/no) as dependent variables.

Results

Association between clozapine and myocarditis using VigiBase IC

Current IC in the entire database and by country

Using the standard criteria of VigiBase, in 1993 when 5 cases were accumulated the association between clozapine and myocarditis became statistically significant after the IC_{025} was above the 0 baseline (Supplementary Fig. 1).

Table 1 describes the current IC as 6.0 and that there were 3572 cases with a mortality of 5.0% (178/3572) and that more than half (50.8%) of the cases were from Australia (a country with less than 26 million people). After Australia, the other countries with the most reports are the United Kingdom (16.5%), Canada (16.5%), the US (8.3%), Germany (4.3%) and New Zealand (2.4%). There were reports from 36 countries. Supplementary Fig. S2 demonstrates that in 19 of

Table 3 Logistic regression models[a] of seriousness and fatal outcome. Dependent variable in models A and B: seriousness (yes/no) and in models C and D: fatal outcome (yes/no).

A Seriousness[b]	Wald statistic	Df	Sig.	OR	95% CI for OR	
					Lower	Upper
Decade	342.0	1	.000	7.91	6.36	9.86
Australia	608.7	1	.000	0.062	0.050	0.077
USA	20.2	1	.000	4.71	2.40	9.26
Days missing	8.6	1	.003	1.58	1.17	2.15
Doses missing	7.9	1	.005	1.56	1.15	2.13
B Seriousness[c]	**Wald statistic**	**Df**	***p***	**OR**	**95% CI for OR**	
					Lower	Upper
Decade	329.8	1	.000	7.86	6.29	9.82
Australia	595.6	1	.000	0.062	0.050	0.077
USA	17.2	1	.000	4.20	2.13	8.26
Days missing	7.1	1	.008	1.53	1.12	2.10
Doses missing	12.7	1	.000	1.79	1.30	2.46
Valproate	8.3	1	.004	1.67	1.18	2.37
Olanzapine	13.6	1	.000	1.90	1.35	2.68
Quetiapine	21.3	1	.000	2.83	1.82	4.40
Infection	18.0	1	.000	2.35	1.58	3.49
C Fatal outcome[d]	**Wald statistic**	**Df**	***p***	**OR**	**95% CI for OR**	
					Lower	Upper
Decade	54.6	1	.000	0.297	0.215	0.410
Australia	18.5	1	.000	0.303	0.176	0.522
USA	13.6	1	.000	2.90	1.65	5.10
Days missing	3.3	1	.069	1.54	0.967	2.45
Age decade	26.1	1	.000	1.44	1.25	1.65
D Fatal outcome[e]	**Wald statistic**	**Df**	***p***	**OR**	**95% CI for OR**	
					Lower	Upper
Decade	55.8	1	.000	0.291	0.211	0.403
Australia	18.2	1	.000	0.306	0.177	0.527
USA	12.4	1	.000	2.78	1.57	4.91
Days missing	3.6	1	.059	1.57	0.983	2.50
Age decade	26.4	1	.000	1.44	1.25	1.65
Quetiapine	4.2	1	.041	2.12	1.03	4.35

CI: confidence interval; Df: degrees of freedom; OR: odds ratio; SPSS: Statistical Package for the Social Sciences; USA: United States of America.

[a] SPSS software, 25th version, was used to calculate univariate ORs and their 95% CIs using seriousness (yes/no) and fatal outcome (yes/no) as dependent variables. The univariate ORs were adjusted by confounding independent variables through the logistic regression model using the backward stepwise selection method; removal testing was based on the probability of the Wald statistic.

[b] The total sample was 3274 in which 1855 were serious and 1419 were non-serious. We initially included 7 variables: decade, Australia, USA, days missing, dose missing, sex, and age in decades. As sex and age in decades were not significant in the backward model and decrease the sample size, we eliminated them from the model.

[c] The prior model included 5 variables: decade, Australia, USA, days missing, and dosses missing. A second model with the same sample size was tried by adding 4 medications with frequency >5% and infection that frequency had >5%. Only risperidone was not significant.

[d] The total sample was 2815 (after 459 were missing age) in which 99 were fatal and 2716 were non-fatal. We initially included 7 variables: decade, Australia, USA, days missing, dose missing, sex, and age in decades. As sex was not significant in the backward model and decreased the sample size, we eliminated it from the model.

[e] The prior model included 5 variables: decade, Australia, USA, days missing, and age in decades. We added 4 medications with frequency >5% and infection that had frequency >5%. Only quetiapine was significant in the model. As missing age reduced the number of fatal cases, we repeated the model with 158 fatal cases and 3116 non-fatal controls; the model indicated that quetiapine was still significant with a similar OR, but Australia was no longer significant.

Table 4 Signs and symptoms most frequently reported in myocarditis cases.

Tachycardia	18.3% (600/3274)
Pyrexia	16.6% (543/3274)
Troponin increase[a]	15.5% (505/3274)
C-reactive protein increase	9.7% (318/3274)
Chest pain	8.2% (270/3274)
Abnormal electrocardiogram	7.9% (258/3274)
Infection	6.7% (219/3274)
Eosinophilia	6.4% (209/3274)
Dyspnea	5.3% (173/3274)
Phosphokinase increase	4.7% (155/3274)
Pericarditis	3.6% (119/3274)
Cardiomyopathy	3.2% (104/3274)

[a] Troponin since 2005.

these 36 countries there was a significant association (IC_{0005} is >0) between clozapine and myocarditis.

Comparing clozapine-associated myocarditis with myocarditis associated with other antipsychotics

Supplementary table* S3 describes 8 other antipsychotic drugs with at least 1 report of myocarditis, but this association was significant only for olanzapine (IC = 2.1; IC_{0025} = 1.8) and quetiapine (IC = 1.8; IC_{0025} = 1.5). The clozapine myocarditis IC (6.0) is obviously statistically higher than these ICs from other antipsychotics due to the lack of overlap of their intervals.

