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Pharmacovigilance Signal Detection of Vortioxetine in Individuals Aged over 65 Years: A Disproportionality FAERS Analysis Versus Other Antidepressants

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Abstract

Background: Recently, vortioxetine has emerged as a potential safe antidepressant alternative in the elderly population. Safety signals of vortioxetine were evaluated against other antidepressants in patients aged over 65. **Methods**: Data from the Food and Drug Administration Adverse Events Reporting System (FAERS) database were analyzed to identify potential safety signals by analyzing patterns and trends in adverse-event reports in which the drug was listed as the primary suspect, extracted up to February 2025. Report characteristics (sex, outcome, year, country, and indication) were described, and disproportionality analyses were conducted to compare vortioxetine adverse events between age groups (18–65 vs. >65) and versus other antidepressants. **Results**: Vortioxetine represented the primary-suspect antidepressant with reporting peaking around 2018. Age-stratified disproportionality analyses showed that older adults had disproportionate reporting of neuropsychiatric events, falls/trauma, cardiovascular rhythm disturbances, and electrolyte/metabolic abnormalities vs. younger adults, suggesting increased vulnerability to multisystem adverse outcomes. Compared to other antidepressants (SSRIs, trazodone, mirtazapine, SNRIs, and the TCAs amitriptyline and nortriptyline), the strongest disproportionality signals for vortioxetine were largely driven by mood-related ADRs, medication errors, and respiratory compromise terms. **Conclusions**: The findings represent pharmacovigilance signals derived from FAERS data and should be considered hypothesis-generating, requiring confirmation through further clinical and epidemiological studies.

Keywords: antidepressants; drug safety; major depressive disorder; pharmacovigilance; vortioxetine

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1. Introduction

Depression is a prevalent and debilitating condition among older adults, significantly affecting their quality of life and exacerbating comorbidities. It is estimated that, globally, approximately 10–15% of individuals over the age of 65 years suffer from depression [1,2], a proportion that likely underestimates the true burden due to underreporting and diagnostic challenges in this age group. The management of depression in elderly populations is particularly challenging due to age-related physiological changes, the presence of multiple comorbidities, cognitive impairment, and increased polypharmacy and sensitivity to medication [2,3].

Antidepressant treatment in older adults necessitates a careful balance between efficacy and medication tolerability, especially in the long term [4,5]. Selective serotonin reuptake inhibitors (SSRIs) have traditionally been the first-line treatment due to their relatively favorable side-effect profile compared to older classes of antidepressants like tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs) [3,4]. However, even SSRIs present side effects in the elderly. Common adverse effects include hyponatremia, increased risk of falls, gastrointestinal disturbances, and potential cardiovascular implications. Furthermore, the polypharmacy typical in this age group increases the risk of drug–drug interactions, complicating antidepressant therapy [3,4,6,7] (Figure 1).

