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Article *in* Schizophrenia Research · November 2023

DOI: 10.1016/j.schres.2023.10.027

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Clozapine-associated pericarditis and pancreatitis in children and adolescents: A systematic literature review and pharmacovigilance study using the VigiBase database

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ARTICLE INFO

Keywords:
Clozapine/administration and dosage
Clozapine/adverse effects
Clozapine/toxicity
Pancreatitis
Pericardial effusion
Pericarditis

ABSTRACT

Background: The literature has paid very little attention to pericarditis, pericardial effusion and pancreatitis during clozapine treatment in children and adolescents.
Methods: Cases of clozapine-associated pericarditis and pancreatitis in children were studied using searches in: 1) PubMed (June 16, 2023), and 2) the World Health Organization's pharmacovigilance database (June 1, 2022), VigiBase. VigiBase uses a logarithmic measure of disproportionality called the information component (IC).
Results: The PubMed search yielded 3 clozapine-associated pericarditis cases, 1 pancreatitis case and 1 with both. VigiBase provided a significant clozapine-associated pericarditis IC = 3.6 with an IC_{025} = 2.9 (only 3 cases were expected while 22 were observed). VigiBase provided a significant clozapine-associated pancreatitis IC = 2.2 with an IC_{025} = 1.4 (only 3 cases were expected while 16 were observed). In VigiBase clozapine-associated pericarditis and pericardial effusion in youth looked similar and on a continuum with myocarditis, as myocarditis, pericarditis and pancreatitis appeared to occur mainly during clozapine titration. Combining PubMed and VigiBase we identified: 1) 29 cases of at least possible clozapine-associated pericarditis/pericardial effusion (6 probable and 23 possible) including 7 cases with and 22 without myocarditis, and 2) 17 cases of clozapine-associated pancreatitis (1 definite and 16 possible). Two of the pancreatitis cases occurred during overdoses. No fatal outcomes were found in any clozapine-associated pericarditis and pancreatitis cases.
Conclusions: Despite the lack of attention in the literature to clozapine-associated pericarditis and pancreatitis, results demonstrate that they can happen in youth, particularly during titration. Pericarditis and pancreatitis appear to be forms of clozapine-associated inflammation during dose titration.

1. Introduction

Clozapine was identified in 1959 and then prescribed by several clinicians who found it relatively toxic. After some small randomized clinical trials (RCTs) clozapine was marketed in German-speaking countries and then in Scandinavian countries (de Leon et al., 2022a). In 1975, a Finnish case series of 18 patients including 16 with agranulocytosis, of which 8 died (Idänpään-Heikkilä et al., 1975), derailed clozapine use and led to the cessation of studies in the United States (US).

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https://doi.org/10.1016/j.schres.2023.10.027
Received 31 July 2023; Received in revised form 25 October 2023; Accepted 25 October 2023

For those who focus on evidence-based medicine (EBM), it would be surprising that a case series, a study with such low-level evidence had this massive impact on a drug's use. On the other hand, the most expert medical scientists (Vandenbroucke, 2004; Ioannidis, 2009) are very aware that the EBM approach used in RCTs has not been successful in the area of adverse drug reactions (ADRs). RCTs are the cornerstone of drug evaluation but are designed to demonstrate efficacy of drugs and not the second element of the risk-benefit balance of ADRs, especially pertaining to low incidence but severe and long-term effects. Thus, the science of ADRs rests much more on what is called pharmacovigilance during post-marketing surveillance (Montastruc et al., 2019) which includes published articles and spontaneous reports to national drug agencies. All national drug agencies send their reports to the pharmacovigilance database of the World Health Organization (WHO), called VigiBase. In a comprehensive review of reasons that 133 drugs were withdrawn between 1990 and 2010, Craveiro et al. (2020) reported that 65 % were due to spontaneous reports and/or case reports while RCTs only accounted for 18 %.

The description of agranulocytosis was the first potentially lethal clozapine ADR identified by pharmacovigilance; it took the effort of Hippius and other continental European supporters of clozapine to keep clozapine barely alive in some European countries (de Leon et al., 2022a). In 1982, clozapine's marketer planned to obtain US approval from the Food and Drug Administration (FDA) by focusing on patients with treatment-resistant schizophrenia (TRS) since it was thought that clozapine, due to the potentially fatal risk of agranulocytosis, was too risky for cases of schizophrenia other than those that were TRS (Honigfeld, 2024). The FDA-approved RCT for clozapine use in TRS: (1) started in 1984 at 16 US sites, (2) was extremely successful, and (3) was published in 1988 (Kane et al., 1988). This positive study showing the superior efficacy of clozapine over chlorpromazine led to US approval including required weekly white blood cell (WBC) monitoring to identify and reduce the risk of agranulocytosis. In 1989, there was limited knowledge of clozapine metabolism, but in 1994 Swedish pharmacologists described clozapine as mainly metabolized by the cytochrome P450 1A2 (CYP1A2) (Bertilsson et al., 1994). The US package insert has not kept up with further advances in clozapine pharmacokinetics (de Leon et al., 2020a).

1.1. The protracted history of clozapine-associated inflammation

Clozapine-associated fever during titrations in the absence of infections was first described in 1972 by German psychiatrists (Blum and Mauruschat, 1972) and developed in approximately 5 % of the early German patients taking clozapine (Gaertner et al., 1989; Naber et al., 1989). Helmchen (1989) described fever occurring between the 5th and 20th treatment days that was frequently associated with an increase in the erythrocyte sedimentation rate; this represented the first article associating clozapine-associated fever with inflammation. Then Vesterby et al. (1980) published the first case of myocarditis associated with clozapine in a patient started on clozapine 300 mg/day without any titration. Kilian et al. (1999) published 23 myocarditis cases associated with clozapine treatment from the Australian pharmacovigilance program. This article further contributed to spreading the notoriety of clozapine toxicity. After initial skepticism from pharmacovigilance agencies, in 2002 a myocarditis warning was added to the US clozapine package insert (de Leon et al., 2020a). The Canadian authors Devarajan et al. (2000) commented on Killian's cases, that "in all cases, daily clozapine doses were increased rapidly" and that the Australian titrations were much faster than their Canadian clozapine titrations.

Currently, it is clear that manifestations of clozapine-associated inflammation due to rapid titration may include a wide variety of presentations including (Verdoux et al., 2019; de Leon, 2022): 1) systemic inflammatory processes: fever, fever with isolated C-reactive protein (CRP) elevation, or lupus erythematosus, 2) localized signs of inflammation: myocarditis, serositis, pneumonitis/alveolitis, hepatitis, pancreatitis, nephritis, colitis and dermatological disorders. This classification is somewhat arbitrary since these presentations may lie on a continuum with no clear-cut boundary between them. In that sense, a series of reviews and pharmacovigilance studies by de Filippis et al. (2020, 2021, 2022) indicated that a clozapine-related drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome may be another manifestation of clozapine-associated inflammation during a dose titration that was too rapid. None of these DRESS cases included children or adolescents.

1.2. The complex problem of defining a rapid clozapine titration

Clozapine metabolism is influenced by 3 sets of variables: 1) ancestry groups, 2) sex-smoking subgroups and 3) the presence or absence of factors associated with clozapine poor metabolizer (PM) status (de Leon et al., 2022b). Thus, there is no easy way to define a rapid titration since the ability to tolerate a rapid titration may be influenced by these three sets of variables. A recent international guideline has proposed 6 titrations for 3 ancestry groups (Asians, Europeans and Africans) and the presence or absence of PM status. Within each of the 6 titrations there are specific recommendations for weeks 3 and 4 for sex-smoking subgroups with female non-smokers having their titration stopped at a lower dose and male smokers treated with the highest clozapine dose within that titration schedule (de Leon et al., 2022b).

