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Association between myocarditis and antipsychotics other than clozapine:

A systematic literature review and a pharmacovigilance study using VigiBase

Running title: myocarditis antipsychotics

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ABSTRACT:

Introduction: Pharmacovigilance studies have definitely established that clozapine can cause myocarditis. Two published reviews suggested that on rare occasions other antipsychotics may induce myocarditis. **Areas covered:** This review explored myocarditis associated with antipsychotics other than clozapine by conducting a systematic search of the literature and critically analyzing the current data in VigiBase compared to the data on clozapine-associated myocarditis. VigiBase is the World Health Organization's global pharmacovigilance database which uses as a statistical signal for associations a logarithmic measure of disproportionality called the information component (IC).

Expert Opinion: For quetiapine, VigiBase provided 106 reports of myocarditis and a significant statistical signal (IC=1.8; IC_{025}=1.5) which was confounded by 48% (51/106) with clozapine co-prescription. Combining the literature and VigiBase cases provided 5 probable myocarditis cases during quetiapine monotherapy (4 after overdose or rapid titration). For olanzapine, VigiBase provided 107 reports of myocarditis and a significant statistical signal (IC=2.1; IC_{025}=1.8) probably explained by 77% (82/107) using clozapine co-prescription. Combining the literature and VigiBase cases provided 1 probable myocarditis case during olanzapine monotherapy. Combining the literature and VigiBase provided another 3 probable cases during therapy with other antipsychotics during overdose or titration with a high dose.

Keywords: antipsychotic agents/administration and dosage; antipsychotic agents/adverse effects; antipsychotic agents/poisoning; antipsychotic agents/toxicity; mortality/drug effects; myocarditis/chemically induced; myocarditis/etiology; olanzapine/adverse effects; quetiapine/adverse effects; quetiapine/poisoning.

Highlights box

- Pharmacovigilance through the publication of case reports and, more importantly, reviews of the databases from the national drug agencies have demonstrated that clozapine causes myocarditis.
- Two published reviews suggested that on rare occasions other antipsychotics may induce myocarditis.
- Quetiapine. By combining published and VigiBase cases we identified 5 probable myocarditis cases associated with antipsychotic monotherapy on quetiapine (4 were after overdose or rapid titration). After controlling for confounders in VigiBase, quetiapine co-prescription was associated with increased odds ratios (ORs) for severity and lethality of myocarditis in clozapine patients. Thus, we recommend that clinicians be aware that on rare occasions quetiapine may contribute to myocarditis.
- Olanzapine. Combining the literature and VigiBase we identified only 1 probable myocarditis case associated with olanzapine. In summary, there is almost no proof that olanzapine is associated with myocarditis.
- Other antipsychotics. By combining published and VigiBase cases, we identified 3 probable myocarditis cases occurring during an overdose or a high-dose titration of other antipsychotics after excluding clozapine, quetiapine and olanzapine.

1. INTRODUCTION

1.1. Pharmacovigilance

Before any new drug is currently introduced in the market, it is well studied for its pharmacokinetic characteristics and adverse drug reactions (ADRs) in a few thousand patients. Rare ADRs may not be detected in these studies before approval but may be recognized by using what is called pharmacovigilance during postmarketing surveillance [1]. This pharmacological term refers to the case reports and studies of ADRs published in medical journals and from reports to the Food and Drug Administration (FDA) and other national drug agencies. The World Health Organization (WHO) has developed a global database called VigiBase. It is located at the Uppsala Monitoring Centre (UMC), Uppsala, Sweden, and currently has >25 million reports of spontaneously reported ADRs from the drug agencies of 145 countries. New reports arrive daily and ADRs are sometimes classified by the reporting clinician but normally those who report would enter free text information and the pharmacovigilance staff at a regional or national center or pharmaceutical company would do the encoding using the categories provided by the database.

1.2. Association of clozapine with myocarditis

1.2.1. Pharmacovigilance on clozapine ADRs

Clozapine was introduced in some European countries in the 1970s before systematic ADR studies [2] were required, but pharmacovigilance led to the identification of an association with agranulocytosis. After its reintroduction in the United States (US) in 1989 after a randomized clinical trial (RCT) in patients with treatment-refractory schizophrenia (TRS) [3], widespread use of clozapine began all over the world for that indication. Pharmacovigilance led to the identification of another ADR, myocarditis. In 1980 Danish authors published in Danish the first case of clozapine-associated myocarditis associated with a rapid titration [4]. In 1992 in another case of clozapine-associated myocarditis during an overdose, the autopsy showed eosinophilic myocarditis [5]. Eosinophilic myocarditis is currently considered the typical presentation of myocarditis associated with clozapine and is a sign of a hypersensitivity reaction [6].

The drug agencies took some time to pay attention to this association between clozapine and myocarditis. Their first article was published in 1993 by the British drug agency [7] and in 2001 articles were published by the FDA [8] and authors linked to the WHO-UMC [9]. In 2002, a myocarditis warning was added to the US clozapine package insert [2].

1.2.2. Data on the association of clozapine and myocarditis in VigiBase data

The first case of clozapine-induced myocarditis was reported to VigiBase in 1986 but only in 1993 did the statistical signal that this database uses to identify potential ADRs (see Section 2.2.1) become significant (Figure 1). In a search on January 15, 2021, there were more than 3000 cases of myocarditis associated with clozapine, indicating a 5% mortality rate (178/3572) [10]. Almost all cases of myocarditis in clozapine patients appear early in treatment with 84% (1309/1560) in the first month and another 5% (82/1560) in the second month. As reports to VigiBase may be overrepresenting the most severe cases, we reviewed the meta-analysis of clozapine-induced myocarditis by Bellisima et al. which studied 359 published clozapine-induced myocarditis cases [11]. Only 79 cases provided time-specific durations and the review suggested that 87% displayed symptoms within 30 days or less of treatment which is similar to the VigiBase search. The outcome for patients was known in 85 cases and 21% were fatal, suggesting that published cases may include a major overrepresentation of the most severe cases of clozapine-induced myocarditis [11]. A more recent meta-analysis of clozapine-induced myocarditis indicated a mortality rate of 12.7% [12].

Based on VigiBase and published cases, it can be concluded that myocarditis occurring during clozapine titration is very likely to be clozapine-induced myocarditis. It has been proposed that clozapine-induced myocarditis may be a hypersensitivity reaction due to titration that was too rapid for that specific patient's clozapine metabolism. Clozapine metabolism, which is influenced by ancestry, presence of genetic poor metabolizers or phenoconversion due to inhibitors, obesity or inflammation, may be influential for the risk of myocarditis [13,14]. Thus, there is no standard definition of rapid titration for clozapine metabolism since it has to be individualized according the metabolism of the individual patient [15]. Myocarditis that occurs after many years on clozapine is a more complicated

diagnosis since there are other causes of myocarditis, including viral infections, comprising worldwide incidences of myocarditis in the general population from 10.2 to 105.6 per 100,000 [16].

1.2.3. Clozapine and myocarditis during intentional overdose

The first case of myocarditis during an intentional overdose was published in 1992 [5]. Our VigiBase clozapine search on January 15, 2021, [10] focused on myocarditis occurring with clinical doses and did not pay specific attention to cases during clozapine overdoses. So next the subsections focus on this topic by conducting an article search and re-analysis from VigiBase.

1.2.3.1. Article search. Table 1 describes 9 published cases [4,5,17-20] of myocarditis possibly associated with clozapine identified by our article search (footnote a of Table 1); they include 2 definitive intentional overdoses.