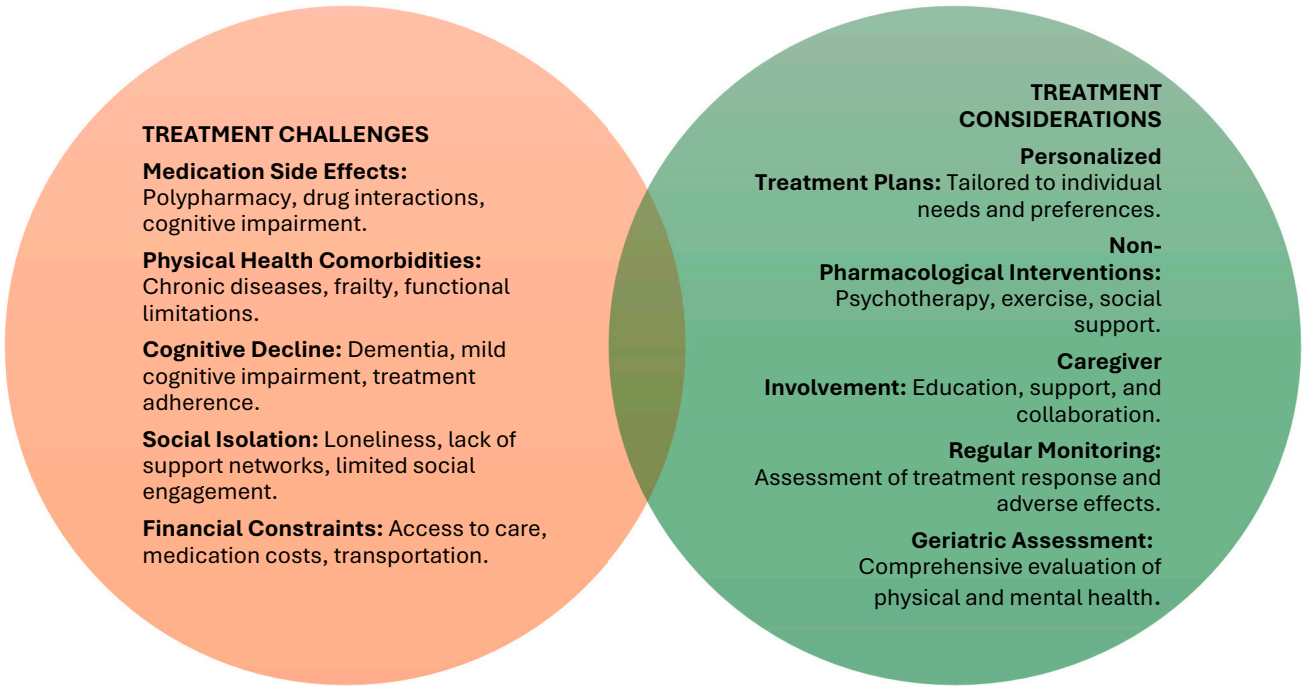


Figure 1. Challenges and Considerations in Treating Depression in the Elderly.

In the past twenty years, compared with other antidepressants, vortioxetine has emerged as a potential alternative [8] (Table 1).

Table 1. Comparator antidepressants included in the analysis and their principal pharmacodynamic mechanisms.

Comparator Antidepressant	Drug Class	Principal Pharmacodynamic Mechanism(s)
Sertraline, citalopram, escitalopram, paroxetine, fluoxetine, fluvoxamine	Selective serotonin reuptake inhibitors (SSRIs)	Selectively inhibit the serotonin transporter (SERT), increasing synaptic serotonin (5-HT) concentrations with minimal direct effects on norepinephrine or dopamine reuptake.
Duloxetine, venlafaxine, and desvenlafaxine	Serotonin–norepinephrine reuptake inhibitors (SNRIs)	Inhibit both the serotonin transporter (SERT) and norepinephrine transporter (NET), increasing synaptic serotonin and norepinephrine concentrations.
Trazodone	Serotonin antagonist and reuptake inhibitor (SARI)	Antagonizes 5-HT2A/5-HT2C receptors and weakly inhibits SERT; also exhibits antagonism at histamine H1 and α1-adrenergic receptors, contributing to its sedative properties.
Mirtazapine	Noradrenergic and specific serotonergic antidepressant (NaSSA)	Antagonizes presynaptic α2-adrenergic autoreceptors and heteroreceptors, enhancing norepinephrine and serotonin release; also blocks 5-HT2, 5-HT3, and histamine H1 receptors.
Amitriptyline	Tricyclic antidepressant (TCA)	Inhibits both SERT and NET; additionally antagonizes muscarinic cholinergic, histamine H1, and α1-adrenergic receptors, accounting for many of its adverse effects.
Nortriptyline	Tricyclic antidepressant (TCA)	Preferentially inhibits NET over SERT, increasing synaptic norepinephrine; also exhibits moderate antagonism at muscarinic cholinergic, histamine H1, and α1-adrenergic receptors, with a lower anticholinergic burden than amitriptyline.

Indeed, vortioxetine is a multimodal antidepressant that acts as a serotonin reuptake inhibitor, with concomitant agonist activity at the 5-HT1A receptor, partial agonist activity at the 5-HT1B receptor, and antagonism at the 5-HT1D, 5-HT7, and 5-HT3 receptors, which may contribute to its antidepressant effects and cognitive benefits. Its peculiar mechanism of action suggests that vortioxetine might offer advantages in terms of both efficacy and tolerability, particularly in the elderly population [8,9]. However, its response and the specific profile of vortioxetine in comparison to SSRIs in individuals over 65 years remain controversial [10]; in a recent study, vortioxetine seemed neither to show a better tolerability profile compared to SSRIs in older adults with Major Depressive Disorder (MDD), nor an advantage in depression-related cognitive symptoms [11].

Post-marketing voluntary reporting systems can complement evidence from clinical trials and observational studies by identifying patterns of adverse-event reporting in larger and more heterogeneous populations. This may be particularly relevant for older adults, who may have greater clinical complexity related to multimorbidity and polypharmacy. The United States Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS), a database of individual case safety reports, provides an opportunity to examine whether specific adverse events are reported disproportionately for vortioxetine across age groups relative to other antidepressants. Disproportionality analysis is intended for pharmacovigilance signal detection and hypothesis generation and does not estimate adverse-event incidence, clinical risk, or comparative safety.