Elevations of CRP and serum clozapine concentrations during rapid titration for the specific ancestry and sex-smoking subgroup of the patient have been described in small samples of clozapine-associated myocarditis in the US (Koenig et al., 2022) and Turkey (Ertuğrul et al., 2022). More recently, individual cases of elevations of CRP and serum clozapine concentrations during rapid titration have been described in patients of Asian ancestry (Danilewitz et al., 2021). Thereafter, a large multicenter study in Japan demonstrated that clozapine-associated inflammatory adverse events were less frequent in Japanese individuals when a titration rate was more gradual than the protocol recommended in the Japanese package insert (Kikuchi et al., 2024).

1.3. Clozapine-associated cases of myocarditis in VigiBase: children and adolescents

In a prior article focused on clozapine-associated myocarditis in children and adolescents (age $\leq$ 18 years), De Las Cuevas et al. (2022a) identified 9 cases from a PubMed search and 72 cases from VigiBase. Of these 72 cases, 67 did not overlap with published cases. These 76 combined cases included 35 doubtful (most with missing information on the day of diagnosis), 19 possible and 22 probable cases, according to the ADR scale. These 41 cases of at least possible clozapine-associated myocarditis indicated that this ADR can definitively occur in youth, particularly in the first 30 days of up-titration. The risk factors appear to be similar in youth (De Las Cuevas et al., 2022a) and adult cases (De Las Cuevas et al., 2022b). After adjusting for confounders, quetiapine increased the risk of seriousness with an odds ratio (OR) of 17.6 (95 % confidence interval CI, 1.56 to 198.6) while Australian origin decreased it with an OR = 0.13 (CI, 0.04 to 0.47) (De Las Cuevas et al., 2022a).

1.4. The neglect of clozapine-associated pericarditis and pancreatitis in children and adolescents

The neglect of clozapine-associated pancreatitis and pericarditis in children and adolescents is evident based on several studies and reviews. In a broad review article about drug-induced pancreatitis Balani and Grendell (2008) explored the few data existing on the mechanisms of drug-induced pancreatitis. The authors concluded that certain subpopulations such as children and adolescents, women, the elderly and patients affected by advanced HIV infection or inflammatory bowel disease may be at higher risk of developing drug-induced pancreatitis,

including clozapine among the possible causes. However, there are no studies investigating the relationship between clozapine and pancreatitis in children and adolescents, although this relationship is known and plausible, and therefore long overdue (Wilmink and Frick, 1996; Sosnowski et al., 2022). A review article (Wehmeier et al., 2005), conducted a Medline search using the key words myocarditis, pericarditis, cardiomyopathy and clozapine with the goal of exploring the frequency of these ADRs in patients treated with clozapine trying to shed further light on the issue. This particular review identified a total of 65 cases of myocarditis, 6 cases of pericarditis, and 52 cases of cardiomyopathy during treatment with clozapine in the literature, but the authors found only one case of pancreatitis followed by pericardial effusion in a 17-year-old adolescent treated with clozapine (Wehmeier et al., 2003).

Therefore, considering the scarcity of information regarding clozapine-associated pericarditis and pancreatitis in children and adolescents (aged ≤18 years), we conducted two separate literature searches. Firstly, we searched in PubMed to identify any published cases. Secondly, we explored VigiBase dataset to find cases reported to national drug agencies, which were subsequently submitted to VigiBase.

2. Methods

2.1. The search for articles

A search was conducted in PubMed on June 16, 2023, to identify cases of clozapine-associated pericarditis, pericardial effusion and pancreatitis in children and adolescents. The search yielded a total of 9 articles, of which 1 contained both a case of pericarditis and pancreatitis and, therefore, counted only once among the cases of pericarditis (Wehmeier et al., 2003) (see Box 1). Of these 9 articles, 4 articles (Sepúlveda Vildósola et al., 1999; Wehmeier et al., 2004; Hebebrand, 2009; McFadden et al., 2016) were excluded, while 5 articles (Frankenburg and Kando, 1992; Kay et al., 2002; Wehmeier et al., 2003; Branik and Nitschke, 2004; Crews et al., 2010) were included for further analysis. Overall, the analysis identified 4 published cases of clozapine-associated pericarditis or pericardial effusion, and 1 published case of clozapine-associated pancreatitis in youth, which are summarized in Table 1.

2.2. VigiBase search

Records dating from the inception of the database until June 1, 2022, were searched by the second and third authors to identify cases of pericarditis (or pericardial effusion) and pancreatitis in children or adolescents taking clozapine. Any cases suspected to be associated with clozapine in patients younger than 19 years of age were selected. Thereafter, all individual reports were scrutinized by the first, second and last authors. The study follows the principles of the Helsinki Declaration. This is a retrospective review of deidentified patient data worldwide that does not require the signed consent of the individual patient according to the ethics of the institutional review board of the second and third author's university. The second and third authors accessed the VigiBase data.

2.3. Significant differences in the VigiBase information component (IC)

A Bayesian confidence propagation neural network provides VigiBase with a statistical indicator called the information component (IC). The IC identifies combinations of particular drugs and ADRs that are present more frequently than expected. The IC is estimated based on all the reports for particular drugs and ADRs, and the total number of reports in the database (Norén et al., 2013). An IC = 0 indicates a drug-ADR combination for which the number of observed cases is the same as those expected from the overall reporting. An IC > 0 indicates that the drug-ADR combinations are reported more frequently than expected. An IC < 0 indicates that the drug-ADR combination are reported less frequently than expected. The sampling variability of ICs is represented by their confidence intervals (CIs). A high IC value, in addition to a high IC_{025} (lower 97.5 % CI), denotes a strong statistical association between the antipsychotic and ADRs in the database. Moreover, when the IC_{025} is positive (>0), this indicates a statistically significant disproportionality between the expected and the reported rates for a drug and an ADR (Norén et al., 2013).

2.4. Scoring other clozapine-associated pancreatitis and pericarditis cases using an ADR scale

Two main causality criteria (exclusion of other causes and a temporal relationship including rechallenge) are used by ADR scales such as the Naranjo scale (Naranjo et al., 1981). When the score of the 10-item Naranjo scale is ≥9, the ADR is definite. When the score is 5–8 the ADR is probable. When the score is 1–4 the ADR is possible. When the score is ≤0, the ADR is doubtful. The first and last authors scored cases obtained from the article and VigiBase searches using the Naranjo scale. They cut and pasted the information relevant for each item into a form developed for each individual patient and justified the score of each item on the form so that it could be reviewed for agreement by the rest of the authors, who were asked to discuss with the first and last authors any

Box 1
PubMed searches (June 9, 2023).

1. Search for clozapine and (pericarditis OR pericardial effusion)
Limit Child: birth-18 years: 6 articles

- 2 were excluded:
  - 1 article included inflammation with other antipsychotics in children (Hebebrand, 2009)
  - 1 article did not include any cases of clozapine-associated pericarditis (Wehmeier et al., 2004).
- 4 were included (Crews et al., 2010; Branik and Nitschke, 2004; Wehmeier et al., 2003; Kay et al., 2002) and were listed in Table 1. One article provided 1 case with both pericarditis and pancreatitis (Wehmeier et al., 2003)

2. Search for clozapine and pancreatitis
Limit Child: birth-18 years: 4 articles

- 3 were excluded:
  - 1 case with both pericarditis and pancreatitis (Wehmeier et al., 2003); it was included in Table 1 as presenting both types of inflammations.
  - 2 cases of pancreatitis by other drugs (McFadden et al., 2016; Sepúlveda Vildósola et al., 1999)
- 1 was included (Frankenburg and Kando, 1992) and was listed in Table 1.

