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Pharmacovigilance in Action: Utilizing VigiBase Data to Improve Clozapine Safety

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Purpose: Clozapine is an antipsychotic which was approved in 1989 for treatment-resistant schizophrenia in the United States (US). There were few randomized trials before its approval and potentially lethal clozapine adverse drug reactions (ADRs), such as agranulocytosis and myocarditis were identified by pharmacovigilance. VigiBase, the WHO global database, is a cornerstone of international pharmacovigilance efforts for ADR identification during post-marketing surveillance. This systematic review of the literature explores additional contributions to the knowledge of clozapine ADRs from recent VigiBase studies.

Methods: Using the terms "clozapine AND VigiBase" we conducted an article search in PubMed on September 5, 2024. Of the 29 articles, 11 were excluded and 18 described in the Results section.

Results: All clozapine ADRs were described in two VigiBase studies. One on pregnancy indicated no increased risk with clozapine compared with other antipsychotics; the other reported 191,557 clozapine ADRs, including 22,956 fatal outcomes through January 15, 2023, and paid attention to the reporting style of the top 4 reporting countries (the US, the United Kingdom, Canada and Australia). Infections were described in three VigiBase studies where clozapine treatment was associated with infections, respiratory aspiration, and pneumonia. Rapid titration can lead to localized clozapine-induced inflammations including myocarditis, pericarditis or pancreatitis, or generalized inflammations such as drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome. Clozapine-induced inflammation was described in four VigiBase studies, two focused on all ages (myocarditis and DRESS) and two on youth (myocarditis and another on pericarditis and pancreatitis). Other specific ADRs were described in nine VigiBase studies (hematological malignancies, rhabdomyolysis, sialorrhea, seizures, diabetes mellitus, drug-induced parkinsonism, withdrawal symptoms, and suicidal behaviors).

Conclusion: The spectrum of respiratory aspiration – aspiration pneumonia – pneumonia and other infections are significant causes of fatal outcomes in clozapine-treated patients. Clozapine had anti-suicidal effects versus other antipsychotics across all VigiBase labels of suicidal behavior.

Plain Language Summary:

Why was the review done? Marketers develop a package insert after a medical drug is licensed for use in each country. The package insert describes the known benefits and risks of the drug at the time it was licensed. After licensing, post-marketing studies are continued to look for possible undetected adverse drug reactions; this process is called pharmacovigilance. These pharmacovigilance studies should be done by the drug agencies in all countries. These national agencies send their reports to the international pharmacovigilance database, VigiBase. VigiBase is managed by the World Health Organization and is located in Uppsala, Sweden. Clozapine is a second-generation antipsychotic medication that was licensed in 1989 in the United States for treatment-resistant schizophrenia and then approved by other countries. In 1989 there was major concern about clozapine causing agranulocytosis (loss of white blood cells), so a hematological monitoring system was required in the United States. Later, myocarditis was associated with clozapine in pharmacovigilance studies.

What did the authors do? They systematically reviewed VigiBase studies on clozapine adverse drug reactions and identified 18 studies that described clozapine adverse drug reactions in detail.

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What do these results mean? These VigiBase studies indicate that the respiratory aspiration – aspiration pneumonia – pneumonia spectrum, along with other infections, are significant causes of fatal outcomes in clozapine-treated patients, but this is not mentioned in any clozapine package insert. On the positive side, VigiBase data confirms other literature that clozapine may have specific anti-suicidal effects not present in other antipsychotics.

Keywords: clozapine/adverse effects, clozapine/therapeutic use, clozapine/toxicity, drug labeling, product surveillance, postmarketing, schizophrenia

Introduction

Introduction to the History of Pharmacovigilance

Pharmacovigilance, the practice of monitoring the effects of medical drugs after they have been licensed for use, has been used for nearly 200 years, years marked by significant events that have shaped its evolution.[1–3] A pivotal moment occurred in the early 1960s when around 10,000 children were born with severe malformations due to thalidomide, a drug commonly used by pregnant women for morning sickness.[4] This historical event underscores the continuous effort to ensure drug safety and the critical importance of systematic monitoring, documentation, and communication in protecting public health.[5]

In response to the thalidomide tragedy, the United Kingdom (UK) pharmacovigilance agency established the Yellow Card Scheme in 1964 for reporting drug toxicities.[6] In 1965, European legislation was enacted to regulate medicinal products. The World Health Organization (WHO) launched the International Drug Monitoring Program in 1968, and by 1978, Sweden assumed its scientific and technical responsibilities, establishing the Uppsala Monitoring Centre (UMC).[7]

Background on Clozapine and Its Clinical Significance

Clozapine is a second-generation antipsychotic medication, primarily indicated for the treatment of treatment-resistant schizophrenia (TRS) and schizoaffective disorder.[8,9] In the United States (US), clozapine was also approved to prevent suicide in schizophrenia psychoses,[10] but the approved indications for clozapine vary widely across the world.[11–16]

Since its introduction in the 1970s, clozapine has been recognized for its superior efficacy to other antipsychotic drugs.[17,18] Clozapine has a unique pharmacological profile, with loose binding to dopamine D_2 receptors,[19] but its mechanism of action is not completely understood.[20] Moreover, clozapine is associated with a lower risk of extrapyramidal side effects and tardive dyskinesia, making it a valuable option for long-term treatment.[21]

However, the clinical utility of clozapine is counterbalanced by its potential to induce severe adverse drug reactions (ADRs), including agranulocytosis,[22] myocarditis,[23] and metabolic disturbances.[24] As clozapine underwent few randomized trials before its approval in the 1970s in German-speaking countries and its resurrection in 1989 in the US for TRS, it is not surprising that potentially lethal clozapine ADRs, such as agranulocytosis and myocarditis, were identified by pharmacovigilance.[25] Clozapine use is complicated by the need for patient adherence to complex monitoring protocols, the risk of drug-drug interactions[26–28] and the management of common ADRs such as sedation, sialorrhea, and constipation.[29,30] It has been suggested recently that clozapine-induced myocarditis is part of a spectrum of clozapine-induced inflammation[31] that may be prevented by slower clozapine titration.[32–35]

The necessity of regular blood testing due to potential agranulocytosis and potentially severe ADRs are barriers that significantly limit clozapine use, highlighting the importance of continued research and improve patient outcomes.[36–39]

Importance of Pharmacovigilance in Medication Safety

Pharmacovigilance is a critical component of medication safety, encompassing the detection, assessment, understanding, and prevention of ADRs and other drug-related problems. It plays a pivotal role in safeguarding public health by ensuring that the benefits of medications outweigh their risks.[40] Effective pharmacovigilance systems enable the early identification of safety signals, facilitating timely interventions to mitigate adverse outcomes.[41]

In the context of clozapine, pharmacovigilance has been particularly vital due to the drug's complex safety profile and very limited studies before its US approval.[25] Continuous monitoring and reporting of ADRs allow for the development of evidence-based guidelines and risk management strategies.

