Respiratory aspiration during treatment with benzodiazepines, antiepileptic and antidepressant drugs in the pharmacovigilance database from VigiBase

Carlos De Las Cuevas, Emilio J. Sanz and Jose de Leon

1. Introduction

The subsections in the Introduction are: 1) respiratory aspiration, 2) the association of respiratory aspiration with antipsychotic (AP) drugs by the Food and Drug Administration (FDA), 3) the contribution of underlying psychiatric disorders to drug-induced aspiration, 4) the association of respiratory aspiration with benzodiazepines, antiepileptic (AED) drugs and antidepressant (AD) drugs in the literature, 5) the confounding effects of APs and opioids and 6) pharmacovigilance.

1.1. Respiratory aspiration

Respiratory aspiration refers to the inflow of material from the oral cavity or upper gastrointestinal tract into the lungs through the larynx. The experts on aspiration describe continuity in the various levels of penetration of foreign material in the respiratory airways until the material penetrates below the vocal cords and is not expelled with the cough reflex, leading to aspiration [1]. The laryngeal cough reflex is very important in preventing aspiration to the lungs and does not decrease with normal aging [2]. Once the aspirated material reaches the lung, three conditions are described by the experts [3]: aspiration, aspiration pneumonitis, and aspiration pneumonia. Obviously, when the aspiration is massive and lethal in a short time (minutes or a few hours), there is little time to develop aspiration pneumonitis and aspiration pneumonia.

1.2. The FDA has associated respiratory aspiration with antipsychotics

In 2005, the FDA brought attention to the association between respiratory aspiration and psychiatric drugs [4]. They observed the association between APs and deaths in patients with dementia caused by pneumonia and required a warning in the package insert about ‘esophageal dysmotility and aspiration’ for new second-generation APs (SGAPs). In June 2008, the FDA further requested the extension of the warning to the first-generation APs (FGAPs) [5]. The interest in this issue has become evident in a recent umbrella review of observational studies that proposed pneumonia may have the strongest association with AP exposure among life-threatening medical events [6]. In a US cohort of 146,552 hospitalizations (median age 56),
antipsychotics were used in 10,377 (7%) hospitalizations. The incidence of aspiration pneumonia was 0.3% in unexposed individuals and 1.2% in those with antipsychotic exposure. The odds ratio (OR) was 3.9, (95% confidence interval, CI, = 3.2–4.8) and the adjusted OR was 1.5 (95% CI = 1.2–1.9). An analysis restricted to those with delirium or dementia provided similar results [7].

Although the AP signal of aspiration and aspiration pneumonia started in dementia [8], the AP most strongly associated with pneumonia and lethality has been clozapine [9] an AP rarely used in demented patients [8]. Clozapine can interfere with swallowing as can other antipsychotics but also may be particularly prone to cause sedation and hyposalivation, further increasing the risk of aspiration [10] and aspiration pneumonia [10,11]. This complexity is apparent, given that clozapine is mainly used in treatment-resistant schizophrenia (TRS) which may pose a particular additional risk for pneumonia [12].

1.3. The contribution of underlying psychiatric disorders to drug-induced aspiration

As TRS can contribute to pneumonia, there are two major groups of psychiatric patients who are very prone to swallowing disturbances and risk of respiratory aspiration [8]: patients with dementia and those with intellectual disability (ID). Multiple drugs can impair oropharyngeal function, saliva production, impair consciousness or cough reflex and thus increase the risk of respiratory aspiration [13,14] in patients with dementia or ID.

1.3.1. Dementia

As indicated, the FDA warning started with antipsychotic use and dementia. Several mechanisms contribute to dysphagia in Alzheimer’s disease and in the elderly with other dementing or neurological conditions [15]. Surprisingly, in 2016, in a systematic review of oropharyngeal dysphagia Takizawa et al. [16] could not identify studies in Alzheimer’s disease. In 2020, Espinosa-Val et al. published a prospective longitudinal study in 255 patients with dementia and found an oropharyngeal dysphagia rate of 86% and almost all patients with dysphagia required fluid thickening or food texture modification [17].

1.3.2. Intellectual disability

In 2017, in a systematic review of dysphagia in adult patients with IDs, Robertson et al. found estimates, based on population-based samples of people with ID from areas of England, of a prevalence around 8.1–11.5% [18]. In two US samples of patients with IDs in residential settings, Sheppard et al. found that mild to severe levels of dysphagia were present in 2/3 and 3/4 of the samples, but the authors acknowledged that they ignored the effects of medications [19]. The same authors, when they tried to develop scales to rank risk factors for the complications of dysphagia in patients with ID, listed medications associated with dysphagia, not only APs, but AEDs, sedatives and medication with anticholinergic or anti-histaminic properties [20]. Many patients with ID have seizures that are difficult to control and aspiration is relatively frequent during seizures. In a retrospective analysis of 1634 adult patients with IDs [21], DeToledo et al. reported that seizures were associated with aspiration pneumonia in a range of 2.5 per thousand (2/806 patients) in the telemetry unit and 2.7 per thousand in (2/733) in the outpatient setting. In 95 institutionalized patients for more than 1 year, there were 17 instances of aspiration pneumonia after a generalized seizure and 32 instances of aspiration unrelated to seizures.

1.4. Respiratory aspiration and benzodiazepines, antiepileptic and antidepressant drugs in the literature

By reviewing mortality in public facilities and during the treatment of patients with ID or dementia, we find that other psychiatric medications can contribute to dysphagia and its complications including respiratory aspiration [8]. Thus, we conducted a PubMed search on respiratory aspiration and benzodiazepines, AEDs and ADs (Supplementary Box S1). Any of these drugs used in overdose can be expected to cause respiratory aspiration, so we were looking for articles on respiration aspiration that occurred during treatment when patients were following prescribed doses.