Table 1
Article search identified 3 cases of pericarditis, one of pericarditis and pancreatitis, and one of pancreatitis in children and adolescents using clozapine.

Author	Case	Age	Sex	Country	Diagnoses of pericarditis or pancreatitis	R/O	Dose/ duration mg/ day for time	Outcome	ADR scale
Branik and Nitschke, 2004	1	17	♀	Switzerland	**Pericarditis** Hypogastric pain (Blumberg's sign), retrosternal pains, nausea, vomiting, diarrheas, fever, ↑ CRP, ↑ Troponin-T, leukocytosis, eosinophilia, EKG, echocardiogram	R/O pathogens, rheumatological cause	Unknown/14 days	Recovery after withdrawn	7 – probable
Crews et al., 2010	2	17	♂	UK	**Pericarditis** Tachycardia, fever, gastrointestinal disturbance, ↑ CRP, echocardiogram, X-ray	R/O viral infection	350[a]/4/ weeks	Recovery after withdrawn. Successful clozapine slow rechallenge without recurrence of pericarditis[b]	3 – possible
Kay et al., 2002	3	16	♀	Australia	**Pericarditis** Mild fever, mild tachypnea, tachycardia, ↑ Troponin-I, EKG	R/O viral and bacterial infections	100/5 weeks[c]	Resolved despite continuation of clozapine	6 – probable
Wehmeier et al., 2003	4	17	♂	Germany	**Pericarditis and Pancreatitis** Mild epigastric pain, ↑ amylase, ↑ lipase,		175/23 days[d]	Recovery after withdrawn	8 – probable
Frankenburg and Kando, 1992	5	17	♀	USA	**Pancreatitis** Fever, nausea, vomiting, right upper quadrant pain, tachycardia, ↑ leucocytes, ↑ eosinophils, ↑ amylase, ↑ ALP, ↑ ESR	R/O gallbladder disease	100/2 weeks	Recovery after withdrawn	9 – definite

ALP, alkaline phosphatase; CRP, c-reactive protein; EKG, electrocardiogram; ESR, erythrocyte sedimentation rate; R/O, rule out.
[a] In divided doses.
[b] Second slower titration up (titration time unknown) to a clozapine dose of 400 mg/day with no adverse effects.
[c] Clozapine, 25 mg daily orally, was commenced 3 weeks prior, and increased to 100 mg daily over 2 weeks.
[d] Clozapine treatment commenced with an initial dose of 25 mg/day. Then, the dose was gradually increased to 175 mg/day in 23 days.

disagreement. Early titration is defined as happening within the first month (De Las Cuevas et al., 2022b) and yields, therefore, a positive score on item 1 ("Are there previous conclusive reports of this reaction?") of the Naranjo scale for a clozapine-associated ADR, during the first month of initiation.

For scoring item 10 ("Was the adverse event confirmed by any objective evidence?") of the Naranjo scale, we would have liked information that an ultrasound was used to diagnose pericarditis or pericardial effusion and pancreatic enzymes were used to diagnose pancreatitis. Most cases did not have precise information that an ultrasound was done but we agreed that currently in developed countries any patient diagnosed with pericarditis or pericardial effusion would require an ultrasound for that diagnosis. Thus, we scored an objective sign to be present when the patient had the diagnoses of pericarditis and/or pericardial effusion. Most cases did not have precise information that pancreatic enzymes were obtained but we agreed that currently in developed countries any patient diagnosed with pancreatitis would require pancreatic enzymes to diagnose pancreatitis. Thus, we score an objective sign to be present when the patient had the diagnosis of pancreatitis.

The forms for each patient (published and VigiBase cases) with detailed scores on the Naranjo scale are available in the Supplementary material. Table 1 describes the Naranjo scores for published cases and Tables S1–S3 the VigiBase cases.

2.5. Consideration of duplicate reports in VigiBase

All VigiBase standard analyses are contaminated by the possibility of some level of duplicate reports, and we have identified duplicate cases in all studies of myocarditis in VigiBase (De Las Cuevas et al., 2022a, 2022b, 2022c). Using VigiBase report IDs to avoid duplicates, the first and last authors identified 34 possible cases of clozapine-associated pericarditis or pericardial effusion in youth. The detailed reviews performed for the Naranjo scale scoring by the first and last authors were used to identify 1 duplicate leading to 33 different cases of clozapine-associated pericarditis or pericardial effusion in children. We grouped together pericarditis and pericardial effusion since they appear to have the same type of clinical presentation. Similarly, the first and last authors identified 2 duplicated cases among 18 possible cases of clozapine-associated pancreatitis in children leading to 16 non-duplicated cases.

2.6. Inability to explore variables associated with fatal and serious outcomes in VigiBase data

We have conducted three studies of myocarditis associated with antipsychotics (De Las Cuevas et al., 2022a, 2022b, 2022c) and we used logistic regression models to explore variables associated with fatal (yes/no) outcomes. There were no fatal outcomes in cases of pericarditis/pericardial effusion or pancreatitis; thus, variables associated with fatal outcomes could not be explored. Similarly, in prior studies (De Las Cuevas et al., 2022a, 2022b, 2022c) logistic regression models were used to explore variables associated with serious (yes/no) outcomes. All cases of pancreatitis with data were serious and all cases except one were serious among those with pericarditis/pericardial effusion. As an alternative to logistic regression models from prior studies, Table 4 was developed with a clinical description of major variables that were potentially associated with seriousness or fatal outcomes in prior VigiBase myocarditis articles (De Las Cuevas et al., 2022a, 2022b, 2022c) including: US (yes/no), Australia (yes/no), sex, age, clozapine dose, duration of clozapine titration, presence/absence of 3 major co-medications: valproate, olanzapine, quetiapine in 4 groups of patients. Three groups came from this present article: pancreatitis, pericarditis/pericardial effusion without myocarditis, pericarditis/pericardial effusion with myocarditis and the fourth group, myocarditis without pericarditis/pericardial effusion, came from a prior article using the same VigiBase search (De Las Cuevas et al., 2022a).

3. Results

3.1. ADR scoring of cases from published articles

Table 1 shows 5 published cases. There were 3 cases of clozapine-associated pericarditis: 2 probable and 1 possible. There was a probable case of clozapine-associated pericarditis and pancreatitis in the same patient. There was a definite case of clozapine-associated pancreatitis.

3.2. Statistical analyses in VigiBase using ICs

In Table 2, clozapine-associated pericarditis occurred in 22 observed cases versus 1 expected, with an IC = 3.6 and with an IC_{025} = 2.9. Pancreatitis occurred in 16 observed cases versus 3 expected with an IC = 2.2 and with an IC_{025} = 1.4. These numbers were lower than those of clozapine-associated myocarditis, which occurred in 72 observed versus only 4 cases expected, with an IC = 4.2 and with IC_{025} = 3.8.

3.3. ADR scoring of VigiBase cases

Supplementary Table S1 describes 10 non-duplicated cases of clozapine-associated pericarditis/pericardial effusion with myocarditis in youth.