Introduction to VigiBase and Its Role in Global Pharmacovigilance

VigiBase, the WHO global database of individual case safety reports (ICSRs), is a cornerstone of international pharmacovigilance efforts for ADR identification during post-marketing surveillance. VigiBase collects and analyzes data from national pharmacovigilance centers worldwide.[42] VigiBase provides a comprehensive overview of drug safety, facilitating cross-country comparisons and the identification of regional differences in ADR reporting.[43]

Description of VigiBase and Its Data Collection Process

VigiBase collects data from over 150 national pharmacovigilance centers worldwide. Each ICSR contains detailed information about ADRs reported by healthcare professionals, patients, and pharmaceutical companies. The reporting person sometimes classifies ADRs, but usually those who report enter free text information and the pharmacovigilance staff at a regional or national center or pharmaceutical company do the encoding, using the categories provided by the database. The data include patient demographics, drug information, reaction details, and outcomes.[44]

The data collection process for VigiBase involves the submission of ICSRs from national pharmacovigilance centers to the UMC. These reports are standardized according to WHO guidelines to ensure consistency and reliability across different reporting systems. The UMC employs advanced data management and signal detection tools, such as VigiFlow and VigiLyze, to process, analyze, and identify potential safety signals from the reported ADRs.

Methodology for Analyzing VigiBase Data

The analysis of VigiBase data involved several systematic steps:

1. ***Data Extraction***: Relevant ICSRs were extracted from VigiBase using specific search criteria aligned with the studies' objectives. Advanced querying tools were used to filter and retrieve pertinent data.
2. ***Descriptive Analysis***: Basic statistical analyses were performed to describe the frequency and distribution of ADRs associated with any drug. This included demographic characteristics of patients, types of ADRs, outcomes, and geographical distribution.
3. ***Disproportionality Analysis***: Disproportionality analysis is a crucial method in pharmacovigilance used to identify potential safety signals associated with drugs. This process involves comparing the observed and expected rates of ADRs to detect unusual patterns that may indicate a safety concern. One of the key metrics used in this analysis is the Information Component (IC) and its confidence intervals (CIs). The IC is a Bayesian measure employed by VigiBase for disproportionality analyses. The IC is designed to identify signals by comparing the actual number of reported ADRs with the expected number based on overall reporting rates. The calculation of the IC involves Bayesian statistics, which allows for the incorporation of prior knowledge and uncertainty in the analysis. Sometimes researchers not having access to the ICs from VigiBase use frequentist methods, such as the proportionality reporting ratio (PRR) or the reporting odds ratio (ROR).[45]

A positive IC value suggests that the observed reporting rate of a particular ADR is higher than what would be expected based on general reporting patterns. This indicates a potential safety signal that warrants further investigation. Specifically, an IC above a certain threshold, such as IC_{025} (the lower bound of the 97.5% confidential interval for the IC), is considered significant. This threshold ensures that the signal is not due to random variation but represents a genuine increase in reporting frequency. Conversely, a negative IC value implies that the observed reporting rate is lower than expected. This may indicate that the ADR is less commonly associated with the drug compared to other drugs in the database.

The IC_{025} value is particularly important in signal detection as it provides a conservative estimate of disproportionality. By focusing on the lower bound of the 97.5% credibility interval, IC_{025} accounts for statistical uncertainty, ensuring

that only robust signals are flagged. An IC_{025} value greater than zero is indicative of a statistically significant higher-than-expected reporting rate, suggesting a potential safety signal that requires further scrutiny.[46,47]

4. ***Comparative Analysis***: The incidence and nature of any drug-related ADR can be compared across different regions and demographic groups to identify patterns and disparities.
5. ***Case Review***: In-depth review of selected case reports, particularly those involving rare or severe ADRs, provides detailed insights into the clinical context and potential risk factors.

As far as the authors understand, the Food and Drug Administration (FDA), the European drug agency (EudraVigilance), and all other national or international databases incorporated into the WHO program share their data with VigiBase and also have access to VigiBase data. Each particular database calculates its statistical measures according to its specific interests. However, each database performs these calculations against its own records, whereas the WHO Database (VigiBase) performs calculations against all records provided by all the participating members/countries. For this reason, the values are different as the background of the data used in the calculations is different, too.

This article summarizes the literature by conducting a systematic review of the VigiBase literature to explore additional contributions to our knowledge of clozapine ADRs.

Methods

Article Search

Pharmacovigilance is a MeSH heading in PubMed but using it would have led to a contamination of the articles from other pharmacovigilance agencies and the authors wanted to limit themselves to VigiBase as they understand its strengths and weaknesses well; thus, after several attempts they decided the best search strategy was to use the terms ”clozapine AND VigiBase”. This PubMed search was conducted in PubMed on September 5, 2024, leading to 29 articles after the elimination of one duplicate article. The initial screening process involved a detailed review of the titles and abstracts by first and last authors and then the whole article was read (Figure 1). Of the 29 articles identified, 11 were excluded due to 1) a focus on drugs other than clozapine (4 articles),[48–51] 2) inclusion in other larger sample articles (3),[11–13] and 3) being commentaries of published samples (4).[52–55] The final selection included 18 articles which are detailed in Table 1[56,57] with two articles including all clozapine ADRs, Table 2[58–60] with three articles on possible clozapine ADRs related to infections, Table 3[61–64] with 4 articles on clozapine-induced inflammation, and Table 4[65–73] with nine articles on other specific clozapine ADRs.

Results

Studies with All Clozapine ADRs

Table 1 shows the findings from two studies that analyzed all clozapine ADRs. Beex-Oosterhuis et al[56] found no significant signal of disproportionate reporting associating clozapine with adverse pregnancy outcomes compared to other antipsychotics. Specifically, they identified 42,236 unique clozapine-related ICSR-ADR combinations, with 494 adverse pregnancy outcomes. The RORs for pregnancy, labor, and delivery complications, termination of pregnancy and risk of abortion, congenital, familial, and genetic disorders, and neonatal disorders were all below 1, indicating no increased risk with clozapine when compared with other antipsychotics. These findings suggest that clozapine may be considered for use during pregnancy with appropriate monitoring.