1.4.1. Benzodiazepines and respiratory aspiration

Supplementary Box S1 describes a retrospective naturalistic study in aged patients in which benzodiazepines were specifically associated with signs of respiratory aspiration [22]. This is not completely surprising since benzodiazepines are sedating agents and have been associated with dysphagia [23,24]. In our experience, they tend to cause dysphagia in high doses [8]. It is interesting that the US package inserts only list risk of respiratory aspiration during overdoses and do not list dysphagia or swallowing disturbances during treatment for lorazepam [25]. The US package inserts for clonazepam [26] and
diazepam [27] do not list aspiration during overdoses nor dysphagia or swallowing disturbances during treatment.

1.4.2. Antiepileptic drugs and respiratory aspiration
Supplementary Box S1 indicates that we did not find articles on AED-induced respiratory aspiration but one article suggests AEDs have been associated with dysphagia [23] and may contribute to additional risks when co-prescribed with APs [28].

1.4.3. Antidepressant drugs and respiratory aspiration
Drugs blocking antimuscarinic receptors by decreasing salivation and those blocking H1 receptors can contribute to dysphagia and sedation [8] and some ADs can block muscarinic or H1 receptors [29]. Supplementary Box S1 shows that we only found one article on AD-induced respiratory aspiration in the context of an overdose [30].

1.5. Confounding drugs: antipsychotics and opioids
In countries with high incomes, particularly in North America, the number of prescriptions of psychiatric drugs has increased dramatically in the last 20 years [31]. More relevant is the fact that many of the patients taking psychotropic drugs take several of them, which is usually called polypharmacy, although it gets defined in different ways. In European patients with schizophrenia, patients were frequently treated with polypharmacy [32] using 3.3 ± 1.8 drugs in a group of Europeans in long-term hospitals [33]. Two European outpatient studies describe the mean number of psychotropic medications as 2.9 ± 1.6 [34] and 3.3 [35]. Similarly, a schizophrenia study in 15 countries in Asia showed that the average psychotropic drug loading of all patients was 2.01 ± 1.64, peaking at 4.1 ± 3.1 in Japan [36].

Therefore, when studying respiratory aspiration associated with benzodiazepines or AEDs or ADs, it is important to consider that other drugs may also be co-prescribed in the patient and there is need to control for the contribution of the two drug classes most definitively associated with respiratory aspiration: APs and opioids.

1.5.1. Antipsychotic drugs and respiratory aspiration
As described, the FDA [4,5] and the literature associates APs with respiratory aspiration [8], so it is not surprising that our search identified four relevant articles (Supplementary Box S1). There were three cases of respiratory aspiration during clozapine treatment [37–39] and one during an AP overdose [40].

1.5.2. Opioids and respiratory aspiration
Opioids can cause sedation and vomiting [41], so they can cause respiratory aspiration during perioperative procedures and, more importantly, during overdose [42]. Thus, our article search (Supplementary Box S1) also identified relevant articles, two discussing respiratory aspiration during perioperative procedures [43,44] and three during overdose or intoxication [42,45,46].

1.6. Pharmacovigilance and VigiBase
Rare adverse drug reactions (ADRs) may not be detected in premarketing studies but may be recognized by using what is called pharmacovigilance during postmarketing surveillance [47]. This pharmacological term refers to the case reports and studies of ADRs published in medical journals and from reports to the FDA and other national drug agencies. The World Health Organization (WHO) has developed a global database called VigiBase which currently has >25 million reports of spontaneously reported ADRs from the drug agencies of 145 countries [48]. It is located at the Uppsala Monitoring Center (UMC), Uppsala, Sweden. New reports arrive daily and ADRs are sometimes classified by the reporting clinician but normally those who report would enter free text information and the pharmacovigilance staff at a regional or national center or pharmaceutical company would do the encoding using the categories provided by the database.

The goal of this review article is to review the association of respiratory aspiration with treatment of 3 psychotropic drugs: benzodiazepines, AEDs and ADs by critically analyzing the current data in VigiBase after considering the confounding effects of polypharmacy. polypharmacy including those of two drug classes, APs and opioids, which have been firmly associated with respiratory aspiration. The word treatment indicates treatment as prescribed, because it would not be surprising that in overdose benzodiazepines, AEDs and ADs can cause respiratory aspiration; they are sedative drugs.

2. Methodological aspects
The Methods subsection focuses on 1) the VigiBase search, 2) standard statistical analyses by VigiBase, 3) the confounding effects of duplicate reports, and 4) the effect of confounding variables.

2.1. VigiBase search
Records dating from the inception of the database until 5 September 2021, were searched to locate aspiration cases suspected to be associated with benzodiazepines, AEDs, and ADs (Table 3). All reports of aspiration associated with these medication groups were scrutinized by the first and second authors. VigiBase classifies a case as serious (defined as an ADR that requires hospitalization or extension of hospital stay, results in persistent or significant disability or incapacity, or is life-threatening). If the case did not meet criteria for seriousness, it was considered non-serious. VigiBase also reports fatal outcomes [48].

This is a retrospective review of deidentified worldwide patient data that does not require the signed consent of the individual patient according to the ethics of the institutional review board of the first author’s university.

2.2. Standard statistical analyses by VigiBase
VigiBase uses a Bayesian confidence propagation neural network that provides a statistical indicator called an information component (IC), which is used to filter out combinations of
particular drugs and ADRs that are present in the database more frequently than expected, according to all reports for the particular drug and ADRs, and the total number of reports in the database [49]. An IC of 0 results from drug-ADR combinations for which the number of observed cases is the same as that which might be expected from the overall reporting in the data set. Positive values represent combinations reported more frequently and negative values more infrequently than expected. The IC measures of disproportionality between the expected and the reported rates of respiratory aspiration are reported in Table 1. CIs of the ICs are provided to account for sampling variability.