Supplementary Table S2 describes 23 non-duplicated cases of clozapine-associated pericarditis/pericardial effusion without myocarditis in youth. Two of them were the same case published by Crews et al. (2010) or Kay et al. (2002) leaving 21 previously unpublished cases.

Supplementary Table S3 describes 16 non-duplicated cases of clozapine-associated pancreatitis in youth. Five of these cases of clozapine-associated pancreatitis were peculiar (1 neuroleptic malignant syndrome in the context of valproic acid co-prescription, 1 clozapine overdose, 1 polydrug overdose with valproic acid and 2 in the presence of valproic acid co-prescription).

3.4. Demographic and clinical characteristics of non-duplicated VigiBase cases

Table 3 describes the demographic and clinical characteristics of the 49 non-duplicated cases from VigiBase. There were 33 cases with clozapine-associated pericarditis/pericardial effusion and 16 with pancreatitis. The age range was from 12 to 17 years old in 33 cases with pericarditis/pericardial effusion and 10 to 17 years old in 16 cases with pancreatitis. Of 33 cases with pericarditis/pericardial effusion, 27 had data on seriousness and all except one were serious. Of 16 cases with clozapine-associated pancreatitis, 10 had data on seriousness and all 10 were serious. There were no fatal outcomes.

There were no myocarditis cases among patients with pancreatitis but almost one third of the 33 cases with pericarditis/pericardial effusion also had myocarditis. In the 33 cases with pericarditis/pericardial effusion, the most frequently reported symptom was chest pain in 21 % of the cases. This was very similar to 22 % (16/72) with chest pain in clozapine-associated myocarditis in children from a prior article (De Las Cuevas et al., 2022a). In cases of pancreatitis, the most frequent symptoms/signs were laboratory abnormalities.

3.5. Comparison of 4 subgroups of inflammations associated with clozapine

Table 4 shows that among clozapine-associated inflammations in youth, the prior article (De Las Cuevas et al., 2022a) described one fatal outcome in 64 patients with myocarditis without pericarditis. On the other hand, no fatal outcomes were reported among the three groups of patients described in this article (16 with pancreatitis, 23 with pericarditis and no myocarditis and 10 with pericarditis and myocarditis). Regarding geographical distribution, the US appears to be relatively overrepresented among pancreatitis cases and Australia appear to be relatively overrepresented in cases of myocarditis without pericarditis. There were no obvious differences in sex and age among the 4 groups.

Duration information is limited by missing data but the median durations in cases of pancreatitis (34 days) and pericarditis without myocarditis (30 days) stand out. Finally, co-medication with olanzapine, quetiapine or valproate appears to be frequently reported.

3.6. At least 29 possible cases of pericarditis/pericardial effusion associated with clozapine

Table 1 reflects that the article search that yielded 3 cases of at least possible clozapine-associated pericarditis (1 probable and 2 possible cases).

Supplementary Tables S1 and S2 describe that the VigiBase search yielding 10 cases of pericarditis with myocarditis and 21 cases of clozapine-associated pericarditis/pericardial effusion without myocarditis that had never been published.

Among cases of pericarditis with myocarditis, there were 3 cases that are doubtful, leaving 7 cases that were at least possible (3 probable and 4 possible). Regarding clozapine-associated cases of pericarditis/pericardial effusion without myocarditis, after duplicate removal, there were 2 cases that were doubtful, leaving 19 that were at least possible (2 probable and 17 possible).

In conclusion, by combining both data sources (PubMed and VigiBase) we had 29 cases of at least possible clozapine-associated pericarditis/pericardial effusion (6 probable and 23 possible) including 7 cases with and 22 without myocarditis.

3.7. At least 17 possible cases of pancreatitis associated with clozapine

Table 1 describes the article search that provided 1 case of a definite clozapine-associated pancreatitis. Supplementary Table S3 shows that VigiBase provided 16 cases of clozapine-associated pancreatitis that had never been published. All 16 cases identified through the VigiBase search were deemed as possible according to the Naranjo scale. Thus, by adding both data sources we identified 17 cases of clozapine-associated pancreatitis (1 definite and 16 possible).

Table 2
Disproportionality results of 2820 clozapine ADRs including myocarditis in children and adolescents (0–18 years) from a total of 2,230,637 ADR reports in children and adolescents. A VigiBase search (June 1, 2022).

	$N_{observed}$	$N_{expected}$	Total reports[a]	IC	IC_{025}
ADRs associated with inflammatory processes					
Myocarditis	72	4	2770	4.18	3.82
Pericarditis	22	1	1119	3.55	2.89
Pancreatitis	16	3	2396	2.22	1.43

ADR: adverse drug reaction; IC: information component; IC_{025}: lower 97.5 % confidence interval of IC.
[a] Total reports is the number of this ADR reported for all drugs in VigiBase.

Table 3
Demographic and clinical variables of VigiBase sample.

	All cases (N = 49)	Pericarditis/pericardial effusion (N = 33)	Pancreatitis (N = 16)
	% (N/N total)	% (N/N total)	% (N/N total)
3 continents and 11 countries			
Oceania	24.5 % (12/49)	30.3 % (10/33)	12.5 % (2/16)
Australia	20.4 % (10/49)	24.2 % (8/33)	12.5 % (2/16)
New Zealand	4.1 % (2/49)	6.1 % (2/33)	–
Europe	49.0 % (24/49)	60.6 % (20/33)	25.0 % (4/16)
United Kingdom	10.2 % (5/49)	15.2 % (5/33)	–
Germany	24.5 % (12/49)	27.3 % (9/33)	18.8 % (3/16)
Finland	4.1 % (2/49)	6.1 % (2/33)	–
France	4.1 % (2/49)	3.0 % (1/33)	6.3 % (1/16)
Italy	2.0 % (1/49)	3.0 % (1/33)	–
Norway	2.0 % (1/49)	3.0 % (1/33)	–
Spain	2.0 % (1/49)	3.0 % (1/33)	–
North America	26.5 % (13/49)	9.1 % (3/33)	62.5 % (10/16)
United States	24.5 % (12/49)	6.1 % (2/33)	62.5 % (10/16)
Canada	2.0 % (1/49)	3.0 % (1/33)	–
Age			
Mean ± SD	15.6 ± 1.7	16.0 ± 1.3	14.6 ± 2.2
Median (P25–P75)	16.0 (15.0–17.0)	16.0 (15.5–17.0)	15.0 (13.3–16.8)
10 years	2.0 % (1/49)	–	6.3 % (1/16)
11 years	2.0 % (1/49)	–	6.3 % (1/16)
12 years	4.1 % (2/49)	3.0 % (1/33)	6.3 % (1/16)
13 years	2.0 % (1/49)	–	6.3 % (1/16)
14 years	12.2 % (6/49)	12.1 % (4/33)	12.5 % (2/16)
15 years	14.3 % (7/49)	9.1 % (3/33)	25.0 % (4/16)
16 years	24.5 % (12/49)	30.3 % (10/33)	12.5 % (2/16)
17 years	38.8 % (19/49)	45.5 % (15/33)	25.0 % (4/16)
Sex			
Male	55.1 % (27/49)	54.5 % (18/33)	56.3 % (9/16)
Female	44.9 % (22/49)	45.5 % (15/33)	43.8 % (7/16)
Psychiatric diagnosis			
*Missing	42.9 % (21/49)	36.4 % (12/33)	56.3 % (9/16)
*Present	57.1 % (28/49)	63.6 % (21/33)	43.8 % (7/16)
Schizophrenia and related disorders	82.1 % (23/28)	90.5 % (19/21)	57.1 % (4/7)
Bipolar disorder	14.3 % (4/28)	4.8 % (1/21)	42.9 % (3/7)
Obsessive compulsive disorder	3.6 % (1/28)	4.8 % (1/21)	–
Diagnoses			
Pericardial effusion/pericarditis			
With myocarditis	20.4 % (10/49)	30.3 % (10/33)	NA
Without myocarditis	46.9 % (23/49)	69.7 % (23/33)	NA
Pancreatitis	32.7 % (16/49)	NA	100 % (16/16)
Seriousness			
*Missing	24.5 % (12/49)	18.2 % (6/33)	37.5 % (6/16)
*Present	75.5 % (37/49)	81.8 % (27/33)	62.5 % (10/16)
Non-serious	2.7 % (1/37)	3.7 % (1/27)	–
Serious but non-fatal	97.3 % (36/37)	96.3 % (26/27)	100.0 % (10/10)
Signs and symptoms			
Chest pain	14.3 % (7/49)	21.2 % (7/33)	–
Fatigue	14.3 % (7/49)	21.2 % (7/33)	–
↑ creatine phosphokinase	12.2 % (6/49)	6.1 % (2/33)	25.0 % (4/16)
Pyrexia (fever according to VigiBase)	12.2 % (6/49)	15.2 % (5/33)	6.3 % (1/16)
↑ lipase	8.2 % (4/49)	–	25.0 % (4/16)
↑ c-reactive protein	6.1 % (3/49)	6.1 % (2/33)	6.3 % (1/16)
↑ hepatic enzymes	6.1 % (3/49)	3.0 % (1/33)	12.5 % (2/16)
↑ troponin	6.1 % (3/49)	9.1 % (3/33)	–
Eosinophilia	4.1 % (2/49)	6.1 % (2/33)	–
Dose (mg/day) at time of diagnosis			
*Missing	40.8 % (20/49)	27.3 % (9/33)	68.8 % (11/16)
*Present	59.2 % (29/49)	72.7 % (24/33)	31.3 % (5/16)
Mean ± SD	325.9 ± 532.1	245.8 ± 138.6	710.0 ± 1283.9
Median (P25–P75)	225.0 (100.0–337.5)	250.0 (112.5–343.8)	125.0 (62.5–1650.0)