De las Cuevas et al[57] highlighted variability in ADR reporting among countries by focusing on all clozapine ADRs and exploring the 4 reporting countries: the US, the United Kingdom, Canada and Australia. Variability across countries complicates cross-national comparisons as they may be contaminated by different levels of underreporting. Until January 15, 2023, they reported 191,557 clozapine ADRs, including 22,956 fatal outcomes, with higher fatality estimates in the UK and Canada after population adjustments. The most frequently reported ADRs involved the blood/lymphatic, nervous, cardiac systems, and infections. Other articles derived from this search are not included in Table 1 but include subanalysis with relatively little data due to major underreporting from Latin America,[13] Western[11] and Eastern Europe.[12]

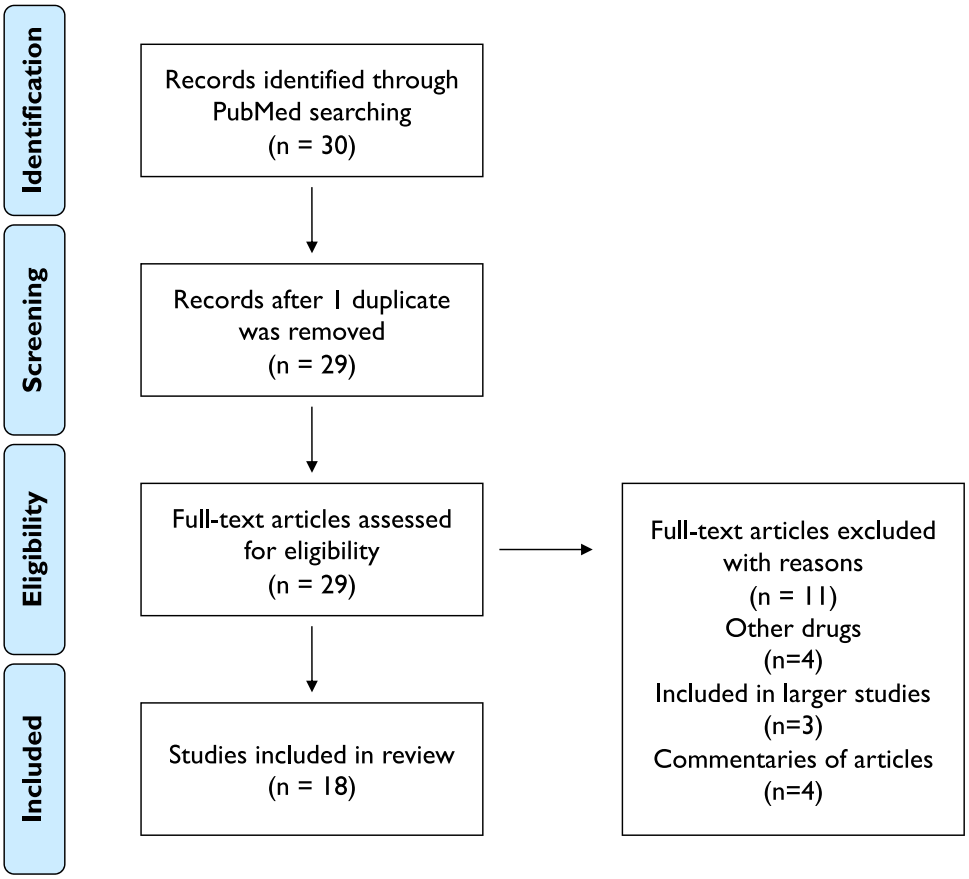

Figure 1 Flow chart with article search.

Studies with Clozapine ADRs Related to Infections

Table 2 shows the findings from three studies that analyzed clozapine ADRs related to infections. After a comprehensive review of 196 labels associated with infections, Chrétien et al[58] identified a statistically significant increase in infection

Table 1 VigiBase Studies with All CLO ADRs

Study	Data Source	Other drugs	Key Findings	Comments
			Metrics	
Beex-Oosterhuis et al[56]	VigiBase Inception -January 1, 2018	No	No significant signal of disproportionate reporting associating CLO with adverse pregnancy outcomes compared to other APs.	The study found no evidence that CLO is less safe during pregnancy compared with other APs. Despite the known serious ADRs of CLO, no significant increase in pregnancy-related adverse events was observed. The findings suggest that CLO can be considered for use during pregnancy with appropriate monitoring and risk-benefit analysis.
			Total unique ICSR-ADR combinations with CLO: 42,236. Adverse pregnancy outcomes with CLO: 494 (compared to 4,645 with other APs). RORs for adverse pregnancy outcomes with CLO versus other APs: Pregnancy, labor, and delivery complications: ROR 0.44 (95% CI, 0.39–0.51); Termination of pregnancy and risk of abortion: ROR 0.56 (95% CI, 0.43–0.73); Congenital, familial, and genetic disorders: ROR 0.37 (95% CI, 0.29–0.47); Neonatal disorders: ROR 0.32 (95% CI, 0.25–0.40)	

(*Continued*)

Table 1 (Continued).

Study	Data Source	Other drugs	Key Findings Metrics	Comments
De las Cuevas et al,[57]	VigiBase Inception -January 1, 2023	No	4 reporting countries (the US, the UK, Canada and Australia) reported CLO ADRs in different ways, making comparisons difficult. 191,557 clozapine ADRs associated with 22,956 fatal outcomes	Blood/lymphatic, nervous system, cardiac, and infections top ADR categories. Higher fatal outcomes were estimated in the UK and Canada after adjusting for population cross-sectional estimates and published CLO use but they may reflect better reporting.

Abbreviations: ADR, adverse drug reaction; AP, antipsychotic; CI, confidence interval; CLO, clozapine; ROR, reporting odds ratio; UK, United Kingdom; US, United States.

Table 2 VigiBase Studies with CLO ADRs Related to Infections

Study	Data Source	Other drugs	Key Findings Metrics	Comments
Chrétien et al[58]	VigiBase Inception-April 11, 2023	No	CLO is linked with a statistically significant increase in reported infections, particularly respiratory and gastrointestinal. 19,404 infections reports. IC of 0.43 [95% CI: (0.41–0.45)]. Notably, 94.3% were serious, and 9.8% fatal.	This signal was of similar magnitude among genders and tested age groups. It was also consistent over time.
De las Cuevas et al[59]	PubMed, VigiBase Inception-September 5, 2021	APs	CLO is more associated with respiratory aspiration than other APs. 746 reports, APs IC=2.1 (IC_{025}= 2.0); CLO IC=3.2 (3.0); Quetiapine IC=2.6 (2.4); Olanzapine IC=2.5 (2.2)	CLO is particularly prone to cause respiratory aspiration through multiple mechanisms, tends to be strongly associated with fatal respiratory aspiration, and most of clozapine respiratory aspiration occurred in non-geriatric patients and during treatment instead of during overdose.
de Leon et al[60]	VigiBase Inception-May 10, 2023	No	Robust association between CLO use and the incidence of pneumonia and aspiration pneumonia. The high misclassification rate of aspiration pneumonia suggests potential overlap in clinical presentations, underscoring the need for refined diagnostic criteria to enhance patient management and safety. 5572 cases of pneumonia, 775 of aspiration pneumonia, and 45 combined. Aspiration pneumonia IC= 3.53 (IC_{025}= 3.42); Pneumonia IC= 1.91 (IC_{025}= 1.87)	In CLO-treated patients: 1) At least 30% of pneumonia cases may be aspiration pneumonia. 2) As co-prescriptions with olanzapine, risperidone, valproic acid or benzodiazepines were associated with signs of aspiration, it is possible that their discontinuation may reduce the risk of aspiration pneumonia. 3) The average lethality rate for pneumonia is 45%, but it may rise to around 75% in geriatric patients undergoing long-term treatment