No age effects

Supplementary table* S4 shows that the association between clozapine and myocarditis was present in all age groups and in no age group does it appear to be remarkably higher or lower.

Sex effect

The myocarditis IC was significant higher in women (the lower IC_{0005} for women 6.0 is higher than the upper IC_{9995} in men 5.6; Supplementary Fig. S3). Although the female OR between observed and expected was higher (100.97) than the male OR (88.8), the female OR was not significantly higher since the CI_{0005} and CI_{9995} overlapped (data available from authors).

Association between clozapine and myocarditis after eliminating duplicates

Table 2 describes the clinical characteristics of 3274 cases after eliminating obvious duplications. Pharmacovigilance databases are known for the problems of incomplete information and missing data.[42] The percentages of relevant missing data include: 13.5% for age, 52.4% for clozapine dose at the time of diagnosis, and 52.4% for days until myocarditis developed. The prevalences of reported co-medications are included in Table 2 while reported signs and symptoms are reported in Table 4. There is no certainty that these co-medications, symptoms or signs are absent in unreported cases; various reported cases appear to have different levels of completion of information. The 5 most frequently reported symptoms or and signs were tachycardia, pyrexia, troponin increase, CRP increase and chest pain (Table 4). Troponin is a specific marker of myocardial damage but troponin data did not start being reported until 2005.

Chronology of the association

Supplementary table* S1 shows that awareness of clozapine-induced myocarditis comes from a combination of published articles and reports to drug agencies. In some countries the first identified case was a published case while in others the first case was reported to the national drug registry. The first case ever reported was a case in the context of an overdose in 1980 in Denmark. In 1986 the first case reported to a national drug agency was reported to the Danish drug agency, making it the first case ever reported to VigiBase. Other countries in which cases were published before any case was reported to VigiBase by their national drug agency include the USA in 2002, Japan in 2012, Venezuela in 2015, China in 2018 and Tunisia in 2019. Some of the national drug registries that include the first case identified in that country include Germany in 1990, the United Kingdom in 1993, Canada in 1999, New Zealand in 2001, Singapore in 2008 (the first in Asia), South Africa in 2010 (the first in Africa), and Turkey in 2018 (the first in Western Asia).

Australia provided half the reported cases (Table 1). Therefore, Supplementary table* S1 has an Australian column comparing it with the rest of the world. Clozapine was marketed in that country in 1994, and in 1995 the first case was reported to the Australian drug agency. In 1999, Kilian et al.[12] reviewed 23 cases from the Australian drug agency in an important article that raised awareness of the topic. In 2007, a clozapine guide[17] was published in Australia which appeared to have further contributed to increasing awareness in that country to the point that every year Australia started to have at least the same number of cases as the rest of the world combined. In 2011, an Australian guideline focused on clozapine-induced myocarditis[18] may have further increased awareness among Australian psychiatrists.

Serious and fatal cases

The 3274 myocarditis cases included 43.4% non-serious, 51.8% serious but non-fatal, and 4.8% fatal outcomes (Table 5). Two countries were obvious outliers: Australia with less relative lethality and the USA with greater relative lethality. Thus, to better explore the time needed for serious and fatal cases to evolve, we stratified the sample into 3 groups. Supplementary Figs. S4 (serious cases) and S5 (fatal cases) present first the rest of the countries, then the USA and lastly, Australia. It is obvious that in the figure (Supplementary Fig. S4) focused on seriousness, the USA appears to have mainly serious cases while in Australia most cases are not serious; these patterns have become more consistent over time. A similar pattern can be observed in the fatal outcomes data (Supplementary Fig. S5).

Table 5 explains that there is probably a difference in reporting practices. Australia reported 79.1% of the non-serious cases; moreover, within the Australian cases 69.2% were non-serious. Due to high volume of Australian cases, it is remarkable that a country with a small population reported 31.6% of all worldwide fatal outcomes. The USA

Table 5 Serious and fatal outcomes based on country.

	N	Non-serious	Serious but non-fatal	Fatal
Total Sample	3274	43.4% (1419/3274)	51.8% (1697/3274)	4.8% (158/3274)
Australia	1621	69.2% (1122/1621)	27.7% (449/1621)	3.1% (50/1621)
Rest of the world	1399	20.5% (287/1399)	74.4% (1040/1399)	5.1% (72/1399)
USA	254	3.9% (10/254)	81.9% (209/254)	14.2% (36/254)
	N	Australia	Rest of the world	USA
Non-serious	1419	79.1% (1122/1419)	20.2% (287/1419)	0.7% (10/1419)
Serious but non-fatal	1697	26.5% (449/1697)	61.3% (1040/1697)	12.3% (208/1697)
Fatal	158	31.6% (50/158)	45.6% (72/158)	22.8% (36/158)

USA: United States of America.

reported 22.8% of fatal outcomes; moreover, within the USA cases, 22.8% were fatal and only 3.9% non-serious.

In order to test whether the effects of Australian and USA cases were not explained by confounding variables such as decade, missing information regarding days (yes/no), missing information regarding dose (yes/no), sex or age (classified by decades). These confounding variables were adjusted using logistic regression models. Table 3, Panel A, shows that for seriousness the multivariate ORs of Australia (0.62) and the USA (4.71) were significant after controlling for 3 other significant variables (decade, missing information regarding days and missing information regarding dose). Table 3, Panel B, shows our exploration of the effect of infections and co-medications. Infection, valproate, olanzapine and quetiapine provided significant ORs and were entered in the model but the multivariate ORs for Australia (0.62) and the USA (4.20) continued to be similar. Table 3, Panel C, reports that for fatal outcomes the multivariate ORs for Australia (0.30) and the USA (2.90) were significant after controlling for 3 other significant variables (decade, missing information regarding days, and age in decades). Among infection and co-medications, only quetiapine has a significant OR, but the multivariate ORs for Australia (0.31) and the USA (2.78) remained similar.