The objective of this pharmacovigilance study was to identify signals of disproportionate adverse-event reporting involving vortioxetine by (1) comparing reporting patterns

among adults aged >65 years with those among adults aged 18–65 years and (2) comparing reporting patterns for vortioxetine with those for other antidepressants, including class-specific and pool comparator groups, using FAERS.

2. Results

A total of 134,137 FAERS reports involving adults treated with vortioxetine or other antidepressants were identified and extracted through February 2025., Preferred Term (PT) filtering, and missing age where applicable. Final analytic samples differed between the age-stratified and antidepressant-comparator analyses because of their respective eligibility criteria. The characteristics of these cases are summarized in Table 2, while the indications reported for the two groups are presented in Table 3.

Table 2. Information regarding Vortioxetine cases extracted from the FAERS dataset (January 2014–February 2025) comparing the two treatment groups (Vortioxetine vs. Other Antidepressants).

Variable	Overall (n = 134,137)	Vortioxetine (n = 4911)	Other Antidepressants (n = 129,226)
Age *			
18–25	11,087	270	10,817
26–35	15,746	485	15,261
36–65	48,177	1649	46,528
>65	22,986	659	22,327
Sex			
Female	76,633	3000	73,633
Male	40,873	1572	39,301
Country of origin (top 10 overall, and frequencies within drug category) *			
United States of America	40,290	2015	38,275
Great Britain	26,657	195	26,462
France	14,647	356	14,291
Germany	8264	46	8218
Canada	7632	232	7400
Italy	6250	164	6086
Spain	3255	151	3104
Japan	3047	492	2555
Sweden	2626	151	2475
Netherlands	1953	37	1916
Outcome			
Hospitalized	49,606	1526	48,080
Died	15,936	284	15,652
Life-threatening	10,956	193	10,763
Disabled	9721	227	9494
Congenital anomaly	3198	12	3186
Required intervention	643	15	628
Other	90,467	3636	86,831

* Missing: age = 36,141; country of origin = 5686, Total missing = 16,631.

Table 3. Information regarding top-10 indications overall and with Vortioxetine.

Overall	Count	Vortioxetine	Count	Other Antidepressants	Count
Product used for unknown indication	64,661	Product used for unknown indication	2430	Product used for unknown indication	62,231
Depression	46,743	Depression	1997	Depression	44,746
Anxiety	13,536	Major depression	739	Anxiety	13,110

Table 3. *Cont.*

Overall	Count	Vortioxetine	Count	Other Antidepressants	Count
Major depression	5490	Anxiety	426	Major depression	4751
Pain	4634	Hypertension	111	Pain	4564
Hypertension	4407	Insomnia	111	Hypertension	4296
Insomnia	3337	Bipolar disorder	83	Insomnia	3226
Bipolar disorder	2146	Sleep disorder	74	Bipolar disorder	2063
Sleep disorder	1754	Pain	70	Sleep disorder	1680
Schizophrenia	1653	Gastroesophageal Reflux Disease	43	Schizophrenia	1628

2.1. Age-Related Signals for Vortioxetine

Subsequently, vortioxetine-related cases (n = 3063) were analyzed by comparing the two age groups (18–65 years and >65 years) (Table 4).

Table 4. Information regarding Vortioxetine cases extracted from the FAERS dataset (up to February 2025) comparing the two age groups 18–65 vs. >65 years.

Variable	Overall (age 18+)	18–65	>65
Count	n = 3063	n = 2404	n = 659
Sex *			
Female	1952	1526	426
Male	1073	854	219
Country of origin (top 10 overall, and frequencies within age group) *			
United States of America	855	714	141
Japan	397	251	146
France	302	215	87
Canada	153	135	18
Great Britain	148	125	23
Sweden	134	119	15
Italy	133	94	39
Spain	121	73	48
South Korea	54	35	19
Switzerland	53	35	18
Outcome			
Other	2198	1758	440
Hospitalized	1005	704	301
Died	209	151	58
Disabled	196	176	20
Life threatening	167	146	21
Required intervention	15	15	0
Congenital anomaly	3	2	1

* Missing: sex = 38, country of origin = 145.

In line with the initial analysis, similar indications were observed among vortioxetine cases, including depression, anxiety, and MDD (Table 5).

Annual adverse event reporting increased from 8365 reports in 2014 to a peak of 16,338 reports in 2019, followed by a decline through 2022 (10,846 reports) and a subsequent increase through 2024 (13,429). Throughout the study period, reports involving comparator antidepressants accounted for the vast majority of submissions, whereas reports involving vortioxetine represented a relatively small proportion of all reports. Vortioxetine reports increased from 176 reports in 2014 to a maximum of 618 reports in 2018, before gradually

declining to 373 reports in 2024. In 2024, vortioxetine reports accounted for 373 of 13,429 total reports (2.8%), while comparator antidepressants accounted for the remaining 13,056 reports (97.2%) (Figure 2).

