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Dementia and Alzheimer's Disease Associated With Aromatase Inhibitors: A Disproportionality Analysis of the WHO Pharmacovigilance Database (VigiBase)

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ABSTRACT

Aromatase inhibitors are used for patients with hormone-receptor positive breast cancer. Alzheimer's disease is the most prevalent cause of dementia. Several studies have suggested an association between the use of aromatase inhibitors and the development of Alzheimer's disease. The objective of this study was to identify potential pharmacovigilance signals associated with dementia and Alzheimer's disease and third-generation aromatase inhibitors in menopausal and postmenopausal women. VigiBase, the global database of individual case safety reports of the World Health Organization, was used to investigate this possible association. A disproportionality analysis was performed for women aged 45 years and older. The reporting odds ratio (ROR) and its 95% CI for reporting dementia are exemestane, 2.08 (1.35–3.19); anastrozole, 1.59 (1.09–2.32); and letrozole, 1.43 (1.05–1.95) and for Alzheimer's disease are exemestane, 0.94 (0.30–2.92); anastrozole: 2.63 (1.55–4.45); and letrozole, 1.33 (0.76–2.35). For senile dementia, only letrozole has cases, with an ROR of 6.77 (2.51–18.31). Signals of disproportionate reporting have been observed between the occurrence of dementia, dementia Alzheimer's type, and senile dementia with aromatase inhibitors, which is in line with estrogen functions and aromatase activity, as well as the findings from preclinical studies. Additional research is required to elucidate this intricate matter.

1 | Introduction

Alzheimer's disease is a progressive neurodegenerative disease that affects the brain and leads to cognitive, memory, and behavioral decline. It has been considered the first cause of dementia. It is more prevalent in women than in men, mainly due to their longer life expectancy [1].

A major advance in the treatment of hormone-receptor positive breast cancer has been the advent of third-generation aromatase inhibitors. Aromatase inhibitors block the production of estrogens by inhibiting the function of aromatase. There are currently three aromatase inhibitors used in clinical practice: anastrozole, letrozole, and exemestane. The introduction of these drugs has had a significant impact on the management of breast cancer, prolonging patient survival, and reducing the rate of tumor recurrence [2].

In preclinical studies, estrogens have demonstrated neuroprotective effects. It has been shown that women have a higher

risk of developing Alzheimer's disease than age-matched men, which is thought to be linked to the decline in estrogen levels after menopause, thereby exacerbating the effects of aging [3].

In light of the aforementioned considerations, aromatase inhibitors could have an impact on cognition and cerebral function. Some studies have found associations of variants of the aromatase gene with the risk of Alzheimer's dementia, particularly in women [4], but clinical studies found contrary results [5].

There is a need to find out whether aromatase inhibitors might have an effect on cognitive function, given the long duration of treatment, usually at a time in life when women are exposed to other important risk factors for dementia, such as age. According to most studies, reporting cognitive deficits in women receiving aromatase inhibitors therapy, a big and open question is whether these women are at a greater risk of developing Alzheimer's disease.

Adverse event reporting databases are important tools for identifying potential new adverse drug reactions or signals and may shed some light on this issue. The aim of this study was to investigate a potential association between aromatase inhibitors and the report of dementia or Alzheimer's dementia using VigiBase, the World Health Organization (WHO) global Individual Safety Case Report (ICSR) database.

2 | Methods

2.1 | Study Design

A disproportionality analysis of ICSR was conducted using VigiBase.

2.2 | Data Description, Access and Preprocessing

VigiBase, the WHO database of reported potential side effects of medicinal products, developed and maintained by Uppsala Monitoring Centre, is the largest spontaneous reporting database in the world, with over 35 million ICSRs—cases of suspected adverse drug reactions (ADRs). Cases were submitted by reporters from the 150 member countries of the WHO Programme for International Drug Monitoring (WHO PIDM) since 1968 [6]. Each ICSR includes information on the patient, the drug (classified as suspect or concomitant), the suspected ADR, and the reporting country. Drugs are coded using the anatomical therapeutic chemical (ATC) classification and ADRs are coded according to the Medical Dictionary for Regulatory Activities (MedDRA) [7].

Reports registered between December 27, 1995—the date of the FDA approval of the first third-generation aromatase inhibitor (anastrozole)—and March 27, 2024 were included in the analysis.

