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

Running title: clozapine myocarditis

Carlos De las Cuevas[a] Emilio J Sanz,[b,c] Can-Jun Ruan,[d,e] Jose de Leon,[f,g,h,i*]

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

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

[c]Hospital Universitario de Canarias, Tenerife, Spain

[d]Laboratory of Clinical Psychopharmacology & The National Clinical Research Centre for Mental Disorders & Beijing Key Lab of Mental Disorders, Beijing Anding Hospital, Capital Medical University, Beijing, China

[e]Department of Psychiatry, The National Clinical Research Centre for Mental Disorders & Beijing Key Lab of Mental Disorders & Beijing Institute for Brain Disorders Center of Schizophrenia, Beijing Anding Hospital, Capital Medical University, Beijing, China

[f]Mental Health Research Center, Eastern State Hospital, Lexington, KY, USA

[g]Psychiatry and Neurosciences Research Group (CTS-549), Institute of Neurosciences, University of Granada, Granada, Spain

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

***Corresponding author:** Jose de Leon, M.D., Mental Health Research Center at Eastern State Hospital, 1350 Bull Lea Road, Lexington, KY 40511, USA e-mail: jdeleon@uky.edu

Phone 1-859-846-8440 Fax 1-859-846-8446

E-mail and ORCID:

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

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

Can-Jun Ruan rcjjenny@msn.com; http://orcid.org/0000-0002-1625-7367

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

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Abstract

Introduction: The incidence of clozapine-associated myocarditis varies by country. These variations are explored in VigiBase, the World Health Organization's global database which has >25 million spontaneously reported adverse drug reaction (ADR) reports from the drug agencies of 145 countries. **Methods:** On January 15, 2021, a search of Vigibase since inception focused on myocarditis in clozapine patients. The 3572 individual reports were studied suing the standard VigiBase logarithmic measure of disproportionality called the 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 myocarditis 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 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 4.8% fatal. There were 41 cases of myocarditis from Asian countries through the end of 2020. **Conclusions:** In pharmacovigilance studies, confounding factors may explain statistical associations, but the strength and robustness of these results are compatible with the theory that myocarditis is definitively associated with early clozapine treatment. Myocarditis reports from Australia reports are over-represented to a major degree. Asian countries may be underreporting myocarditis to their drug agencies.

Key words: clozapine/adverse effects; clozapine/metabolism; clozapine/toxicity; mortality/drug effects; myocarditis/chemically induced; myocarditis/etiology.

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. Unidentified ADRs are more problematic for drugs approved before 1996, as they were not well-studied. Terfenadine was a second-generation antihistaminic that was considered safe in the RCTs, but in 1996 the FDA became aware that terfenadine had caused 125 deaths in the general United States (US) population. At that time, it became clear that terfenadine, when co-prescribed with inhibitors of its metabolism, may cause death from Torsades de Pointes.[3] Thus, since 1996 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 rested in postmarketing surveillance to decrease potentially lethal ADRs. Clozapine was marketed in some European countries in the early 1970s[6] 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 the 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[8-22]). In 1980, Danish authors[4] 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.[5] The first "rapid titration by a doctor" was described in a German patient in 1995.[7] 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.[8] 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.[9] 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 3,262 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 3,262 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,[36] 250 cases,[28] or 359 cases.[37]

VigiBase is the World Health Organization's global ADR database.[65] 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 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 contaminated by the possibility of some level of duplicated reports.

Statistical analyses calculated for this article using non-duplicated 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 which are described in Table 2 which include most frequent reported co-medications. 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 of seriousness, it was considered as non-serious.

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 Figure 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 Figure S2 demonstrates that in 19 of 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 that 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 Figure 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 Figures 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 Figure 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 Figure 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 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 to 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 to 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 to 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 to 15.19).

Days to diagnosis

Less than half of the sample provided data regarding days to diagnosis. Supplementary Figure S4 shows that 84% (1,309/1,560) 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 to 21 had >50 cases/day. Fatal outcomes are grouped between days 11 to 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 to 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 to 359 cases).

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 Figure 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 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.

Major underreporting from Asian countries

A prior VigiBase study[48] 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.

The are no myocarditis reports in VigiBase from China. Clozapine was introduced in China in 1976[49] and for many years clozapine was the most frequently prescribed antipsychotic in China.[50] However, Chinese psychiatrists have always prescribed approximately half the dosage used in Western countries.[51] 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[52] 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.[53] Japanese titration appears extremely rapid for these patients because the prevalence of fever during titration appears extremely high, as articles describe prevalences of 29%[52] or 38%.[54]

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.[55] 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.[56] As a matter of fact, patients with

undiagnosed inflammation cannot tolerate normal titrations and can develop additional clozapine-induced inflammation, making titration very risky.[57]

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 overrepresented 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.[56,58-62]

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[12,28,31-40,45,47,55,62-82] proposes that this seven-fold difference between Australia and other countries can be understood if clozapine-induced myocarditis is a hypersensitivity reaction.

Relevance clozapine-associated myocarditis in context of its toxicity

FDA data from 1998-2005 indicated that clozapine was associated with 3,277 deaths or serious non-fatal outcomes, making it the third most toxic drug in the US, after oxycodone and fentanyl.[4] In our VigiBase search on July 15, 2019, myocarditis was the fourth leading cause of death in clozapine patients.[61] 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 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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Table 1 Reports of myocarditis and lethality (including duplicates)[a]

Countries[b]	Frequency %	Myocarditis N	Seriousness[c]	Relative lethality[d]	IC[e] IC_{005}-IC_{995}
Australia	50.8	1813	34.0% (617/1813)	2.9% (53/1813)	4.6 4.5-4.8
United Kingdom of Great Britain	16.5	590	87.6% (517/590)	4.2% (25/590)	4.0 3.8-4.2
Canada	9.3	331	90.0% (298/331)	4.5% (15/331)	5.0 4.7-5.2
United States of America	8.3	295	96.6% (285/295)	17.3% (51/295)	4.9 4.6-5.2
Germany	4.3	155	65.2% (101/155)	5.2% (8/155)	5.2 4.8-5.6
New Zealand	2.4	85	5.9% (5/85)	5.9% (5/85)	5.3 4.8-5.6
18 other European countries < 1%	6.8	244	86.8% (212/244)	6.7% (17/244)	-
6 Asian[f] countries < 1%	1.2	42	76.2% (32/42)	7.1% (3/42)	-
1 Western Asian[g] country < 1%	0.36	13	53.8% (7/13)	7.7% (1/13)	-
2 African countries < 1%	0.06	2	50% (1/2)	0% (0/2)	-
1 South American country < 1%	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, CI, confidence interval; Food and Drug Administration; 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]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.

