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ORIGINAL RESEARCH

Investigating in VigiBase over 6000 cases of pneumonia in clozapine-treated patients in the context of the literature: focus on high lethality and the association with aspiration pneumonia

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ABSTRACT

Background: The literature associates clozapine with pneumonia/aspiration pneumonia.

Research design and methods: The international pharmacovigilance database (VigiBase™) uses the information component (IC) as statistical signal. VigiBase clozapine reports were analyzed for pneumonia/aspiration pneumonia from introduction to 10 May 2023.

Results: There were 6392 cases of all types of pneumonia (5572 cases of pneumonia, 775 of aspiration pneumonia, and 45 combined). The IC was 3.52 for aspiration pneumonia, introduced as a VigiBase label in 2003, and 1.91 for pneumonia. Patients were reclassified as 3628 with no signs of aspiration and 1533 with signs. Signs of aspiration were strongly associated with some co-medications: olanzapine, odds ratio (OR) = 23.8, 95% confidence interval (CI), 14.9–38.0; risperidone OR = 18.6, CI, 11.4–30.4; valproic acid, OR = 5.5, CI, 4.5–6.6; and benzodiazepines OR = 5.5, CI, 4.5–6.6. In 2415 cases with completed data, fatal outcomes made up 45% (signs of aspiration made no difference), but there was wide variability from 0% (females <45 years of age; duration ≤30 days) to 76% (males >64 years of age; duration >1 year). During the first week, pneumonia was associated with 1) very high titration doses, 2) very small doses in Parkinson's disease, and 3) Japan vs other countries.

Conclusions: In clozapine-treated patients: 1) at least 30% of pneumonia cases may be aspiration pneumonia, 2) stopping some co-medications may decrease the risk of aspiration pneumonia, 3) average lethality in pneumonia was 45% but may be around 75% in geriatric patients with long-term treatment, and 4) safer titrations may sometimes require 5-mg tablets.
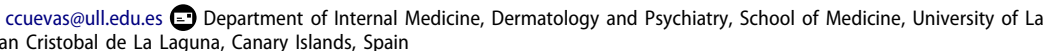
1. Introduction

1.1. Pneumonia and aspiration pneumonia

Pneumonia is a major global public health concern, significantly contributing to healthcare costs and mortality rates. In the United States alone, there are approximately 6 million cases of pneumonia annually, leading to over a million hospitalizations, and 50,000 people die from this disease [1–3]. Pneumonia manifests through a diverse range of causative factors and clinical presentations. This variability in both its origins and symptoms underscores the complexity of pneumonia, making accurate diagnosis and targeted treatment crucial in managing the disease effectively [4]

Within the spectrum of pneumonia, aspiration pneumonia has been considered a distinct entity [5]. More recently, this notion has been challenged and it is suggested that aspiration pneumonia should be regarded as part of a continuum, which includes community- and hospital-acquired pneumonias [6]. This paradigm shift underscores the complexity of diagnosing and understanding aspiration pneumonia, revealing that it is not a separate entity but rather a subset within the broader pneumonia spectrum. Aspiration pneumonia accounts for 5% to 15% of community-acquired pneumonia cases [5,7–9]. Unfortunately, comparable figures for hospital-acquired pneumonia are not readily available, emphasizing the knowledge gaps in this area. Robust diagnostic criteria for aspiration

pneumonia remain elusive, leading to a lack of clarity and consistency in its diagnosis [10]. Consequently, studies investigating this condition encompass heterogeneous patient populations.

1.2. Pneumonia in psychiatric patients

Recent meta-analyses in psychiatric journals have brought attention to pneumonia as a major cause of fatal outcomes in schizophrenia [11] and as consistently associated with antipsychotics [12,13]. Attention was first brought to the topic in 2005 by the Food and Drug Administration (FDA), as a boxed warning was included in the package insert of all second-generation antipsychotics due to increased mortality in the elderly with dementia, including pneumonia [14]. The FDA also added a specific statement in all these package inserts except for clozapine's that one of the possible mechanisms was interference from swallowing. The difference was that, because clozapine was approved for treatment-resistant schizophrenia (TRS) and not indicated for dementia, its package insert received the boxed warning but not the statement on swallowing [15].

When the antipsychotic literature on swallowing disturbances through 2018 was reviewed, three major findings were identified: 1) swallowing disturbances can manifest as a spectrum of disorders extending from aspiration to aspiration pneumonia to pneumonia, 2) the association with clozapine appeared stronger than with other second-generation antipsychotics, and 3) the mechanism explaining dysphagia associated with antipsychotics was complex [15]. In the

studied 45 published cases of dysphagia caused by antipsychotics: roughly ¼ of the cases were explained by four major causes [15]: 1) parkinsonism, 2) acute dystonic reactions, 3) hypersalivation, and 4) tardive dyskinesia. Sedation and xerostomy appeared important in a very few cases.

1.3. Pneumonia in clozapine treated-patients

Clozapine in the absence of co-prescription of other antipsychotics carries little risk for parkinsonism, acute dystonic reactions, tardive dyskinesia, or xerostomy. On the other hand, clozapine can interfere with swallowing as can any other antipsychotic but also may be particularly prone to cause sedation and hypersalivation, further increasing the risk of the spectrum aspiration-aspiration pneumonia-pneumonia. Other clozapine adverse reactions (ADRs) can contribute to or complicate pneumonia in clozapine-treated patients [15]. Clozapine-induced gastrointestinal hypomotility (CIGH) can lead to vomiting and aspiration pneumonia [16].

The amount of articles on the association between clozapine and pneumonia or clozapine and aspiration pneumonia is overwhelming to review in detail. There are three major article groups with progressively smaller sample sizes from pharmacovigilance databases [17–20], national registries [21–27] and clinical samples [28–34] which are described in Box 1.

1.4. Pneumonia and clozapine pharmacology

It is not easy to summarize the complex literature on clozapine and pneumonia in a few words [35]. Infectious pneumonia in the absence of aspiration may be mainly explained by TRS, which is associated with smoking, obesity, and poor adherence to medical treatment, while the contribution of clozapine may be small; it has been proposed that clozapine may decrease immunoglobulin synthesis in some patients [36]. On the other hand, aspiration pneumonia appears to be definitively a clozapine-associated ADR.

The pathophysiology of the fatal outcomes may have common elements in both infectious pneumonia and aspiration pneumonia [35]. Once there is a systemic inflammation there is massive release of cytokines that inhibit the cytochrome P450 (CYP) 1A2 (CYP1A2) and other CYPs, which can lead to clozapine intoxication [37,38]. Box 2 describes four variables that may influence fatal outcomes in clozapine-treated patients during pneumonia, the severity of the systemic inflammation [38–41], the effect of anti-infective agents [42], smoking cessation [43,44] and arrythmias [42,43,45,46].