(*continued on next page*)

Table 3 (*continued*)

	All cases (N = 49)	Pericarditis/pericardial effusion (N = 33)	Pancreatitis (N = 16)
	% (N/N total)	% (N/N total)	% (N/N total)
Days until inflammation			
*Missing	57.1 % (28/49)	57.8 % (19/33)	56.3 % (9/16)
*Present	42.9 % (21/49)	42.4 % (14/33)	43.8 % (7/16)
Mean ± SD	45.3 ± 50.9	53.4 ± 59.6	31.1 ± 24.2
Median (P25–P75)	28.0 (15.5–49.0)	27.5 (18.5–58.5)	34.0 (12.0–54.0)
≤30 days	57.1 % (12/21)	64.3 % (9/14)	42.9 % (3/7)
>30 days and ≤ 60 days	23.8 % (5/21)	14.3 % (2/14)	42.9 % (3/7)
>60 days	19.0 % (4/21)	21.4 % (3/14)	14.3 % (1/7)
Reported co-medication			
Only clozapine	67.3 % (33/49)	63.6 % (21/33)	75 % (12/16)
Clozapine + valproate + no antipsychotic	2.0 % (1/49)	3.0 % (1/33)	–
Clozapine + valproate +1 antipsychotic	2.0 % (1/49)	–	33.3 % (2/16)
Clozapine + valproate + ≥ 2 antipsychotics	12.2 % (6/49)	9.1 % (3/33)	33.3 % (2/16)
Clozapine + 1 antipsychotic + no valproate	14.3 % (7/49)	21.2 % (7/33)	–
Clozapine + ≥2 antipsychotics + no valproate	2.0 % (1/49)	3.0 % (1/33)	–
Valproate	16.3 % (8/49)	12.1 % (4/33)	25.0 % (4/16)
Aripiprazole[a]	12.2 % (6/49)	15.2 % (5/33)	6.3 % (1/16)
Olanzapine[a]	12.2 % (6/49)	15.2 % (5/33)	6.3 % (1/16)
Quetiapine[a]	12.2 % (6/49)	12.1 % (4/33)	12.5 % (2/16)
Haloperidol[a]	10.2 % (5/49)	9.1 % (3/33)	12.5 % (2/16)
Risperidone[a]	10.2 % (5/49)	3.0 % (1/33)	25.0 % (4/16)

NA, Not applicable; P25, 25th percentile; P75, 75th percentile; SD, standard deviation.
[a] Co-prescribed antipsychotic with at least 3 cases.

Table 4
Demographics and clinical variables: comparisons among groups of clozapine-associated inflammation in children in VigiBase.

Variable	Pancreatitis N = 16	Pericarditis without myocarditis N = 23	Pericarditis with myocarditis N = 10	Myocarditis without pericarditis N = 64
Fatal outcome (yes)	0 % (0/10)	0 % (0/17)	0 % (0/10)	1.6 % (1/64)
Seriousness (yes)	100.0 % (10/10)	100.0 % (17/17)	90 % (9/10)	53.1 % (34/64)
Australia (reporting country)	12.5 % (2/16)	26.1 % (6/23)	20 % (2/10)	43.8 % (28/64)
US (reporting country)	62.5 % (10/16)	8.7 % (2/23)	0 % (0/10)	7.8 % (5/64)
Female sex	43.8 % (7/16)	52.2 % (12/23)	30 % (3/10)	22.6 % (14/62)
Age (median, years)	15.0	17.0	16.0	17.0
Median duration (days)	34.0 (N = 7)	30.0 (N = 7)	19.0 (N = 7)	16.0 (N = 39)
Onset within 30 days	50 % (4/8)	57.1 % (4/7)	60 % (6/10)	85.0 % (34/40)
Median clozapine dose (mg/day)	125.0 (N = 5)	175.0 (N = 17)	300.0 (N = 7)	200.0 (N = 44)
Olanzapine co-prescription	6.3 % (1/16)	8.7 % (2/23)	30 % (3/10)	9.4 % (6/64)
Quetiapine co-prescription	12.5 % (2/16)	4.3 % (1/23)	30 % (3/10)	7.8 % (5/64)
Valproate co-prescription	25 % (4/16)	8.7 % (2/23)	20 % (2/10)	1.6 % (1/64)

mg: milligrams; US: United States.

3.8. At least 1 possible pericarditis and pancreatitis associated with clozapine

Table 1 identifies a probable case of clozapine-associated pericarditis followed by pancreatitis. No similar cases with both types of inflammations in youth were reported to VigiBase.

4. Discussion

4.1. Other clozapine-associated inflammations can definitively occur in youth

This article demonstrates that there are cases of clozapine-associated pericarditis/effusion in youth and that by combining the article and VigiBase search we were able to identify 29 cases that were at least possibly clozapine-associated cases. In order to assess our contribution to the literature we reviewed 5 relevant articles with information on clozapine ADRs in youth including a multicenter study (Steinauer et al., 2018), a clozapine protocol for children (Towbin et al., 1994), two systematic reviews of clozapine ADRs in children (Schneider et al., 2014; Adnan et al., 2022) and a clozapine narrative review (Rachamallu et al., 2019). Of these 5 articles, 3 did not mention clozapine-associated pericarditis or pericardial effusion. One of these articles (Rachamallu et al., 2019) described one of the published cases of clozapine-associated pericarditis (Branik and Nitschke, 2004) and another article (Schneider et al., 2014) listed another of the published cases (Wehmeier et al., 2004).