A high IC value, in addition to IC<sub>25</sub> (lower 97.5% CI), denotes a strong statistical association between the antipsychotic and myocarditis in the database. Moreover, when the IC<sub>25</sub> (lower 97.5% CI) is positive (>0) it indicates a statistically significant disproportionality between the expected and the reported rates for a drug and an ADR. Similarly, the 95% CI of two drugs can be used for comparison and when they do not overlap this indicates that they are significantly different with at least a p value <0.05 [50].

2.3. The confounding effects of duplicate reports

All of these VigiBase standard analyses are contaminated by the possibility of some level of duplicate reports. The first and second authors downloaded the files of aspiration associated with benzodiazepines (N = 469), AEDs (N = 429) and ADs (N = 875). By combining these three files, the cases numbered 1773, so when the first author combined them into a single file, he found 1004 cases after eliminating 769 duplicated cases, according to the coding system used by VigiBase.

The first and last authors have extensive experience in working together using VigiBase data [9,10,48,51]. Based on this experience they decided to review the 1004 VigiBase aspiration cases associated with these 3 drug classes. Each case was reviewed to identify duplicates by discussing them using their extensive clinical experience (>30 years each working as psychiatrists) and making decisions by agreement. They decided that 44 cases were duplicates, leading to 960 unduplicated cases. In the review, they also identified 60 cases of aspiration in neonates exposed during pregnancy or in small children (age <10 yo). They eliminated these 60 cases, leading to 900 cases as the study sample.

2.4. The effect of confounding variables

The information in many cases reported to VigiBase is limited but based on the authors’ extensive experience with VigiBase, they thought it was probable that in 364 cases aspiration occurred in the context of an overdose and/or suicide attempt. They also identified 596 cases of aspiration in the context of major medical problems not obviously explained by aspiration and probably present before aspiration. They realized that this variable of major medical problems might be biased since many patients appear to have been found dead with a sign of aspiration for which there was no prior clinical data. VigiBase provide the opportunity to classify patients as demented but by reviewing individual cases we found that many other patients were also taking treatment for dementia so we included them in that category.

Table 1. ICs for respiratory aspiration and drug class (5/20/09).

| Benzodiazepine class (defined by ATC as N05BA) and 6 top individual drugs | N<sub>observed</sub> | N<sub>expected</sub> | N<sub>drug</sub> | IC<sub>25</sub> | IC | N<sub>serious</sub> | N<sub>total</sub> | Without Duplicates | Used Alone | Aspiration Pneumonia | Overdose or Suicide |
|---|---|---|---|---|---|---|---|---|---|---|---|
| N05BA group<sup>2</sup> | 344 | 50 | 200126 | 2.6 | 2.8 | | | | | | |
| Diazepam | 86 | 10 | 39531 | 2.7 | 3.1 | 74 | 66 | 76 | 11% (8/76) | 42% (32/76) | 8% (6/76) |
| Lorazepam | 68 | 9 | 35730 | 2.5 | 2.9 | 63 | 22 | 68 | 19% (13/68) | 40% (27/68) | 21% (14/68) |
| Clonazepam | 65 | 10 | 39457 | 2.3 | 2.7 | 60 | 33 | 55 | 13% (7/55) | 46% (25/55) | 24% (13/55) |
| Alprazolam | 65 | 14 | 54438 | 1.8 | 2.2 | 60 | 44 | 56 | 11% (6/56) | 55% (31/56) | 20% (11/56) |
| Oxazepam | 18 | 2 | 8724 | 2.0 | 2.8 | 17 | 8 | 18 | 17% (3/18) | 56% (10/18) | 11% (2/18) |
| Nordiazepam | 6 | 0 | 1125 | 1.3 | 2.8 | 5 | 5 | 6 | 0% (0/6) | 17% (1/6) | 0 |
| AED class (defined by ATC as N03A) and 6 top individual drugs | | | | | | | | | | | |
| N03A group<sup>2</sup> | 618 | 199 | 79415 | 1.5 | 1.6 | | | | | | |
| Valproic acid | 72 | 22 | 87819 | 1.3 | 1.7 | 64 | 34 | 64 | 19% (12/64) | 23% (15/64) | 22% (14/64) |
| Pregabalin | 66 | 35 | 140895 | 0.5 | 0.9 | 64 | 27 | 66 | 26% (17/66) | 35% (23/66) | 27% (27/66) |
| Gabapentin | 58 | 22 | 88156 | 1.0 | 1.4 | 50 | 22 | 55 | 35% (19/55) | 38% (21/55) | 18% (10/55) |
| Lamotrigine | 43 | 16 | 65942 | 0.9 | 1.4 | 36 | 23 | 43 | 44% (19/43) | 39% (17/43) | 21% (9/43) |
| Levetiracetam | 27 | 12 | 47236 | 0.6 | 1.2 | 25 | 9 | 34 | 1% (6/34) | 5% (2/43) | 23% (10/43) |
| Topiramate | 25 | 8 | 32986 | 0.9 | 1.5 | 21 | 9 | 32 | 9% (3/32) | 38% (12/32) | 19% (6/32) |
| AD class (defined by ATC as N06A) and 6 top individual drugs | | | | | | | | | | | |
| N06A group<sup>2</sup> | 520 | 197 | 78742 | 1.3 | 1.4 | | | | | | |
| Venlafaxine | 67 | 18 | 70491 | 1.5 | 1.9 | 59 | 39 | 59 | 19% (11/59) | 56% (33/59) | 10% (6/59) |
| Citr palopram | 65 | 11 | 42290 | 2.2 | 2.5 | 54 | 37 | 65 | 26% (27/65) | 63% (41/65) | 9% (6/65) |
| Bupropion | 60 | 18 | 71145 | 1.3 | 1.7 | 53 | 37 | 56 | 36% (20/56) | 77% (43/56) | 5% (3/56) |
| Amitriptyline | 54 | 9 | 35243 | 2.1 | 2.5 | 45 | 30 | 48 | 15% (7/48) | 48% (22/48) | 10% (5/48) |
| Trizactone | 51 | 6 | 24226 | 2.5 | 3.0 | 46 | 31 | 46 | 8% (3/36) | 42% (15/36) | 6% (2/36) |
| Sertraline | 49 | 20 | 81142 | 0.8 | 1.3 | 45 | 30 | 42 | 31 (13/42) | 33% (14/42) | 19% (8/42) |