Myocarditis in Asian countries

There were 41 cases of myocarditis from Asian countries (30 from Japan, 5 from Korea, 3 from Malaysia, 2 from Singapore and 1 from Thailand) until the end of 2020. No cases were reported from China but the first case from India was reported during the early days of 2021. The 41 cases include 25% (10/41) non-serious, 68% (28/31) serious but non-fatal and 7% (3/41) fatal. The 30 Japanese cases included 17% non-serious (5/30), 77% (23/30) serious but non-fatal and 7% fatal (2/30).

Asian countries have a significantly higher frequency of seriousness, 75% (31/41) vs. 56% (1824/3233) in the rest of the world ($p = 0.017$; univariate OR = 2.40, CI 1.17–4.90). When adjusted using logistic regression models, after controlling for 3 other significant variables (decade, missing information regarding days and missing information regarding dose), differences remained significant ($p = 0.02$; adjusted OR = 2.39, CI 1.11–5.17).

Concerning fatal outcomes, Asian countries registered higher figures, 7% (3/41) vs. 4.8% in the rest of the world (155/3233) ($p = 0.46$; OR = 1.57, CI 0.48–5.13), which become statistically significant differences when adjusted using 3 other significant variables (decade, missing information on days and missing information on dose) ($p = 0.021$; adjusted OR = 4.35, CI 1.25–15.19).

Days to diagnosis

Less than half of the sample provided data regarding days to diagnosis. Supplementary Fig. S4 shows that 84% (1309/1560) of cases of myocarditis with reported time data were diagnosed in the first 30 days. Supplementary table* S5 presents the same data by month and indicates that another 5% (82/1560) were diagnosed in the second month. Supplementary table* S6 describes the daily frequencies during the first month. Days 12–21 had >50 cases/day. Fatal outcomes are grouped between days 11 and 24; relative lethality was 2% in the first month.

Clozapine dose on the last day of treatment

Supplementary Tables S5 and S6 present the clozapine dosage on the last day of treatment. The median dosage during the first week appears definitively inappropriate on some days including 112.5 mg/day on days 1 and 2, and 212.5 mg/day on day 4. The maximum dose on day 1 of 175 mg/day indicated a patient was started on that dose. Other very high maximum daily doses were 300 mg/day on days 2, 5 and 7; 400 mg/day on day 4; and 500 mg/day on day 6. The maximum dosage on some days of weeks 2–3 are also highly inappropriate with values of 600 mg/day on days

10 and 20, 650 mg/day on day 15, 800 mg/day on day 11, and 1600 mg/day on day 13 (Supplementary table* S6).

Discussion

This sample includes >3000 patients with clozapine-induced myocarditis from 36 countries and with >1500 of them with data on the timing of diagnosis. In spite of all its limitations, this sample is much larger than prior samples reported in review articles (ranging from 23[12] to 359 cases[37]).

Clozapine-induced myocarditis mainly occurs during titration

Clozapine appears to definitively have a strong association with myocarditis not present in other antipsychotics (Supplementary table* S3). The first clozapine case was published in 1980 but since 1993 the VigiBase statistical signal of the association between clozapine and myocarditis has become significant and currently is very strong (Supplementary Fig. 1). In pharmacovigilance studies, statistical associations can be explained by confounding factors, but most of the myocarditis cases occurring in clozapine patients happen during titration. This is compatible with what we know about hypersensitivity reactions associated with rapid titration. Furthermore, the strength of the association and robustness[42,43] across time and in various countries suggest that clozapine may be a relevant contributing factor or even a causal factor during titration. Myocarditis occurred mostly (84%) in the first month, plus another 5% in the second month. Supplementary table* S7 suggests that the number of cases drops precipitously after 4 months. There are other causes of myocarditis, particularly viral infections[44]; thus, it is possible that many of the cases not occurring during clozapine titration may be mainly explained by other causes and clozapine may be merely a contributing factor.

The role of rapid titration

To correctly interpret the speed of titration in each patient with myocarditis,[45,46] there is need to know information such as ancestry, sex, smoking status, obesity and co-medication[47] that is missing. Most psychiatrists looking at Supplementary table* S6 maximum doses would easily agree that 175 mg/day of clozapine is not a safe dose for the first day. Similarly, reaching 300 mg on day 2, 400 mg on day 4 or 500 mg on day 6 is not safe. In 2014, Schulte et al.[48] emphasized the definitive risk of rapid clozapine titrations for seizures, orthostatic hypotension or even collapse may also be relevant for myocarditis.[48]

Minimum doses reported in VigiBase

Many of the minimum doses reported in Supplementary table* S6 are very low during the first month. The readers need to understand that this is the last dose that was reported to the national drug agency which sent them to VigiBase. We cannot rule out that patients had much higher doses prior to that, which were first reduced and then finally stopped. Most cases did not have enough detail concerning titration or how doses were discontinued.

Another issue that clinicians need to remember when interpreting these values is that we have found that some clozapine PMs can get therapeutic concentrations with very low doses, even lower than 100 mg/day, due to co-medication with inhibitors, the presence of inflammation, obesity or, more rarely, genetic PM status.[46,49–52] These patients require much slower titrations and much lower final doses.