1.2.3.2. VigiBase search. In our January 15, 2021, search of VigiBase, we identified 3274 non-duplicated cases of myocarditis associated with clozapine. Australia provided more than one half of the myocarditis cases and one third of the lethality. Similarly, a 2020 meta-analysis of clozapine-induced myocarditis found an event rate of 2% in 9 Australian samples and of 0.3% in 15 non-Australian samples [12].

The clozapine dosage amount at the time of discontinuation was recorded in 1907 of these 3274 cases. Although clozapine therapeutic dosages may vary according to ancestry, the US package insert considers 900 mg/day as the maximum recommended dose [21]. Thus, it appears a conservative, but reasonable, approach to consider any clozapine dose >900 mg/day as definitively excessive and a potential sign in VigiBase that the myocarditis was possibly associated with an overdose. There were 3 possible overdose cases using this definition (2 with 950 mg/day and 1 with 1600 mg/day) or 0.16% among the 1907 cases of clozapine myocarditis in which dosages were available. Thus, myocarditis associated with clozapine overdose may be relatively rare and most cases of myocarditis associated with clozapine in VigiBase appeared to be associated with early treatment during titration.

1.3. Limited data on the association between myocarditis and other antipsychotics

In summary, there is general agreement in the literature that clozapine is associated with myocarditis. As previously described, this is usually considered to happen in the context of a hypersensitivity

reaction in which the titration was too rapid for the patient [13,14], but some cases appear to be due to overdoses (published cases in Table 1 and 0.16% in VigiBase). On the other hand, there is limited data on myocarditis associated with antipsychotics other than clozapine. As far as we know, two review articles commented on them. In 2001, using the statistical methods used by VigiBase (see Section 2.2.1), Coulter et al. [9] found 231 reports of myocarditis and/or cardiomyopathy in patients on clozapine and proposed that there was a strong association with clozapine. They also suggested the need for further investigation related to other antipsychotics: risperidone (16 cases), chlorpromazine (14 cases), haloperidol (11 cases) and fluphenazine (8 cases) [9]. In a review article in 2009, Raedler [22], based on the article by Coulter et al. [9], proposed that myocarditis may also be associated with other antipsychotics besides clozapine.

The goal of this review article is to provide an update on the association between myocarditis and antipsychotics other than clozapine by conducting a systematic search of the literature (Table 2 and 3) and by critically analyzing the current data in VigiBase (Figure 1 and Tables 4 to 6), comparing it to the data on clozapine-associated myocarditis [10].

2. METHODOLOGICAL ASPECTS

This section has two subsections: 1) a description of the search for articles, and 2) a focus on the statistical methods used in VigiBase.

2.1. The search for articles

The literature was searched for cases of myocarditis occurring during treatment with other antipsychotics as long as clozapine was not present (Table 2). On July 30, 2021, 31 PubMed searches of other antipsychotics AND “myocarditis” were completed. Instead of providing 31 PRISMA flow charts, we summarized these 31 searches in Table 2. The search “olanzapine” AND “myocarditis” provided the 9 articles [22-30] leading to 1 case [30] included in Table 3. The search “quetiapine” AND “myocarditis” provided the 13 articles [26, 27, 31, 32-41] leading to 6 cases [36-41] included in Table 3. The search “aripiprazole AND myocarditis” provided 4 articles [29, 30, 42, 43] leading to 1 case [29, 30] included in Table 3. The search “asenapine AND myocarditis” provided 1 article which provided 1 case included in Table 3 [44]. The search “haloperidol AND myocarditis” provided 6 articles [9, 23,

45-48] leading to 1 case [48] included in Table 3. The search "perphenazine AND myocarditis" provided 1 article which provided 1 case included in Table 3 [49].

Twelve searches provided no articles for Table 3 since all articles [9, 20, 22-25, 27, 43, 48, 50-65] were excluded (Section 7 of Table 2). Thirteen searches provided no articles (Section 8 of Table 2).

2.2. VigiBase search

Records dating from the inception of the database until April 7, 2021, were searched to locate myocarditis cases suspected to be associated with antipsychotics. They are classified in VigiBase as N05A or the Antipsychotic Anatomical Therapeutic Chemical Classification System code (Table 4). All reports of myocarditis and antipsychotics other than clozapine were scrutinized by the first and second authors. This was a retrospective review of deidentified cases (see Table 5, footnote a). VigiBase classifies a case as serious (defined as an ADR that requires hospitalization or extension of hospital stay, results in persistent or significant disability or incapacity, or is life-threatening). If the case did not meet criteria for seriousness, it was considered non-serious. VigiBase also reports fatal outcomes [10].

2.2.1. Statistical analyses using standard VigiBase's disproportionality approach

VigiBase uses a Bayesian confidence propagation neural network that provides a statistical indicator called an information component (IC), which is used to filter out combinations of particular drugs and ADRs that are present in the database more frequently than expected, according to all reports for the particular drug and ADRs, and the total number of reports in the database [66]. An IC of 0 results from 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 data set. Positive values represent combinations reported more frequently and negative values more infrequently than expected. The IC measures of disproportionality between the expected and the reported rates of myocarditis related to antipsychotics are reported in Figure 1 and Table 4. Confidence intervals (CIs) of the ICs are provided to account for sampling variability.

2.2.2. Significant differences in VigiBase ICs

A high IC value, in addition to IC_{025} (lower 95% CI), denotes a strong statistical association between the antipsychotic and myocarditis in the database. Moreover, when the IC_{025} (lower 95% CI) is positive (>0) it indicates a statistically significant disproportionality between the expected and the reported rates for a drug and an ADR. Similarly, the 95% CI of two drugs can be used for comparison and when they do not overlap this indicates that they are significantly different with at least a p value <0.05 [67].

2.2.3. Review of non-duplicate reports

All of these VigiBase standard analyses are contaminated by the possibility of some level of duplicate reports. All reports were scrutinized by the first author and discussed with the last author in cases of doubt. The first author reviewed each case carefully for possible duplicates and for myocarditis unique cases associated with antipsychotics other than clozapine. They are described in Table 5. It was decided that, in any myocarditis case including clozapine and another antipsychotic, clozapine would be considered the cause of the myocarditis and excluded.

2.3. Interpreting single myocarditis cases as associated with other antipsychotics

The article search and the review of non-duplicated cases in VigiBase led to a short list of myocarditis patients receiving various antipsychotic monotherapies, but the interpretation of these individual cases of myocarditis as drug-related is complex. Pharmacovigilance data using clinical diagnosis and the published case reports or VigiBase cases do not require diagnostic criteria for myocarditis. The ADR scale had several criteria that are fundamental for making assumptions about causality such as exclusion of other causes (non-drug-related and drug-related) and a temporal relationship preferentially demonstrated by rechallenge [68]. Thus, we used Naranjo et al.'s scale, which has 10 items for assessing these cases. This scale classified the ADRs as definite (≥ 9), probable (5-8), possible (1-4) and doubtful (≤ 0) [68]. After reviewing published cases and VigiBase cases, we figured out that the cases of myocarditis caused by other antipsychotics were justified because clozapine causes myocarditis. We thought that assumption was not correct so we decided, based on the literature and our VigiBase review of myocarditis associated with clozapine [10], and became convinced that clozapine is definitively associated with clozapine during overdoses or early titration. Thus, we

assumed that this would be the expected pattern for myocarditis associated with antipsychotics. For scoring item 1 ("Are there previous conclusive reports on this reaction?") of the Naranjo scale for other antipsychotics we decided that when the case was associated with overdose or early titration of that antipsychotic, we would score it as 1.