In light of this evolving perspective on pneumonia and aspiration pneumonia, this study embarks on an exploration of their association with clozapine in the international pharmacovigilance database. By distinguishing between pneumonia and aspiration pneumonia, this study aims to provide valuable insights into the clinical presentation, risk factors, and potential mechanisms underlying clozapine-associated pneumonia. In doing so, we aspire to contribute to a more nuanced understanding of the interplay between clozapine, aspiration pneumonia, and pneumonia in general, ultimately enhancing the clinical management and safety of patients receiving this critical antipsychotic medication.

Box 1. Summary of the literature on CLO and pneumonia

1. Pharmacovigilance databases
- The AP studies from pharmacovigilance databases have established that CLO:
  - has a stronger relationship with pneumonia [17,18] or aspiration [19], and
  - pneumonia, including aspiration pneumonia, is associated with many fatal outcomes, approximately 4 times more than severe neutropenia, which has been the focus of the CLO package insert [20].

2. National registries
- In the Taiwanese national registry [21,22], it has been established that:
  - CLO's association with pneumonia may be stronger than that of other APs and it is particularly true in patients with Parkinson's disease [23].
  - benzodiazepines by themselves were also associated with ↑ risk of pneumonia in patients with schizophrenia [24].
  - the risk of pneumonia in CLO-treated patients was ↑ by benzodiazepines and valproate co-prescription in patients with schizophrenia [25] and valproate co-prescription in patients with bipolar disorder [22].
- In the Danish National Registry, Rohde et al. completed a mirror-image study compared with AP-naïve patients [26]. The rate of pneumonia was significantly higher after initiation of CLO than for other SGAPs, but risperidone also had a lower but significantly increased pneumonia rate.
- In an extension of this Danish study [27], the annual pneumonia incidence increased:
  - from 0.76% in AP-naïve patients with schizophrenia
  - to 1.40% in TRS the year before CLO and
  - to 2.12% 1 year after CLO was started for TRS. This increase indicated that, before taking CLO, patients with TRS and taking other APs and presumably other medications with ↑ pneumonia risk and that adding CLO further ↑ the risk.
- It was estimated that in CLO-treated patients during the first year the increased risk is 64% compared with CLO-naïve patients:
  - of which 45% came from TRS and associated variables and
  - CLO added another 19% risk [27].

3. Clinical studies
- Many of the clinical studies only describe case reports of aspiration pneumonia [28,29], some reported that aspiration pneumonia can be an ADR during titration [30].
- In Japan, Kikuchi et al. studied 214 titrations of which 54 (25%) had some form of CLO-induced inflammation [31]. There were four pneumonia cases and a hypersensitivity pneumonia case in the context of DRESS syndrome.
- In 1408 CLO titrations in a Korean tertiary hospital, Kang et al. found
  - the incidence of pneumonia was 3.7% (52/1408), much > than the incidence of 0.3% (4/1408) for severe neutropenia and of 0.1% (2/1408) for myocarditis [32].
  - The 52 pneumonia cases were associated with no fatal outcomes and appeared to be a combination of aspiration pneumonia, infectious pneumonia, and hypersensitivity pneumonia [33]. This Korean inpatient study provides a strong indication that pneumonia and/or aspiration pneumonia may be an important CLO-associated ADR.
- In a study on myocarditis in the Danish registry, Rohde et al. reviewed 3262 outpatient CLO titrations and focused on the absence of fatal outcomes associated with myocarditis during the first 2 months, but on the other hand, they found 7 fatal outcomes (0.2%) associated with pneumonia [34].

ADR: adverse drug reactions; AP: antipsychotic; CLO: clozapine; DRESS: drug reaction with eosinophilia and systemic symptoms; SGAP: second-generation antipsychotic; TRS: treatment-resistant schizophrenia.

2. Methodological aspects

2.1. Pharmacovigilance database

VigiBase® is a comprehensive global pharmacovigilance database operated by the World Health Organization (WHO) [47]. The reporting clinician 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.

This vast repository of ADRs provides a unique opportunity to delve into real-world clinical data, allowing researchers and healthcare professionals to scrutinize nuanced differences between these conditions. Given the challenges associated with diagnosing aspiration pneumonia and the lack of robust diagnostic criteria, VigiBase® offers a wealth of valuable information encompassing heterogeneous patient populations across the world [48]. By meticulously analyzing the ADRs reported within this database, there is the possibility of exploring patterns, risk factors, and potential mechanisms specific to aspiration pneumonia, differentiating it from other forms of pneumonia.

2.2. VigiBase® search

On 10 May 2023, a retrospective pharmacovigilance cohort analysis was undertaken utilizing VigiBase® by comprehensively including all cases labeled 'pneumonia' or 'aspiration pneumonia' in clozapine-treated patients since the drug's introduction into clinical practice in the 1970s. Each case was meticulously examined for critical details, such as patient demographics (including age and sex), reporting region, and date of the report, alongside drug-related information encompassing the indication and types and numbers of suspected drugs. Additionally, ADR specifics, including the time of occurrence, severity of the event, and associated mortality, were analyzed when available. This study followed the principles of the Declaration of Helsinki and adhered to stringent data anonymization protocols including grouping ages to avoid the identification of single patients, which eliminated the need for ethics committee approval at the university of the authors who downloaded the files.

Box 2. Variables that may contribute to fatal outcomes during pneumonia in CLO-treated patients

1. Severity of the systemic inflammation: ↑ CLO concentrations
- Severe systemic inflammation during infections may lead to doubling or tripling CLO concentration in serum/plasma.
- This is not specific to pneumonia or the infectious agent since it can occur with all systemic inflammations. Therefore, ↑ in serum/plasma CLO concentration has been described in:
  - other infections [38,39],
  - pneumonia associated with influenza [40],
  - non-infectious systemic inflammations [40], and
  - with severe COVID-19 infections with or without pneumonia [41].

2. Anti-infective agents
- Most but not all anti-infective agents are safe for CLO-treated patients, but ciprofloxacin and other compounds in the family are extremely dangerous and potentially lethal for patients taking CLO as they are powerful inhibitors of CLO metabolism [42].

3. Smoking cessation: can ↑ CLO concentrations
- Tobacco smoking induces CLO metabolism and ↓ CLO concentrations in serum/plasma.
- Many published articles state that if the CLO-treated patient is a smoker and discontinues smoking during pneumonia, this may contribute to a CLO intoxication without considering that de-induction for several days and its effects may not be complete until the second week in average patients [43].
- Several published cases describe CLO intoxication occurring 2–4 weeks after smoking cessation [44].

3. Arrythmias
- It has not been studied in CLO-treated patients, but in schizophrenia patients with pneumonia in the Taiwanese registry, Liao et al. found that cardiac arrhythmia may be an important mechanism underlying fatal outcomes during pneumonia [45].
- This is not surprising as CLO is an inhibitor of the potassium channel and other cardiac ion channels [46].
- As the CLO concentration in plasma/serum ↑ the blocking of these heart channels and these effects are additive with the direct effect of the infective agents in the heart and those of some anti-infective agents that also can block the cardiac ion channels [42,43].

CLO: clozapine.