Major underreporting from Asian countries

A prior VigiBase study[53] of all ADRs indicated that a greater proportion of Japanese reports in VigiBase are serious in nature and this is compatible with the small number of myocarditis cases reported from Japan. It appears to us that Japan and other Asian countries may be underreporting cases of myocarditis associated with clozapine. The current limited data suggests that severity (adjusted OR = 2.39) and lethality (adjusted OR = 4.35) of those currently reported may be greater than in non-Asian countries but these findings will need to be revisited when VigiBase receives many more myocarditis cases from Asian countries.

There are no myocarditis reports in VigiBase from China. Clozapine was introduced in China in 1976[54] and for many years clozapine was the most frequently prescribed antipsychotic in China.[55] However, Chinese psychiatrists have always prescribed approximately half the dosage used in Western countries.[56] The first case of myocarditis published in Chinese was in 2001 in the context of an overdose.[16] In 2018 an article listed in PubMed reviewed the autopsies of 24 sudden unexpected deaths in psychiatric patients in Shanghai; 2 of them appear to be cases of clozapine-induced myocarditis.[21]

Clozapine was introduced in Japan in 2009 and restricted to special inpatient institutions. The first published clozapine trial[57] used up to 600 mg/day, the maximum approved dose in Japan. This is an extremely high dose for an average Japanese patient, who probably metabolizes clozapine like other Asians.[58] Japanese titration appears extremely rapid for Japanese patients because the prevalence of fever during titration appears extremely high, as articles describe prevalences of 29%[57] or 38%.[59]

Limitations including reporting bias

Pharmacovigilance databases are hampered by reporting biases and two of them may be important in this myocarditis study: the effect of the country and of missing data.

VigiBase data supports the idea that Australian physicians are much more aware of clozapine-induced myocarditis than physicians in other countries. They report many more mild cases. After reviewing the clinical diagnosis in one area of Australia, Winckel et al.[60] proposed that this diagnosis included cases of inflammation that did not strictly meet the diagnosis of myocarditis and cases with concomitant viral infections. We propose that 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.[61] As a matter of fact, patients with undiagnosed inflammation cannot tolerate normal titrations and can develop additional clozapine-induced inflammation, making titration very risky.[52]

VigiBase data also supports the idea that US physicians apparently only report the most severe cases of clozapine-induced myocarditis; US relative lethality was higher than in the rest of the world. The patients with missing data concerning the day of the treatment and the dose were over-represented among those with serious cases and among fatal cases. The adjustment of US ORs for serious and fatal cases based on the presence of missing data did not appear to explain the high US ORs for seriousness or fatality. Other limitations are described in Supplementary Box S1.[50,61–65]

Hypothesis: clozapine-associated myocarditis as a possible hypersensitivity reaction

Our data from VigiBase suggest an overrepresentation from Australian reports which is compatible with the published meta-analysis describing a seven-fold difference in incidence between Australia and other countries.[30] Supplementary Box S2[25,47,51,60,65–84] proposes that this seven-fold difference between Australia and other countries can be understood if clozapine-induced myocarditis is a hypersensitivity reaction. Supplementary Box S3[13,47,85] discusses the difficulty in exploring the differences in rapid titration although this may be crucial in understanding incidence differences for clozapine-induced myocarditis.

Relevance clozapine-associated myocarditis in context of its toxicity

FDA data from 1998 to 2005 indicated that clozapine was associated with 3277 deaths or serious non-fatal outcomes, making it the third most toxic drug in the US.[4] In our VigiBase search on July 15, 2019, myocarditis was the fourth leading cause of death in clozapine patients.[64] Thus, raising awareness of clozapine-associated myocarditis may be important in reducing clozapine toxicity.

Conclusions

Clozapine appears to definitively have a strong association with myocarditis not present in other antipsychotics (Supplementary table* S3). In pharmacovigilance studies, statistical associations can be explained by confounding factors, but most of the myocarditis cases occurring in clozapine patients happen during titration in the first and second months, which is compatible with what we know about hypersensitivity reactions associated with rapid titration. VigiBase records through December 31, 2020, included 3274 different patients with myocarditis which were 43.4% non-serious, 51.8% serious but non-fatal and 4.8% fatal. More than half of the reports come from Australia. This is possibly explained by the combination of high attention to its diagnosis, the report of non-serious cases and too-rapid titration. Asian countries are underreporting myocarditis, but the limited VigBase data suggest that their myocarditis cases may be more serious and lethal.

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Conflict of interest

The authors have declared that there are no conflicts of interest in relation to the subject of this study.

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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 thank Lorraine Maw, M.A., at the Mental Health Research Center at Eastern State Hospital, Lexington, KY, USA for editorial assistance and G. Niklas Norén at the Uppsala Monitoring Centre, Uppsala, Sweden, for helping with the correct interpretation of the results and providing comments to improve the final version of the article.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.rpsm.2021.07.004.

References

1. Ioannidis JP. Adverse events in randomized trials: neglected, restricted, distorted, and silenced. Arch Intern Med. 2009;169:1737–9, http://dx.doi.org/10.1001/archinternmed.2009.313.
2. Shader RI. Some thoughts on pharmacovigilance and postmarketing surveillance. Clin Ther. 2016;38:2509–10, http://dx.doi.org/10.1016/j.clinthera.2016.11.008.
3. Flockhart DA. Drug interactions, cardiac toxicity, and terfenadine: from bench to clinic? J Clin Psychopharmacol. 1996;16:101–3, http://dx.doi.org/10.1097/00004714-199604000-00001.
4. Moore TJ, Cohen MR, Furberg CD. Serious adverse drug events reported to the Food and Drug Administration, 1998–2005. Arch Intern Med. 2007;167:1752–9, http://dx.doi.org/10.1001/archinte.167.16.1752.
5. Crilly J. The history of clozapine and its emergence in the US market: a review and analysis. Hist Psychiatry. 2007;18:39–60, http://dx.doi.org/10.1177/0957154X07070335.
6. Idänpään-Heikkilä J, Alhava E, Olkinuora M, Palva I. Letter: clozapine and agranulocytosis. Lancet. 1975;2, http://dx.doi.org/10.1016/s0140-6736(75)90206-8.
7. Kane J, Honigfeld G, Singer J, Meltzer H. Clozapine for the treatment-resistant schizophrenic: a double-blind comparison with chlorpromazine. Arch Gen Psychiatry. 1988;45:789–96, http://dx.doi.org/10.1001/archpsyc.1988.01800330013001.