3. RESULTS

The two subsections focus on the article and VigiBase searchers.

3.1. Article search

3.1.1. Olanzapine and myocarditis in the article search

A myocarditis case associated with olanzapine [30] was considered a probable ADR (Table 3, Case 1).

3.1.2. Quetiapine and myocarditis in the article search

There were 6 myocarditis cases from 6 different countries associated with quetiapine (Table 3, Cases 2 to 8) [36-41]. Of the 4 cases left [69, 70] after exclusions, Case 2 was considered possible (scored as 1) [41]. The other 3 cases were considered probable: 1) Case 4 (score of 7) was remarkable because it was definitively caused by rapid titration, as the 300-mg dose was started with no uptitration [39]; 2) Case 6 (score of 7) occurred within 3 weeks of initiation [37] and 3) Case 7 (score of 6) started after 2 months of initiation and was fully developed after another 2 months [36].

3.1.3. Other antipsychotics and myocarditis in the article search

Four other myocarditis cases associated with antipsychotics are reviewed in Table 3: a haloperidol intentional overdose (Case 8) [48], an aripiprazole case (Case 9) [29, 30], an asenapine case (Case 10) [44], and a perphenazine case (Case 11) [49]. Only the haloperidol overdose (Case 8) was considered a possible myocarditis case (score 3); it was confounded by the presence of chlorpromazine in the intentional overdose [48].

3.2. VigiBase search

3.2.1. Comparing myocarditis cases associated with clozapine

Table 4 shows that in April 7, 2021, there were 3836 myocarditis reports that were associated with antipsychotics, when only 276 should be expected. Most of them were due to clozapine which has

3665 myocarditis reports when only 57 should be expected. Olanzapine was next with 107 myocarditis reports versus 24 expected. Quetiapine was third with 106 myocarditis reports versus 30 expected.

The antipsychotics group had an IC=3.8 with IC_{025}=3.7. This value may be mainly explained by clozapine, with an IC=6.0 and IC_{025}=5.9. In the next level are olanzapine IC=2.1 with IC_{025}=1.8 and quetiapine IC=1.8 with IC_{025}=1.5. The rest of the antipsychotics had values not compatible with a significant association; some have an IC < 1 and a few of them had IC >1.0 but an extremely low number of reports had IC_{025}<0.

In summary, Table 4 suggests that olanzapine and quetiapine ICs are suggestive of the potential for a statistically significant association with myocarditis but they are contaminated by two major confounding factors, duplicate cases and the co-prescriptions (particularly with clozapine).

Figure 1 shows clozapine ICs since 1986 but the value became significant in 1993 (IC_{025} >0) with a value around 2.0; since 2005 it has been at least 5.0 and had a very narrow CI. Since 2013, olanzapine IC has reached close to or higher than 2 and become significant (IC_{025} >0). As the upper CI of the olanzapine IC has never reached the lower CI of the clozapine IC, clozapine has a stronger statistical association with myocarditis than olanzapine with a p value <0.05.

Since 2016 quetiapine IC has almost reached 2 and become significant (IC025 >0). As the upper CI of the quetiapine IC has never reached the lower CI of the clozapine IC, clozapine has a stronger statistical association with myocarditis than quetiapine with a p value <0.05.

3.2.2. Olanzapine and myocarditis in VigiBase

Table 4 explains that the olanzapine IC signal in VigiBase is likely to be explained by clozapine co-prescription since in 77% (82/107) of cases of myocarditis associated with olanzapine, the patient was also taking clozapine. Only 11% (12/107) of olanzapine reports have no description of an antipsychotic co-prescribed. As the difference between observed and expected myocarditis in olanzapine is only 83 (107-24=83), the 82 cases with clozapine co-prescription can easily explain the difference. Since 2013, the olanzapine IC became significant for olanzapine but had a consistent pattern from half to more than 2/3 of the cases explained by the clozapine co-prescription.

Table 5 shows that after eliminating the 107 duplicated olanzapine reports, 76 different olanzapine patients remained, 11 myocarditis cases associated with olanzapine in the absence of antipsychotic co-prescription and only 3 cases that were scored 0 (doubtful).

3.2.3. Quetiapine and myocarditis in VigiBase

Table 4 explains that the quetiapine IC signal in VigiBase is likely to be partly explained by 48% (51/106) clozapine co-prescription. Only 44% (47/106) of quetiapine reports have no antipsychotic co-prescription. As the difference between observed and expected myocarditis in quetiapine was only 76 (106-30=76), the 51 cases with clozapine co-prescription can easily explain 2/3 of this difference. Furthermore, since 2016 when the quetiapine IC became significant, approximately half the cases were consistently explained each year by clozapine co-prescription.

Table 5 demonstrates that after eliminating [71, 72] the 106 duplicated quetiapine reports, 55 different quetiapine patients remained, and 15 myocarditis cases in the absence of antipsychotic co-prescription and only 4 were scored (2 possible and 2 probable). One of the probable cases listed a dose above the recommended range (1000 mg/day) for an unknown time and the other an even higher dose on day 9 (1200 mg/day), compatible with rapid titration.

3.2.4. Other antipsychotics and myocarditis in VigiBase

Other antipsychotics generated a small number of reports in the absence of clozapine (Table 4). After excluding duplications and co-prescriptions, Table 6 describes 27 myocarditis cases potentially associated with antipsychotic monotherapy other than olanzapine and quetiapine and 3 scored cases (1 possible and 2 probable). The two probable cases included an intentional overdose on loxapine and the use of a high dosage (850 mg/day) for 6 days on an antipsychotic mainly used in France, called cyamemazine.

4. CONCLUSION

The subsections of the conclusion section focus on 1) limitations, 2) olanzapine monotherapy, 3) quetiapine monotherapy, 4) other antipsychotic monotherapy, 5) antipsychotics as a class, and 6) a final summary.

4.1. Limitations

The limitations include: 1) interpreting myocarditis in the context of polypharmacy, 2) the small number of cases on monotherapy that were left after duplications and co-prescription were eliminated, and 3) the use of clinical diagnosis.

Antipsychotic polypharmacy is increasingly common in schizophrenia [73, 74], with a median rate of 19.6% (interquartile range, 12.9%-35.0%) [75], and a prevalence of nearly 60% in some settings [76]. Antipsychotics are also used for schizophrenia spectrum disorders [77], bipolar disorder [78], and a range of other psychiatric disorders [79]. In situations of polypharmacy, it may be impossible to distinguish which one may be causing an ADR [80]. Thus, we made methodological decisions (Section 2.3) to best interpret cases of myocarditis associated with other antipsychotics in the absence of co-prescription of clozapine.

After duplications and co-prescription were eliminated, on monotherapy we only identified in the published literature 11 cases of potential myocarditis leading to 2 possible and 4 probable cases (footnote a of Table 3) and in VigiBase 53 potential cases other than those from clozapine, leading to 3 doubtful, 3 possible and 4 probable cases (Footnote b of Table 6). Furthermore, the VigiBase ICs of olanzapine and quetiapine are seriously contaminated by duplicate reports.

These cases described in the published literature or VigiBase are based on a reported clinical diagnosis but we have no way of verifying that the myocarditis diagnoses were correct.