Abbreviations: ADRs, adverse drug reactions; AP, antipsychotic; CLO, clozapine; IC, information component; IC_{025}, lower 97.5% confidence interval of the IC.

reports associated with clozapine, particularly respiratory and gastrointestinal infections. They recorded 19,404 infection reports, with an IC of 0.43 (95% CI: 0.41–0.45), noting that 94.3% of these infections were serious and 9.8% were fatal. The signal was consistent across genders, age groups, and over time.

De las Cuevas et al[59] found that clozapine was more associated with respiratory aspiration than other antipsychotics. The clozapine ICs (and IC_{025}) were 3.2 (and 3.0) for clozapine while the ICs for antipsychotics were 2.1 (and 2.0), for quetiapine 2.1 (and 2.0) and for olanzapine 2.5 (and 2.2). After controlling other variables using logistic regression models, increased fatal outcomes were associated with clozapine versus other antipsychotics and with geriatric age in

clozapine-treated patients. Multiple antipsychotic pharmacological mechanisms may explain respiratory aspiration. Clozapine 1) is an antipsychotic particularly prone to cause respiratory aspiration through multiple mechanisms, 2) tends to be strongly associated with fatal respiratory aspiration, and 3) most of its respiratory aspiration occurs in non-geriatric patients and during treatment instead of during overdose. There were 333 cases of respiratory aspiration in clozapine-treated patients (many of these patients were taking other medications that can interfere with swallowing) and 25% (82/333) developed pneumonia. Massive respiratory aspiration can lead to immediate fatal outcomes, precluding the development of pneumonia. There were 89 non-fatal respiratory aspirations in clozapine-treated patients and 38% (36/95) developed pneumonia. Thus, clozapine appears to be associated with an ADR spectrum from respiratory aspiration to aspiration pneumonia to pneumonia.

In a further study of this spectrum, de Leon et al[60] reported a robust association between clozapine use and pneumonia, including aspiration pneumonia, with 5,572 pneumonia cases and 775 aspiration pneumonia cases. They observed a high misclassification rate between aspiration pneumonia and infectious pneumonia without aspiration, suggesting the need for refined diagnostic criteria, but concluded at least 30% of pneumonia cases in clozapine-treated patients were aspiration pneumonia. Signs of aspiration pneumonia were strongly associated with some co-medications: olanzapine, risperidone, valproic acid, and benzodiazepines indicating that the discontinuation of these co-medications could reduce this risk of repeated aspiration pneumonia. The average lethality rate for pneumonia was 45%, potentially rising to 75% in geriatric patients undergoing long-term treatment.

Studies of ADRs Related to Clozapine-Induced Inflammation

Table 3 shows the findings from four studies that analyzed clozapine-induced inflammation-related ADRs.[31] De las Cuevas et al[61] reported a strong association between clozapine and myocarditis, with 3,572 reports and an IC of 6.0 (IC_{025}= 5.9). They found that 43% of myocarditis cases were non-serious, 52% were serious but non-fatal, and 5% were fatal. Myocarditis was particularly associated with early clozapine treatment, with over-representation of reports from Australia and potential underreporting in Asian countries. In an extension of this prior study only focused on children and

Table 3 VigiBase Studies of ADRs Related to CLO-induced Inflammation

Study	Data Source	Other drugs	Key Findings Metrics	Comments
De las Cuevas et al[61]	VigiBase Inception -January 15 2021	APs	Strong association between CLO and myocarditis compared to other APs 3,572 reports, IC= 6.0 (IC_{025}= 5.9); 43% non-serious, 52% serious but non-fatal, and 5% fatal cases	Myocarditis is definitively associated with early CLO treatment. Myocarditis reports from Australia are over-represented to a major degree while Asian countries may be underreporting myocarditis to their drug agencies.
De las Cuevas et al[62]	PubMed, VigiBase Inception -June 1, 2022	No	CLO-induced myocarditis can occur in children and presents similarly to cases in adults 76 cases, IC= 4.2 (IC_{025}= 3.8)	Fatal outcomes were lower in children (1.4% of 72) compared to the overall sample (4.8% of 3274). After adjusting for confounders, quetiapine significantly increased the risk of serious outcomes (OR = 17.6, 95% CI: 1.56-198.6).
de Filippis et al[63]	PubMed, VigiBase Inception -June 1, 2022	No	Despite the lack of attention in the literature to CLO-associated pericarditis and pancreatitis, results demonstrate that they can happen in youth, particularly during titration. 22 reports of CLO-associated pericarditis IC= 3.6 (IC_{025} = 2.9) and 16 reports of pancreatitis IC= 2.2 (IC_{025}= 1.4)	CLO-associated pericarditis and pancreatitis during CLO titrations probably 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 CLO titration schedules and CRP monitoring.

(*Continued*)

Table 3 (Continued).

Study	Data Source	Other drugs	Key Findings	Comments
			Metrics	
de Filippis et al[64]	VigiBase Inception -July 1, 2022	APs	CLO is associated with a significant number of reports of DRESS syndrome.	The study found a significant association between CLO and DRESS syndrome, which emphasizes the need for increased vigilance and monitoring for this serious ADR. CLO-associated DRESS syndrome presents with a unique clinical pattern that includes fever, eosinophilia, and internal organ involvement, requiring timely identification and management to prevent severe outcomes.
			800 reports of DRESS syndrome associated with CLO with a ROR= 2.3 (95% CI 2.1–2.5) and a IC=1.2 (95% CI 1.1–1.3).	

Abbreviations: ADRs, adverse drug reactions; AP, antipsychotic; CI, confidence interval; CLO, clozapine; CRP, c-reactive protein; DRESS, drug reaction with eosinophilia and systemic symptoms; IC, information component; IC_{025}, lower 97.5% confidence interval of the IC; OR, odds ratio; ROR, reporting odds ratio.

adolescents, De las Cuevas et al[62] found 76 cases of clozapine-induced myocarditis and an IC of 4.2 (IC_{025}= 3.8). Fatal outcomes were lower in children (1%) compared to the overall sample (4.8%), and quetiapine significantly increased the risk of serious outcomes.