8. Vesterby A, Pedersen JH, Kaempe B, Thomsen NJ. Pludselig død under behandling med klozapin (Leponex) [Sudden death during treatment with clozapine (Leponex)]. Ugeskr Laeger. 1980;142:170–1 [in Danish].
9. Meeker JE, Herrmann PW, Som CW, Reynolds PC. Clozapine tissue concentrations following an apparent suicidal overdose of Clozaril. J Anal Toxicol. 1992;16:54–6, http://dx.doi.org/10.1093/jat/16.1.54.
10. Committee on Safety of Medicines. Myocarditis with antipsychotics: recent cases with clozapine (Clozaril). Curr Probl Pharmacovigilance. 1993;19:9–10.
11. Bandelow B, Degner D, Kreusch U, Rüther E. Myocarditis under therapy with clozapine. Schizophr Res. 1995;17:293–4, http://dx.doi.org/10.1093/jat/16.1.54.
12. Kilian JG, Kerr K, Lawrence C, Celermajer DS. Myocarditis and cardiomyopathy associated with clozapine. Lancet. 1999;354:1841–5, http://dx.doi.org/10.1093/jat/16.1.54.
13. Devarajan S, Kutcher SP, Dursun SM. Clozapine and sudden death. Lancet. 2000;355:841, http://dx.doi.org/10.1016/s0140-6736(00)00035-0.
14. Coulter DM, Bate A, Meyboom RH, Lindquist M, Edwards IR. Antipsychotic drugs and heart muscle disorder in international pharmacovigilance: data mining study. BMJ. 2001;322:1207–9, http://dx.doi.org/10.1136/bmj.322.7296.1207.
15. La Grenade L, Graham D, Trontell A. Myocarditis and cardiomyopathy associated with clozapine use in the United States. N Engl J Med. 2001;345:224–5, http://dx.doi.org/10.1056/NEJM200107193450317.
16. Zhang HG. One case of pulmonary edema and myocarditis caused by clozapine toxicity. J Rare Uncommon Dis. 2001;8:49–50 [in Chinese].
17. Berk M, Fitzsimons J, Lambert T, Pantelis C, Kulkarni J, Castle D, et al. Monitoring the safe use of clozapine: a consensus view from Victoria, Australia. CNS Drugs. 2007;21:117–27, http://dx.doi.org/10.2165/00023210-200721020-00003.
18. Ronaldson KJ, Fitzgerald PB, Taylor AJ, Topliss DJ, McNeil JJ. A new monitoring protocol for clozapine-induced myocarditis based on an analysis of 75 cases and 94 controls. Aust NZ J Psychiatry. 2011;45:458–65, http://dx.doi.org/10.3109/00048674.2011.572852.
19. Kikuchi Y, Ataka K, Yagisawa K, Omori Y, Shimizu K, Kanbayashi T, et al. Clozapine-induced cardiomyopathy: a first case in Japan. Schizophr Res. 2013;150:586–7, http://dx.doi.org/10.1016/j.schres.2013.08.032.
20. Baptista T, Rojas N, Dávila DF. Heterogeneity of clozapine-associated myocarditis: an opportunity for novel preventing strategies. Aust N Z J Psychiatry. 2015;49, http://dx.doi.org/10.1177/0004867415585584.
21. Ye X, Shi C, Shen YW, Zhao ZQ, Jiang Y, Li LL. Forensic analysis of 24 cases of long-term antipsychotics use-induced sudden unexpected deaths. Fa Yi Xue Za Zhi. 2018;34:644–7, http://dx.doi.org/10.12116/j.issn.1004-5619.2018.06.014.
22. Masmoudi R, Baati I, Ksouda K, Abida I, Sellami R, Affes H, et al. Clozapine-induced myocarditis: a rare adverse drug reaction not to ignore. Therapie. 2019;74:441–4, http://dx.doi.org/10.1016/j.therap.2018.07.006.
23. Anıl Yağcıoğlu AE, Ertuğrul A, Karakaşlı AA, Ağaoğlu E, Ak S, Karahan S, et al. A comparative study of detection of myocarditis induced by clozapine: with and without cardiac monitoring. Psychiatry Res. 2019;279:90–7, http://dx.doi.org/10.1016/j.psychres.2019.07.008.
24. Cohen D, Bogers JP, van Dijk D, Bakker B, Schulte PF. Beyond white blood cell monitoring: screening in the initial phase of clozapine therapy. J Clin Psychiatry. 2012;73:1307–12, http://dx.doi.org/10.4088/JCP.11r06977.