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

[e]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.

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

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

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					
- 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	52.4% (1714/3274)				
- Present	47.6% (1560/3274)	224±130	150	200	300
Days until myocarditis					
- Missing	52.4% (1714/3274)				
- Present	47.6% (1560/3274)	167±725	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.

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

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.

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

SUPPLEMENTARY MATERIAL

Table of Contents

Supplementary Box S1 Other limitations of this study

1. Limitation of the VigiBase database
• Inclusion of mainly spontaneous reports (e.g., the reporting clinician decides whether to report the ADR including myocarditis in the patient taking clozapine, another antipsychotic, or another drug). • Lack of certainty that clozapine caused the ADR or its fatal outcomes because other coincidental causes, or co-medications, may explain them. • Lack of control for presumably greater severity of illness in clozapine patients compared to those taking other antipsychotics. We think that in pneumonia the effect of treatment-resistant schizophrenia may be more important[58] while in myocarditis during clozapine titration the crucial issue is the relative speed of titration; the main reasons may be that the psychiatrist is too aggressive and/or the patient cannot tolerate the clozapine titration. • Lack of detailed data on titrations. Reasons for the patient's inability to tolerate titration may be a different DNA ancestry than the average patient in the country, co-medication with inhibitors such as oral contraceptives or valproate, obesity, or rare genetic PMs.[59] • Lack of data on race or ancestry.
2. Limitations of the concept
• This study focused on clozapine-associated myocarditis. • We did not try to analyze clozapine cardiomyopathy, which is a very poorly defined syndrome.[60] VigiBase has >1000 cases of cardiomyopathy.[61] Approximately 3% of 3274 patients (Table 4) with myocarditis were also diagnosed with cardiomyopathy. Future clozapine studies of VigiBase need to study the patients diagnosed with cardiomyopathy and not myocarditis. • We propose that clozapine-associated myocarditis is part of a major syndrome called clozapine-induced inflammation, associated with rapid titration for a given patient. The syndrome includes clozapine-induced CRP elevations, clozapine-induced fever, and other local manifestations, such as serositis, pneumonitis, hepatitis, pancreatitis, nephritis and colitis.[56,62] Different clozapine ADRs are reported to VigBase with varying probability and VigiBase uses complex terminology with the possibility of overlap; thus, it is not possible to study all of these manifestations together.
3. Limitations of the used statistical analyses used
• VigiBase uses IC for disproportionality analyses that consider the number of reports across drugs and within that drug, but does not control for confounders and for duplicates. • Our logistic regression models corrected by available confounding variables, but may not have accounted for disproportionality in reporting.

ADR, adverse drug reaction; CRP, c-reactive protein; IC, information component; PM, poor metabolizer.

Supplementary Box S2 Clozapine-associated myocarditis as a hypersensitivity reaction

1. Hypersensitivity reactions associated with rapid titration

- The lamotrigine-induced Stevens-Johnson syndrome, which is a hypersensitivity reaction, was reduced substantially when the company slowed the recommended titration in average patients with further slowing in half in patients taking an inhibitor, valproate.[63]
- In 2015, two articles[64,65] independently proposed that clozapine-associated myocarditis is a similar hypersensitivity reaction, in this case associated with rapid titration of clozapine.

2. The hypersensitivity model[47] can be simplified into 3 phases

- In the first phase, the titration is too fast for a specific patient, as the psychiatrist was too aggressive with it, and/or the patient's clozapine PM status; this leads to a release of cytokines.
- In the second phase, a positive feedback loop develops, the cytokines inhibit CYP1A2, the main metabolic enzyme for clozapine metabolism, which further ↑ serum clozapine concentrations.
- In the third phase, if the titration continues, the inflammation becomes complicated by the development of auto-antibodies which leads to myocarditis.

3. Clozapine-induced inflammation

- The initial symptom is ↑ CRP; then frequently fever develops and in the late stage local signs of inflammation became obvious, most frequently myocarditis, but other local inflammations including serositis, pneumonitis, hepatitis, pancreatitis, nephritis or colitis can occur.[62]
- Clozapine-induced fever in the absence of any concomitant infection was first described in Germany in 1972[66] in approximately 5% of the patients[67] between the 5th and 20th treatment days and was frequently associated with ↑ the ESR.[68] In the US, a 5% rate of benign hyperthermia[69] was considered normal during clozapine titration and should resolve spontaneously, or in more severe cases stopping clozapine and restarting it again would be required.[70] In clozapine patients from Hong-Kong,[71] ORs associated with fever were 18.9 for a rate of titration >50 mg/week, 3.6 for valproate and 3.2 for the presence of physical illness.