2.3 | Cases Identification

ICSRs reported in women aged ≥45 years (menopausal and postmenopausal) from any country were considered. Standardized MedDRA queries (SMQs) from MedDRA were used to identify the ADRs of interest. Thus, any ICSRs containing a term from the SMQ "Dementia" were considered a case (MedDRA [version 27.0]). The SMQ "Dementia" contains the following terms: "Clinical dementia rating scale score abnormal," "Dementia," "Dementia Alzheimer's type," "Dementia Alzheimer's type, uncomplicated," "Dementia Alzheimer's type, with delirium," "Dementia Alzheimer's type, with delusions," "Dementia Alzheimer's type, with depressed mood," "Dementia with Lewy bodies," "Early onset familial Alzheimer's disease," "Frontotemporal dementia," "Hippocampal atrophy," "Mini mental status examination abnormal", "Mixed dementia," "Presenile dementia," "Progressive supranuclear palsy," "Senile dementia," and "Vascular dementia." The ICSRs registered under the terms "Corticobasal degeneration," "Creutzfeldt-Jakob disease," "Hippocampal sclerosis," "Korsakoff's syndrome," "Prion disease," "Scatolia," and "Variant Creutzfeldt-Jakob disease" have been excluded because they are not related to Alzheimer's dementia. Noncases were all other reports (ICSRs) in Vigibase during the same period, occurring in women > 45 years. ICSRs with unknown sex and age were excluded.

ICSRs for which anastrozole, letrozole or exemestane were reported as suspected, interacting, or concomitant drugs were considered exposed. Fixed combination products were included. Prior to conducting any analysis, a deduplication process was applied.

2.4 | Statistical Methods

The main analysis estimated the risk of reporting "Dementia" associated with third-generation aromatase inhibitors compared with all other drugs (called "nonusers") using a disproportionality analysis. The measure of this disproportionality used was the *reporting odds ratio* (ROR) with its 95% confidence interval (CI). The ROR is a homologue of the odds ratio for case–control studies and corresponds to the ratio of the reporting odds for persons exposed to the drug of interest compared to those not exposed [8]: $ROR = ad/bc$, where a represents drug and ADR of interest, b represents drug of interest with other ADRs, c represents other drugs with ADR of interest, and d represents other drugs and ADRs. There is disproportion when an ROR is > 1, and it is statistically significant if the lower bound of the 95% CI of the ROR (–ROR) was ≥1. We defined a potential signal when –ROR > 1, and there were at least three cases reported in the period of interest. A positive disproportionality signal for a particular drug–ADR association in a pharmacovigilance database is potentially suggestive of a drug–ADR association and warrants further investigation via case–control or cohort studies to verify the associations [8].

The disproportionality analysis was conducted for each drug individually (anastrozole, letrozole, or exemestane) and for the drug class at the ATC level 4 (aromatase inhibitors: anastrozole, letrozole, and exemestane together).

The reporting frequencies for the following variables were estimated using the Microsoft Excel software: age group, origin

TABLE 1 | Characteristics of the reported cases of dementia in women aged ≥ 45 who were taking anastrozole, exemestane, or letrozole. (VigiBase, December 1995–March 2024).

	Anastrozole	Letrozole	Exemestane
Total cases (suspected)—*n*	42 (27)	56 (20)	23 (16)
Origin of reports—*n* (%)			
Americas	32 (76)	38 (68)	18 (78)
Asia	1 (2)	6 (11)	1 (4)
Europe	7 (17)	11 (20)	4 (17)
Oceania	2 (5)	1 (2)	0 (0)
Age group—*n* (%)			
45–64 years	5 (12)	6 (11)	0 (0)
65–74 years	14 (33)	19 (34)	5 (22)
≥ 75 years	23 (55)	31 (55)	18 (78)
Serious—*n* (%)			
Yes	28 (67)	54 (96)	23 (100)
No	9 (21)	1 (2)	0 (0)
Unknown	5 (12)	1 (2)	0 (0)
Drug treatment duration—*n* (%)			
≤ 1 year	3 (7)	3 (5)	1 (4)
1–3 years	1 (2)	2 (4)	0 (0)
≥ 3 years	2 (5)	0 (0)	0 (0)
Unknown	36 (86)	51 (91)	22 (96)
Time to onset—*n* (%)			
≤ 15 days	0 (0)	1 (2)	0 (0)
16–30 days	0 (0)	0 (0)	0 (0)
31–90 days	1 (2)	0 (0)	0 (0)
91–365 days	0 (0)	1 (2)	0 (0)
> 1 year	3 (7)	4 (7)	1 (4)
Unknown	38 (90)	50 (89)	22 (96)
Reaction outcome—*n* (%)			
Fatal	2 (5)	1 (2)	0 (0)
Not recovered	11 (26)	15 (27)	2 (9)
Recovered/recovering	2 (5)	1 (2)	2 (9)
Recovered with sequelae	1 (2)	0 (0)	0 (0)
Died—unrelated to reaction	0 (0)	1 (2)	0 (0)
Unknown	26 (62)	38 (68)	19 (83)
Withdrawal outcome—*n* (%)			
Fatal	1 (2)	1 (2)	0 (0)
No effect observed	5 (12)	4 (7)	2 (9)
Not applicable	2 (5)	1 (2)	0 (0)