4.2. Is olanzapine associated with myocarditis?

Table 3 describes only 1 published probable olanzapine case [30]. The current myocarditis IC for olanzapine of 2.1 with an IC_{025} of 1.8 may appear impressive, but this high value is seriously contaminated by duplicates (which reduced myocarditis cases from 107 to 76) and, more importantly, 2/3 of the cases since 2016, when the IC became significant, may be explained by clozapine co-prescription. In summary, in spite of the significant olanzapine IC, the difference between observed and expected cases is probably completely explained by clozapine co-prescription. Table 6 presents 11

myocarditis cases with no antipsychotic co-prescription, but the 3 rated cases were considered doubtful. We conclude that currently we have almost no proof that olanzapine is associated with myocarditis.

4.3. Is quetiapine associated with myocarditis?

Table 3 describes six published myocarditis cases from six countries which had the potential to be associated with quetiapine; three of them were scored as probable. The three probable cases include: 1) a US case started on quetiapine 300 mg/day for 5 days quetiapine (Table 3, Case 4) [39]; 2) a UK case was diagnosed in the third week after starting quetiapine (Table 2, Case 6) [37]; and 3) a German case after quetiapine 600 mg/day for 2 months (Table 3 case 7) [36].

Although the quetiapine IC of 1.8 with an IC_{025} of 1.5 may appear impressive, there is significant contamination by duplicates (which reduced the myocarditis cases from 106 to 56) and, more importantly, half the cases since 2016 when the IC became significant may be explained by clozapine co-prescription. Therefore, there is no current good statistical proof in VigiBase that quetiapine has a significant association with myocarditis in VigiBase.

Table 6 describes 15 VigiBase quetiapine cases but only 2 were rated as probable including an Oceanian case with a high dose of 1000 mg/day for an unknown time and a European case with a high dose of 1200 mg/day for 9 days.

After considering the 3 probable published cases (Table 3) and 2 probable VigiBase cases in VigiBase (Table 6), we recommend that psychiatrists be alert for the very rare case in which quetiapine may be associated with myocarditis. Of the 5 probable quetiapine cases, 4 were after an intentional overdose or a rapid titration.

4.4. Myocarditis and other antipsychotic monotherapy

In our exhaustive search combining published and VigBase cases we found 3 probable myocarditis cases (an intentional overdose of haloperidol and chlorpromazine, Case 8 in Table 3; an intentional overdose of loxapine in Table 5; and a titration using a high dose of cyamemazine in Table 6) and one possible case (on aripiprazole, Table 6).

4.5. The VigiBase association of myocarditis with clozapine may completely explain the association of myocarditis with antipsychotics as a class

Sections 4.3 to 4.5 raise serious doubts that antipsychotics as a class may be associated with myocarditis. Table 4 clearly demonstrates that clozapine IC is extremely high at 6.0 and IC_{025} of 5.9; the number of observed clozapine myocarditis cases is a higher order of magnitude, with 3665 cases, than the 107 cases featuring other antipsychotics in the absence of clozapine. This strong attention to reporting myocarditis in clozapine patients may have spuriously contaminated the myocarditis reports of the antipsychotic class and may explain the IC of the antipsychotic class of 3.8 with an IC_{025} of 3.7.

4.6. Final summary

Two published reviews [9, 22] have suggested that on rare occasions antipsychotics other than clozapine may induce myocarditis. Our VigiBase search identified 106 reports of myocarditis in quetiapine patients, indicating a significant statistical signal (IC=1.8; IC_{025}=1.5). Clozapine co-prescription reached 48% (51/106) and appears to explain an important part of this statistical signal. By combining published and VigiBase cases we identified 5 probable myocarditis cases associated with antipsychotic monotherapy on quetiapine (four were after overdose or rapid titration). After controlling for confounders in VigiBase, quetiapine co-prescription was associated with increased ORs for severity and lethality of myocarditis in clozapine patients. Thus, we recommend that clinicians be aware that occasionally quetiapine may contribute to myocarditis.

Our Vigibase search identified 107 reports of myocarditis in olanzapine patients, indicating a significant statistical signal (IC=2.1; IC_{025}=1.8), but most of the signal appears to be explained by the 77% (82/107) with clozapine co-prescription. After excluding duplicates and patients taking other antipsychotics, 11 myocarditis cases were reviewed in detail leading to 3 cases scored as doubtful. The literature search identified a case scored as probable olanzapine-induced myocarditis. It can be concluded that currently we have almost no proof that olanzapine is associated with myocarditis.

By combining published and VigiBase cases, we identified 3 probable myocarditis cases associated with antipsychotic therapy other than clozapine, quetiapine or olanzapine. The 3 cases were

due to overdose or high-dose titration. Thus, it is possible that any antipsychotic overdose may on rare occasions be associated with myocarditis, but well-studied cases with postmortem histopathology need to definitively establish whether a causal association exists, or not.

The statistical association between myocarditis and antipsychotics as a class was mainly explained by clozapine since 1) 95% of myocarditis cases (3665/3838) were probably explained by clozapine, and 2) the statistical signal (IC=3.8; IC_{025}=3.7) associating the antipsychotic class with myocarditis was probably completely explained by the clozapine statistical signal (IC=6.0; IC_{025}=5.9).

5. EXPERT OPINION

The subsections of this expert opinion section focus on 1) olanzapine and clozapine co-prescription, 2) quetiapine and clozapine co-prescription, and 3) a five-year perspective.

5.1. Olanzapine and clozapine co-prescription

Table 5 shows that 77% of olanzapine reports with myocarditis are contaminated by clozapine and, as previously described, clozapine co-prescription may explain the effects of olanzapine on myocarditis identified by VigiBase IC. In our prior clozapine study, we also saw that after eliminating duplicates, olanzapine co-prescription was a frequent contaminant, 8.7% (284/3274), of clozapine myocarditis. Moreover, in a logistic regression model with seriousness of clozapine myocarditis (yes/no) as the dependent variable, olanzapine was associated with a significant ($p<0.001$) odds ratio (OR) of 1.90 (95% CI 1.35 to 2.68) [10]. This association of olanzapine co-prescription increasing the severity of clozapine myocarditis has not been previously described in the literature and may be explained because olanzapine is mainly metabolized by CYP1A2 [81].

Thus, olanzapine may compete for CYP1A2 with clozapine in situations in which the metabolism of clozapine is compromised (competitive inhibition) [81]. In the same logistic regression model, valproate was also significant ($p=0.004$) with a OR of 1.67 (95% CI 1.18 to 2.37) [10]. Valproate can also inhibit clozapine metabolism, particularly during early titration [82], and has been described as a risk for developing myocarditis in patients taking clozapine [13, 14, 83].

5.2. Quetiapine and clozapine co-prescription

Table 5 shows that 51% of quetiapine reports included clozapine co-prescription, but as described before, clozapine co-prescription may not explain all the increased numbers of quetiapine myocarditis in VigiBase.