4. Clozapine-associated myocarditis in the context of clozapine metabolism

- Clozapine is mainly metabolized by CYP1A2;[72] it follows the same pattern as other CYP1A2 drugs,[73] with need for lower doses in female non-smokers and higher in male smokers.[74]
- People of Asian ancestry (ranging geographically from Pakistan to Japan), have lower CYP1A2 activity[73] and lower clozapine metabolism.[74-77] This ancestral classification is based on DNA;[78] the original inhabitants of the Americas, or Amerindians, who are descended from Asians, also have lower clozapine metabolism.[79]
- Three facts may explain the greater incidence of myocarditis in Australian clozapine patients:
  - greater attention to diagnosis in Australia;[55]
  - the risk of Australian titration for people of Asian ancestry who have dramatically increased in population in Australia in recent years[80] and have lower clozapine metabolism[74-77] than patients of European ancestry;[81] and
  - the risk of Australian titrations for patients of European ancestry who are clozapine PMs, including those taking valproate.[45,82]

5. The role of rapid titration according to prior reviews of clozapine-associated myocarditis

- Table S1 described 12 reviews:
  - 5 ignore the role of rapid titration as a risk,[12,31-33,39]
  - 1 criticizes this hypothesis,[40]
  - 1 doubts this hypothesis,[34]
  - 1 mentions that it may be important in Australia, but Australian titrations are no more rapid than others,[28]
  - 3 mention this hypothesis[36-38] and
  - only 1 supports it.[35]

CRP, c-reactive protein; CYP, cytochrome P450; ESR, erythrocyte sedimentation rate; OR, odds ratio; PM, poor metabolizer; US, United States.

Supplementary Table S1 Chronology of myocarditis reports and published articles

			Non-Australian		Australian	
Year	Total	N	Approval after 1975[a]	Published articles	N	Published article
1980	0	0		Danish self-overdose[8]		
1986	1	1 (Denmark)				
1989			USA, UK			
1990	1	1 (Germany)				
1991			Canada			
1992				USA overdose[9]		
1993	3	3 (2 Germany + 1 UK)	Turkey, NZ	4 cases in UK (Drug agency)[10]		
1994	6	6 (All of Europe)			0	Approved
1995	10	4 (All of Europe)		German overdose by doctor[11]	6	
1996	14	14 (All of Europe)			0	
1997	11	8 (All of Europe: 7 Germany)			3	
1998	12	8 (All Europe: 6 Germany)			4	
1999	12	10 (9 Europe: 1 Canada)			2	Kilian: 23 cases[12]
2000	16	8 (5 Europe + 2 USA + 1 Canada)		Canadian:[13] rapid titration may explain Kilian's cases	8	
2001	45	11 (7 Europe+3 NAm+ 1 NZ)		Vigibase article[14] FDA article[15] Overdose in China published in Chinese[16]	34	
2002	28	13 (10 Europe + 3 NAm)			15	
2003	50	41 (29 Europe + 12 NAm)			9	
2004	33	31 (22 Europe + 9 NAm)			0	
2005	110	32 (17 Europe + 11 NAm+ 4 NZ)			78	
2006	62	38 (26 Europe + 8 NAm+ 4 NZ)			24	
2007	20	3 (1 Europe + 2 NAm)			17	Clozapine guide[17]
2008	158	68 (32 NAm + 32 Europe + 3 NZ + 1 Asia[b])			90	
2009	177	110 (92 Europe + 16 NAm + 2 NZ)	Japan		67	
2010	100	59 (33 Europe + 20 NAm + 5 NZ + 1Africa[c])			41	
2011	207	91 (56 Europe + 28 NAm + 6 NZ + 1 Asia[d])			116	Myocarditis guide[18]
2012	126	64 (33 Europe + 26 NAm + 5 NZ)		First Japanese case[19] and first published Asian case in English	62	
2013	196	75 (45 Europe + 8 NAm + 18 NZ + 4 Asia[e])			124	

2014	132	58 (48 Europe + 8 NAm + 2 Asia)			74	
2015	238	108 (60 Europe + 18 NAm + 25 NZ+ 5 Asia)		First Venezuelan case which is the first case in SAm[20]	130	
2016	279	172 (107 NAm + 54 Europe + 5 NZ + 5 Asia + 1 SAm[f])			107	
2017	218	136 (84 Europe + 35 NAm + 5 NZ + 1 SAm + 10 Asia + 1 Turkey[g])			82	
2018	322	178 (87 NAm + 82 Europe + 2 NZ + 6 Asia[h] +1 Turkey)		Two first cases[21] from China in a journal listed in PubMed	144	
2019	448	201 (105 NAm + 81 Europe + 5 Asia[j] +10 Turkey)		First Tunisian case[22] and first published case in Africa. First article in Turkey with 10 cases.[23]	247	
2020	238	101 (77 Europe + 20 NAm + 2 Asia + 1 Turkey+ 1 Africa[k])			137	

NAm: North America including the USA and Canada; NZ: New Zealand; SAm: South America; UK, United Kingdom; USA, United States of America.

[a]In 1975 cases of agranulocytosis were described in Finland and clozapine was withdrawn from several European countries and the pre-marketing studies in Canada and the USA were stopped.

[b]First case in Singapore and in Asia. Asia was defined based on the definition of Asians as those people whose ancestry comes from countries ranging geographically from Pakistan to Japan and who are one of the 5 main ancestral groups according to DNA evolution.

[c]First case in South Africa and in Africa.

[d]First case in Korea.

[e]First case in Japan.

[f]First case in South America, which was in Venezuela.

[g]First case in Turkey. According to DNA ancestry people from Turkey are Western Asians, who are different from Asians and from the same ancestry group as Europeans.

[h]First 2 cases in Malaysia.

[i]Clozapine was marketed in China in 1976 and has been the antipsychotic of first choice for many years.

[j]First case in Thailand.

[k]First case in Tunisia.

Supplementary Table S2 Review articles on clozapine-associated myocarditis

Author	Country	Specialty[a]	Description	Mention of rapid titration[b]	Our comments
Kilian et al., 1999[12]	Australia	Cardiology, psychiatry and forensics	Review of 23 myocarditis cases on clozapine patients reported to Australian drug agency	No	In a comment on this article, Dejeveran et al.[9] stated that the Australian titrations were much faster than their Canadian titrations
Hagg et al., 2001[31]	Norway and Sweden	Clinical pharmacology	Review of 24 myocarditis cases in clozapine patients reported to VigiBase	No	
Merrill et al., 2005[32]	USA	Psychiatry and cardiology	Review of 69 published cases of clozapine cardiac ADRs (including myocarditis) in PubMed	No	Quotes Dejeveran et al.[9]
Wehmeier et al., 2005[33]	Germany	Psychiatry	Review of 65 published cases of myocarditis, pericarditis and cardiomyopathy in clozapine patients in PubMed	No	
Haas et al., 2007[34]	Australia	Epidemiology and pharmacy	Review of 116 myocarditis cases reported in clozapine patients to Australian drug agency	Unclear whether or not it is a risk factor	
De Berardis et al., 2012[35]	Italy	Psychiatry and pharmacy	Review of published cases of myocarditis in clozapine patients in the literature	Suggested risk factor	
Ronaldson et al., 2015[28]	Australia	Epidemiology and psychiatry	Review of 250 published cases of myocarditis in clozapine patients in PubMed	Risk factor in her case-control study. "More than usually rapid dose titration is not the practice in Australia".	