2.3. Statistical analyses

2.3.1. Statistical analyses in VigiBase® using the information component (IC)

VigiBase® utilizes a Bayesian confidence propagation neural network to generate a statistical measure known as the IC. This unique metric is instrumental in identifying drug-ADR combinations that are observed more frequently than expected, based on all the drug reports. ICs are calculated based on all drug reports, specific drug reports, country reports, and their sample sizes [49]. To account for sampling variability, the ICs are accompanied by confidence intervals (CIs), particularly the IC_{025} the lowest CI at 97.5% (see footnote a from Table 1).

2.3.2. Machine learning analyses

The R software was used in a first approximation by calculating two machine learning analyses: Random Forest (RF) [50–52] and Gradient Boosting (GB) [53] described in Supplementary Box S1.

2.3.3. Logistic regression models

The SPSS software, 29th version, was used to calculate adjusted odds ratios (ORs) and their 95% CIs using pneumonia with/without signs of aspiration and fatal/non-fatal outcome as the dependent variables. The ORs were adjusted by confounding independent variables through the logistic regression model using the backward stepwise selection method; removal testing was based on the probability of the Wald statistic.

Table 1. Disproportionality analysis results for pneumonia and aspiration pneumonia.

	Reports for all drugs	Observed for CLO	Expected for CLO	IC	IC_{025}	IC_{975}
Pneumonia	260832	5621	1492	1.912	1.874	1.950
Aspiration pneumonia	12455	823	71	3.521	3.420	3.617
Combined	272451	6400	1558	2.037	2.002	2.0724
All ADRs	34005278	194558				

ADR: adverse drug reaction; CI: confidence interval; CLO: clozapine; IC: information component.
[a]When the observed occurrences match the expected numbers of reports, an IC of 0 is assigned to the drug-ADR combination. Conversely, an IC > 0 signifies that the reported combinations are more commonly observed than expected, indicating a possible significant occurrence. On the other hand, an IC < 0 indicates that the reported combinations are rarer than expected. To account for sampling variability, the ICs are accompanied by CIs, enhancing the precision of the statistical analysis. IC_{025} has the lowest CI at 97.5%. When the IC and IC_{025} are both positive, it indicates a statistically significant increased disproportionality between the expected and the observed rates for this drug-ADR combination. When the IC and IC_{025} are both negative, it indicates a statistically significant decreased disproportionality between the expected and the observed rates for this drug-ADR combination [49].

3. Results

3.1. ICs

Pneumonia had an IC = 1.91 and IC_{025} = 1.87, aspiration pneumonia had an IC = 3.52 and IC_{025} = 3.42, and their combination had an IC = 2.03 and IC_{025} = 2.00, indicating notable discrepancies between expected and observed clozapine-associated cases, e.g. for the combined category there were 1558 expected cases versus the 6400 observed cases (Table 1). Supplementary Figure S1 illustrates the evolution of ADR reports related to clozapine-associated types of pneumonia over time, showing an overall increasing trend with notable peaks in 2011–2012, and highlights the fact that aspiration pneumonia was not recognized as an independent ADR in VigiBase® until 2003.

3.2. Descriptive analyses

There were 5572 cases of pneumonia, 775 of aspiration pneumonia, and 45 combined cases leading to 6,392 cases of all types of pneumonia. Supplementary Table S1 presents data on the six top reporting countries of pneumonia cases to VigiBase®, which accounted for 94% of global reports. The United Kingdom (UK) with 35% and the United States (US) with 26% were the primary reporting countries; five other countries with large number of reports were Canada, Australia, Japan, Germany, and Ireland.

Supplementary Tables S2 and Table S3 presenting socio-demographic and clinical variables compared across three groups: pneumonia, aspiration pneumonia, and cases involving both types. These categories include sex, age groups, seriousness of cases (non-serious, serious but non-fatal, fatal), laboratory analysis results, clinical signs and symptoms, and details of drug treatments (dose of clozapine, duration of treatment, use of other antipsychotics, mood stabilizers, antidepressants, benzodiazepines, and anticholinergics). Supplementary Table S1 indicates that agranulocytosis was present in 188 of 6392 pneumonia cases, which provides a 3% prevalence in pneumonia and means that 97% of pneumonia occurred in the absence of agranulocytosis.

3.3. Machine learning analyses

The RF analysis used 500 trees and five predictor variables per iteration, showing a low out-of-bag error (12.2%) and 99.9% accuracy in predicting pneumonia. However, it demonstrated a 99.6% misclassification rate for aspiration pneumonia. Supplementary Figure S2 displays the RF classification tree, focusing on 'WBC Increased' and 'Aspiration' as key variables.

The GB analysis accurately identified 68.9% of pneumonia cases but was less effective with aspiration pneumonia, misclassifying 63.5% of cases. Similarly, the RF analysis showed a negligible error rate (0.01%) for pneumonia but a significant misclassification rate (99.6%) for aspiration pneumonia. This indicates both models' high accuracy in identifying pneumonia but also highlights a challenge in distinguishing between pneumonia types, reflecting a potential limitation in the clinical profiling's ability to differentiate between the VigiBase labels 'pneumonia' and 'aspiration pneumonia.' The out-of-bag error matrix underscored the need for improved modeling techniques to better categorize pneumonia subtypes.

3.4. Improving the classification by using those with or without signs of aspiration

An experienced clinician reviewing Supplementary Table S1 would easily conclude that some of the lung infections classified as 'pneumonia' in VigiBase® need to be more correctly classified as aspiration pneumonia, which is not surprising since the term 'aspiration pneumonia' was not added until 2003. For example, all 805 'pneumonia' cases with the additional label 'aspiration' should be considered 'aspiration pneumonia.' All 'pneumonia' cases with the additional label 'salivary hypersecretion,' 'dysphagia,' 'vomiting,' or 'choking' are also cases indicating high risk for aspiration and should be considered aspiration pneumonia. This concept is further and independently supported by the poor classification performance of aspiration pneumonia by the machine learning methods.

All adult patients with complete data were classified into 1533 likely to be aspiration pneumonia as they had these signs of aspiration and into 3628 pneumonia cases missing any sign of aspiration. Table 2 describes the variables associated with pneumonia with signs of aspiration. The univariate OR shows 10 significant results but these may be confounded by other variables. A logistic regression corrected by confounders provided seven very significant ORs ($p < 0.001$) higher than 1: geriatric age (OR = 1.36, CI, 1.20–1.61), olanzapine (OR = 23.8, CI 14.9–380), risperidone (OR = 18.6, CI 11.4–30.4), valproic acid (OR = 5.5, CI 4.5–6.6), and benzodiazepines (OR = 6.7, CI, 5.2–8.8). All of these co-medications appear to have potential to disturb swallowing and have been associated with aspiration in the context of polypharmacy [19,54]. Thus, it appears reasonable to interpret this reclassification as perhaps compatible with what should be expected for aspiration pneumonia. Four significant ORs were <1, before 2003 (OR = 0.56), female sex (OR = 0.73, 0.63–0.84), quetiapine (OR = 0.12, 0.07–0.21), and antidepressants (OR = 0.58, CI 0.44–0.76). They can be interpreted as protecting for aspiration pneumonia or increasing the risk of other types of pneumonia that are not associated with aspiration.