By combining the article and VigiBase search we identified 17 at least possible cases of clozapine-associated pancreatitis in youth. Our contribution to the literature is needed since none of these 5 relevant articles mentioned that clozapine ADR. Finally, our PubMed search identified a probable pediatric case of clozapine being associated with both pancreatitis and pericarditis. Five of the 16 cases of VigiBase clozapine-associated pancreatitis were complex in their presentation, including one with neuroleptic malignant syndrome, two associated with overdoses and four cases being complicated by co-prescribed valproic acid.

4.2. The possible problem of lack of diagnostic awareness

The data from Table 4 on duration is limited by missing data but appears to suggest that cases of pancreatitis and pericarditis without

myocarditis were associated with longer duration until identification than those of myocarditis. We suspect that myocarditis during clozapine titration is easier to identify because there is awareness of myocarditis among child and adolescent psychiatrists. Moreover, the Australian protocols include troponin measures that facilitate the diagnosis of subclinical myocarditis. Pancreatitis and pericarditis without myocarditis may be less expected by child and adolescent psychiatrists who may take longer to diagnose them. This interpretation of a lack of awareness contributing to a delay in the diagnosis is suggested by a Turkish study focused on myocarditis (Anıl Yağcıoğlu et al., 2019). All 9 cases of myocarditis were identified by an echocardiogram within the first few days after the symptoms started and always before day 30 of titration. On the other hand, a patient had signs of inflammation at day 14 but her ultrasound was normal on that day, so clozapine was continued until day 34, when the treating psychiatrist finally realized that the emerging pancreatitis (and hepatitis) were associated with the clozapine titration (Yildiz et al., 2021; Ertuğrul et al., 2022). The Turkish psychiatrists were aware of myocarditis during clozapine titrations after a fatal outcome had occurred in their hospital but were not expecting other types of inflammation during clozapine titrations. Thus, even in this Turkish study with high awareness of myocarditis, pancreatitis was not expected and took longer to be diagnosed.

In that regard, we recommend that child and adolescent psychiatrists measure and pay attention to CRP elevations during clozapine titrations (Wagner et al., 2023), which are the first signs of clozapine-associated inflammation. Once the CRP is elevated during the titration, slowing or stopping the clozapine titration may prevent further progression to myocarditis, pericarditis, pancreatitis or any other type of clozapine-associated inflammation (Shelton et al., 2022).

4.3. Limitations

First, pharmacovigilance databases are hampered by reporting biases from spontaneous reports and two of these may be important in this study: missing data and the effect of the country. If we assume that clozapine-associated inflammation events occurring in the first 30 days are typical of rapid titration, the lack of data regarding the day of the inflammation diagnosis is a problem. Table 3 indicates that more than half of the 49 patients were missing information on the time of diagnosis, including 27 % among pericarditis/pericardial effusion cases and 69 % in pancreatitis cases.

The effect of country includes the proneness of physicians and other people to report ADRs to their national drug agencies. Australian psychiatrists are very sensitive to mild cases of myocarditis (De Las Cuevas et al., 2022b) and this includes sensitivity to cases in children and adolescents, too (De Las Cuevas et al., 2022a). However, Australian psychiatrists do not appear to pay so much attention to pancreatitis (Table 4). The US provided more than half of the clozapine-associated pancreatitis cases (Table 4). This fact may reflect the US position as the top reporter of clozapine ADRs to VigiBase (De Las Cuevas et al., 2024).

Second, the interpretation of 5 of the 16 VigiBase cases of pancreatitis was extremely complex because the reporting did not provide time lines to aid in understanding the progression of complex presentations and also because of the contribution of valproic acid in four of these cases. The literature agrees that pancreatitis has been consistently associated with valproic acid (Gerstner et al., 2007) and this is true for children, too (Cofini et al., 2015). Two of the 16 pancreatitis cases occurred in the context of overdoses, while none of the 31 pericarditis cases that we reviewed in VigiBase were associated with overdoses. Overdoses can be considered massive rapid titrations. In adults, clozapine overdoses have been occasionally associated with myocarditis (De Las Cuevas et al., 2022b, 2022c). In adults, a few cases of quetiapine overdoses and very rarely massive overdoses of other antipsychotics have been associated with myocarditis (De Las Cuevas et al., 2022c).

Third, using a 30-day threshold for determining the presence or absence of ongoing titration in VigiBase was based on our VigiBase study of myocarditis (De Las Cuevas et al., 2022b). This threshold appeared wise for cases including myocarditis but it may not have been correct for pericarditis without myocarditis and pancreatitis. In these two presentations of clozapine-associated inflammation (i.e. pericarditis without myocarditis and pancreatitis), there were several cases where clozapine was discontinued a few days after day 30. This situation probably reflects delay in the diagnosis, but we did not want to modify the 30-day limit for diagnosing clozapine titration in VigiBase that we have established for myocarditis (De Las Cuevas et al., 2022b). In retrospect, future studies in VigiBase on clozapine-associated pancreatitis or clozapine-associated pericarditis without myocarditis may need to use a 40-day threshold for titration to allow for the longer time until diagnosis of these unexpected manifestations of clozapine-associated inflammation in youth.

Finally, VigiBase uses ICs for disproportionality analyses that consider the number of reports across drugs and within a drug, but that does not control for confounders and for duplicates, so that the ICs in Table 2 are somewhat confounded by duplicates. As far as we can tell, however, duplicates were a minor problem because our careful review of cases found only 1 duplication regarding cases with clozapine-associated pericarditis/pericardial effusion and 2 regarding clozapine-associated pancreatitis.

4.4. Implications

Previously published articles (Towbin et al., 1994; Schneider et al., 2014; Steinauer et al., 2018; Rachamallu et al., 2019; Adnan et al., 2022) provided limited or no mention of cases of clozapine-associated pericarditis/pericardial effusion in clozapine-treated youth. On the other hand, by combining published cases and never-published cases from VigiBase, we identified 23 cases with at least possible clozapine-associated pericarditis/pericardial effusion during the first 30 days of up-titration in youth. Based on these findings, clozapine-associated pericarditis in youth needs to receive more attention from child and adolescent psychiatrists.

The previously published articles (Towbin et al., 1994; Schneider et al., 2014; Steinauer et al., 2018; Rachamallu et al., 2019; Adnan et al., 2022) actually ignored clozapine-associated pancreatitis. By combining published cases and never-published cases from VigiBase, we identified 17 cases with at least possible clozapine-associated pancreatitis. Child and adolescent psychiatrists need to know that clozapine-associated pancreatitis occurs in youth.

4.5. Current guidelines for preventing clozapine-induced inflammation in youth

In our opinion, clozapine-associated pericarditis and pancreatitis during clozapine titrations are part of a broader pro-inflammatory syndrome that includes myocarditis, DRESS and other signs of inflammation. Manifestations of inflammation may be preventable by using slower, personalized clozapine titration schedules. Studies are starting to be published in adults, including studies in Japan (Kikuchi et al., 2024), Korea (Kang et al., 2024a, 2024b), Australia (Carswell et al., 2024), Canada (Danilewitz et al., 2021) and the US (Leung et al., 2024) indicating the need for raising awareness among psychiatrists across the world regarding this issue (de Leon, 2024).