By focusing on VigiBase and published cases, De Filippis et al[63] highlighted that clozapine-associated pericarditis and pancreatitis can occur in youth, particularly during titration, with 22 reports of pericarditis (IC= 3.6, IC_{025}= 2.9) and 16 reports of pancreatitis (IC= 2.2, IC_{025}= 1.4). Another study by de Filippis et al[64] found a significant association between clozapine and drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome, with 800 reports and an IC of 1.2 (95% confidence interval CI 1.1–1.3).

Studies of Other Specific Clozapine ADRs

Table 4 shows the findings from nine studies that analyzed other specific clozapine-induced ADRs. Chrétien et al[65] identified a significant association between clozapine and hematologic malignancies, reporting 493 cases of malignant lymphoma with an adjusted ROR (aROR) of 9.14 with 95% CI of 7.75–10.77 and 275 cases of leukemia (aROR 3.54, 95% CI 2.97–4.22). The median time to onset was 5.1 years for malignant lymphoma and 2.5 years for leukemia. They proposed that clozapine should be used at the lowest effective dose to mitigate these risks. Star et al[66] found that clozapine was significantly associated with rhabdomyolysis in children and adolescents with 26 total reports. The 26

Table 4 VigiBase Studies of Other Specific CLO ADRs

Study	Data Source	Other drugs	Key Findings	Comments
			Metrics	
Chrétien et al[65]	VigiBase Inception -March 3, 2019	No	CLO was significantly associated with hematologic malignancies	The median time to onset was 5.1 years (IQR 2.2–9.9) for malignant lymphoma and 2.5 years (IQR 0.6–7.4) for leukemia. CLO should be used at the lowest effective dose.
			For CLO: 493 malignant lymphoma cases (aROR 9.14, 95% CI 7.75–10.77) and 275 leukemia cases (aROR 3.54, 95% CI 2.97–4.22)	
Star et al[66]	VigiBase Inception -February 5, 2010	APs	CLO was significantly associated with rhabdomyolysis.	Monitoring should be intensified when CLO dose is increased. Seemingly nonserious symptoms such as abdominal pain, muscle pain, weakness, and dark urine should be followed up as they could be precursors to rhabdomyolysis which may develop into acute renal failure
			26 total AP reports on children and adolescents, 20 reports of rhabdomyolysis without NMS and 6 reports of rhabdomyolysis with NMS	

(*Continued*)

Table 4 (Continued).

Study	Data Source	Other drugs	Key Findings Metrics	Comments
Man et al[67]	VigiBase Inception -May 5, 2016	APs	CLO was associated with a significantly higher frequency of sialorrhea (excessive salivation) compared to other APs. CLO registered 2,732 reports of sialorrhea (1.1% of clozapine ADRs) with ROR= 3.60 (95% CI, 3.41–3.79)	The study found that sialorrhea was reported almost 4 times more frequently with CLO use than with other AP use. The issue was significantly underreported by healthcare professionals compared to patients, suggesting a need for increased awareness and discussion of this ADR when initiating CLO therapy.
Kumlien and Lundberg.[68]	VigiBase Inception -2006	Other including APs	CLO was associated with a significant proportion of seizures among neuroactive drugs. CLO had 3,758 reports of seizures making up 9.0% of drug-induced seizures by neuroactive drugs.	The study emphasized that seizure risk of CLO is high and place it in the context of other neuroactive drugs.
Montastruc et al[69]	VigiBase Inception -March 29, 2013	APs	CLO was the top AP associated with diabetes mellitus (possibly explained by 5-HT_{2C} and H_1 binding). CLO explained 53% of diabetes mellitus reports. Among APs 5-HT_{2C} receptor occupancy had a AOR=:2.13 (95% CI, 1.72–2.64) and H1 receptor occupancy AOR=2.04 (95% CI, 1.46–2.84).	The study emphasized the need for monitoring glycemic disturbances in patients treated with CLO.
Linselle et al[70]	VigiBase Inception -May 2015	Other including APs	CLO was one of the drugs associated with induction or aggravation of sleep apnea syndrome CLO registered 104 of 3325 total reports. CLO ROR = 2.4 (95% CI, 2.0–2.9).	The study emphasizes the need for physicians to monitor for sleep apnea syndrome in patients prescribed clozapine, especially considering its sedative properties that may contribute to respiratory depression.
de Germay et al[71]	VigiBase Inception -December 31, 2017	Other including APs	CLO had the lowest disproportionality value for drug-induced parkinsonism among studied drugs. CLO provided 160 of 4565 reports of drug-induced parkinsonism. The ROR ordered from high to low were for sulpiride and haloperidol followed by risperidone, aripiprazole, paliperidone, metoclopramide, olanzapine, quetiapine and CLO.	The authors propose that CLO may have a unique pharmacological profile, particularly its affinity to D_4.
Storck et al[72]	VigiBase From 2000 to 2022	APs	CLO was associated with a lower risk of all kinds of withdrawal syndromes compared with other APs. CLO provide 281 (13%) of 2151 AP withdrawal syndrome reports. Clozapine ROR=0.30 (95% CI 0.26–0.34). CLO, along with chlorpromazine and fluphenazine had lower risks.	This may be due to lower affinity for dopamine D_2 receptors.

(*Continued*)

Table 4 (Continued).

Study	Data Source	Other drugs	Key Findings Metrics	Comments
De las Cuevas et al[73]	VigiBase Inception -January 1, 2024	APs	CLO appears to display a much stronger and possibly protective safety profile on the suicidality spectrum when compared with other APs. CLO anti-suicidal effects may overcome its potential toxicity in intentional overdoses.	CLO is a drug considered to be "toxic" by many prescribers, with huge overreporting to VigiBase when compared to its worldwide use, and potentially overrepresented in suicide attempters because of its indications. In spite of these biases, this VigiBase study supports other non-overlapping published studies and strongly supports CLO's anti-suicidal activity.
			2391 CLO-treated patients on the suicidality spectrum (627 with suicidal ideation, 752 with suicide attempt, 488 with intentional overdose and 731 with completed suicide. The CLO IC for suicidal ideation, suicide attempt; intentional overdose and completed suicide were significantly lower than those of other APs	

Abbreviations: 5-HT_{2C}: serotonin 2C receptor; ADR, adverse drug reaction; AOR, adjusted odds ratio; AP, antipsychotic; aROR, adjusted reporting odds ratio. CI, confidence interval; CLO: clozapine; D_2: dopamine 2 receptor; D_4: dopamine 4 receptor; H_1: histamine 1 receptor; IQR: interquartile range; NMS, neuroleptic malignant syndrome; ROR, reporting odds ratio.

cases included 6 with neuroleptic malignant syndrome (NMS) and 20 without NMS. Man et al[67] reported that clozapine was associated with a significantly higher frequency of sialorrhea compared to other antipsychotics, with 2,732 reports (1.1% of clozapine ADRs) and a ROR of 3.60 (95% CI, 3.41–3.79). This ADR was reported almost four times more frequently with clozapine than with other antipsychotics, and it was significantly underreported by healthcare professionals compared to patients.