(Continues)

TABLE 1 | (Continued)

	Anastrozole	Letrozole	Exemestane
Reaction diminished	1 (2)	0 (0)	2 (9)
Unknown	33 (79)	50 (89)	19 (82)
Rechallenge outcome—*n* (%)			
Not applicable	3 (7)	1 (2)	0 (0)
Unknown	39 (93)	55 (98)	23 (100)

TABLE 2 | ROR for the association between "Dementia" and third-generation aromatase inhibitors, restricted to women ≥45 years (VigiBase, December 1995 to March 2024).

	Anastrozole (*n* = 24 344)		Letrozole (*n* = 41 066)		Exemestane (*n* = 14 481)		All aromatase inhibitors	
Adverse reaction (total cases)	***n***	**ROR (95% CI)**	***n***	**ROR (95% CI)**	***n***	**ROR (95% CI)**	***n***	**ROR (95% CI)**
Dementia (6543)	27	1.59 (1.09–2.32)	41	1.43 (1.05–1.95)	21	2.08 (1.35–3.19)	86	1.60 (1.29–1.97)
Dementia Alzheimer's type (2057)	14	2.63 (1.55–4.45)	12	1.33 (0.76–2.35)	3	0.94 (0.30–2.92)	28	1.65 (1.14–2.40)
Senile dementia (138)	0	NA	4	6.77 (2.51–18.31)	0	NA	4	3.57 (1.32–9.66)
Dementia with Lewy bodies (111)	1	3.49 (0.49–24.96)	0	NA	0	NA	1	1.09 (0.15–7.80)
Frontotemporal dementia (74)	1	5.25 (0.73–37.79)	0	NA	0	NA	1	1.64 (0.23–11.80)
Progressive supranuclear palsy (34)	1	11.62 (1.59–84.94)	0	NA	0	NA	1	3.63 (0.50–26.53)
Terms grouped (9000)[a]	42	1.80 (1.33–2.44)	56	1.42 (1.09–1.85)	23	1.65 (1.10–2.49)	117	1.58 (1.31–1.89)

Abbreviations: CI, confidence interval; NA, not applicable; ROR, reporting odds ratio.
[a]More than one of the terms of interest may be included in an ICSR.

of reports, seriousness, reaction outcome, time to onset, dechallenge outcome, rechallenge outcome, and duration of drug treatment.

3 | Results

Among the 9 356 370 ICSRs registered in VigiBase in women aged ≥45 years between December 27, 1995, and March 27, 2024 that matched the "Dementia" SMQ, 117 included an aromatase inhibitor. Forty-two of these ICSRs included letrozole, 23 exemestane, and 56 letrozole. Table 1 shows the main characteristics of these cases.

The Americas had the highest number of reports among all reporting countries. Almost all of the reactions were serious and occurred in patients aged ≥75 years. In most cases, the reaction outcome was "unknown" followed by "not recovered." There was slight information on the time to onset; when available, it was very long, in most cases more than a year. The effect of drug withdrawal was also scarce and varied for each drug; in the majority of cases, no effect was seen after the drug was stopped. No information was found on re-exposition to the drugs.

The disproportionality analysis is presented in Table 2. Signals of disproportionate reporting were found for the drug-event pairs anastrozole–dementia (27 cases, ROR [95% CI] = 1.59 [1.09–2.32]), anastrozole–dementia Alzheimer's type (14 cases, ROR [95% CI] = 2.63 [1.55–4.45]), letrozole–dementia (41 cases, ROR [95% CI] = 1.43 [1.05–1.95]), letrozole–senile dementia (4 cases, ROR [95% CI] = 6.77 [2.51–18.31]), and exemestane–dementia (21 cases, ROR [95% CI] = 2.08 [1.35–3.19]). For all these associations, the Information Component (IC) and its 95% lower limit were > 0, also indicating disproportionality.