25. Ronaldson KJ, Fitzgerald PB, Taylor AJ, Topliss DJ, Wolfe R, McNeil JJ. Rapid clozapine dose titration and concomitant sodium valproate increase the risk of myocarditis with clozapine: a case–control study. Schizophr Res. 2012;141:173, http://dx.doi.org/10.1016/j.schres.2012.08.018.
26. Bogers JP, Schulte PF, Van Dijk D, Bakker B, Cohen D. Clozapine underutilization in the treatment of schizophrenia: how can clozapine prescription rates be improved? J Clin Psychopharmacol. 2016;36:109–11, http://dx.doi.org/10.1097/JCP.0000000000000478.
27. Netherlands clozapine collaboration group [Internet]. Guideline for the use of clozapine. http://www.clozapinepluswerkgroep.nl/wp-content/uploads/2013/07/Guideline-for-the-use-of-Clozapine-2013.pdf [accessed 14.03.21].
28. Ronaldson KJ, Fitzgerald PB, McNeil JJ. Clozapine-induced myocarditis, a widely overlooked adverse reaction. Acta Psychiatr Scand. 2015;132:231–40, http://dx.doi.org/10.1111/acps.12416.
29. Rohde C, Polcwiartek C, Kragholm K, Ebdrup BH, Siskind D, Nielsen J. Adverse cardiac events in outpatients initiating clozapine treatment: a nationwide register-based study. Acta Psychiatr Scand. 2018;137:47, http://dx.doi.org/10.1177/0004867419898760.
30. Siskind D, Sidhu A, Cross J, Chua YT, Myles N, Cohen D, et al. Systematic review and meta-analysis of rates of clozapine-associated myocarditis and cardiomyopathy. Aust N Z J Psychiatry. 2020;54:467–81, http://dx.doi.org/10.1177/0004867419898760.
31. Hägg S, Spigset O, Bate A, Soderström TG. Myocarditis related to clozapine treatment. J Clin Psychopharmacol. 2001;21:382–8, http://dx.doi.org/10.1097/00004714-200108000-00005.
32. Merrill DB, Dec GW, Goff DC. Adverse cardiac effects associated with clozapine. J Clin Psychopharmacol. 2005;25:32–41, http://dx.doi.org/10.1097/01.jcp.0000150217.51433.9f.
33. Wehmeier PM, Heiser P, Remschmidt H. Myocarditis, pericarditis and cardiomyopathy in patients treated with clozapine. J Clin Pharm Ther. 2005;30:91–6, http://dx.doi.org/10.1111/j.1365-2710.2004.00616_1.x.
34. Haas SJ, Hill R, Krum H, Liew D, Tonkin A, Demos L, et al. Clozapine-associated myocarditis: a review of 116 cases of suspected myocarditis associated with the use of clozapine in Australia during 1993–2003. Drug Saf. 2007;30:47–57, http://dx.doi.org/10.2165/00002018-200730010-00005.
35. De Berardis D, Serroni N, Campanella D, Olivieri L, Ferri F, Carano A, et al. Update on the adverse effects of clozapine: focus on myocarditis. Curr Drug Saf. 2012;7:55–62, http://dx.doi.org/10.2174/157488612800492681.
36. Curto M, Girardi N, Lionetto L, Ciavarella GM, Ferracuti S, Baldessarini RJ. Systematic review of clozapine cardiotoxicity. Curr Psychiatry Rep. 2016;18, http://dx.doi.org/10.1007/s11920-016-0704-3.
37. Bellissima BL, Tingle MD, Cicović A, Alawami M, Kenedi C. A systematic review of clozapine-induced myocarditis. Int J Cardiol. 2018;259:122–9, http://dx.doi.org/10.1016/j.ijcard.2017.12.102.
38. Knoph KN, Morgan RJ 3rd, Palmer BA, Schak KM, Owen AC, Leloux MR, et al. Clozapine-induced cardiomyopathy and myocarditis monitoring: a systematic review. Schizophr Res. 2018;199:17–30, http://dx.doi.org/10.1016/j.schres.2018.03.006.
39. Yuen JWY, Kim DD, Procyshyn RM, White RF, Honer WG, Barr AM. Clozapine-induced cardiovascular side effects and autonomic dysfunction: a systematic review. Front Neurosci. 2018;12:203, http://dx.doi.org/10.3389/fnins.2018.00203.
40. Patel RK, Moore AM, Piper S, Sweeney M, Whiskey E, Cole G, et al. Clozapine and cardiotoxicity – a guide for psychiatrists written by cardiologists. Psychiatry Res. 2019;282:112491, http://dx.doi.org/10.3389/fnins.2018.00203.
41. Norén GN, Hopstadius J, Bate A. Shrinkage observed-to-expected ratios for robust and transparent large-scale