Curto et al., 2016[36]	Italy and USA	Psychiatry and cardiology	Systematic review of 88 published cases of cardiac clozapine ADRs (including myocarditis) in PubMed and other databases	Not in the text except for description that in rechallenge cases slower titrations have been used.	Rapid titration is listed in tables with cases and references
Bellissima et al., 2018[37]	New Zealand	Clinical pharmacology, cardiology and psychiatry	Systematic review of 359 published cases of clozapine-associated myocarditis in PubMed and other databases	Comments that it is reported in studies and rechallenge cases of clozapine-induced myocarditis	Rapid titration is listed in references
Knop et al., 2018[38]	USA	Pharmacy and psychiatry	Systematic review of clozapine monitoring protocols for myocarditis and cardiomyopathy in PubMed and other databases	Reported risk factor for myocarditis. "It is therefore plausible that slow initial titration and retitration may mitigate the risk of myocarditis".	
Yuen et al., 2018[39]	Canada	Pharmacology and psychiatry	Systematic review of clozapine cardiovascular ADRs (including myocarditis) in PubMed and other databases	No	It refers only peripherally to myocarditis and comments it may be a hypersensitivity reaction to clozapine.
Patel et al., 2019[40]	UK	Cardiology and psychiatry	Narrative review of clozapine-associated myocarditis and dilated cardiomyopathy	"It is the authors' opinion that since myocarditis occurs early with the initiation of any causative drug, up-titration is more of a coincidence than a risk during this time period."	

ADR, adverse drug reaction; UK, United Kingdom; USA, United States of America.
[a]Authors were classified according to their specialty.
[b]This column is summarized in Supplementary Box 2.

Supplementary Table S3 Myocarditis and other antipsychotics[a]

Active ingredient	$N_{observed}$	$N_{expected}$	IC_{025}	IC	N_{fatal}
Olanzapine	103	24	1.8	2.1	13
Quetiapine	103	30	1.5	1.8	33
Risperidone	59	38	0.2	0.6	10
Aripiprazole	37	23	0.2	0.7	4
Paliperidone	25	15	0.1	0.7	2
Asenapine	7	2	0.1	1.4	1
Loxapine	3	1	-1.0	1.0	0
Brexpiprazole	1	2	-4.8	-1	0

[a]Patients could be taking other medications including clozapine.

Supplementary Table S4 Age and clozapine-associated myocarditis

Patient age	**$N_{observed}$**	**$N_{expected}$**	**IC_{0005}**	**IC**	**IC_{9995}**
12 - 17 years	72	1	5.0	5.6	6.1
18 - 44 years	2087	59	5.0	5.1	5.2
45 - 64 years	834	14	5.7	5.8	6.0
65 - 74 years	85	2	4.6	5.2	5.7
≥ 75 years	26	1	3.5	4.6	5.4
Unknown	467	6	6.0	6.2	6.4

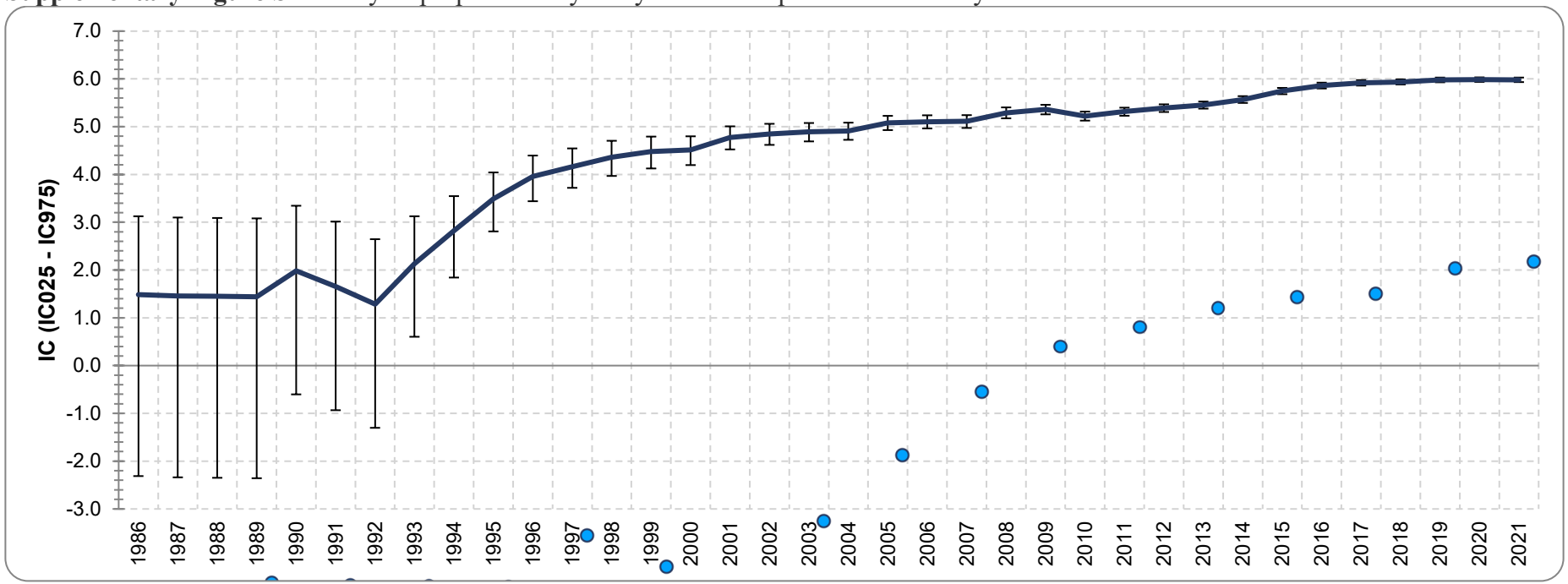
Supplementary Table S5 Clozapine-associated myocarditis outcomes by month