AD: antidepressant; AED: antiepileptic drug; ATC: Anatomical Therapeutic Chemical.

<sup>1</sup>ATC system of the World Health Organization where the active substances are divided into different groups based on the organ or system on which they act and their therapeutic, pharmacological, and chemical properties.

<sup>2</sup>This class is contaminated by a few benzodiazepines (diazepam, lorazepam, clonazepam, and midazolam)
2.4.1. Logistic regression models on fatal outcomes
Based on prior experience in VigiBase [48] the SPSS software, 27th version, was used to calculate adjusted ORs and their 95% CIs using fatal outcome (yes/no) as the dependent variable. 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. As the authors were interested in the fatal outcomes not associated with overdose and/or suicide, they divided the file between those with no data suggesting overdose and/or suicide, which were those of interest for us, and those with overdose and/or suicide, which served as controls.

2.4.2. Logistic regression models comparing each drug class versus the other 2 drug classes
Logistic regression models were also used to explore the variables associated with each drug category, ADs, benzodiazepine, or AEDs, versus the other 2 drugs.

3. Results
The subsections of the Results section focus on 1) ICs, 2) logistic regression models in non-duplicated cases of aspiration, and 3) the review of 172 non-duplicated and non-confounded cases.

Table 2. Demographic and clinical variables of sample analyzed after eliminating duplicates.

|                              | Total sample | Overdose/suicide No | Overdose/suicide Yes |
|------------------------------|--------------|---------------------|----------------------|
| North America                | 65.2% (387/900) | 63.1% (349/553)     | 68.6% (238/347)      |
| Europe                       | 27.3% (246/900) | 26.2% (145/553)     | 29.1% (101/347)      |
| Asia                         | 4.3% (39/900)   | 6.1% (34/553)       | 1.4% (5/347)         |
| Oceania                      | 2.8% (25/900)   | 4.1% (23/553)       | 0.6% (2/347)         |
| South America                | 0.2% (2/900)    | 0.2% (1/553)        | 0.3% (1/347)         |
| Africa                       | 0.1% (1/900)    | 0.2% (1/553)        | 0% (0/347)           |
| Age                          |               |                     |                      |
| • Missing                    | 15.4% (139/900) | 18.6% (103/553)     | 10.4% (36/347)       |
| • Present                    | 84.6% (761/900) | 81.4% (450/553)     | 89.6% (311/347)      |
| • Mean±SD                    | 47.2 ± 19.0    | 52.0 ± 18.8         | 40.4 ± 17.1          |
| Geriatric age (≥65 yo)       | 16.7% (150/761) | 21.9% (121/540)     | 8.4% (29/311)        |
| Sex                          |               |                     |                      |
| • Missing                    | 5.1% (46/900)   | 4.7% (26/553)       | 5.8% (20/347)        |
| • Present                    | 94.9% (854/900) | 95.3% (527/553)     | 94.2% (327/347)      |
| Male                         | 55.4% (473/854) | 57.5% (304/527)     | 51.7% (169/327)      |
| Female                       | 44.6% (381/854) | 42.3% (223/527)     | 48.3% (158/327)      |
| Seriousness¹                 |               |                     |                      |
| • Non-serious                | 7.4% (67/900)   | 9.2% (51/553)       | 4.6% (16/347)        |
| • Serious but non-fatal      | 42.2% (380/900) | 41.6% (230/553)     | 43.2% (150/347)      |
| • Fatal                      | 50.3% (453/900) | 49.2% (272/553)     | 52.2% (181/347)      |
| Benzodiazepines              | 49.7% (447/900) | 47.9% (265/553)     | 52.4% (182/347)      |
| Antiepileptics               | 41.4% (373/900) | 47.6% (263/553)     | 31.7% (110/347)      |
| Antidepressants              | 51.7% (465/900) | 44.7% (247/553)     | 62.8% (218/347)      |
| Antipsychotics               | 42.8% (385/900) | 51.5% (285/553)     | 28.8% (100/347)      |
| Opioids                      | 31.1% (280/900) | 23.0% (127/553)     | 44.1% (153/347)      |
| Number of suspected drugs    | 2.86 ± 1.73    | 2.82 ± 1.66         | 2.91 ± 1.84          |
| Major medical problem        | 66.2% (596/900) | 69.1% (382/553)     | 61.7% (214/347)      |
| Dementia                     | 2.0% (18/900)   | 3.1% (17/553)       | 0.3% (1/347)         |
| Parkinsonism                 | 2.4% (2/900)    | 3.8% (1/553)        | 0.3% (1/347)         |
| Choking                      | 4.6% (41/900)   | 6.1% (34/553)       | 2.0% (7/347)         |

SD, standard deviation.
¹VigiBase reports fatal outcomes. VigiBase may classify a case as serious (defined as an adverse event or reaction that requires hospitalization or extension of hospital stay, results in persistent or significant disability or incapacity, or is life-threatening). If the case did not meet criteria for seriousness, it was considered non-serious.
approximately 2/3 of the total cases and those with or without probable overdoses. The mean number of suspected drugs from the 5 groups (benzodiazepines, AEDs, ADs, APs, and/or opioids) was almost 3 and this number was similar in probable overdoses. The fatal outcomes were around 50% and this number was similar in probable overdoses.