pattern discovery. Stat Methods Med Res. 2013;22:57–69, http://dx.doi.org/10.1177/0962280211403604.
42. Bate A, Lindquist M, Edwards IR. The application of knowledge discovery in databases to post-marketing drug safety: example of the WHO database. Fundam Clin Pharmacol. 2008;22:127–40, http://dx.doi.org/10.1111/j.1472-8206.2007.00552.x.
43. Hopstadius J, Norén GN. Robust discovery of local patterns: subsets and stratification in adverse drug reaction surveillance. In: Published in IHI 2012 (IHI '12 Proceedings of the 2nd ACM SIGHIT International Health Informatics Symposium). 2012. p. 265–74, http://dx.doi.org/10.1145/2110363.2110395.
44. Heymans S, Eriksson U, Lehtonen J, Cooper LT Jr. The quest for new approaches in myocarditis and inflammatory cardiomyopathy. J Am Coll Cardiol. 2016;68:2348–64, http://dx.doi.org/10.1016/j.jacc.2016.09.937.
45. Chopra N, de Leon J. Clozapine-induced myocarditis may be associated with rapid titration: a case report verified with autopsy. Int J Psychiatry Med. 2016;51:104–15, http://dx.doi.org/10.1177/0091217415621269.
46. de Leon J, Rhee DW, Kondracke A, Diuguid-Gerber J. Rapid titration and decreased clozapine clearance may help explain five cases of clozapine-induced myocarditis in a New York hospital. Psychosomatics. 2020;61:102–3, http://dx.doi.org/10.1016/j.psym.2019.08.008.
47. de Leon J, Ruan CJ, Schoretsanitis G, De Las Cuevas C. A rational use of clozapine based on adverse drug reactions, pharmacokinetics, and clinical pharmacopsychology. Psychother Psychosom. 2020;89:200–4, http://dx.doi.org/10.1159/000507638.
48. Schulte PF, van Dijk D, Cohen D, Bogers J, Bakker B. Comment on 'effectiveness and safety of rapid clozapine titration in schizophrenia'. Acta Psychiatr Scand. 2014;130:69–70, http://dx.doi.org/10.1111/acps.12274.
49. Ruan CJ, Zang YN, Cheng YH, Wang CY, de Leon J. Around 3% of 1,300 levels were elevated during infections in a retrospective review of 131 Beijing hospital in-patients with more than 24,000 days of clozapine treatment. Psychother Psychosom. 2020;89:255–7, http://dx.doi.org/10.1159/000506355.
50. Ruan CJ, de Leon J. Is there a future for CYP1A2 pharmacogenetics in the optimal dosing of clozapine? Pharmacogenomics. 2020;21:369–73, http://dx.doi.org/10.2217/pgs-2020-0015.
51. Ruan CJ, Zang YN, Wang CY, Cheng YH, Sun C, Spina E, et al. Clozapine metabolism in East Asians and Caucasians: a pilot exploration of the prevalence of poor metabolizers and a systematic review. J Clin Psychopharmacol. 2019;39:135–44, http://dx.doi.org/10.1097/JCP.0000000000001018.
52. Ruan CJ, Wang CY, Tang YL, Lin SK, Lee ST, Hong KS, et al. Exploring the prevalence of clozapine phenotypic poor metabolizers in 4 Asian samples: they ranged between 2% and 13. J Clin Psychopharmacol. 2019;39:644–8, http://dx.doi.org/10.1097/JCP.0000000000001125.
53. Wakao R, Taavola H, Sandberg L, Iwasa E, Soejima S, Chandler R, et al. Data-driven identification of adverse event reporting patterns for Japan in VigiBase, the WHO Global Database of individual case safety reports. Drug Saf. 2019;42:1487–98, http://dx.doi.org/10.1007/s40264-019-00861-y.
54. Potter WZ, Ko GN, Zhang LD, Yan WW. Clozapine in China: a review and preview of US/PRC collaboration. Psychopharmacology (Berl). 1989;99 Suppl.:S87–91, http://dx.doi.org/10.1007/BF00442568.
55. Tang YL, Mao PX, Jiang F, Chen Q, Wang CY, Cai ZJ, et al. Clozapine in China. Pharmacopsychiatry. 2008;41, http://dx.doi.org/10.1055/s-2007-993224.
56. Wang C, Li L. Proper use of clozapine: experiences in China. Shanghai Arch Psychiatry. 2012;24:108–9, http://dx.doi.org/10.3969/j.issn.1002-0829.2012.02.006.
57. Kishi T, Fujita K, Furukawa O, Suzuki T, Moriwaki M, Nitta M, et al. Efficacy and tolerability of clozapine in Japanese patients with treatment-resistant schizophrenia: results from a 12-week, flexible dose study using raters masked to antipsychotic choice. Asian J Psychiatry. 2013;6:200–7, http://dx.doi.org/10.3969/j.issn.1002-0829.2012.02.006.
58. Yada Y, Kitagawa K, Sakamoto S, Ozawa A, Nakada A, Kashiwagi H, et al. The relationship between plasma clozapine concentration and clinical outcome: a cross-sectional study. Acta Psychiatr Scand. 2021;143:227–37, http://dx.doi.org/10.1111/acps.13264.
59. Tsukahara M, So R, Yada Y, Kodama M, Kishi Y. Clinical utility and safety of slower-than-recommended titration of clozapine for treatment-resistant schizophrenia: a retrospective cohort study. Psychiatr Q. 2021;92:703–13, http://dx.doi.org/10.1007/s11126-020-09841-3.
60. Winckel K, Siskind D, Hollingworth S, Wheeler A. Clozapine-induced myocarditis: separating the wheat from the chaff. Aust N Z J Psychiatry. 2015;49:188, http://dx.doi.org/10.1177/0004867414554269.
61. de Leon J, Ruan CJ, Verdoux H, Wang C. Clozapine is strongly associated with the risk of pneumonia and inflammation. Gen Psychiatr. 2020;33:e100183, http://dx.doi.org/10.1136/gpsych-2019-100183.
62. Villasante-Tezanos AG, Rohde C, Nielsen J, de Leon J. Pneumonia risk: approximately one-third is due to clozapine and two-thirds is due to treatment-resistant schizophrenia. Acta Psychiatr Scand. 2020;142:66–7, http://dx.doi.org/10.1111/acps.13184.
63. Alawami M, Wasywich C, Cicovic A, Kenedi C. A systematic review of clozapine induced cardiomyopathy. Int J Cardiol. 2014;176:315–20, http://dx.doi.org/10.1016/j.ijcard.2014.07.103.
64. De Leon J, Sanz EJ, De Las Cuevas C. Data from the World Health Organization's pharmacovigilance database supports the prominent role of pneumonia in mortality associated with clozapine adverse drug reactions. Schizophr Bull. 2020;46:1–3, http://dx.doi.org/10.1093/schbul/sbz093.
65. Verdoux H, Quiles C, de Leon J. Clinical determinants of fever in clozapine users and implications for treatment management: a narrative review. Schizophr Res. 2019;211:1–9, http://dx.doi.org/10.1016/j.schres.2019.07.040.
66. Wang XQ, Lv B, Wang HF, Zhang X, Yu SY, Huang XS, et al. Lamotrigine-induced severe cutaneous adverse reaction: update data from 1999–2014. J Clin Neurosci. 2015;22:1005–11, http://dx.doi.org/10.1016/j.jocn.2015.01.016.
67. Freudenreich O. Clozapine-induced myocarditis: prescribe safely but do prescribe. Acta Psychiatr Scand. 2015;132:240–1, http://dx.doi.org/10.1111/acps.12425.
68. de Leon J, Tang YL, Baptista T, Chen D, Schulte PFJ. Titrating clozapine amidst recommendations proposing high myocarditis risk and rapid titrations. Acta Psychiatr Scand. 2015;132:242–3, http://dx.doi.org/10.1111/acps.12421.
69. Blum A, Mauruschat W. Temperaturanstiege und Bluteiweiβveränderungen unter der Therapie mit Neuroleptika- unter besonderer Berücksichtigung des neuartigen Dibenzodiazepin-Derivates Clozapin. Pharmacopsychiatry. 1972;5:15–69.
70. Naber D, Leppig M, Grohmann R, Hippius H. Efficacy and adverse effects of clozapine in the treatment of schizophrenia and tardive dyskinesia – a retrospective study of 387 patients. Psychopharmacology (Berl). 1989;99 Suppl.:S73–6, http://dx.doi.org/10.1007/BF00442564.
71. Helmchen H. Clinical experience with clozapine in Germany. Psychopharmacology (Berl). 1989;99 Suppl.:S80–3, http://dx.doi.org/10.1007/BF00442566.
72. Safferman A, Lieberman JA, Kane JM, Szymanski S, Kinon B. Update on the clinical efficacy and side effects of clozapine. Schizophr Bull. 1991;17:247–61, http://dx.doi.org/10.1093/schbul/17.2.247.