In the context of study of drug-induced seizures, Kumlien and Lundberg[68] reported that clozapine was significantly associated with seizures accounting for 3,758 reports, which is 9% of the total reports of drug-induced seizures. In the context of study of antipsychotic-induced diabetes mellitus, Montastruc et al[69] found clozapine was the most frequently suspected antipsychotic drug for diabetes, accounting for 54% of diabetes mellitus reports. They found adjusted odds ratios (AOR) of 2.13 (95% CI 1.72–2.64). They estimated the affinity of the antipsychotics for neurotransmitter receptors and found significant effects for serotonin 5-HT_{2C} and histamine H_1 receptor occupancy. In the context of study of drugs that induce or aggravate sleep apnea syndrome, Linselle et al[70] identified 104 reports associated with clozapine and an ROR of 2.4 (95% CI 2.0–2.9). In the context of the study of drug-induced parkinsonism, De Germay et al[71] found that clozapine had the lowest disproportionality value among studied antipsychotics. In the context of study of all kinds of antipsychotic-induced withdrawal syndromes, Storck et al[72] reported that clozapine had a lower risk.

A recent article[73] presents a comprehensive review of clozapine's anti-suicidal effects from the literature and analysis using data from VigiBase including other antipsychotics. Clozapine has significantly lower information IC values for suicidal ideation, suicide attempts, intentional overdose, and completed suicides compared to other antipsychotics like aripiprazole, olanzapine, quetiapine, and risperidone. This stark contrast highlights clozapine's unique protective benefits against suicidal behaviors. Despite its known toxicity in overdoses, the data indicate that clozapine's anti-suicidal properties may outweigh these risks. The study also highlighted the frequent co-prescription of clozapine with other antipsychotics, which could contaminate the IC values. The authors called for further detailed studies to compare the lethality of clozapine overdoses when compared with the overdoses of other second-generation antipsychotics and advocate for considering clozapine earlier in the treatment of schizophrenia due to its potent anti-suicidal effects. They emphasize the importance of understanding clozapine's benefits and risks to enhance public health and suicide prevention strategies.

Discussion

Interpretation of the Results in the Context of Existing Literature

The findings of this literature review provide substantial evidence supporting the critical role of pharmacovigilance in enhancing medication safety, particularly for drugs with complex safety profiles like clozapine.[74] Clozapine is a drug approved by the Food and Drug Administration (FDA) in the late 1980s with very limited studies; therefore, much of what we know about its ADRs comes from pharmacovigilance studies.[25] These limited early studies may explain why it has required these recent VigiBase studies: the spectrum of respiratory aspiration – aspiration pneumonia and pneumonia,[59,60] along with other infections,[58] are important causes of fatal outcomes in clozapine-treated patients. Package inserts worldwide and the published literature focus on the risk of fatal outcomes associated with severe neutropenia but, according to VigiBase, agranulocytosis is only the 35th leading cause worldwide of fatal outcomes in clozapine-treated patients while pneumonia ranks second after the nonspecific label "death". Thus, the various levels of hematological monitoring around the world have been successful in reducing fatal outcomes associated with severe neutropenia while the association with fatal outcomes during pneumonia and other infections has been neglected.[75,76] This may have contributed to unnecessary morbidity and mortality during the recent COVID-19 pandemic.[77–79]

There is some data that clozapine-treated patients may be more prone to infections; the contributions of clozapine versus those of TRS are currently unknown.[80] On the other hand, there is no doubt that infections may be frequent in clozapine patients as they were present 2% of the time in an inpatient study with 131 Chinese patients, which totaled more than 67 patient-years (24,798 patient-days). Mild infections without systemic inflammation may not have relevant effects on clozapine metabolism but those associated with relevant systemic inflammation release cytokines that impair clozapine metabolism. In that Chinese study, 3% of the steady-state clozapine levels were elevated during the infections.[81]

The recent VigiBase studies have also shed new light on rapid clozapine titration without personalized dosing, indicating that it may be associated with clozapine-induced myocarditis[61,62] and other clozapine-induced inflammations,[63,64] Thus, they have presented a new means of prevention by using slow personalized titration.[32] Patients of Asian ancestry have lower clozapine metabolism and need approximately half of the clozapine dosage approved in the US.[82,83] The original people of the Americas are descendants of Asians and also need lower clozapine doses.[84] A recent study in the UK[85] has verified that patients of African ancestry may need high clozapine doses to get therapeutic concentrations.[86] Therefore, an international titration guideline proposed to stratify clozapine titrations and dosing according to ancestry, the lowest doses for patients of Asian ancestry and those original peoples from the Americas, intermediate for those of European ancestry and highest for those of African ancestry.[32,85] Within each ancestry group,[32,85] there is a slower titration for those who have impaired clozapine metabolism, poor metabolizers (PMs) due to obesity, and those who use inhibitors such as oral conceptives[87,88] or valproate.[89,90] Clozapine-induced inflammations impair clozapine metabolism; thus, it is important to add weekly c-reactive protein (CRP) during titration[91,92] to identify patients in which the titration has been too rapid for their metabolism,[93] as some patients may be genetic clozapine PMs. They may be PMs due to the presence of rare genetic mutations.[94] Co-medication with olanzapine or quetiapine,[86] has also been identified by VigiBase studies as risk factors for clozapine-induced inflammation during titrations.[49,61,62]

These new findings on pneumonia and clozapine-induced inflammation are supported by recent VigiBase studies and underscore the necessity for continuous monitoring and analysis of pharmacovigilance data.[95,96] The high incidence and mortality rates associated with these clozapine ADRs align with previous literature, highlighting the importance of robust pharmacovigilance systems such as VigiBase in identifying and addressing drug-related risks.