In our prior clozapine study, we saw that after eliminating duplicates, quetiapine co-prescription was frequent, and contaminated 5.2 % (171/3274) of clozapine myocarditis. In the logistic regression model, using seriousness (yes/no) of clozapine myocarditis as the dependent variable, the quetiapine OR was 2.83 (95% CI 1.82 to 4.40). This association of co-prescription of quetiapine with increased severity of myocarditis in clozapine patients was completely unexpected. The logistic regression model, using fatal outcomes (yes/no) of clozapine myocarditis as the dependent variable, had much less power (158 fatal outcomes vs. 3116 non-fatal cases), but quetiapine still had a significant ($p<0.041$) OR, 2.12 (95% CI 1.03 to 4.35) [10]. We did not expect that quetiapine may be more consistently associated with clozapine myocarditis than olanzapine. Quetiapine was associated with both seriousness and fatality, while olanzapine is only associated with seriousness. As quetiapine is mainly metabolized by CYP3A4 [81], these effects on clozapine myocarditis should not be mediated by inhibiting clozapine metabolism. As quetiapine may occasionally cause myocarditis by itself and co-prescription may increase the risk of myocarditis in clozapine patients, this suggests that quetiapine may have some pharmacodynamic effects at the immunological level that contribute to risk of myocarditis. These pharmacodynamic effects of quetiapine associated with myocarditis appear much lower than those of clozapine, but they may be more important than those of the rest of the antipsychotics.

5.3. Five-year perspective

Based on our review of myocarditis cases in patients taking quetiapine antipsychotic monotherapy, we recommend that psychiatrists be skeptical that quetiapine is the cause of myocarditis unless it happens after an overdose or a rapid titration. In the rest of the cases, other causes of myocarditis, particularly viral myocarditis, should be ruled out in a quetiapine patient before blaming quetiapine. Future quetiapine studies and case reports with detailed information including post-mortem autopsies when available should verify the possible association between quetiapine and myocarditis. Future quetiapine

studies need to explore its pro-inflammatory potential in *in vitro* models as a recent study suggested that unmetabolized quetiapine can have complex effects in neutrophils and some pro-inflammatory effects in inactivated macrophages but may have anti-inflammatory effects on activated macrophages [84].

Future studies on clozapine-induced myocarditis should explore whether or not co-prescription of olanzapine or quetiapine contribute to the severity and/or lethality of clozapine-induced myocarditis. If they do, slower clozapine titrations may be required [15] when titrating clozapine in patients taking olanzapine or quetiapine.

In order to clarify whether or not other antipsychotics besides clozapine and quetiapine can occasionally cause myocarditis during overdoses, in the next five years published cases should provide postmortem microscopic examinations documenting the presence of eosinophilic myocarditis suggestive of hypersensitivity drug reaction and paying close attention to other possible myocarditis causes and co-medications. Finally, after five years, it may be important to replicate this type of study in VigiBase after more cases have accumulated and more definitive conclusions can be established.

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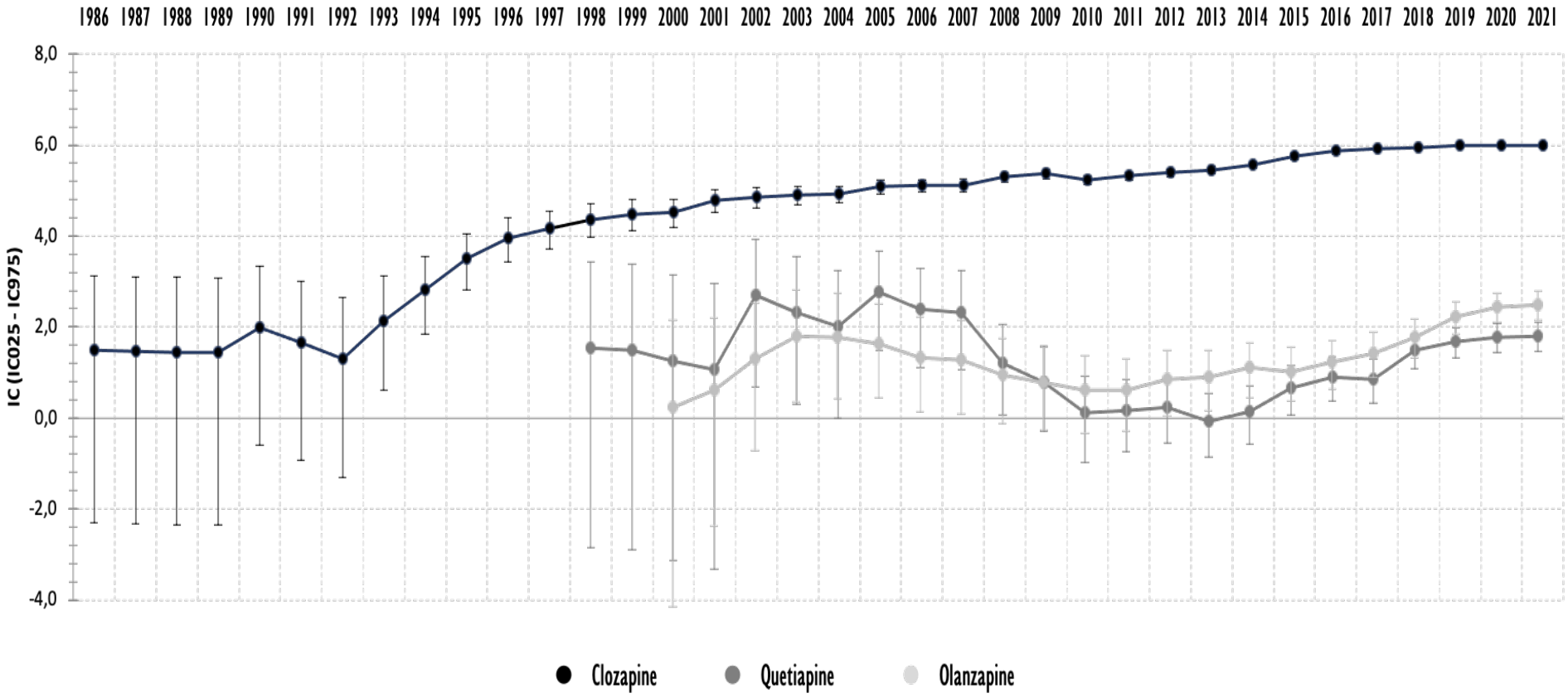
Figure 1. Yearly IC for clozapine-, quetiapine- and olanzapine-associated myocarditis until April 7, 2021.



CI, confidence interval; IC, information component.

Table 1. Cases of postmortem diagnosis of myocarditis after possible clozapine overdoses identified in article search.[a]

Authors	*Case*	*Age*	*Sex*	*Diagnosis*	*Country*	*Comment*
Vesterby et al., 1980 [4]	1	22	♂	Schizophrenia	Denmark	Patient was prescribed 300 mg/day for 10 days until death[b]
Meeker et al., 1992 [5]	2	22	♂	Schizophrenia	USA	Recently started and intentional overdose (2000 mg)[c]
Worm et al., 1993 [17]	3	44	♂		Denmark	Unknown dose but postmortem C was considered toxic
Worm et al., 1993 [17]	4	41	♀		Denmark	350 mg/day dose but postmortem C was considered toxic
Worm et al., 1993 [17]	5	27	♂	Psychosis[d]	Denmark	Unknown dose but postmortem C was considered toxic
Zhang, 2001 [18]	6	38	♀		China	Intentional overdose: 1000 mg (myocarditis, pulmonary edema and coma)[e]
Flanagan et al., 2005 [19]	7				UK/Eire	One case had eosinophilic myocarditis
Ye et al., 2018 [20]	8	64	♀	Schizophrenia	China	Only drug detected in toxicological screen was clozapine
Ye et al., 2018 [20]	9	67	♂	Schizophrenia	China	Drugs detected in toxicological screen: clozapine and paroxetine

C: concentration.