If this hypothesis is correct, clozapine-associated pericarditis and pancreatitis during clozapine titration can be avoided by adjusting the titration speed to the anticipated clozapine clearance of a specific youth. Information is currently limited concerning how to do this, therefore we provide a comprehensive discussion of the current role of 1) pharmacogenetic testing, 2) non-genetic clozapine PMs, 3) antipsychotic co-medications, 4) therapeutic drug monitoring (TDM), 5) CRP

monitoring, and 6) the international adult titration guideline that can be applied for adolescents.

4.5.1. Pharmacogenetic testing

Currently available commercial tests for CYP1A2 genotyping cannot be recommended for clozapine (Ruan and de Leon, 2020). These tests do not identify differential CYP1A2 activity levels based on ancestry or some rare mutation that may explain clozapine genetic PM status.

It is not currently known why there are differential CYP1A2 activity levels per ancestry group, lower in those of Asian ancestry, intermediate in those of European ancestry and highest in those of African ancestry. This difference in activity level may be explained by changes in the CYP1A2 gene or at other genes that modify CYP1A2 activity (Ruan et al., 2019a).

Rare mutations are associated with lower or no CYP1A2 activity but these mutations probably vary per ancestry group. The limited information that we have in adults is that a clozapine PM needs approximately half of the minimum therapeutic dose compared with their ancestry group and sex-smoking subgroup. Clozapine doses range from 75 (female non-smokers) to 150 mg/day (male smokers) in patients of Asian ancestry, and 75 (female non-smokers) to 200 mg/day (male smokers) in patients of European ancestry. Clozapine genetic PMs account for approximately <10 % of clozapine patients (de Leon, 2023). In East Asians 4 alleles can result in lower metabolic activity (CYP1A2*8, CYP1A2*11, CYP1A2*15 and CYP1A2*16) and probably <1 % of clozapine patients may have each of these alleles and other unknown alleles may need to be identified (de Leon, 2023). In patients of European ancestry, unknown alleles may need to be identified but two alleles are likely to be candidates associated with clozapine genetic PMs. These gene variants include CYP1A2*7, which is very rare and was identified in one clozapine patient (Allorge et al., 2003), and CYP1A2*6, with no or little activity and which is present in approximately 1 % of the European general population (Zhou et al., 2017).

4.5.2. Non-genetic clozapine PMs

The existing studies are not of sufficient quality, but the limited published information suggests that non-genetic clozapine PMs may be more frequent than genetic clozapine PMs (de Leon et al., 2020b). This phenomenon is called phenoconversion by pharmacologists (de Leon, 2015). In the case of clozapine there are three major causes of phenoconversion that explain non-genetic PM status: obesity, co-medication with inhibitors of clozapine metabolism and inflammation.

Clozapine deposits in the fat tissue and this can lead to an inhibition of the metabolism of clozapine (Diaz et al., 2018). Thus, cases of clozapine PMs associated with obesity or a high body mass index (BMI) close to the limit of obesity of 30 kg/m^2 have been described in patients of Asian (Ruan et al., 2019b) and European ancestry (Ruan et al., 2024).

Co-medication with moderate-to-potent inhibitors of clozapine metabolism can lead to phenoconversion. This can happen with potent inhibitors such as fluvoxamine but also with moderate inhibitors such as oral contraceptives (Schoretsanitis et al., 2020), as the estrogen component of oral contraceptives are CYP1A2 inhibitors (Schoretsanitis et al., 2022). Valproate can be an inhibitor or an inducer of clozapine metabolism (Diaz et al., 2008), but during the clozapine titration the inhibitory effects may be more relevant since induction may take several weeks to manifest (de Leon, 2020).

The cytokines released during inflammation can inhibit CYP1A2 and other CYPs. Thus, cases of clozapine intoxication during infections have been described since the early 2000s (Raaska et al., 2002; de Leon and Diaz, 2003). Initially, they have not received sufficient attention (Ruan and de Leon, 2019), but these reports are becoming more frequent in the literature (Clark et al., 2018). The key element is whether the infection is associated with systemic inflammation or not, manifested by CRP elevations (Ruan et al., 2020; Arrojo-Romero et al., 2022). Moreover, systemic inflammations in the absence of infection can cause elevations of plasma clozapine concentrations (Ruan et al., 2018). This contributes to the complexity of this phenomenon because when clozapine causes any kind of inflammation, including pericarditis and pancreatitis, this inflammation releases cytokines leading to a positive feedback mechanism, further reducing clozapine metabolism.

Currently, there is no information on the role of genetic or non-genetic clozapine PM status in other forms of localized inflammation in children or adults. Based on the limited information we have on clozapine-induced myocarditis in adults, we can predict that cases of clozapine-induced inflammation during normal clozapine titrations in genetic PMs exist but are not frequent; we are aware of two possible cases (de Leon et al., 2020c; Koenig et al., 2022). Most cases of clozapine-induced myocarditis in adults appear to be explained by a combination of rapid titration with non-genetic clozapine PM status, mainly due to obesity and/or valproate co-medication. In a few patients, infections that occurred before starting clozapine or during the clozapine titration were an additive factor (Danilewitz et al., 2021; Ertuğrul et al., 2022; Koenig et al., 2022).

To avoid clozapine-induced pericarditis, pancreatitis or other inflammations, child and adolescent psychiatrists need to remember that obese patients or those taking inhibitors of clozapine metabolism (e.g., oral contraceptives, valproic acid or even high caffeine intake) may be clozapine PMs and need slower clozapine titrations schedules.

4.5.3. Antipsychotic co-prescription

Currently, there is no information about the role of antipsychotic co-prescription in other forms of localized inflammation in children or adults, but a possible role is based on the limited information we have about clozapine-induced myocarditis in adults. Olanzapine and quetiapine were associated with increased severity of clozapine-induced myocarditis based on data from VigiBase in adults (De Las Cuevas et al., 2022b). Moreover, quetiapine has been associated with myocarditis severity in children in the VigiBase data (De Las Cuevas et al., 2022a) and in some adult clinical samples (Nachmani Major et al., 2020). These two antipsychotics were frequent in these youth patients with clozapine-induced inflammation, with or without myocarditis (Table 4).

Olanzapine does not appear to cause myocarditis by itself during rapid titration, but may compete for CYP1A2 with clozapine, further decreasing CYP1A2 metabolism in patients in whom the CYP1A2 activity may already be compromised (De Las Cuevas et al., 2022a). High doses of perphenazine may also inhibit CYP1A2 (Cooke and de Leon, 1999; Ruan et al., 2020), so it cannot be ruled out that high doses of perphenazine may contribute to other forms of clozapine-induced inflammation.

Quetiapine appears to cause myocarditis by itself during rapid titration but it does not compete for CYP1A2; therefore, it may contribute to inflammation (De Las Cuevas et al., 2022a). It cannot be ruled out that quetiapine may contribute to other forms of clozapine-induced inflammation.

To avoid this risk, child and adolescent psychiatrists may need use the titration schedules for clozapine PMs, when the patient is co-prescribed olanzapine or quetiapine, or even in youth taking high doses of perphenazine (Schoretsanitis and de Leon, 2022).

4.5.4. Clozapine TDM in children and adolescents

A recent systematic review of clozapine TDM in children and adolescents indicated that there is very limited data and most of the data is in adolescents of European ancestry who appear to metabolize clozapine similarly to adults of European ancestry (Jiménez-Fernández et al., 2023).