3.2.1. Lethality in respiratory aspirations which were not associated with overdoses

Table 3 describes the variables associated with fatal outcomes on those 553 non-duplicated cases of aspiration in which there was no data supporting overdoses. The fatal outcomes were associated with choking (OR = 2.27) and the presence of at least one drug from 3 classes: APs (OR = 3.12), opioids (OR = 2.13) and ADs (OR = 2.08).

3.2.2. Lethality in respiratory aspirations which were associated with overdoses

In those with fatal aspiration during overdose, the most important associated variable was the number of suspected drugs (OR = 1.23, CI 1.08 to 1.4 p = 0.002).

3.2.3. Exploring variables associated with aspiration in each drug class

When ADs were compared to the other 2 drug classes in the 900 patients, the OR for the number of suspected drugs was significant (OR = 1.31, CI 1.20 to 1.43, p < 0.001) and three other dichotomous variables were significant: lethal outcomes (OR = 1.55, CI 1.17 to 2.04, p = 0.002), major medical problems (OR = 1.48, CI 1.11 to 1.99, p = 0.009) and overdose (OR = 2.20, CI 1.66 to 2.93, p < 0.001).

When repeating the analyses by comparing benzodiazepines or AEDs, the number of suspected drugs was significant but some of the other dichotomous variables significant in the antidepressant class were significant but protective; this is looking at the other side of the ‘AD coin,’ namely, looking at the non-ADs. Thus, the association appears to be driven by the variables that the AD logistic regression model showed have a significant effect.

3.3. The review of 171 non-duplicated and non-confounded cases

Figure 1 describes 171 cases which were not duplicated and were not associated with the presence of data suggesting overdose or major medical problems. Table 4 indicates that in most cases (82%, 140/171) more than 1 drug was involved; it suggests that aspiration in the absence of data indicating overdose or major medical problems, involves several drugs. In the 21 cases involving 5 or more drugs 81% (17/21) of outcomes were fatal.

Supplementary Table S1 describes all the available information from the 32 cases in monotherapy with a specific benzodiazepine, AED or an AD which was associated with aspiration in the absence of overdose or major medical problems. Only 5 cases of benzodiazepines were associated with aspiration, three of them with lorazepam. Only three cases had data on age and the three of them were of geriatric age but there was no information about whether or not these patients were demented. Only 10 cases of AEDs were associated with aspiration: 3 with gabapentin and 2 with pregabalin. There were 17 cases of ADs associated with aspiration: 4 with sertraline, 3 with fluoxetine and 2 with citalopram.

4. Conclusion

The subsections of the Conclusion section focus on: 1) benzodiazepines, 2) AEDs, 3) ADs, 4) AP co-medication, 5) opioid comedication, and 6) limitations.

4.1. Benzodiazepines

The benzodiazepine ICs were 2.8 and IC_{0.25} 2.6, higher than the AP ICs; this appeared to suggest that benzodiazepines may as a group be associated with aspiration. Six individual benzodiazepine ICs were also suggestive. It must be remembered that these ICs were contaminated by duplicates and co-medications. In the logistic regression models on fatal outcomes in aspiration cases not associated with overdoses, the presence of one or more benzodiazepines was not significant.

### Table 3. Logistic regression model\(^1\) fatal outcome in patients with no overdoses/suicide.

| \(N = 553\) whole sample (sex or geriatric age not included)\(^1\) (272 fatal vs 284 non-fatal) | Wald Statistic | Df | P     | OR  | 95% CI for OR |
|---|---|---|---|---|---|
| Antipsychotics | 37.4 | 1 | <0.001 | 3.131 | 2.171-4.514 |
| Antidepressants | 16.5 | 1 | <0.001 | 2.109 | 1.471-3.025 |
| Opioids | 11.9 | 1 | <0.001 | 2.155 | 1.392-3.335 |
| Choking | 4.4 | 1 | 0.037 | 2.289 | 1.052-4.982 |

| \(N = 445\) sex and geriatric age included\(^2\) (234 fatal vs 211 non-fatal) | Wald Statistic | Df | P     | OR  | 95% CI for OR |
|---|---|---|---|---|---|
| Antipsychotics | 15.3 | 1 | <0.001 | 2.265 | 1.503-3.413 |
| Antidepressants | 16.7 | 1 | <0.001 | 2.382 | 1.571-3.611 |
| Opioids | 6.8 | 1 | 0.009 | 1.857 | 1.166-2.958 |
| Choking | 3.7 | 1 | 0.054 | 2.379 | 0.986-5.741 |

\(^{1}\text{Variable(s) entered in step 1: number of suspected drugs, antipsychotics, benzodiazepines, antiepileptics, antidepressants, opioids, parkinsonism, dementia, major medical problems and choking. The model fit well as measured by the Hosmer and Lemeshow test } \chi^2 = 3.6, df = 5, p = 0.59. \text{ We used a } p \text{ value of entry 0.05 and removal 0.06.}\)

\(^{2}\text{Variable(s) entered in step 1: number of suspected drugs, antipsychotics, benzodiazepines, antiepileptics, antidepressants, opioids, parkinsonism, dementia, major medical problems, choking, sex and geriatric. The model fit well as measured by the Hosmer and Lemeshow test } \chi^2 = 3.9, df = 8, p = 0.79. \text{ We used a } p \text{ value of entry 0.05 and removal 0.06.}\)
Supplementary Table S1 shows that only five cases of benzodiazepines were associated with aspiration in the absence of other drugs. It is remarkable that only three of these five cases had data on age and these three were of geriatric age; but there was no information indicating whether or not these patients were demented. There were 17 patients with aspiration in the absence of overdose who were clearly identified as demented. Benzodiazepines were nearly equally present in those who died, 54% (7/13), and in those who did not, 50% (2/4).