	Dose (mg/day)						Severity	
	N	P_{25}	Median	P_{75}	Min.	Max.	Seriousness	Fatalities
Month 1	1309	150.0	200.0	250.0	12.5	1600	40.9% (535/1309)	2.1% (27/1309)
Month 2	82	150.0	237.5	300.0	25.0	600	25% (38/82)	0% (0/82)
Month 3	27	200.0	300.0	400.0	12.5	500	29.6% (8/27)	0% (0/27)
Month 4	22	187.5	300.0	400.0	40.0	600	50.0% (11/22)	9.1% (2/2)
Month 6	9	337.5	425.0	500.0	300.0	600	33.3% (3/9)	0% (0/9)
Month 7	6	287.5	337.5	450.0	250.0	450	50.0% (3/6)	0% (0/6)
Month 8	8	175.0	275.0	350.0	50.0	375	25.0% (2/8)	0% (0/8)
Month 10	4	225.0	312.5	587.5	225.0	650	75.0% (3/4)	0% (0/4)
Month 11	2		450.0		400.0	500	0% (0/2)	0% (0/2)
Year 2	3		325.0		300.0	400	66.6% (2/3)	0% (0/3)
Year ≥ 3	99	275.0	425.0	550.0	12.5	950	47.5% (47/99)	9.1% (9/99)
Total	1560	150	200	300	12.5	1600	41.6% (649/1560)	2.4% (38/1560)

Supplementary Table S6 Clozapine-associated myocarditis outcomes in the first 30 days

	Dose (mg/day)						Severity	
	N	P_{25}	Median	P_{75}	Min.	Max.	Seriousness	Fatalities
Day 1	4	34.375	112.5	162.5	12.5	175	25% (1/4)	0% (0/4)
Day 2	12	12.5	112.5	200.0	12.5	300	25% (3/12)	0% (0/12)
Day 3	6	12.5	37.5	100.0	12.5	100	0% (0/6)	0% (0/6)
Day 4	10	100.0	212.5	350.0	37.5	400	20% (2/10)	0% (0/10)
Day 5	11	100.0	150.0	225.0	25.0	300	36.4% (4/11)	0% (0/11)
Day 6	9	62,5	150.0	200.0	50	500	44.4% (4/9)	0% (0/9)
Day 7	17	37.5	125.0	237.5	12.5	300	23.5% (4/17)	0% (0/17)
Day 8	26	75.0	100.0	250.0	12.5	400	50% (13/26)	0% (0/26)
Day 9	19	100.0	175.0	225.0	25.0	350	26.3% (5/19)	0% (0/19)
Day 10	33	112.5	200.0	243.5	12.5	600	36.4% (12/33)	0% (0/33)
Day 11	34	118.5	200.0	250.0	25.0	800	35.3% (12/34)	2.9% (1/34)
Day 12	63	100.0	200.0	275.0	12.5	450	28.6% (18/63)	0% (0/63)
Day 13	89	150.0	175.0	265.0	12.5	1600	37.1% (33/89)	2.2% (2/89)
Day 14	118	131.5	200.0	250.0	12.5	500	39.0% (46/118)	2.5% (3/118)
Day 15	112	150.0	200.0	250.0	12.5	650	35.7% (40/112)	3.6% (4/112)
Day 16	96	153.5	200.0	300.0	12.5	500	44.8% (43/96)	1% (1/96)
Day 17	118	150.0	200.0	250.0	12.5	400	39.8% (47/118)	2.5% (3/118)
Day 18	102	150.0	200.0	275.0	12.5	500	47.1% (48/102)	2.9% (4/102)
Day 19	80	150.0	200.0	250.0	12.5	400	45.0% (36/80)	1.3% (1/80)
Day 20	81	150.0	200.0	250.0	12.5	600	49.4% (40/81)	3.7% (3/81)
Day 21	75	150.0	200.0	262.5	12.5	900	46.7% (35/75)	0% (0/75)
Day 22	45	175.0	225.0	300.0	37.5	475	48.9% (22/45)	6.7% (3/45)
Day 23	27	150.0	225.0	300.0	12.5	400	37.0% (10/27)	3.7% (1/27)
Day 24	34	175.0	225.0	300.0	37.5	600	38.2% (13/34)	2.9% (1/34)
Day 25	29	100.0	200.0	262.5	12.5	400	51.7% (15/29)	0% (0/29)
Day 26	12	150.0	200.0	300.0	50.0	400	41.7% (5/12)	0% (0/12)
Day 27	12	150.0	250.0	300.0	75.0	400	66.7% (8(12)	0% (0/12)
Day 28	12	150.0	212.5	300.0	25.0	350	41.7% (5/12)	0% (0/12)
Day 29	5	125.0	300.0	325.0	75.0	350.0	20.0% (1/5)	0% (0/5)
Day 30	18	200.0	300.0	350.0	75.0	550	55.6% (10/18)	0% (0/18)
Total	1309	150	200.0	250.0	12.5	1600	40.9% (535/1309)	2.1% (27/1309)