73. Tham JC, Dickson RA. Clozapine-induced fevers and 1-year clozapine discontinuation rate. J Clin Psychiatry. 2002;63:880–4, http://dx.doi.org/10.4088/jcp.v63n1005.
74. Pui-yin Chung J, Shiu-yin Chong C, Chung KF, Lai-wah Dunn E, Wai-nang Tang O, Chan WF. The incidence and characteristics of clozapine-induced fever in a local psychiatric unit in Hong Kong. Can J Psychiatry. 2008;53:857–62, http://dx.doi.org/10.1177/070674370805301211.
75. Bertilsson L, Carrillo JA, Dahl ML, Llerena A, Alm C, Bondesson U, et al. Clozapine disposition covaries with CYP1A2 activity determined by a caffeine test. Br J Clin Pharmacol. 1994;38:471–3, http://dx.doi.org/10.1111/j.1365-2125.1994.tb04385.x.
76. Ghotbi R, Christensen M, Roh HK, Ingelman-Sundberg M, Aklillu E, Bertilsson L. Comparisons of CYP1A2 genetic polymorphisms, enzyme activity and the genotype–phenotype relationship in Swedes and Koreans. Eur J Clin Pharmacol. 2007;63:537–46, http://dx.doi.org/10.1007/s00228-007-0288-2.
77. de Leon J, Rajkumar AP, Kaithi AR, Schoretsanitis G, Kane JM, Wang CY, et al. Do Asian patients require only half of the clozapine dose prescribed for Caucasians? A critical overview. Indian J Psychol Med. 2020;42:4–10, http://dx.doi.org/10.4103/IJPSYM.IJPSYM_379_19.
78. Suhas S, Kumar V, Damodharan D, Sharma P, Rao NP, Varambally S, et al. Do Indian patients with schizophrenia need half the recommended clozapine dose to achieve therapeutic serum level? An exploratory study. Schizophr Res. 2020;222:195–201, http://dx.doi.org/10.1016/j.schres.2020.05.057.
79. Nielsen R, Akey JM, Jakobsson M, Pritchard JK, Tishkoff S, Willerslev E. Tracing the peopling of the world through genomics. Nature. 2017;541:302–10, http://dx.doi.org/10.1038/nature21347.
80. González-Esquivel DF, Jung-Cook H, Baptista T, de Leon J. Amerindians may need clozapine dosing similar to that of Asians. Rev Psiquiatr Salud Ment. 2020, http://dx.doi.org/10.1016/j.rpsm.2020.11.002. S1888-9891(20)30125-7 [Epub ahead of print].
81. Mostafa S, Kirkpatrick CMJ, Byron K, Sheffield L. An analysis of allele, genotype and phenotype frequencies, actionable pharmacogenomic (PGx) variants and phenoconversion in 5408 Australian patients genotyped for CYP2D6, CYP2C19, CYP2C9 and VKORC1 genes. J Neural Transm (Vienna). 2019;126:5–18, http://dx.doi.org/10.1007/s00702-018-1922-0.
82. Schoretsanitis G, Smith RL, Molden E, Solismaa A, Seppälä N, Kopeček M, et al. European Caucasians may need lower minimum therapeutic clozapine doses than those customarily proposed. J Clin Psychopharmacol. 2021;41:140–7, http://dx.doi.org/10.1097/JCP.0000000000001341.
83. de Leon J. Future studies on the interaction between clozapine and valproic acid should aspire to include longitudinal designs and free valproate concentrations, and should consider that inducer and/or inhibitory effects may vary with time, the individual, and the auto-induction of valproic acid. Ther Drug Monit. 2020;42:159–61, http://dx.doi.org/10.1097/FTD.0000000000000705.
84. Golpour A, Patriki D, Hanson PJ, McManus B, Heidecker B. Epidemiological impact of myocarditis. J Clin Med. 2021;10:603, http://dx.doi.org/10.3390/jcm10040603.
85. de Leon J, Ruan CJ, Schoretsanitis G, Kane JM. Dose and safety concerns of clozapine: worldwide package inserts need revisions. Schizophr Res. 2020;216:2–4, http://dx.doi.org/10.1016/j.schres.2019.12.009.