As there is no published data on clozapine TDM during titration, it is not clear that it can be used in children and adolescents to prevent clozapine-induced inflammations. To interpret clozapine TDM it is important to have trough and steady-state concentrations, but that rarely happens during titration. Moreover, typically the results require several days to arrive, so CRP monitoring is more important in

diagnosing clozapine-induced inflammation and reducing its risk for progression.

4.5.5. CRP monitoring

The international titration guidelines for adults proposes the use of baseline and weekly CRP monitoring at the same time that blood is collected for the WBC (white blood cell) count (de Leon et al., 2022b). A recent meta-analysis supports the use of CRP during the clozapine titration (Leung et al., 2023). A CRP that is elevated before starting clozapine indicates a possible undiagnosed inflammation that may impair clozapine metabolism and provides an indication to wait until the inflammatory process is resolved before starting clozapine. If the baseline CRP is normal and elevation occurs during the clozapine titration, this indicates a clozapine-induced inflammation, that an infection has developed, or both. Child and adolescent psychiatrists may need to become familiar with CRP monitoring during clozapine titrations.

4.5.6. International clozapine titration guideline for adults may be used for adolescents

The international clozapine titration guideline for adult use not only recommends CRP monitoring but 6 personalized titrations according to ancestry and clozapine PM status (de Leon et al., 2022b). Based on the limited information we have on clozapine TDM in adolescents (Jiménez-Fernández et al., 2023), this adult guideline may be helpful for adolescents who are influenced by the effects of sex hormones. Until more data or a specific guideline is developed, adolescent psychiatrists may cautiously follow the adult titration guideline which provides rather conservative titration schedules.

4.6. Need for an international clozapine titration guideline for adolescents and children

Obviously, there is need to develop a guideline for personalizing clozapine titration in children and adolescents. The major limitation is that large prospective studies of clozapine titration in youth are not likely to be published soon. As indicated, a cautious use of the adult guideline for adolescents based on their ancestry and presence or absence of clozapine PM status is recommended. There is very little data in children, but if clozapine is really needed in children a very slow titration combining the recommendation of the adult guideline with a correction for the weight of the patient appears reasonable. We hope to be able to develop a clozapine titration guideline for children and adolescents within 5 years.

4.7. Need for further VigiBase studies of other clozapine-induced inflammations in adults

This study on clozapine-induced inflammations other than myocarditis focuses on youth and does not include adults. As the introduction describes, there was a need for this study because the topic is neglected in the pediatric literature. A second reason for focusing on youth is that we have found that in VigiBase clozapine ADRs in children and adolescents have more complete data and comprise a lower number of cases than in adults. Thus, it was easier to study non-myocarditis forms of localized clozapine-induced inflammation during clozapine titration that was not myocarditis in children. In youth the topic is mainly exhausted by studying clozapine-induced myocarditis in a prior article (De Las Cuevas et al., 2022a) and by adding this current second article about clozapine-induced pericarditis and pancreatitis. Other forms of clozapine-induced inflammation have extremely few youth cases in VigiBase. There are many more reports of localized clozapine-induced inflammation in adults that are not myocarditis, but they are split among many headings including pericarditis, pericardial effusion, serositis, pneumonitis, alveolitis, hepatitis, pancreatitis, nephritis, colitis and some dermatological disorders. Into VigiBase the concept of clozapine-induced inflammations does not exist and is split in many categories of localized inflammation and may include some of the cases of systemic signs of inflammation during clozapine titration such as DRESS, fever or CRP elevations. Moreover, our list is not exhaustive since more rare forms of clozapine-induced inflammation are being published, such as two recent cases with inflammation in some muscle tissues (Escobedo-Aedo et al., 2023). In summary, although there is need for a study of other forms of inflammation during clozapine titration in adults beside myocarditis, this would be a complex enterprise due to the large number and heterogeneity of labels that would need to be considered.

5. Conclusion

As far as we can tell based on the current state of knowledge, clozapine-associated pericarditis and clozapine-associated pericardial effusion manifest clinically in a similar way in children and adolescents and these two labels are used in VigiBase essentially to describe the same type of presentation. Moreover, clozapine-associated pericarditis overlaps with clozapine-associated myocarditis and these presentations may be on a continuum. When only pericarditis is present, it appears that it may take longer to be diagnosed, as pericarditis is not expected and troponin measurements do not contribute to the diagnostic process.

In spite of the lack of attention by the literature to clozapine-associated pancreatitis, published and VigiBase cases demonstrate that it can occur in children and adolescents. Some of the cases may possibly be associated with rapid titrations, but we found two clozapine-associated cases during overdoses.

Finally, our prior VigiBase search found one fatal outcome in an adolescent with clozapine-associated myocarditis (De Las Cuevas et al., 2022a), but we were relieved that no additional fatal outcomes were associated with pericarditis or pancreatitis in the presence of clozapine treatment, at least not in the published cases or cases reported to VigiBase.

CRediT authorship contribution statement

CDLC and JdL proposed the design of this article to EJS. EJS and CDLC downloaded the files. CDLC worked on cleaning the files. RdF and JdL scored all the Naranjo scales by agreement. Other authors reviewed and agreed with the scores. RdF and JdL wrote the first draft of this article. All the co-authors reviewed, provided modifications and approved the final version.

Funding

The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors. Open access funding provided by Università degli Studi Magna Graecia di Catanzaro within the CRUI-CARE Agreement.

Declaration of competing interest

No commercial organizations had any role in the writing of this paper for publication. In the last 3 years, RdF has received speaker fee from Janssen Pharmaceutica and travel support from Janssen Pharmaceutica and ROVI; CUC has been a consultant and/or advisor to or has received honoraria from: AbbVie, Acadia, Alkermes, Allergan, Angelini, Aristo, Biogen, Boehringer-Ingelheim, Cardio Diagnostics, Cerevel, CNX Therapeutics, Compass Pathways, Darnitsa, Denovo, Gedeon Richter, Hikma, Holmusk, IntraCellular Therapies, Jamjoom Pharma, Janssen/J&J, Karuna, LB Pharma, Lundbeck, MedAvante-ProPhase, MedInCell, Merck, Mindpax, Mitsubishi Tanabe Pharma, Mylan, Neurocrine, Neurelis, Newron, Noven, Novo Nordisk, Otsuka, Pharmabrain, PPD Biotech, Recordati, Relmada, Reviva, Rovi, Sage, Seqirus, SK Life Science, Sumitomo Pharma America, Sunovion, Sun Pharma, Supernus,

Takeda, Teva, Tolmar, Vertex, and Viatris. He provided expert testimony for Janssen and Otsuka. He served on a Data Safety Monitoring Board for Compass Pathways, Denovo, Lundbeck, Relmada, Reviva, Rovi, Supernus, and Teva. He has received grant support from Janssen and Takeda. He received royalties from UpToDate and is also a stock option holder of Cardio Diagnostics, Kuleon Biosciences, LB Pharma, Mindpax, and Quantic; GS has received speaker/consultation fees from Dexcel Pharma, HLS Therapeutics and Thermo Fisher. In the last 3 years, the remaining authors report no conflicts of interest.

Data availability

VigiBase does not allow the distribution of the data file but the Supplementary material has all the detailed information needed to score the Naranjo scale in each published case and each VigiBase case.

Acknowledgments

The authors are indebted to the national centers which make up the World Health Organization (WHO) Program for International Drug Monitoring and contribute reports to VigiBase. 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 or of the WHO.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.schres.2023.10.027.

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