[a]On July 23, 2021, two PubMed searches were conducted. The first search, using the words "Drug overdose"[Mesh] AND "clozapine" AND myocarditis, provided 4 articles, of which only Meeker et al. [4] was relevant. The second search, using the words "Clozapine/poisoning"[Mesh] AND myocarditis, provided 4 articles, of which only two were relevant: Vesterby et al. [3] and Meeker et al. [4]. Another 4 articles [17-20] were identified in the last author's file. Worm et al. [17] studied 10 patients who died in Denmark and had toxic or therapeutic clozapine concentrations. The three included in this table had a histopathological diagnosis of myocarditis and were considered to have toxic concentrations, but there was no information on whether they overdosed or not. Zhang [18] described a case with pulmonary edema and myocarditis after a self-inflicted overdose. Flanagan et al. [19] studied 7 fatal overdoses with high clozapine concentrations, but their anatomopathological findings were not reported. Another 26 deaths during clozapine treatment were studied; eosinophilic myocarditis was diagnosed in one case, but demographic data and clozapine concentrations were not provided. Ye et al. [20] studied 24 patients who suddenly died in Shanghai; eleven of them had a postmortem diagnosis of myocarditis. Of these eleven patients, only two had clozapine identified in their toxicological screen, but no information was provided on their concentrations.

[b]This article was published in Danish. In prior published articles, following the MESH heading "Clozapine/poisoning" used by PubMed, led us to believe that it was a clozapine overdose. The third author gave access to the original article and provided an English translation that allowed us to reinterpret the case. The patient was prescribed 300 mg/day. A very high postmortem clozapine concentration was found in blood (4,500 ng/ml). The clozapine quantity found in the entire stomach contents was only 0.4 mg (30 ml). The authors concluded that suicide was very unlikely.

[c]The patient had a history of prior overdose on antipsychotics.

[d]The patient had psychosis possibly associated with substance abuse.

[e]The patient was rapidly taken to the hospital and recovered. The diagnosis of myocarditis was based on the electrocardiogram and serum levels of heart enzymes.

Table 2. PubMed searches (July 30, 2021).

1. "olanzapine" AND "myocarditis": 9 articles leading to 1 case
• 5 articles provided no cases [22-26]; • 2 articles were excluded due to cases of myocarditis associated with clozapine [27,28]; • 1 case of myocarditis was excluded due to being explained by aripiprazole [29]; and • 1 article [30] led to 1 case included in Table 3.
2. "quetiapine" AND "myocarditis": 13 articles leading to 6 cases
• 3 articles provided no cases [26,31,32]; • 4 articles that were excluded due to cases of myocarditis associated with clozapine [27, 33-35]; and • 6 articles [36-41] led to 6 cases included in Table 3.
3. "aripiprazole AND myocarditis": 4 **articles leading to 1 case**
• 1 article was excluded because they were cases of myocarditis associated with clozapine [42]; • 1 article [43] described a study of cardiovascular ADRs with no cases of myocarditis associated with aripiprazole, but reported 2 cases of myocarditis associated with antipsychotics other than clozapine. One case was associated with the combination of haloperidol and perazine; the other combined haloperidol and pipamperone. As these cases were not described in detail, they were not included in Table 3; and • 2 articles [29, 30] with only 1 aripiprazole case that was included in Table 3.
4."asenapine AND myocarditis": 1 article leading to 1 case
• 1 article which provided 1 case included in Table 3 [44].
5."haloperidol AND myocarditis": 6 articles leading to 1 case
• 4 articles provided no cases [9, 23,45,46]; • 1 article with a case of myocarditis associated with clozapine [47]; and • 1 article [48] with 1 haloperidol case that was included in Table 3.
6."perphenzine AND myocarditis": 1 article leading to 1 case
• 1 article which provided 1 case included in Table 3 [49].
7. 12 searches with no included articles
• The 5 articles from the risperidone search were excluded due to no cases [9, 23, 25] or cases due to clozapine [50, 51]. • The 4 articles from the ziprasidone search were excluded due to no cases [43, 52-54]. • The only article from the zotepine search was excluded due to no cases [55]. • The 2 articles from the amisulpride search were excluded due to no cases [23, 24]. • Of the 8 articles in the chlorpromazine search, 6 were excluded due to no cases [9, 22, 56-59], 1 case due to haloperidol [48] and another with 2 cases due to clozapine [20]. • The 6 articles in the thioridazine search were excluded due to no cases [52, 53, 55, 60-62]. • The 2 articles from the pimozide search were excluded due to no cases [53, 55]. • The 2 articles from the trifluoperazine search were excluded due to no cases [63, 64]. • The article in the sulpiride search included cases associated with clozapine [27]. • The only article on fluphenazine search was excluded due to no cases [9]. • The only article in the levomepromazine search was excluded due to no cases [24]. • The only article from the loxapine search was excluded due to no cases [65].
8. 13 searches with no identified articles
• Following antipsychotics: brexpiprazole, bromperidol, cariprazine, cyamemazine, flupentixol, lurasidone, paliperidone, perazine, periciazine, pipamperone, prochlorperazine, promazine, and zuclopenthixol.

Table 3. Cases of myocarditis from other antipsychotics identified in the article search.

Author	*Case*	*Age*	*Sex*	*Country*	*Psychiatric Diagnoses*	*Diagnoses of Myocarditis*	*Dose/Duration mg/day for time*	*Other medications*	*ADR scale*[a]
OLANZAPINE									
Vang et al., 2016 [30]	1	39	♂	Denmark	S & Subst	Autopsy	40 for 54 days	morphine, VEN, oxazepam	5 – probable
QUETIAPINE									
Hagiwara et al., 2018 [41]	2	37	♂	Japan	BPD	Within DRESS		lithium	1 – possible
Giuntoli et al., 2019 [40]	3	27	♀	Italy	None		Int overdose		no myocarditis[b]
Bhogal et al., 2018 [39]	4	31	♂	USA	GAD	Echocardiography	300 for 5 days		7 – probable
Gosselin et al., 2017 [38]	5	18	♀	Canada	PD	Autopsy	Int overdose	caused by acetaminophen[c]	no myocarditis
Wassef et al., 2015 [37]	6	18	♂	UK	ADHD	Cardiac MRI	ND for 3 weeks	methylphenidate (years)	7 – probable
Roesch-Ely et al., 2002 [36]	7	35	♀	Germany	S	ECG and labs	600 for 2 months		6 – probable/
HALOPERIDOL									
Bhatia et al., 2009 [48]	8	65	♀	India	S	EKG, CPK	80 Int overdose[c]	CPZ 1200 mg[d]	3 – possible
ARIPIPRAZOLE									
Christoffersen et al., 2011 [29] Vang et al., 2016 [30]	9	36	♂	Denmark	S	Autopsy	30 for 6 months	olanzapine 20 mg/day	arrhythmia[e]
ASENAPINE									
Lim et al., 2015 [44]	10	52	♀	Australia	S	Unclear symptom Echocardiography	15 for 19 days[f] 5 days[f]	quetiapine 50 mg/day	quetiapine may be cause[f]
PERPHENAZINE									
Ansari et al., 2003 [49]	11	66	♀	USA	S	Echocardiography	2 for 10 years	amitriptyline	myocardiopathy[g]

ADHD: Attention-deficit hyperactivity disorder; ADR; adverse drug reaction; BPD: bipolar disorder; CPK: creatinine phosphokinase; CPZ: chlorpromazine; DRESS: Drug Reaction with Eosinophilia and Systemic Symptoms; EKG: electrocardiogram; GAD: generalized anxiety disorder; Int: intentional; MRI: magnetic resonance imaging; ND: dose not described; PD: personality disorder; S: Schizophrenia; Subst: substance abuse; VEN: venlafaxine.