In summary, although benzodiazepine ICs appear impressive, no other information in our analyses suggested that benzodiazepines had a specific effect in the context of the major polypharmacy found in these patients with aspiration in the absence of overdose. Therefore, the limited data from VigiBase suggests that benzodiazepines may contribute to respiratory aspiration when overdose is present and in cases associated with polypharmacy, but there was little support for the association of respiratory aspiration and benzodiazepine monotherapy in therapeutic doses. Based on VigiBase data and the literature, new studies of the association of benzodiazepine monotherapy and respiration aspiration in geriatric patients are needed.

### 4.2. Antiepileptic drugs

The AED IC values were intermediate between and close to the IC values of the ADs and opioids. In the logistic regression on fatal outcomes in aspiration cases not associated with overdose, the presence of one or more AEDs was not significant.

Among individual ICs, gabapentin had an IC of 1.4 and IC\textsubscript{25} of 1.0. Gabapentin explained 3 of the 9 cases of AEDs
 associated with aspiration in monotherapy in the absence of overdose. Two other cases were from the analogous compound pregabalin. The information on these gabapentin (or pregabalin) cases is too limited to be able to make any causal connection between the drug and the aspiration. Furthermore, a PubMed search on 6 June 2022, provided no published cases of aspiration associated with gabapentin or pregabalin. However, the search identified a swallowing study in 26 patients with oropharyngeal cancer; it proposed that gabapentin had minimal effects on swallowing [52].

As indicated in the Introduction, patients with ID taking AEDs are at high risk of aspiration and aspiration pneumonia. These aspirations can often occur during seizures but at other times can occur in the absence of seizures. VigiBase data rarely includes details regarding time sequence, so whenever we saw an aspiration and the data indicated a seizure had occurred, we decided to consider the aspiration to be explained by seizure and the presence of a major medical problem. In summary, VigiBase provided little support for a specific effect of AED monotherapy on aspiration in the absence of overdose or major medical problems including seizures. Therefore, the limited data from VigiBase suggests that AEDs may contribute to respiratory aspiration when including overdose or in cases associated with polypharmacy, but there was little support for an association between respiratory aspiration and AED monotherapy in therapeutic doses. Moreover, respiratory aspiration may occur during seizures and most of these patients may be taking one or more AEDs. VigiBase usually provides no details on the chronological relationship between aspiration and seizures.

4.3. Antidepressant drugs

The AD IC values were intermediate between and close to the IC values of AEDs and opioids. In the logistic regression on fatal outcomes in aspiration cases not associated with overdose, the presence of at least one AD was very significant (OR = 2.1, CI 1.45 to 2.97). APs were also significantly associated with fatal outcomes, suggesting that the AD signal for lethality may be real. In the logistic regression of aspiration from AD versus those from benzodiazepines and/or AEDs, it was remarkable that, for ADs with significant effects on fatal outcomes in aspiration cases not associated with overdose, the presence of at least one AD was very significantly associated with fatal outcomes, major medical problems and overdose. This appears to suggest that ADs may be a contributing factor to lethality in aspiration across all types of aspiration: those associated with overdoses and those in the context of major medical problems.

Among individual ICs contaminated by duplicates and polypharmacy, three ADs appeared to have relatively high values: trazadone with an IC of 3.0 (IC_{925} = 2.5), amitriptyline with an IC of 2.5 (IC_{925} = 2.1) and citalopram with an IC of 2.5 (IC_{925} = 2.0). Trazadone and amitriptyline are ADs with high affinity for blocking muscarinic and H1 receptors, contributing to aspiration by producing dry mouth, sedation and possibly swallowing disturbances [29].

Supplementary Table S1 presents 17 cases of ADs in monotherapy associated with respiratory aspiration but only one case each for trazadone and amitriptyline were identified. VigiBase provided little information to make causal connections between them and respiratory aspiration. The trazadone case was fatal in a 39-year-old female and included the word ‘dysphagia’ in the description. In search of additional cases, a PubMed search on 8 June 2022, provided only one case of aspiration associated with trazadone but the patient suffered a fatal overdose mainly caused by oxycodone and clonazepam [53]. The amitriptyline case was fatal in a 66-year-old female and included the word ‘choking’ in the description. In search of additional cases, a PubMed search on 8 June 2022, identified a review of 225 TCA self-inflicted overdose (70% including amitriptyline) cases; 3% involved aspiration of the stomach contents [54].

Nine of the 17 AD cases on monotherapy were due to SSRIs: 4 used sertraline, 3 fluoxetine and 2 citalopram. SSRIs are not usually considered to be associated with respiratory aspiration and/or swallowing disturbances. In search of additional cases, a PubMed search on 6 June 2022, provided only one case of aspiration associated with citalopram; it occurred in the presence of an overdose of oxazepam [55]. A PubMed search on 6 June 2022, produced only one case of aspiration associated with fluoxetine, that of a patient in which a stroke had impaired his automatic breathing [56]. A PubMed search on 6 June 2022, revealed only one case of aspiration associated with sertraline, a patient with a methadone overdose associated with serotonin syndrome [57].

In summary, VigiBase provided little support for a specific effect of AD monotherapy on respiratory aspiration but suggested that an AD added to other medications may increase lethality in all cases of aspiration including those associated with overdose, polypharmacy, and/or major medical problems.