3.5. Exploring fatal outcomes

There were 2415 adult cases with no missing data in the three most relevant variables associated with fatal outcomes (sex, age, and duration of clozapine treatment). The prevalence of fatal outcomes was 45% in the combined samples (1090/2145) and in those with or without signs of aspiration pneumonia. Table 3 describes the univariate OR and the adjusted OR using logistic regression with the variables associated with fatal outcomes. The logistic regression model identified sex (female decreased the fatal outcomes with an OR = 0.72), duration (divided into three steps: <31 days as baseline, 31 to 365 days with an OR = 3.1, and >365 days with an OR = 7.0),

Table 2. Variables associated[a] with pneumonia with signs of aspiration (N = 1533)[b] versus those without (N = 3628).

Variable (yes/no)	Univariate analysis			Logistic regression analysis		
	OR	95% CI	P value	OR	95% CI	P value
Before 2003	0.490	0.406–0.592	<.001	0.556	0.449–0.689	<.001
Female sex	0.771	0.679–0.874	<.001	0.730	0.632–0.843	<.001
Age ≥65 years	1.177	1.033–1.341	.014	1.386	1.195–1.607	<.001
Olanzapine	18.173	11.574–28.534	<.001	23.840	14.942–38.035	<.001
Risperidone	17.127	10.779–27.212	<.001	18.658	11.449–30.407	<.001
Quetiapine	0.550	0.351–0.861	.009	0.123	0.072–0.211	<.001
Haloperidol	1.457	1.056–2.009	.022	-	-	-
Valproic acid	4.153	3.502–4.926	<.001	5.526	4.4594–6.647	<.001
Benzodiazepines	2.823	2.419–3.294	<.001	6.794	5.217–8.847	<.001
Antidepressants	1.538	1.358–1.742	<.001	0.580	0.443–0.759	<.001-

CI: confidence interval; OR: odds ratio, SPSS: Statistical Package for the Social Sciences.
[a]SPSS software, 29th version, was used to calculate multivariate ORs and their 95% CIs using fatal outcome (yes/no) as the dependent variable. The multivariate ORs were adjusted by confounding independent variables through the logistic regression model using the backward stepwise selection method; removal testing was based on the probability of the Wald statistic (a p value of entry 0.05 and removal 0.06). The total sample of this logistic regression model is 5,161 divided in 1533 (30%) with signs of aspiration and 3628 (70%) without aspiration. From the total sample of 6392, 1231 were excluded due to age <18 years or missing sex or age.
[b]From 1533 with signs of aspiration include 1319 with aspiration, 652 with aspiration pneumonia, 130 with vomiting, 124 with dysphagia, 124 with salivary hypersecretion, 145 vomiting, and 12 choking.

Table 3. Variables associated with 1090 fatal and 1325 non-fatal outcomes in 2415 cases with completed data.

Variable (yes/no)	Univariate analysis[a]			Logistic regression analysis[b]		
	OR	95% CI	P value	OR	95% CI	P value
Before 2003	1.207	0.969–1.503	.093	1.703	1.315–2.206	<.001
Female sex	0.892	0.755–1.053	.178	0.720	0.595–0.871	<.001
Age 18–44 years			<.001			<.001
Age 45–64 years	2.838	2.243–3.591	<.001	2.611	2.037–3.346	<.001
Age >64 years	8.443	6.585–10.826	<.001	8.039	6.178–10.460	<.001
Duration <31 days			<.001			<.001
Duration 31–365 days	3.457	2.583–4.626	<.001	3.124	2.289–4.263	<.001
Duration >365 days	7.140	5.445–9.363	<.001	6.955	5.202–9.298	<.001

CI: confidence interval; OR: odds ratio.
[a]There were six variables (olanzapine, risperidone, haloperidol, valproic acid, antidepressants, and anticholinergics) with p value > .25 in the univariate analyses that were not introduced in the logistic regression analysis.
[b]There were two medications (quetiapine and benzodiazepines) with p value < .25 that were introduced in the logistic regression analysis using the backward stepwise selection method but were removed. Removal testing was based on the probability of the Wald statistic (p value of entry 0.05 and removal 0.06).

Table 4. Rates of fatal outcomes by age, sex, and duration of clozapine treatment across 2415 pneumonia cases.

	Total sample			Male			Female		
	<31 days	31–365 days	>365 days	<31 days	31–365 days	>365 days	<31 days	31-365 days	>365 days
18–44 years	2.3% (4/176)	20% (37/190)	34% (80/234)	3% (4/121)	21% (24/116)	32% (55/173)	0% (0/55)	18% (13/74)	41% (25/61)
45–64 years	14% (23/180)	35% (91/262)	54% (307/571)	15% (17/115)	38% (64/168)	58% (213/374)	12% (8/65)	29% (27/94)	48% (94/197)
>64 years	44% (46/105)	65% (142/220)	75% (358/477)	59% (37/63)	68% (96/141)	76% (196/258)	21% (9/42)	58% (46/70)	74% (162/219)

andage (divided into three steps: 18–44 years as baseline, 45 to 64 years with an OR = 2.0 and >64 years with an OR = 6.2).

Table 4 provides the percentages of fatal outcomes after stratification by age, duration, and sex. The average percentage of fatal outcome was 45% but after stratification ranged from a low of 0% in females younger than 44 years of age and with treatment duration of less than or equal to a month and a high of 76% in males older than 64 years and with a treatment duration of more than 1 year.

3.6. Relevance of titration for pneumonia during clozapine treatment

VigiBase does not provide details on titration, and usually there is only one dosage reflecting when the clozapine-associated ADR was diagnosed and reported to VigiBase. Of 2461 pneumonia cases during the duration of the clozapine treatment, there were 19% (512/2641) in the first month, which suggests that titration may be a high-risk period for developing pneumonia.

To explore the combined effects of dosing and duration during clozapine titration, we focused on the first 7 days since, based on the experience with clozapine-induced myocarditis [55], it is relatively easy to identify very high doses in the first week of titration. There were 134 pneumonia cases in the first 7 days, but 53 (40%) were missing the clozapine dose.

Of the 134 cases, three appeared unusual. One was a case in the context of agranulocytosis and two appeared to be overdoses on day 2 with 1750 or 7500 mgs. There were 45 cases of pneumonia reported on day 1, with 17 fatal outcomes (38%); some had shockingly high initial doses. There were nine cases with a first dose of 200 mg/day or higher with no titration. On the other hand, in the first week in patients older than 65 years, we identified five cases, including three fatal outcomes. Three of these five geriatric cases were associated with very low doses (6–13 mg/day) and possibly compatible with aspiration pneumonia associated with the use of very low doses of clozapine for Parkinson's disease which impairs swallowing.