When analyzing aromatase inhibitors as a group, statistically significant disproportionality was observed for dementia (86 cases, ROR [95% CI] = 1.60 [1.29–1.97]), Alzheimer's disease (28 cases, ROR [95% CI] = 1.65 [1.14]), and Senile dementia (4 cases, ROR [95% CI] = 3.57 [1.32]) (Table 2).

4 | Discussion

4.1 | Key Results

To our knowledge, this is the first study to investigate the potential association between dementia or Alzheimer' dementia and third-generation aromatase inhibitors by analyzing VigiBase data. Aromatase inhibitors were significantly associated with the reporting of dementia, Alzheimer's dementia, and senile dementia in the present study. This is consistent with previous knowledge of the cognitive effects of aromatase [9].

Most identified cases were considered serious and occurred in patients aged ≥ 75 years, suggesting older age as a risk factor for the development of dementia associated with aromatase inhibitor treatment, as is expected. The majority of the reports came from the Americas, as is usually the case with Vigibase data. Treatment duration, time to onset, and effect of dechallenge were unknown variables in most of the cases. The slow onset of this condition, the long duration of treatments, and the fact that it is likely irreversible or very slowly evolving could explain the lack of information: reactions were reported when they were suspected, but no subsequent follow-up has been conducted. In the few cases where information is available, drug withdrawal has no effect for most patients, but, surprisingly, improvement after drug removal was observed in three patients. There is no information on the effects of reexposure to the drug in any of the cases.

A multitude of research studies have demonstrated the relevance of estrogens in brain function and their neuroprotective properties against neurodegenerative disorders, including Alzheimer's disease [10]. Studies in humans have shown that endocrine therapy resulted in a decline in cognitive abilities in breast cancer patients [11]. However, new research shows that aromatase inhibitors and other endocrine therapies have no significant effect on cognitive function or neurodegenerative diseases in these patients compared with no treatment [5].

As the use of aromatase inhibitors as a therapy for breast cancer and other clinical conditions continues to grow, it would be beneficial to conduct further research to determine whether there is a heightened risk of Alzheimer's disease in women who have received these drugs.

One of the major limitations of studies based on pharmacovigilance databases is underreporting. This, together with the lack of data on drug use, makes it impossible to estimate the true incidence of the reported ADRs. Another limitation is that it is not possible to control for other risk factors that may act as confounders for the events studied. Finally, Vigibase only contains suspicions, so it is important to note that a causal relationship between the drug and the ADR studied has not been established. With regard to the specific adverse reaction studied, dementia, indication bias should be considered. As aromatase inhibitors are prescribed to postmenopausal women, there are other risk factors for dementia, such as age and naturally low estrogen levels. To minimize this bias, disproportionality analysis was restricted to women > 45 years, so that the comparators are in the same conditions and have the same risk factors.

Still, spontaneous reporting systems present several advantages: they cover all types of authorized drugs; it is a simple, quick, and economical method enabling the generation of hypotheses and identification of new potential safety concerns involving drugs, notably rare, infrequent, or unexpected events.

5 | Conclusions

A data analysis of the world's largest pharmacovigilance database, Vigibase, revealed signals of disproportionate reporting for dementia, dementia Alzheimer's type, and senile dementia with aromatase inhibitors. This is in line with what is known about the functions of estrogens and aromatase, and preclinical studies; although, surprisingly, this has not been shown in large pharmacoepidemiological studies. More research is needed to understand this complex issue. Meanwhile, healthcare professionals should be aware of this possibility when prescribing or monitoring patients using these medicines.

Author Contributions

M.T. Yuste was responsible for the conceptualization, design, and analysis of data for this study, and the preparation of the paper. P. Marín acquired data. The study was conceptualized by M. Sainz-Gil, P. Marín, and E. Escudero, who also reviewed the manuscript. All authors have approved the final version for publication and agree to be held accountable for all aspects of the work.

Disclosure

Vigibase is managed by the Uppsala Monitoring Centre (UMC), the WHO Collaborating Centre for International Drug Monitoring. The information comes from a variety of sources, and the probability that the suspected adverse effect is drug related is not the same in all cases. The discussion and conclusions of this study are the authors' considerations and do not represent the opinion of the UMC or the WHO.

Ethics Statement

The authors have nothing to report.

Consent

This study does not involve the participation of human subjects or animals.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the Uppsala Monitoring Centre. The data supporting the conclusions of this article will be made available by the corresponding author upon reasonable request.

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