4.4. Antipsychotic co-medication

The FDA decided that pharmacovigilance data was enough to raise awareness of the risk of APs in association with aspiration in patients with dementia. The current VigiBase IC of 2.1 (IC_{925} = 2.0) indicated that there is good reason to suspect that APs, as a class, may contribute to respiratory aspiration. Moreover, although this study was not focused on APs, Table 2 indicates the importance of including them as confounders since at least one AP was used in 43% (385/900) of the total sample. In 52% (286/533) of the cases respiratory aspiration did not appear to be associated with overdose. The logistic regression model also indicated that APs may increase the lethality of respiratory aspiration in the absence of overdose.

4.5. Opioid co-medication

The VigiBase IC of 1.6 (IC_{925} = 1.5) indicates that there is some reason to suspect that opioids as a class may contribute to respiratory aspiration. Moreover, although this study was not focused on opioids, Table 2 indicates that it is important to include them as confounders since at least one opioid was used in 31% (280/900) of the total sample and 23% of (127/
553) cases in which respiratory aspiration did not appear to be associated with overdose. The logistic regression model also indicated that opioids may increase the lethality of respiratory aspiration in the absence of overdose.

4.6. Limitations

The limitations of this study include those associated with the authors’ biases, VigiBase and the field.

4.6.1. Limitations associated with the authors

The authors have been interested in the association between APs and swallowing disturbances, aspiration or pneumonia-associated aspiration [8–12]. That led them to explore the neglected area of the association between benzodiazepines, AEDs and ADs with respiratory aspiration. After reviewing the neglect of this topic in the literature, the authors may be considered biased for starting this exploratory study, but VigiBase ICs provided some basis to justify this exploration. In the process of exploring a neglected area some decisions were made that can be considered arbitrary but were justified by the clinical judgment of the authors. VigiBase has a variable that declares the drug suspected in the aspiration. The authors thought, in this large sample of respiratory aspiration in which patients were taking, on average, nearly 3 drugs in the categories of benzodiazepines, AEDs, ADs, APs or opioids, it was difficult to determine whether a drug was ‘suspected’ or not. This led the authors to ignore this VigiBase variable and just add all cases in which they were treated with at least benzodiazepine, AED or AD, which contributed to increasing the number of patients in combined cases to 900. VigiBase considers that in 300 cases at least one benzodiazepine was suspected to be associated with respiratory aspiration, but the authors’ files included 469 cases taking a benzodiazepine, of which 169 cases featured benzodiazepines co-prescribed with AEDs or ADs. In 293 cases at least one AED was suspected by VigiBase to be associated with respiratory aspiration, but the authors’ files included 429 cases taking AEDs. In 360 cases at least one AD was suspected by VigiBase to be associated with respiratory aspiration, but the authors’ files included 875 cases taking ADs.

4.6.2. Limitations associated with VigiBase data

VigiBase data was limited in three ways: standard statistical parameters (ICs), missing data and limited availability of clinical and temporal data. In prior studies, we have found that VigiBase ICs can be seriously distorted by duplicates and polypharmacy and that significant ICs may merely reflect these distortions, particularly when another medication could explain the association [51].

Table 2 indicates that in the 900 non-duplicated cases age was missing in around 15% of them and sex in 5% of them. Due to these missing data, these two variables were not initially introduced in the backward logistic regression analyses but adding them appears to show similar results (Table 3).

In the review of individual cases, we rarely found the patient identified as having ID (or mental retardation) so we could identify this category as a confounder. Many of the patients with AED polypharmacy appear to be patients with ID but this diagnosis was not specified.

In a prior VigiBase study [51], the Naranjo ADR scale [58] was used to establish the probability of an association between a drug and ADRs. Thus, it was planned to use the Naranjo scale in monotherapy cases from Supplementary Table S1 but the clinical and chronological data were limited so the cases could not be scored using the Naranjo scale.

4.6.3. Limitations associated with the field

After 10 sessions of 3–4 hours each in which the first and last authors reviewed each case to select the 900 non-duplicated cases, it appeared that many cases suggested that patients who were found dead may have had aspiration. Even with a very thorough autopsy it would not be possible to conclude whether aspiration led to death or whether aspiration happened in the process of losing consciousness or having a seizure. Similarly, some of these fatal cases may be secondary to unidentified overdose. Thus, in this area, particularly when dealing with patients found dead, it is not possible to know some of the details surrounding the aspiration. Therefore, our analysis may be confounded by unidentified overdose or seizures producing respiratory aspiration. These limitations are part of working in this field independently of whether data comes from VigiBase or not.

5. Expert opinion

The subsections of this Expert Opinion section focus on respiratory aspiration 1) during overdoses, 2) associated with polypharmacy, and with other topics such as 3) need for longitudinal swallowing studies in ID patients, 4) aspiration pneumonia and pneumonia, 5) choking, and 6) a five-year perspective.

5.1. Respiratory aspiration during overdoses

VigiBase has a data field that identifies cases associated with overdose and/or suicide. Many more cases of possible overdose were identified by the careful review of each case by two authors of the 900 non-duplicated cases. Thus, up to 39% (347/900) were probably associated with an overdose but there is no certainty that other cases which were not included in this category were not overdose cases, since for many patients the clinical information was limited.

There is no doubt in our minds that overdose, benzodiazepines, AEDs and ADs may be associated with respiratory aspiration but one must remember that it is difficult to establish an association with an individual drug since, in VigiBase, for aspiration aspiration associated with overdose, the patients were taking on average nearly three suspected drugs among benzodiazepines, AEDs, ADs, APs, or opioids. As a matter of fact, when combining these five drug classes, each suspected drug increased lethality by odds of 1.23; this means that for each additional drug the risk increases by 1.23 so that patients taking three of these drugs may have odds of 3.7 (3 × 1.23 = 3.7). It must be remembered that lethality in these overdose cases may not necessarily be explained by respiratory aspiration; other mechanisms may also have contributed to these fatal outcomes.
5.2. Polypharmacy may be important in respiratory aspiration

Table 2 clarifies that polypharmacy is important in respiratory aspiration in the absence of overdose since, on average, patients were taking nearly three drugs from among the five suspected drug classes (benzodiazepines, AEDs, ADs, APs, or opioids).