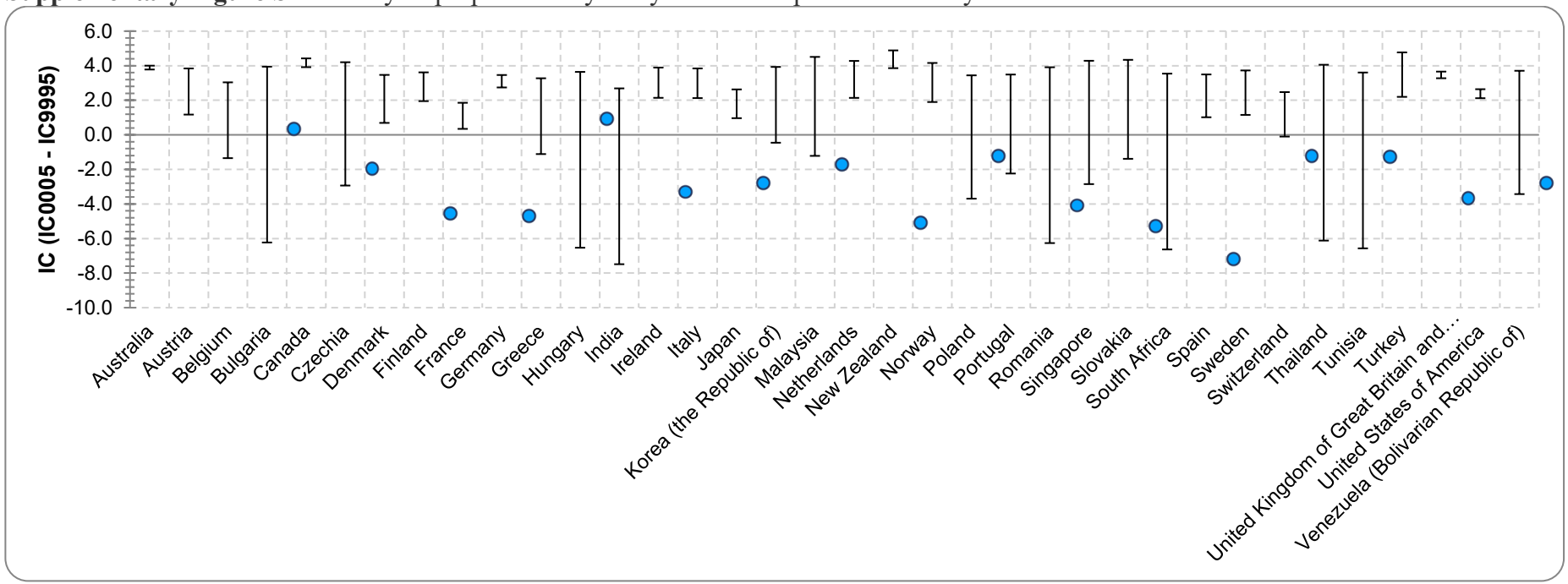
Supplementary Figure S1 Yearly disproportionality analysis for clozapine-associated myocarditis[a]



CI, confidence interval; IC, information component.

[a]Graphic representation of the strength of association between clozapine and myocarditis using IC until January 15, 2021.

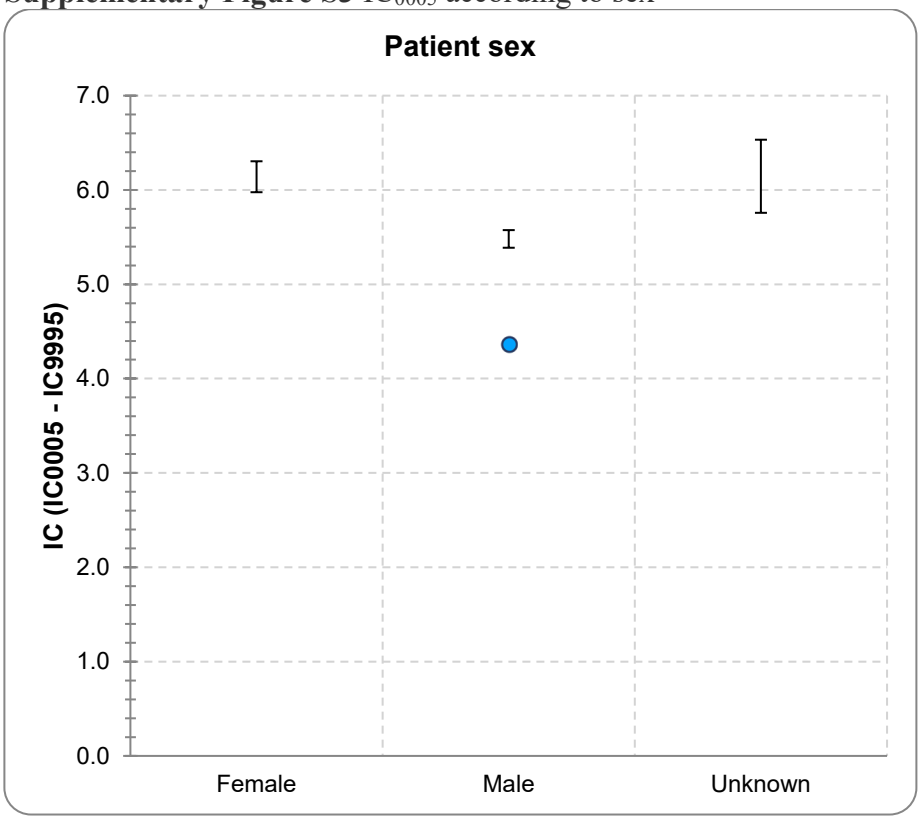
Supplementary Figure S2 Country disproportionality analysis for clozapine-induced myocarditis[a]