[a]Eleven published cases of potential myocarditis on other antipsychotics besides clozapine: five were excluded and only six were rated (two possible and four probable).

[b]Definitive quetiapine overdose but no obvious signs of myocarditis.

[c]The patient overdosed on acetylsalicylic acid and ethanol, which had not been associated with eosinophilic myocarditis [69]. The patient had a serious acetaminophen overdose. The literature on acetaminophen overdoses is complex. Sheikh et al. [69] does not include acetaminophen among the drugs associated with eosinophilic myocarditis. Khabazian Zadeh et al. [70] conducted a systematic review of myocardial lesions during acetaminophen overdoses leading to 23 reviewed articles, they found that myocardial lesions were not rare but myocarditis was rare. Gosselin et al., 2017 [38] blamed the myocarditis on acetaminophen rather than quetiapine and we agree with them.

[d]On the day of overdose, the haloperidol dose went from 15 to 80 mg/day and the dose of CPZ went from 100 to 1200 mg/day. We considered haloperidol to be the more likely cause of myocarditis, but we cannot rule out that CPZ contributed.

[e]The authors suspected the patient died because of arrythmia. The diagnosis of eosinophilic myocarditis was unclear: “the changes were of different ages, - in the areas with newer changes, there was infiltration of inflammatory cells dominated by eosinophilic granulocytes” [29].

[f]Clozapine had been discontinued before starting asenapine. "On asenapine, she experienced nausea, appetite loss, rhinorrhoea, diarrhoea and ankle oedema. These symptoms were initially thought to be side effects of asenapine, and thus it was ceased. She was then commenced on quetiapine 50 mg. After 5 days on quetiapine, she presented to the ED with dyspnoea, tachycardia, ankle oedema, and examination revealed bibasal crepitations and an S3 gallop" [44]. Although the authors argued that asenapine was the cause of myocarditis, we thought that quetiapine was more likely to be the cause. Due to the complexity of the case, we did not list this case in the quetiapine section.

[g]"histologic findings met the Dallas criteria for toxic myocarditis with fibrosis" [49]. The discontinuation of the drugs was not associated with improvement and the patient died two years later even after the discontinuation of both drugs. The patient also had chronic nonspecific hepatitis. The authors did not describe cardiac enzyme elevations during the drug treatment, which would suggest myocarditis.

Table 4. ICs for antipsychotics and myocarditis (April 7, 2021).

Antipsychotic	$N_{observed}$	$N_{expected}$	N_{drug}	IC_{025}	IC	$N_{country}$	$N_{serious}$	N_{fatal}
NO5A Group	3838	276	820929	3.7	3.8	34	2203	245
Clozapine	3665	57	170578	5.9	6.0	34	2077	178
Olanzapine	107	24	71675	1.8	2.1	14	84	13
Quetiapine	106	30	89926	1.5	1.8	13	88	33
Risperidone	63	38	113499	0.3	0.7	12	47	10
Aripiprazole	37	23	68794	0.2	0.7	7	29	4
Haloperidol	35	12	35814	1.0	1.5	7	23	6
Paliperidone	26	15	44523	0.2	0.8	7	24	2
Amisulpride	16	2	7368	1.7	2.5	5	5	2
Chlorpromazine	16	4	12882	1.0	1.8	4	10	6
Zuclopenthixol	13	1	4354	1.9	2.8	4	10	2
Fluphenazine	10	2	4882	1.3	2.3	5	6	6
Asenapine	7	2	7085	0.1	1.4	2	6	1
Cyamemazine	5	2	4956	-0.2	1.3	1	5	0
Lurasidone	5	4	10922	-1.1	0.4	3	5	1
Perphenazine	4	1	3293	-0.3	1.5	2	4	4
Flupentixol	4	1	3509	-0.3	1.4	2	1	0
Thioridazine	4	2	5010	-0.7	1.0	3	1	2
Loxapine	3	1	3681	-1.0	1.0	1	3	0
Perazine	2	0	998	-1.0	1.6	2	1	0
Levomepromazine	2	2	5604	-2.5	0.1	2	1	1
Prochlorperazine	2	3	8662	-3.0	-0.4	2	2	2
Ziprasidone	2	5	15451	-3.8	-1.2	1	2	2
Bromperidol	1	0	294	-2.5	1.3	1	0	1
Periciazine	1	0	765	-2.8	1.0	1	0	0
Pimozide	1	0	1087	-3.0	0.8	1	0	1
Promazine	1	0	1223	-3.1	0.7	1	0	0
Pipamperone	1	1	2165	-3.5	0.3	1	1	1
Trifluoperazine	1	1	2946	-3.8	0.0	1	0	1
Sulpiride	1	2	4981	-4.3	-0.5	1	1	1
Brexpiprazole	1	3	7485	-4.8	-1.0	1	0	0
Other drugs listed in the same category[a]								
Valproic acid	75	29	85587	1.0	1.4	7	59	23
Lithium	28	10	29678	0.9	1.4	11	21	4
Carbamazepine	23	23	69225	-0.7	0.0	11	14	6

IC: information component; IC_{025}: lower 95% confidence interval of IC; $N_{country}$: number of countries providing reports of myocarditis; N_{drug}: number of ADRs reported for this drug in VigiBase; $N_{expected}$: number of myocarditis cases expected, based on average numbers of myocarditis cases per drug reported to VigiBase; N_{fatal}: number of myocarditis cases that were fatal in VigiBase; NO5A Group: antipsychotic group; $N_{observed}$: number of myocarditis cases observed for this drug (or group); $N_{serious}$: number of myocarditis cases that were considered serious by VigiBase.

[a]Vigibase has included the myocarditis associated with these 3 drugs in the NO5A Group, so the total number of 3838 is mildly contaminated by these 3 drugs.

Table 5. VigiBase cases of myocarditis associated with antipsychotics potentially contaminated by duplicates.[a]

	N	Clozapine	Olanzapine	Quetiapine	Risperidone	Aripiprazole	Haloperidol	Paliperidone	Amisulpride	Chlorpromazine	Zuclopenthixol	Fluphenazine
Olanzapine	107	77%[b] (82/107)	11%[c] (12/107)	16	24	12	15	0	1	7	4	5
Quetiapine	106	48%[b] (51/106)	24	44%[c] (47/106)	9	6	5	0	1	0	3	1
Risperidone	63	73%[b] (46/63)	24	9	14%[c] (10/63)	3	13	0	1	6	1	6
Aripiprazole	37	86%[b] (32/37)	13	6	3	8%[c] (3/37)	2	0	3	0	3	0
Haloperidol	35	77%[b] (27/35)	15	5	13	2	11%[c] (4/35)	0	1	7	1	5
Paliperidone	26	62%[b] (16/26)	5	2	2	1	1	15%[c] (4/26)	1	1	1	0
Amisulpride	16	94%[b] (15/16)	1	1	1	3	1	0	0%[c] (0/16)	0	0	0
Chlorpromazine	16	69%[b] (11/16)	7	0	6	0	7	0	0	19%[c] (3/16)	2	5
Zuclopenthixol	13	77%[b] (10/13)	4	3	1	3	1	0	0	2	8%[c] (1/13)	0
Fluphenazine	10	60%[b] (6/10)	5	1	6	0	5	0	0	5	0	10%[c] (1/10)

[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. Only antipsychotics with at least 10 myocarditis reports are listed in the table.