Not all VigiBase findings are bad news, as the study on suicidal behavior suggested that clozapine has major potential to save lives due to its anti-suicidal effect in patients with schizophrenia and in other patients with the most severe mental illnesses, including bipolar disorder[97] and borderline personality disorder.[98] The studies from the national registries of Taiwan[99] and the Scandinavian countries, such as Denmark[100] Finland,[101] and Sweden,[102] indicated that clozapine saves lives of patients with schizophrenia, compared with other antipsychotics, probably due to its anti-suicidal effects but also by decreasing other natural deaths since clozapine is associated with better adherence than other oral antipsychotics[103] and may be associated with better adherence to medical medications, thus decreasing cardiovascular deaths.[104,105] These VigiBase studies suggest that in Taiwan and the Scandinavian countries more lives may be saved by paying attention to

the risk of the aspiration – aspiration pneumonia – pneumonia spectrum by preventing them and better managing them. Similarly, slower personalized titration may lead to the avoidance of clozapine-induced inflammations; more successful titrations will lead to more long-term clozapine treatments with the potential for anti-suicide effects. Suicide is one of the greatest causes of death in patients with schizophrenia.[106]

Implications for Clinical Practice and Medication Safety

The insights gained from VigiBase data have important implications for clinical practice. Healthcare providers should be aware of the heightened risks associated with clozapine, particularly in vulnerable populations such as the elderly and those with comorbid conditions. The identification of significant regional variations in ADR reporting suggests the need for standardized reporting practices to ensure comprehensive monitoring.[107] Moreover, the protective effect of clozapine against suicidal behaviors[73] emphasizes its potential benefits in specific patient populations, warranting careful consideration in treatment planning.

Limitations

Limitations of Our Article Search

Our search focuses on clozapine ADRs in VigiBase, the international pharmacovigilance database. We are aware of other pharmacovigilance studies for clozapine that did not use the VigiBase database but accessed data from drug agencies including the FDA,[108–121] EudraVigilance[122–124] and the Japanese drug agency.[125] As these pharmacovigilance studies included international data, we assume that they accessed data similar to that in VigiBase, but currently, we do not understand the overlap and lack of overlap between international data accessed through VigiBase versus the international data accessed from other pharmacovigilance agencies.

Underreporting is a Major Limitation of VigiBase Studies

Underreporting is the most important limitation of spontaneous reporting systems used for pharmacovigilance, including any VigiBase study.[126–129]

Based on these published data it is clear that clozapine pharmacovigilance varies widely around the world. The top reporting countries for clozapine ADRs are the UK, Canada, the US and Australia.[57] The Yellow Card system used by the UK appears to provide the best country data in VigiBase. As clozapine ADRs account for 3.5% of all drug ADRs this suggests that the UK may be the best reporter quantitatively. On the other hand, as the UK has no unified national registry including all health data, there is no way to estimate the underreporting of clozapine ADRs. The comparison with Canada suggests that the UK may be the best reporter of clozapine ADRs qualitatively as well. Considering estimates of use and population, Canada may have more fatal outcomes than the UK but the quality of the data appears worse as 45% of the deaths there is no additional information (versus 21% in the UK). In Canada, clozapine ADRs account for 1.9% of all drug ADRs. In Australia, clozapine ADRs account for 2.8% of all drug ADRs and there was a very important relative increase of clozapine-induced myocarditis, as this country with 26 million people accounts for half of the worldwide reports and 1/3 of the fatal outcomes. It is likely this relative increase in reporting may reflect a real increase in incidence of clozapine-induced myocarditis in Australia. The US is the top reporter of all drugs, but appears to have underreported clozapine ADRs when compared to the other 3 top reporting countries as clozapine ADRs account only for 0.4% of all drug reports.[57] It is possible that US seriously underreports the less severe clozapine ADRs, as in clozapine-induced myocarditis only severe cases appeared to be reported.[61]

Other Western European countries besides the UK also have national health systems providing free care and relatively good outcomes. Thus, it was surprising to find that 11 of these countries probably do major underreporting of clozapine ADRs when compared with the UK and after adjusting for population and clozapine use they appear to only report from 1–10% when the UK's reporting is considered to be 100%.[11] This is particularly perplexing in reference to Finland and Germany. Finland appears to be the top country in the world for clozapine prescriptions.[130] In a Finnish clozapine-treated cohort of patients from 1972 to 2014 who were followed until 2017, there were 2285 pneumonias.[131] Until 2017 VigiBase includes 57 pneumonia cases with 6 fatal outcomes.[60] This appears to indicate that only 2.5% (57/2285=0.25) of the pneumonia cases described in the Finnish registry may have been reported to VigiBase. Thus, the underreport in

Finland, at least for pneumonia in clozapine-treated patients is 97.5%. German-speaking psychiatrists have a long tradition of pharmacovigilance using hospital records.[11] Their most recent German study[132] described 38,349 inpatients treated with clozapine, but this data appears to be seriously hampered by underreporting as only 2% or 589 with severe clozapine ADRs were documented, which means that 98% or 37,763 had no severe clozapine ADRs. No pneumonia was reported in this large study, probably because the German-speaking psychiatrists did not associate pneumonia with clozapine treatment.[11]

VigiBase has received extremely few clozapine ADRs from Eastern Europe,[12] Latin America,[13] Asia[125] or Africa.[125] Clozapine is frequently used in Russia[15] but this country has never sent a report of a clozapine ADR to VigiBase.[12] It is currently unknown how the massive underreport from these large areas of the world has confounded the VigiBase data on clozapine. When analyzing the limited Asian data on clozapine pharmacovigilance, Hatano et al[125] have recently proposed that in Asia there are increased concentration-dependent ADRs which may be compatible with the theory that current dosing among Asians may be too high. The doses approved in the US were developed without considering that patients of Asian ancestry may need lower doses, approximately half of the US-recommended clozapine dosage.[82,83] In some Asian countries influenced by the clozapine dosages used in Western countries, it is becoming obvious that the previously official doses were too high. Published studies in Korea,[133,134] Japan[34,35] and India[135] are describing the need for using lower clozapine doses than the officially recommended doses in some of these Asian countries, since the official clozapine doses followed US recommended doses.

Other VigiBase Limitations

Other VigiBase limitations are reporting bias, confounding factors, variation in reporting practices and lack of: 1) ancestry data, 2) number of exposed individuals, and 3) limited clinical detail.[57]