When compared with other countries, Japan had an increased number of pneumonia cases in the first week with 22 cases but only 1 fatal outcome. In these Japanese cases, dosages during the first week of titration were much lower than in cases in Western countries. Japan appeared to have an increased number of pneumonia cases during titration with 16% (80/512) during the first month of treatment versus 3% (73/2129) of Japanese patients after the first month, giving an OR = 5.2 (CI 3.7 to 7.3; $p < 0.001$).

4. Discussion

This study has undertaken a comprehensive analysis of pneumonia in clozapine-treated patients with a focus on distinguishing between pneumonia and aspiration pneumonia and fatal outcomes.

4.1. ICs

The large number of cases and, more importantly, the high ICs and IC_{025} indicate a significant excess for clozapine in the number of observed versus expected cases for pneumonia and aspiration pneumonia.

4.2. Descriptive analyses

From descriptive information (distributed across Supplementary Tables S1 to Table 3), the most relevant finding is that UK provides 35% of all reports of pneumonia in clozapine-treated patients and the US is second with 26%.

4.3. Machine learning analyses and reclassification by using the presence of signs of aspiration

The RF and GB analyses provided insightful results, achieving high prediction accuracy for pneumonia but a high misclassification rate for aspiration pneumonia. This led to a clinical reclassification of pneumonia with signs of aspiration for any 'pneumonia' with any of the following labels: 'aspiration,' 'salivary hypersecretion,' 'dysphagia,' 'vomiting,' or 'choking.' Of the total of 5,161 pneumonia patients with complete data and age ≥18 years, 1533 (30%) patients had pneumonia with signs of aspiration and 3628 (70%) had pneumonia without signs of aspiration. To interpret these data, it must be remembered that before 2003, the label 'aspiration pneumonia' was not available in VigiBase, so before 2003 there is major under-reporting of aspiration pneumonia (OR = 0.56, CI 0.45 to 0.69; Table 2). Therefore, it is highly likely that aspiration pneumonia accounted for more than 30% of the more than 6000 pneumonia cases in VigiBase until May of 2023.

The limited logistic regression from Table 2 indicates that the several co-medications including olanzapine, risperidone, valproic acid and benzodiazepines increase the risk of the presence of any signs of aspiration in pneumonia in clozapine-treated patients reported to VigiBase®.

4.4. Age and clozapine-treatment duration had strong effects on fatal outcomes

Average fatal outcome was 45% in 2415 patients with completed data, but Table 4 shows three variables (sex, age, and duration of clozapine treatment) had a major impact in lethality with a low of 0% and a high of 76%. The high lethality in the geriatric patients after more than 1 year (76% in males and 74% in females) (Table 4) may be partly explained by aspiration pneumonia in patients with Parkinson's disease but most cases with pneumonia during long-term maintenance appeared to be patients with TRS (the mean clozapine dose was extremely high for Parkinson's disease in 96 females 221 ± 154 mg/day and in 113 males 205 ± 174 mg/day).

4.5. Pneumonia during titration

As 19% of pneumonia cases occurred within the first 30 days, this suggests that the titration period is associated with a high risk of pneumonia. Two cases seem to be related to an overdose by the patient, but many others appear to be due to highly inappropriate titration protocols prescribed by healthcare professionals. Limited data indicate that geriatric patients, especially those with Parkinson's disease, may develop aspiration pneumonia within the first week, even when administered extremely low doses of clozapine (6 or 12.5 mg/day).

The official Japanese titration guidelines were developed based on the US protocols [56], but these titrations may be too rapid for the metabolism of clozapine in Japanese patients, who show a clozapine metabolism similar to those of patients of Asian ancestry [57,58]. According to the recent multicenter study in Japan [31], the official Japanese titration schedule and a slower titration (by 0.70) were linked with a total prevalence of more than 30% for fever and other forms of clozapine-induced inflammation, some of which were pneumonia, possibly aspiration pneumonia or hypersensitivity pneumonia. In our VigiBase search, Japan reported a 52% rate (80 out of 153 cases) of pneumonia during titration, much higher than the 19% pneumonia rate during titration in the global sample. The VigiBase® Japanese data suggest that a portion of clozapine-associated ADRs during titration were pneumonia, but detail is lacking on how many of these cases

are aspiration pneumonia versus eosinophilic pneumonia due to hypersensitivity. Clozapine-induced myocarditis during titration was also higher in Japan than in other countries according to VigiBase® data [55].

Table 5 indicates that the lowest lethality after correcting for the effects of sex and age was during the titration. This is not surprising since in many countries most of the clozapine titrations are in the inpatient setting facilitating the early diagnosis and treatment of pneumonia. On the other hand, Denmark appears to have a very good record of clozapine use [56,59], with approximately 40% titrations done from the start in the outpatient setting [56]. These Danish outpatient titrations can benefit for paying attention to signs of aspiration and pneumonia since Rohde et al. found only 26 deaths during the first 2 months among 3262 outpatient titrations but 7 of these 26 deaths were identified as pneumonia [34].

4.6. Limitations

This is an extremely large sample of clozapine-associated pneumonia with more than 6000 cases, which is larger than the combination of all prior published clinical samples but still has the limitations described in Supplementary Box S2 related to any pharmacovigilance sample [59–61] and the statistical analyses.

5. Expert opinion

The subsections of this Expert Opinion section focus on 1) worldwide fatal outcomes in clozapine-treated patients associated with severe neutropenia versus pneumonia, 2) a critical review of the lack of reference of the US clozapine package insert to lethality during pneumonia, 3) clinical implications of our results, and 4) the need for further advances.

5.1. Worldwide fatal outcomes: severe neutropenia and pneumonia

Traditionally, drug agencies and clinicians have focused on clozapine-induced agranulocytosis as the major risk for fatal outcomes in clozapine-treated patients [62,63]. In a VigiBase® search focused on clozapine-treated patients through 15 July 2019, when all the forms of severe neutropenia were combined, it was evident that awareness worldwide is extremely high since there were 34,391 cases when all labels for severe neutropenia were combined. This high level of awareness worldwide is associated with a very low relative lethality of 2% (550/34931). In the same search, pneumonia by any label in clozapine-treated patients accounted for approximately 4 times more fatal cases (2077 out of 6983) cases by including pneumonia, aspiration pneumonia, and lower respiratory tract infections [20]. Future VigiBase studies need to better explore these cases labeled 'lower respiratory tract infections,' a label frequently used in the UK. Currently, it is not known whether the VigiBase® label 'lower respiratory tract infections' overlaps with the label 'aspiration pneumonia.' Until 15 January 2023, there were 2231 cases worldwide with 319 fatal outcomes using the label 'lower respiratory tract infections' among clozapine-treated patients [64].

The best comparison of the relative importance of agranulocytosis and pneumonia is that agranulocytosis was only the 35th highest cause of fatal outcomes in clozapine-treated patients while pneumonia was the second highest in a search through 15 January 2023 [64]. In summary, it appears that the different levels of hematological monitoring in different countries and the generalized awareness of the risk of severe neutropenia have been successful in substantially reducing the number of lethality reports associated with severe neutropenia submitted to VigiBase in clozapine-treated patients [65].