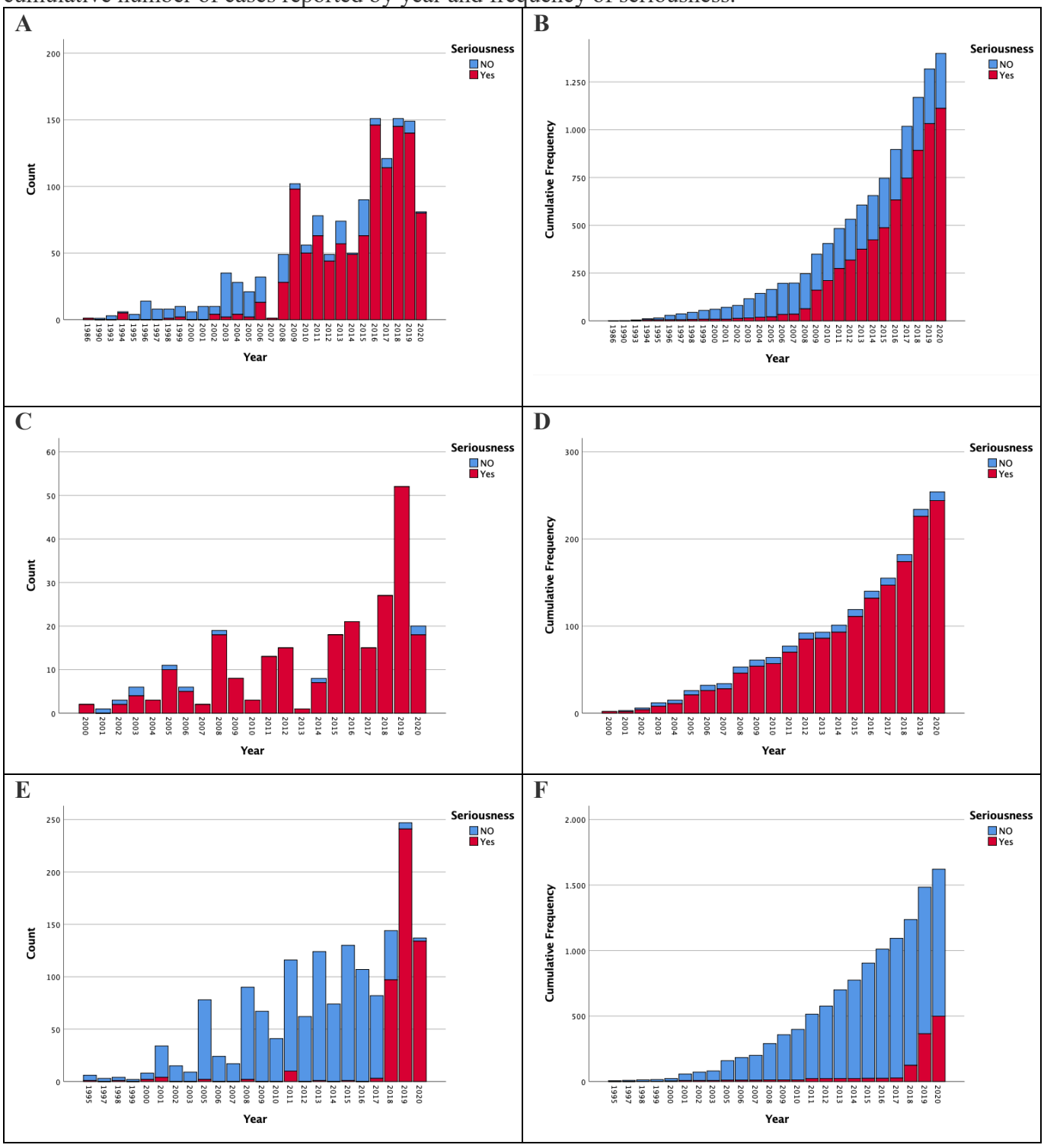
CI, confidence interval; IC, information component, IC.

[a]IC_{0005} is used to support analysis of subgroup-specific associations between substances and effects.

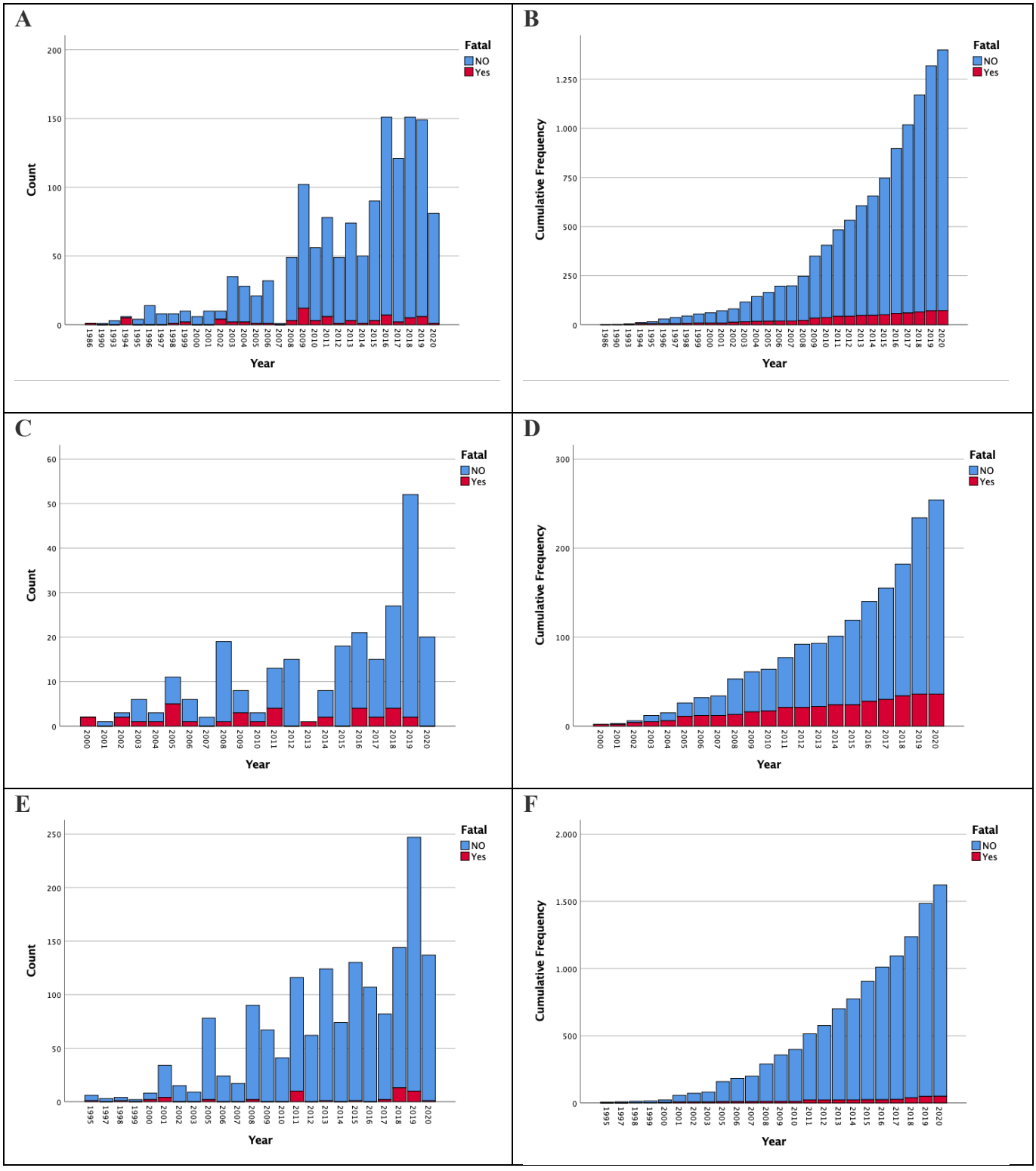
Supplementary Figure S3 IC_{0005} according to sex