When focusing on the lethality of aspiration, the backward logistic regression of lethality in the absence of overdose provided significant effects for three drug classes, APs, ADs, and opioids, but the number of suspected drugs was not significant (Table 3). When a univariate OR = 1.28 (CI 1.14 to 1.43) was calculated, the number of suspected drugs was significantly associated (p < 0.001) with lethal outcomes, but the significance disappeared after introducing the model the effect of the presence of at least 1 drug from the AP and AD classes.

VigiBase data reflects the generalized prescription of psychiatric medications in situations of polypharmacy. Clinicians may need to remember that although polypharmacy may be justified in some cases, this data suggests that combining benzodiazepines, AEDs or ADs, or even adding them to APs or opioids may not only contribute to respiratory aspiration but to its lethality. The prescription of multiple psychiatric drugs also provides more drugs to use in self-inflicted overdoses and, according to VigiBase, this was also associated with greater risk of lethality in the overdoses that were accompanied by respiratory aspiration.

5.3. Need for longitudinal swallowing studies in intellectual disability patients on benzodiazepines, antiepileptic, or antidepressant drugs

As the Introduction indicates, in patients with ID [20] it is generally accepted that medications such as benzodiazepines, AEDs, or ADs with anticholinergic or anti-histaminic properties may contribute to dysphagia. Unfortunately, the literature does not describe longitudinal swallowing studies in individual patients with on-off medication data that definitively establishes that adding or discontinuing a specific medication from these drug classes specifically interferes with swallowing for a specific individual. This type of study is not easily conducted under controlled conditions, but even when clinicians may conduct one, it is not being published. This type of longitudinal swallowing study would be ideal in definitively establishing that benzodiazepines, AEDs, or ADs would cause respiratory aspiration but, in its absence, this VigiBase study or a similar pharmacovigilance study may be the only data available.

5.4. Respiratory aspiration versus aspiration pneumonia and pneumonia

This VigiBase search focused on respiratory aspiration which in VigiBase overlaps with the terms aspiration pneumonia or pneumonia. Those patients with respiratory aspiration who died in a short period of time minutes to a few hours probably died because of a massive aspiration; those who survive may have developed aspiration pneumonia [59]. Future VigiBase studies should focus on the association of benzodiazepines, AEDs, or ADs with aspiration pneumonia. Similarly, future studies need to explore the association of benzodiazepines, AEDs, or ADs with pneumonia and other types of polypharmacy in pneumonia [60,61].

5.5. Choking and aspiration

Duck et al. [62] define choking (or foreign body airway obstruction) as occurring when an object partially or completely obstructs the passage of air exchange between the upper airway and the trachea. In adults it is almost always associated with food and is considered accidental, although impaired consciousness or swallowing disturbances may be contributing factors [63]. Choking can sometimes also be associated with respiratory aspiration, meaning that some material penetrates below the vocal cords [64]. Moreover, attempts to resuscitate a person who is choking can lead to vomit aspiration. As far as we can tell, some of the cases described as respiratory aspiration in VigiBase included in the descriptions the word ‘choking’ or foreign body aspiration, which was classified by the first and last authors as choking in 4.6% (41/900) total cases of aspiration and in 6.1% (34/553) aspiration cases in the absence of overdose (Table 2). In most cases, it was not clear whether in the strict sense it meant ‘choking’ with no aspiration or both choking and aspiration happening at the same time. Thus, it is possible that some of these cases were of choking and not aspiration but were not correctly classified in VigiBase, but with limited available information there is no certainty of that possibility.

5.6. Five-year perspective

In 2005, the FDA raised awareness that APs may cause swallowing disturbances and aspiration in patients with dementia [4]. This VigiBase study suggests that there are reasons to consider that, in the absence of overdose, benzodiazepines, AEDs and ADs may contribute to respiratory aspiration but these drugs appear to mainly work as contributing factors in the context of polypharmacy.

The authors hope that this pharmacovigilance study in VigiBase focused on benzodiazepines, AEDs and ADs may stimulate new studies in the area. As longitudinal studies using swallowing studies are not likely to be published, other pharmacovigilance studies may be easier to conduct. The role of monotherapy with benzodiazepines as contributing factors in respiratory aspiration in geriatric patients or those with dementia needs urgent attention. Benzodiazepines have been associated with risk of death in patients with dementia [65], but the studies do not provide data concerning to what extent respiratory aspiration may contribute to these deaths. There is need to study respiratory aspiration in patients with ID and try to assess the contribution of aspiration during seizures versus aspiration in the absence of seizures and their relative lethality.

This VigiBase study only focused on APs and opioids as co-medications but there is need for VigiBase studies focused on them as primary medications. These future studies will need to
consider the confounding effects of benzodiazepines, AEDs and ADs on respiratory aspiration.

The FDA started to raise awareness concerning the problem of aspiration and APs in 2005 [4], but it was not until 2019 that an umbrella review firmly established the association between pneumonia and APs [6]. The authors hope that it does not take 14 years to gain more attention on the role of respiratory aspiration in the absence of overdose during treatment with benzodiazepines, AEDs, and ADs.

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ORCID

Carlos de Las Cuevas http://orcid.org/0000-0001-5742-905X
Emilio J. Sanz http://orcid.org/0000-0001-6788-4435
Jose de Leon http://orcid.org/0000-0002-7756-2314

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