5.2. Critical review of the lack of reference of the US clozapine package insert to lethality during pneumonia

The Food and Drug Administration (FDA) uses boxed warnings to bring attention to serious ADRs [66].

As a matter of fact, the US clozapine package insert since its introduction in 1990 has had a boxed warning for agranulocytosis and four other boxed warnings have been added, but there is no boxed warning for pneumonia [67]. The FDA should be using pharmacovigilance data in the decision-making process regarding boxed warnings in the clozapine package insert. The reader will be perplexed by our prior section describing fatal outcomes in clozapine-treated patients as four times higher in the various forms of pneumonia with no boxed warning while severe neutropenia has had a boxed warning since clozapine's introduction in 1990.

It is not possible to present here a detailed discussion of all the complex issues relevant to the lack of a boxed warning for pneumonia in the US clozapine package insert or even a detailed chronological history of the development of the US clozapine package insert and its limitations [68]. In this subsection, a brief summary will be presented by briefly discussing 4 relevant topics: 1) the package insert of another drug producing a metabolism similar to clozapine, theophylline, describes the risk of intoxication during infections; 2) a brief discussion of the extensive limitations of the US package insert, which does not included the advances in pharmacokinetics since 1990; 3) a succinct chronological history of the literature on the risk of clozapine intoxication during infections; and 4) a critical view based on US pharmacovigilance during the first 10 years of clozapine's marketing.

5.2.1. Theophylline intoxication during infections
The literature on theophylline intoxication during infections has accumulated since the 1970s: 1) first was the description that acute respiratory viral illness decreases theophylline metabolism [69]; 2) Shilalukey et al.. (1993) proposed that when a child taking theophylline develops an upper respiratory infection, the theophylline dose should be halved [70], and 3) theophylline was found to be mainly metabolized by the cytochrome P450 1A2 (CYP1A2) [71]. Thus, it is not surprising that the US package insert for theophylline includes a warning of the risk of intoxication during infections.

In the 1990s, in vitro studies found that the release of cytokines during infection decreases the activity and synthesis of CYP1A2 [72]. Thus, similar effects should be found with any other drug mainly metabolized by CYP1A2 and recent well-controlled studies using phenotyping have confirmed that on average CYP1A2 activity decreases by half on average during acute inflammation [73].

5.2.2. The lack of pharmacokinetic advances in the US package insert

Clozapine was approved by the FDA in 1990 for TRS and marketed in 1990. At that time pharmacokinetic knowledge was limited so it was introduced with a very limited number of drug metabolism studies. In 1994, Swedish researchers established using phenotyping and drug–drug interaction studies that in vivo clozapine is mainly metabolized by CYP1A2 and is essentially a CYP1A2-dependent drug in clinical doses. In vitro studies detected other metabolic pathways including cytochrome P450 3A4 (CYP3A4) and cytochrome P450 2D6 (CYP2D6). CYP3A4 may be more relevant in toxic concentrations but is a minor pathway in clinical concentrations [68]. There is general agreement in the literature that CYP2D6 is a minor pathway. It is unclear why the FDA in 2004 added to the US package insert that CYP2D6 poor metabolizers (PMs) need lower clozapine doses. There is no literature to support that [68]. More importantly, it is perplexing that this statement still persists in the US clozapine package insert in 2024 when package inserts from other countries or pharmacogenetic organizations do not agree with the FDA decision to recommend lower clozapine doses for CYP2D6 PM [74].

The advances in pharmacokinetics mean that the US package insert is seriously outdated in too many areas to be able to describe succinctly but, as another major example, in 1997 two studies indicated that patients of Chinese ancestry receiving approximately half the dosage used in Western countries had the same serum/plasma concentrations [75,76]. This knowledge was progressively supported by more studies [56] but was never incorporated into the US package insert. Neither is the current understanding that DNA ancestry should be using in clozapine dosing since metabolism is lower in patients from Asian and Indigenous American ancestry, intermediate in those of European ancestry and highest in those of African ancestry [77–79].

5.2.3. Clozapine intoxication during infections: a succinct literature review

As clozapine is mainly dependent for its metabolism on CYP1A2, it is expected that during infections with systemic inflammation it should behave like theophylline and be associated with intoxications. As a matter of fact, cases of clozapine intoxication during infections were described in the early 2000s [37,80]. Following the recommendations for theophylline, it was proposed that clozapine doses should be halved to prevent clozapine intoxications during severe infection [81]. Twenty years later, the case reports had accumulated [38], the warning about the risk of lethality during infection in clozapine patients had been published [82] and finally the first cohort studies proposed that the risk of clozapine intoxication is determined by the severity of the systemic inflammation [39]. Similarly, a cohort

studied during COVID-19 found that clozapine intoxication occurred in patients with elevated c-reactive protein (CRP), while in those with no or mild elevations there were no obvious increases in serum/plasma concentrations [41].

The role of CRP as a marker of systemic inflammation has a long history in clozapine-treated patients. In 2009, Pfuhlmann et al. proposed using increased CRP as a marker of the risk that an inflammation may lead to increases in plasma/serum clozapine concentrations [83]. The Australian experts added CRP monitoring to the clozapine titration to prevent myocarditis [84]. Their data suggested that CRP elevations happened on average 5 days earlier than troponin elevations [85]. Thus, CRP was proposed as a marker of all clozapine-induced inflammations that are associated with titrations that are too rapid for that specific patient; these inflammations can include fever, myocarditis, other localized inflammations, or DRESS [86]. A recent systematic review recommended CRP monitoring during clozapine titrations [87]

5.2.4. A critical review of US pharmacovigilance during the first 10 years of clozapine marketing

According to Meltzer [88], the US marketer stopped marketing clozapine in the US around 2003. This is important in understanding the lack of recent updates in the US package insert. Once a drug becomes generic and the marketer does not support further studies or changes in the package insert, there is little economic incentive to improve the package insert of any drug; package inserts then easily become outdated [89].

There is no doubt that during the first 10 years of marketing until 1999, clozapine's marketer in the US and the FDA should have been attentive to the fatal outcomes in clozapine-treated patients in the US pharmacovigilance data. Any reader of this article can see in Supplementary Figure S2 that until 1999 there were 140 fatal outcomes worldwide associated with pneumonia in clozapine-treated patients. Supplementary Figure S2 does not present the US data. In the US, until 1999, 929 deaths in clozapine-treated patients were reported to the FDA. All forms of severe neutropenia accounted for 48 deaths, which was only 5% of the 929 fatal outcomes. Currently, it is not known why the US clozapine marketer and the FDA did not pay attention to the fact that pneumonia was associated with more than twice the fatal outcomes as severe neutropenia with 112 fatal outcomes or 12% of the total of 929 deaths [64].