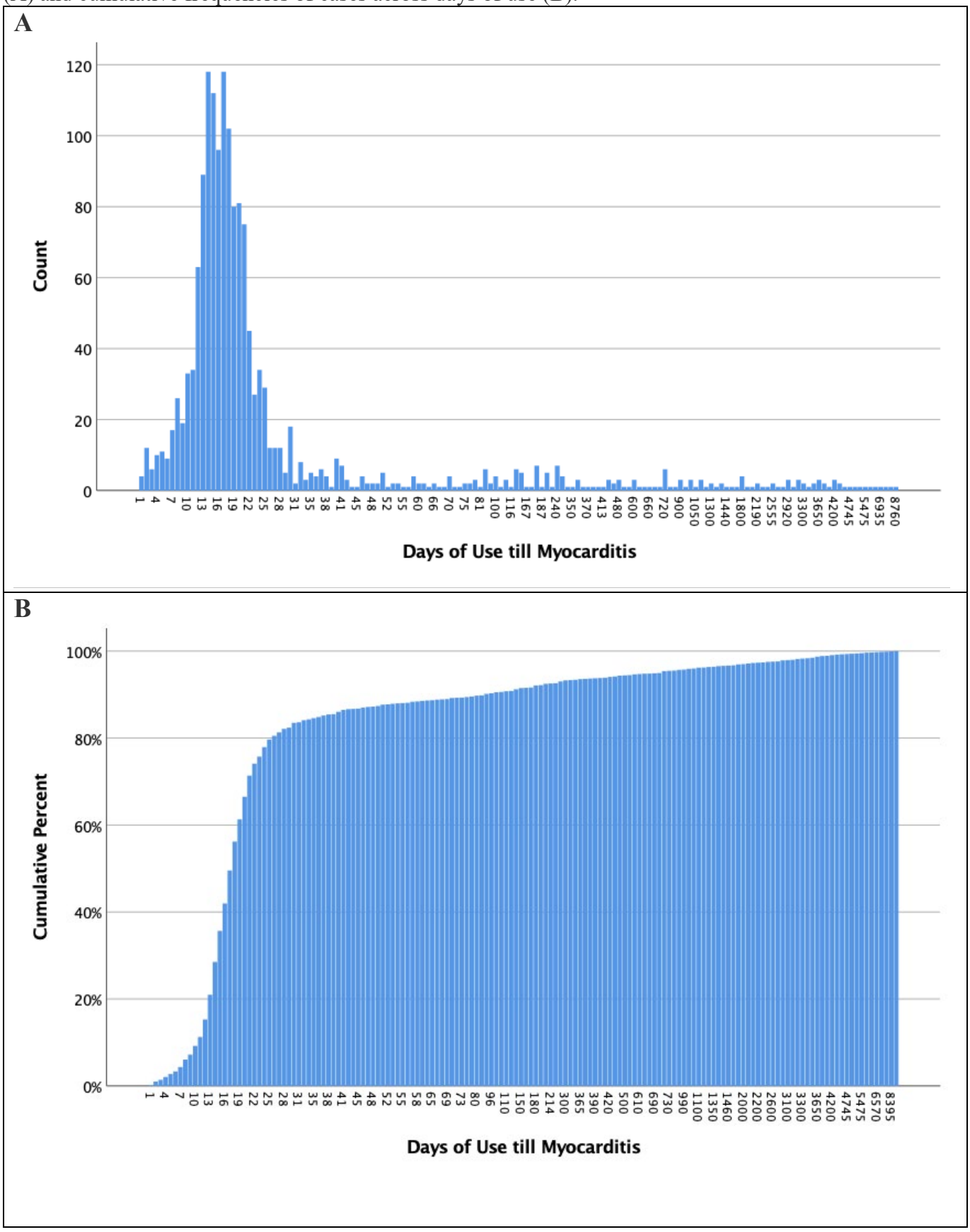
Supplementary Figure S4 Yearly evolution of clozapine-associated myocarditis and seriousness of outcome. After excluding Australia and the USA (A, B), in the USA (C, D), and in Australia (E, F), A, C & E show stacked bar charts representing annual reporting cases by seriousness. B, D & F show the cumulative number of cases reported by year and frequency of seriousness.



Supplementary Figure S5 Years of evolution of clozapine- associated myocarditis and fatal outcomes. After excluding Australia and the USA (A, B), in the USA (C, D), and in Australia (E, F), A, C & E show stacked bar charts representing annual reporting cases by fatality. B, D & F show the cumulative number of cases reported by year and frequency of fatality.



Supplementary Figure S6 Days of clozapine use until diagnosis of myocarditis.
(A) and cumulative frequencies of cases across days of use (B).



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