In the authors' experience with VigiBase data, interpreting clozapine ADRs can be hampered by a lack of clinical detail. The significance of insufficient clinical detail varies depending upon the ADR, so their experience in myocarditis, pneumonia and suicide is described. In clozapine-associated myocarditis, polypharmacy appeared to be the most important issue, but other antipsychotics may also be contributing factors. In the first article all cases of myocarditis were allegedly associated with clozapine, so logistic regression models were calculated to estimate the effects of other antipsychotics in serious and fatal outcomes.[61] Due to the thousands of cases, using ADR scales to establish causal relationships in each case was not possible. In a second step to further understand the issue, the myocarditis cases associated with other antipsychotics were studied after controlling for the effects of clozapine co-prescription; an ADR scale was used to establish causal relationships between the antipsychotic and the myocarditis, as the number of cases was manageable.[49] The third article focused on clozapine-associated myocarditis in children and adolescents where clinical details were much more frequently described, so it was possible to determine much more accurate causal relationships using the ADR scale.[62] In the study of pneumonia associated with clozapine the major problem was the lack of availability of the term *aspiration pneumonia* in VigiBase for many years. To control for that the authors developed a new analysis dividing the pneumonia cases into those with and without any sign of aspiration.[60] In the study on suicide, to control for the effect of other antipsychotics, the ICs were compared. However, all ICs in VigiBase are contaminated by antipsychotic co-medications, so additional published articles were used to strengthen the interpretation that clozapine may have a specific anti-suicidal effect. The major problem of that suicide article is confounding by indication, as antipsychotics are associated with severe mental illnesses that have different levels of association with suicide behavior (severe mood disorders are more strongly associated with suicide behavior than schizophrenia).[73] Thus, the lack of psychiatric diagnoses was stressed as a major limitation and a future study focused on other antipsychotics was recommended.[73] In summary, the lack of clinical detail in VigiBase is a problem, but the solutions are complex; they vary from ADR to ADR and frequently require additional studies.

Finally, all pharmacovigilance databases including VigiBase pose limitations on interpreting ADR fatal outcomes: 1) there is no information on the proportion of ADRs that occurred versus those actually reported, 2) there is a lack of information regarding the proportion of fatal outcomes compared to non-fatal outcomes in the reported ADRs, and 3) the number of patients taking a specific drug, adjusted for the size of the population, remains unknown.[136]

Enhancing Medication Safety and Increasing Patient Adherence

Pharmacovigilance is an essential part of increasing medication safety but provides no data on patient adherence or on the opinion of patients regarding clozapine ADRs. Thus, none of these VigiBase studies provide information on the level of medication adherence of patients taking clozapine. A subgroup of patients on clozapine appear to like clozapine because of its efficacy and lack of extrapyramidal symptoms.[25] Thus, patient surveys on clozapine tend to indicate that many patients like clozapine[137,138] and data from the Finnish registry that persistence in filling prescriptions of clozapine is better than refills for other oral antipsychotics.[103] On the other hand, non-adherence to oral antipsychotics is a major problem for patients with schizophrenia and predictors of poor adherence include taking the medication for more than 1 year, dislike of medications in general (pharmacophobia) and skepticism about specific antipsychotics.[139] There is limited data on clozapine adherence. In the best study, in a Canadian clozapine clinic at an academic department, Takeuchi et al[140] estimated that only 1/3 of the patients took clozapine consistently based on pill counts and an electronic system that established that the patient had opened the vial containing the clozapine. Even with this type of complex system to assess pill use, there is no guarantee that the patient who opened a vial also swallowed a pill. Therefore, measuring clozapine in serum/plasma, called therapeutic drug monitoring (TDM), is probably the best way to explore clozapine adherence.[141] Unfortunately, clozapine TDM values reflect not only the intake of clozapine but the ability of that specific patient to clear clozapine from his/her body. In that sense, if the patient is prescribed a definitive therapeutic dose and no clozapine is present in his/her body, it is easy to diagnose complete non-adherence, but it gets very complicated to determine partial non-adherence when low concentrations are present. That makes it important to develop TDM parameters to diagnose non-adherence.[141] Recently, three TDM indexes have been proposed as potential measures of clozapine non-adherence.[142] Most cases of low clozapine plasma/serum concentrations in relation to the prescribed dose are explained by non-adherence, but on rare occasions they may be explained by patients with increased clozapine metabolism.[143]

Future VigiBase Studies

Strategies for improving clozapine prescribing, monitoring, and adherence based on VigiBase findings include enhanced monitoring protocols, patient education and support, interdisciplinary collaboration, and the use of pharmacovigilance data. Implementing stringent monitoring protocols, especially during the initial titration period, can mitigate the risk of severe ADRs such as myocarditis and pneumonia, with regular follow-up and prompt management of early symptoms being crucial.[32]

Educating clozapine experts worldwide on the advances provided by pharmacovigilance and pharmacokinetics is crucial[32] as they need to educate their patients and caregivers about potential risks and the necessary precautions that can improve adherence and early detection of ADRs. Support systems, including regular check-ins and easy access to healthcare providers, can enhance adherence in patients with schizophrenia.[144] Encouraging collaboration between psychiatrists, primary care providers, and specialists can ensure a holistic approach to patient care, addressing both psychiatric and physical health needs.[145] Additionally, clozapine experts should continue to leverage pharmacovigilance data from VigiBase and other sources to keep clinicians informed about emerging safety concerns and adjust treatment strategies accordingly.[146]

Recommendations for healthcare professionals and regulatory bodies include staying informed of the latest pharmacovigilance data, integrating this knowledge into clinical decision-making, and promoting standardized ADR reporting practices.[147,148] Healthcare professionals should prioritize patient education and regular monitoring to detect and manage ADRs promptly.[149] Regulatory bodies should enhance the accessibility of pharmacovigilance data to healthcare providers and support research initiatives aimed at understanding and mitigating drug-related risks.

Conclusion

The key points and findings of this literature review are the following: 1) clozapine is associated with severely neglected ADRs, including pneumonia, myocarditis, and respiratory aspiration, with significant regional variations in reporting; 2) clozapine shows a protective effect against suicidal behaviors compared to other antipsychotics; and 3) pharmacovigilance in the 20th century played a crucial role in identifying clozapine ADRs[25] that were incorporated in the package insert. The

21st century findings in VigiBase also need to be incorporated in clozapine package inserts worldwide.[75,76] As lack of adherence is a major problem for long-term clozapine use, it is important that clinicians 1) consider clozapine TDM to verify adherence,[141,142] and 2) incorporate the knowledge of these clozapine ADRs recently described into the education of their schizophrenia patients. The education should be based on what we know about the variables associated with adherence.[150] Each patient should specifically be asked about their adherence to clozapine instead of assuming it, and asked for their personal assessment[151] of the risk and presence of clozapine ADRs.

Continuous pharmacovigilance efforts, facilitated by comprehensive databases like VigiBase, are essential for ensuring the safe use of all medications, including clozapine. These systems enable the early detection of safety signals and support evidence-based decision-making, ultimately improving patient outcomes. Clozapine pharmacovigilance is weakened by very limited data from large areas of the world including continental Europe, Latin America, Asia and Africa; therefore, improving pharmacovigilance in these areas may provide major improvements in the validity and reliability of the results and aid our understanding of which clozapine ADRs need more attention in various countries. Future research should focus on enhancing the granularity of clozapine pharmacovigilance data, exploring the underlying mechanisms of ADRs, and developing more effective risk management strategies. Ongoing efforts to standardize reporting practices and integrate pharmacovigilance data into clinical workflows will be crucial for advancing medication safety and optimizing clozapine therapy.

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