5.2.5. Recent changes in clozapine package inserts

In 2020, the UK pharmacovigilance agency recommended monitoring clozapine levels for situations leading to toxicity, including when 'a patient has pneumonia or other serious infection' [90]. The FDA has never included a recommendation for clozapine levels in the US package insert despite this recommendation by international experts [91] and US experts [92]. On the other hand, in May 2023, the FDA modified the US clozapine package insert providing no recommendations for clinicians and a confusing message, 'Published case reports describe examples where pneumonia or other inflammatory conditions may increase clozapine concentrations. The clinical significance, the impact of treatments to modulate this inflammation, and mechanism of this potential increase in clozapine concentrations

have not been fully characterized but may involve reduced cytochrome P450 1A2 activity.' [67]. Currently, it is not known why the FDA only focused on published case reports but did not look at the US pharmacovigilance data in clozapine-treated patients, which indicates there are many more fatal outcomes associated with pneumonia than with severe neutropenia. Until 15 January 2023, there were 9,587 fatal outcomes in US clozapine-treated patients, 2% (218/9587) associated with agranulocytosis versus 7% (674/9587) associated with pneumonia [64].

5.3. Clinical implications of our results

Our findings may have major clinical relevance in four aspects of managing clozapine-treated patients: 1) at least 30% of pneumonia cases may be aspiration pneumonia, 2) stopping some co-medication (olanzapine, quetiapine, valproate, and benzodiazepines) may decrease the risk of aspiration pneumonia, 3) the average lethality of 45% during pneumonia does not make it clear that the lethality rate in patients over 65 years of age and experiencing more than 1 year of treatment may be 75%, and 4) 5-mg tablets may be required to safely titrate some patients.

5.3.1. At least 30% of pneumonia cases in clozapine-treated patients may be aspiration pneumonia

This VigiBase® study indicates it is possible that at least 30% of pneumonia in clozapine-treated patients may be aspiration pneumonia. Aspiration pneumonia clearly appears to be a clozapine-associated ADR while infectious pneumonia in the absence of aspiration may be more related to the comorbidity and co-medications associated with TRS and less influenced by clozapine. It is possible that the percentage of aspiration pneumonia may be even higher than 30% in clozapine-treated patients and it is very likely that it may be much higher during titration, in geriatric patients and in those co-medicated with olanzapine, risperidone, benzodiazepines, or valproate (Tables 2 and 3). VigiBase® does not reflect psychiatric diagnosis very well in clozapine-treated patients, but aspiration pneumonia instead of infectious pneumonia in the absence of aspiration should be suspected in patients at major risk for a swallowing impairment, including those with intellectual disability [93] or Parkinson's disease [23]. The limited VigiBase® data also suggest that during titration, pneumonia is a clozapine-associated ADR; this includes aspiration pneumonia associated occasionally with voluntary overdoses and more frequently with too-rapid titration by the prescriber. According to the literature, some pneumonia during titration can be hypersensitivity pneumonia manifested as eosinophilic pneumonia in the absence of an infectious agent [94] or in the context of the more complex DRESS presentation [95].

5.3.2. Some co-medications may suggest that the pneumonia is an aspiration pneumonia

The limited data from the logistic regression seen in Table 2 indicate that several co-medications including olanzapine, risperidone, valproic acid, and benzodiazepines have extremely high ORs, indicating they increase the risk that an associated pneumonia has signs compatible with aspiration pneumonia. This is very important since

aspiration pneumonia has a high risk of recurrence. In the Danish registry, risperidone by itself was associated with increased pneumonia risk [26]. In the Taiwan registry, clozapine was associated with increased risk of recurrence of pneumonia [96] and comedication such as a benzodiazepine [25] or valproate [22] increased the risk of pneumonia in clozapine-treated patients. Thus, if the patient had survived pneumonia and this was developed in the presence of olanzapine, risperidone, valproic acid, or benzodiazepines, it appears reasonable to stop all of these co-medications that may be further interfering with swallowing.

5.3.3. Using an average of 45% may obscure the high mortality rate in geriatric patients

In the sample with complete data on pneumonia, we observed a high average lethality rate of 45% (1090/2415). The average of 45% can be misleading since Table 4 indicates that the range after considering age, duration of clozapine treatment and sex varies widely from 0 to 76%. In patients of geriatric age (>64 years), lethality was very high, from 59% to 76% in males and 21% to 74% in females. It appears very important to prevent pneumonia in this geriatric population. Clozapine clearance decreases as renal function decreases [79,97]; thus, patients who had been stable on a clozapine dose for 10–20 years may end up with very high serum/plasma concentrations when they reach geriatric age and their renal functions start to decline. Thus, when a patient who is stable on clozapine becomes older, his/her serum/plasma concentrations may increase at least 1.4 to 1.6-fold when reaching 80 years of age [79]. The addition of pneumonia may lead to doubling or tripling baseline clozapine concentrations. Thus, the 75% lethality, according to the VigiBase® data described in Table 4, may reflect the combination of keeping the same maintenance doses in spite of the progressive age-related decrease in clozapine clearance as renal function decreases plus the clozapine intoxication associated with severe systemic inflammation during any type of pneumonia.

Other important interventions for preventing pneumonia and its lethality in all clozapine-treated patients include 1) using the lowest possible therapeutic dosage by monitoring clozapine levels [98], 2) educating patients and families about the risk of infection and the need to contact the clozapine prescriber when there are signs of infection [99], and 3) treating risk factors such as i) constipation [100,101] that may lead to CIGH [16] and secondarily to vomiting and aspiration pneumonia and ii) hypersalivation [100,102,103].

5.3.4. 5-mg clozapine tablets may be needed for safer clozapine prescribing

The limited data on titration suggest that clozapine tablets of 5 mg may be needed, but they are not available [104]. In most countries around the world, the smallest dosage available for clozapine is the 25-mg tablet, although in some countries these 25-mg tablets can be divided in half [105–107]. The high rate of pneumonia during titration published in studies from Asian countries such as Korea [32,33] or Japan [31] and the VigiBase Japanese data indicate the need for very low starting doses in patients of Asian ancestry. Similar low doses

may be required for patients of Indigenous American ancestry who are descended from East Asians [108]. The international clozapine titration guideline [77] recommends starting with 6.25 mg and increasing by 6.25 mg during the first week for any patients of Asian (or Indigenous American) ancestry with obesity or using co-medications including oral contraceptives, valproate, quetiapine, or olanzapine [78]. This extremely slow titration would be much easier with 5-mg tablets than with 25-mg tablets. Similarly, 5-mg tablets may be helpful for clozapine titrations in patients with Parkinson's disease that, according to our limited data from VigiBase®, fatal cases in the first week of titration were reported after several days on low doses of 6.25 to 12.5 mg/day. That those extremely low clozapine doses contributed to fatal outcomes in Parkinson's disease probably reflects the fact that dysphagia is extremely frequent in this disease. In a systematic review, Takizawa et al. reported that dysphagia was present in 11–81% of patients with Parkinson's disease [109]. Thus, as most patients with severe Parkinson's disease probably have some level of swallowing disturbance, even very small clozapine doses can further exacerbate the problem and, more importantly, lead to fatal aspiration pneumonia.