[b]These percentages represent the number of myocarditis cases using the antipsychotic and clozapine divided by the number of myocarditis cases reported for that antipsychotic.

[c]These percentages represent the number of myocarditis cases using only that antipsychotic divided by the number of myocarditis cases reported for that antipsychotic. Other drugs besides antipsychotics could be co-prescribed.

Table 6. After eliminating duplicates in VigiBase: myocarditis cases in patients on monotherapy with an antipsychotic other than clozapine.

Case	*Year*	*Region*[a]	*Sex*	*Age*	*Seriousness*	*Comments*	*ADR scale*[b]
76 olanzapine non-duplicated reports and 11 on olanzapine monotherapy (15%, 11/76)							
1	2000	North America	♀	40	Fatal	Infection was present	Possible viral myocarditis
2	2002	Europe	♂	42	No	Prior treatment with digoxin	Worsening of heart problem
3	2003	Europe	♂	42	Fatal	After 5 years on olanzapine	0 – doubtful
4	2003	North America	♂	8	Fatal	Ventricular fibrillation, arrest	Limited information
5	2008	Europe	♂	28	Fatal	After 5 years on olanzapine	0 – doubtful
6	2009	Europe	♀	32	Yes, but not fatal	Important medical conditions	0 – doubtful
7	2011	Europe	♂	50	Yes, but not fatal	Important medical conditions	Inconsistent information
8	2014	Europe	♂	32	Fatal	Important medical conditions	Possible NMS/catatonia
9	2017	Europe	♂	-	Yes, but not fatal	Important medical conditions	Limited information
10	2020	Europe	♀	34	Yes, but not fatal		Limited information
11	2020	Oceania	♂	60	Yes, but not fatal		Limited information
55 quetiapine non-duplicated reports and 15 on quetiapine monotherapy (27%, 15/55)							
1	2002	Europe	♂	35	No	Infection was present	Possible NMS
2	2002	Europe	♀	68	Fatal	Found after cardiac arrest	Limited information
3	2005	Oceania	♂	35	No	1000 mg/day unknown time	6 – probable
4	2008	North America	♂	45	Fatal	Sepsis and pancreatitis (VPA)	Completed suicide
5	2011	Europe	-	-	No		Limited information
6	2011	North America	♀	54	Fatal	Abdominal hernia repair	Limited information
7	2012	North America	♀	15	Yes, but not fatal	Complex overdose	Limited information
8	2012	Europe	♂	35	Yes, but not fatal	Eosinophilia/pancytopenia	2 – possible
9	2014	Europe	-	-	Yes, but not fatal	Prolonged hospitalization	Limited information
10	2014	Europe	♂	57	Yes, but not fatal	On 9th day: 1200 mg/day	5 – probable
11	2015	Europe	♂	18	Yes, but not fatal		3 – possible
12	2018	Europe	♂	17	Yes, but not fatal	300 mg/day for 38 days	Other possible cause[c]
13	2018	North America	♀	18	Fatal		Case 5 of Table 3
14	2018	North America	♂	31	Yes, but not fatal	Prolonged hospitalization	Limited information
15	2019	Asia	♂	37	Yes, but not fatal		Case 2 of Table 3
42 risperidone non-duplicated reports and 10 on risperidone monotherapy (24%, 10/42)							
1	1999	Europe	♂	40	No		Limited information
2	2000	North America	-	14	No	Prescribed for 4 years	Limited information
3	2000	North America	♀	55	Fatal		Limited information
4	2002	North America	♂	12	No	Pleural effusion/myocarditis	Limited information

5	2004	Europe	♂	-	No	AV blockade/myocarditis	Limited information
6	2006	North America	♂	23	Yes, but not fatal	Prescribed for >4 months	Limited information
7	2009	North America	♂	71	Yes, but not fatal	↑ troponin in dementia	Limited information
8	2014	Europe	♀	21	Yes, but not fatal	2 other antipsychotics	Limited information
9	2014	North America	-	-	Fatal	MI/myocarditis	Limited information
10	2017	Europe	♂	18	Yes, but not fatal		Limited information
25 aripiprazole non-duplicated reports and 2 on aripiprazole monotherapy (8%, 2/25)							
1	2009	North America	♂	15	Yes, but not fatal	20 mg/day for 18 months	3 – possible
2	2013	Oceania	♀	57	Fatal		Limited information
26 haloperidol non-duplicated reports and 3 on haloperidol monotherapy (12%, 3/26)							
1	1984	Oceania	♀	23	Fatal	120 mg/day	Limited information
2	1988	North America	♀	46	Fatal	With TCAs for15 months	Limited information
3	1988	North America	♀	49	Fatal		Limited information
15 paliperidone non-duplicated reports and 4 on paliperidone monotherapy (27%, 4/15)							
1	2011	North America	♂	-	Yes, but not fatal		Limited information
2	2014	Europe	♀	-	Yes, but not fatal		Limited information
3[d]	2017	Europe	♀	-	Yes, but not fatal	↑ liver enzymes and myopericarditis	Limited information
4[d]	2021	Europe	♂	24	Yes, but not fatal	Myocarditis (left sequelae)	Limited information
11 chlorpromazine non-duplicated reports and 3 on chlorpromazine monotherapy (27%, 3/11)							
1	1979	Europe	♂	26	Fatal		Limited information
2	2008	North America	♀	31	Fatal	1 day of treatment for rash	Limited information
3	2017	Europe	♀	48	Yes, but not fatal		Caused by carboplatin[e]
11 fluphenazine non-duplicated reports and 1 on fluphenazine monotherapy (9%, 1/11)							
1[f]	2011	Europe	♂	33	No		Limited information
1 pimozide non-duplicated report and 1 on pimozide monotherapy (100%, 1/1)							
1	1984	Europe	♀	-	Fatal		Limited information
3 loxapine non-duplicated reports and 1 on loxapine monotherapy (33%, 1/3)							
1	2008	Europe	♀	21	Yes, but not fatal	Intentional overdose	6 – probable
2 perphenazine non-duplicated reports and 1 on perphenazine monotherapy (50%, 1/2)							
1	2005	North America	♀	66	Fatal	TCA and chronic hepatitis	Limited information
4 cyamemazine non-duplicated reports and 1 on cyamemazine monotherapy (25%, 1/4)							
1	2020	Europe	♂	48	Yes, but not fatal	850 mg/day for 6 days	6 – probable

AV: atrioventricular; MI: myocardial infarct; NMS: neuroleptic malignant syndrome; TCA: tricyclic antidepressant; VPA: valproic acid.
[a]The region is provided instead of country to avoid identifying the case.

[b]53 VigiBase cases of potential myocarditis while on antipsychotics other than clozapine: 43 were excluded and only 10 were rated (3 doubtful, 3 possible and 4 probable).
[c]The patient was also taking a tetracycline (lymecycline). Tetracyclines have been repeatedly associated with drug hypersensitivity including myocarditis [71]. The patient recovered after discontinuing quetiapine and lymecycline.
[d]Paliperidone palmitate.
[e]Carboplatin has been associated with myocarditis [72].
[f]Fluphenazine decanoate.