5.4. Need for further advances

There is a great need of studies on the lethality of pneumonia in clozapine-treated patients. The national registries in Scandinavia and Taiwan need to explore this issue. It is not easy to retrospectively diagnose between aspiration pneumonia versus infectious pneumonia. We suspect that aspiration pneumonia accounts for more than 30% of pneumonia in clozapine-treated patients. It is important to pay attention to signs compatible with aspiration such as history of salivary hypersecretion, dysphagia, vomiting, or choking. Our limited data also suggest that pneumonia during titration or in patients of geriatric age should be suspected to be aspiration pneumonia unless there is a reason to suspect an infectious pneumonia. Very importantly, our limited data suggest that co-medication with olanzapine, risperidone, valproic acid, or benzodiazepines indicates very high risk that it is aspiration pneumonia and serious consideration should be given to the risk of a repeated aspiration pneumonia.

Our proposed pharmacological interventions for reducing the risk of pneumonia in clozapine-treated patients focus on reducing risk associated with 1) rapid clozapine titration, 2) high maintenance doses of clozapine that may be lower by using clozapine levels, and 3) co-medications potentially promoting aspiration and then aggressively decreasing the risk of clozapine intoxication once pneumonia or aspiration pneumonia has developed. It appears to us that it is not easy to use other drugs to target the pharmacological mechanisms that may explain the risk of aspiration pneumonia in clozapine-treated patients. The mechanisms are not well understood but, using the literature, one can propose that the effects of clozapine on aspiration and aspiration pneumonia are probably explained by multiple pharmacodynamic mechanisms [15] including the following risks: 1) H_1 antagonism may contribute to sedation and swallowing disturbances, 2) agonism

of the salivary muscarinic receptors may contribute to hypersalivation, 3) antagonism of the intestinal muscarinic receptors may contribute to severe constipation which may lead to aspiration of vomit and, 4) antagonism of D_2 receptors may contribute to swallowing disturbances. These multilevel pharmacodynamic actions make it difficult to prescribe other drugs to decrease these risks of using clozapine. A good example of this complexity is prescribing an anticholinergic such as benztropine in tablet or capsule form because it may decrease the risk of aspiration by decreasing the risk of hypersalivation, but it may also further increase the risk of aspiration if severe constipation develops and the patient has an aspiration of vomit secondary to the CIGH.

As Subsection 5.2 indicates, there is a need for major updates of the US clozapine package insert [110], including moving away from a high risk of lethality due to agranulocytosis and toward a high risk of lethality due to pneumonia and other severe systemic infections [111].

As Subsection 5.3.4 indicates, Korean researchers [32,33] and Japanese researchers [31] are starting to realize that clozapine titrations developed in the US may not be suitable for patients of Asian ancestry, as they have lower clozapine clearance and may need the slower titrations proposed by the international clozapine guideline [77]. Ideally, these slower titrations and lower therapeutic dosages should be incorporated into the clozapine package inserts of these Asian countries, but as clozapine is a generic drug it is not easy to acquire funding for prospective studies that would convince the drug agencies of these and other Asian countries. Until the package inserts are changed, the clozapine experts of these Asian countries should be encouraged to publish new studies to educate their clozapine prescribers. For instance, the multi-center research group developed by Kikuchi et al. in seven hospitals in Japan [31] should be followed as an example; their more recent studies [112–114] have further accumulated data on the benefits of slower clozapine titration.

6. Conclusion

This is an extremely large sample of clozapine-associated pneumonia with more than 6000 cases, which is larger than the combination of all prior published clinical samples, but it has all the limitations of pharmacovigilance data. In spite of the limitations, it provides important insights for clozapine-treated patients including the following: 1) to reduce the fatal outcomes it is much more important to focus on pneumonia (45% lethality) than on severe neutropenia (2% lethality), 2) at least 30% of pneumonia may be aspiration pneumonia, 3) stopping some co-medications (olanzapine, quetiapine, valproate, and benzodiazepines) may decrease the risk of aspiration pneumonia, 4) average pneumonia lethality was 45% but may be around 75% in geriatric patients in long-term treatment, and 5) 5-mg tablets may be required to safely titrate patients with Parkinson's disease or of Asian ancestry.

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Declaration of interest

J de Leon personally develops his presentations for lecturing, has never lectured using any pharmaceutical or pharmacogenetic company presentations, and has never been a consultant for pharmacogenetic or pharmaceutical companies. In the past, J de Leon received researcher-initiated grants from Eli Lilly (one ended in 2003 and the other, as co-investigator, ended in 2007); from Roche Molecular Systems, Inc. (ended in 2007); and, in a collaboration with Genomas, Inc., from the NIH Small Business Innovation Research program (ended in 2010). J de Leon has been on the advisory boards of Bristol-Myers Squibb (2003/04) and AstraZeneca (2003). Roche Molecular Systems supported one of his educational presentations, which was published in a peer-reviewed journal (2005). His lectures were supported once by Sandoz (1997), twice by Lundbeck (1999 and 1999), twice by Pfizer (2001 and 2001), three times by Eli Lilly (2003, 2006, and 2006), twice by Janssen (2000 and 2006), once by Bristol-Myers Squibb (2006), and seven times by Roche Molecular Systems, Inc. (once in 2005 and six times in 2006). G Schoretsanitis has received speaker/consultation fees from Dexcel Pharma, HLS Therapeutics, and Thermo Fisher. E Spina has participated in speakers/advisory boards and received support from Angelini, ArcaPharma, Janssen Pharmaceuticals, Lundbeck, Otsuka, and Rovi. E Sanz has never been a consultant for any pharmaceutical industry and his lectures have never been supported by any pharmaceutical company. On several occasions he has been invited to speak at conferences that might have been supported by the industry, but the invitation and reimbursements were given by the scientific society organizing the conference in all cases. He has a signed agreement with the WHO-Uppsala Monitoring Center as member of the external clinical experts Group. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

Author contributions

C De Las Cuevas and J de Leon proposed the design of this article to EJ Sanz. EJ Sanz and C De Las Cuevas downloaded the files. C De Las Cuevas worked on cleaning the files. C De Las Cuevas and J de Leon wrote the first draft of this article. M Betancort completed the machine learning analyses. J de Leon completed the logistic regression model analysis, discussed them and the issue of the missing data with A Villasante-Tezanos who completed the statistical commentary on that issue. All the coauthors critically reviewed the article, provided modifications, approved the first and final versions and any significant changes at the proofreading stage, approved with the submission to this journal and agreed to take responsibility and be accountable for the contents of the article and to share responsibility to resolve any questions raised about the accuracy or integrity of the published work.

Data availability statement

VigiBase does not allow the distribution of their file.

Reviewer disclosures

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Ethics statement

This study followed the principles of the Declaration of Helsinki and adhered to stringent data anonymization protocols including grouping ages to avoid the identification of single patients, which eliminated the need for ethics committee approval at the university of the authors who downloaded the files

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