Table 5. Information regarding top-10 indications for Vortioxetine overall and within each age group.

Overall	Count	18–65 Years	Count	>65 Years	Count
Depression	1565	Depression	1192	Depression	373
Product used for unknown indication	1154	Product used for unknown indication	870	Product used for unknown indication	284
Major depression	543	Major depression	464	Major depression	79
Anxiety	345	Anxiety	296	Anxiety	49
Insomnia	99	Insomnia	81	Hypertension	47
Hypertension	95	Bipolar disorder	59	Insomnia	18
Bipolar disorder	66	Hypertension	48	Pain	15
Sleep disorder	60	Sleep disorder	46	Sleep disorder	14
Pain	53	Pain	38	Diabetes mellitus	13
Gastroe-sophageal Reflux Disease	33	Generalized anxiety disorder	30	Atrial fibrillation	11

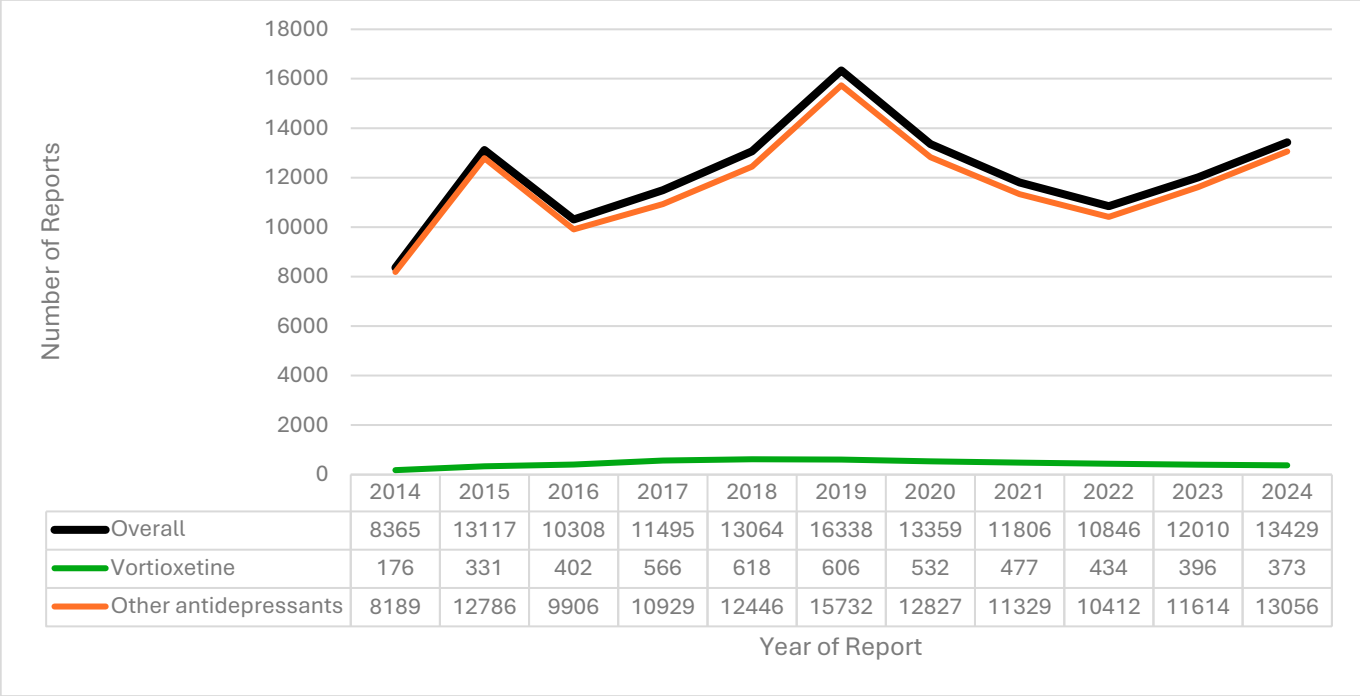
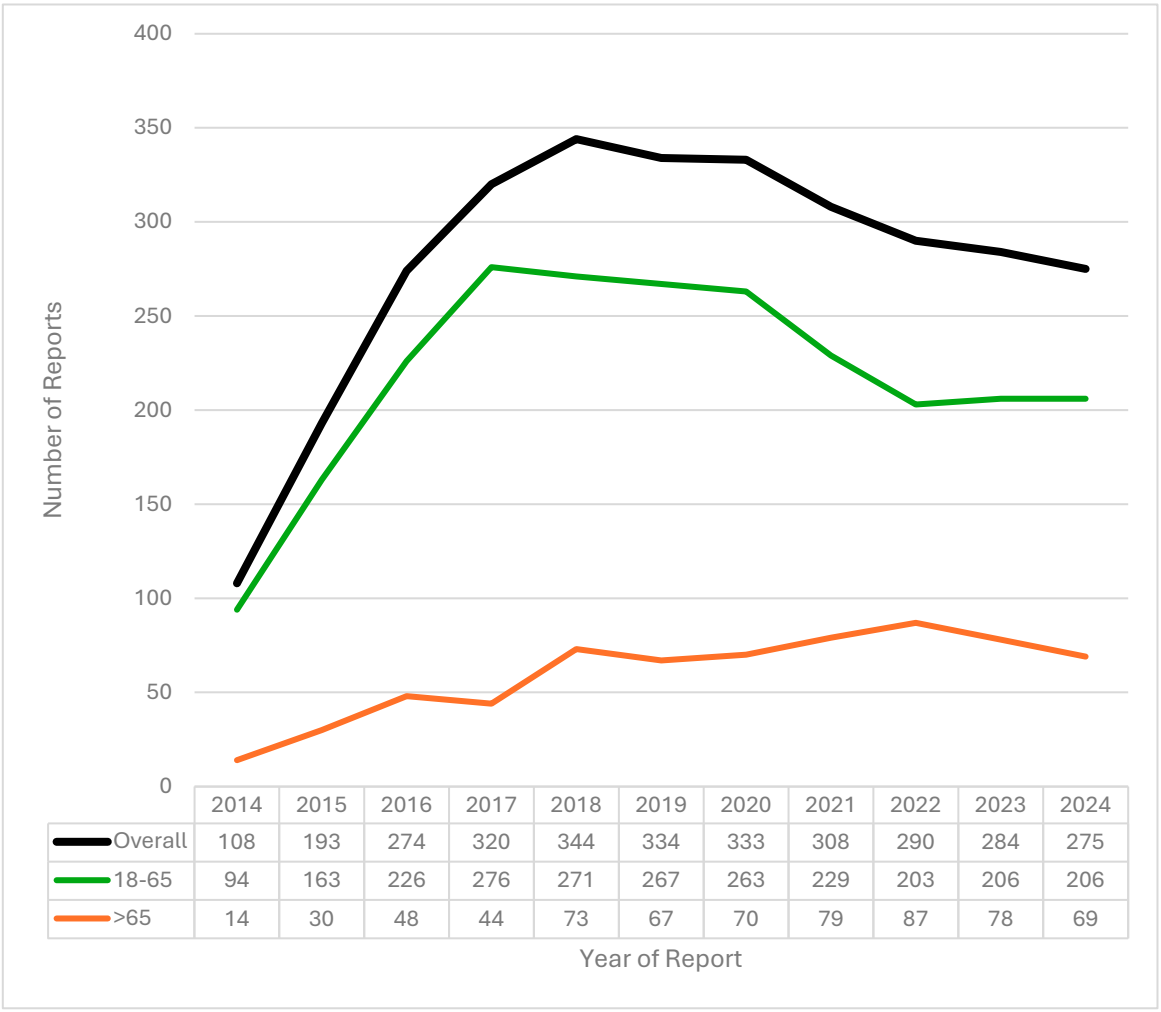


Figure 2. Number of FDA Adverse Event Reports—Overall and by Drug Group (recorded as Primary Suspect drug).

Focusing specifically on vortioxetine, reports increased from 108 in 2014 to a peak of 344 reports in 2018, followed by a gradual decline to 275 reports in 2024. Reports among adults aged 18–65 years consistently accounted for the majority of submissions. The contribution of the >65-year age group increased from 21.2% of reports in 2018 (73/344) to 30.0% in 2022 (87/290) before declining slightly to 25.1% in 2024 (69/275) (Figure 3).



	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023	2024
Overall	108	193	274	320	344	334	333	308	290	284	275
18-65	94	163	226	276	271	267	263	229	203	206	206
>65	14	30	48	44	73	67	70	79	87	78	69

Figure 3. Number of FDA Adverse Event Reports for Vortioxetine (recorded as Primary Suspect drug) for age 18+—Overall and by Age Group.

The analysis of disproportionate adverse-event reporting in older adults (>65 years old) compared to those aged 18–65, specifically concerning vortioxetine, showed the top disproportionate reactions as determined by the reporting odds ratio (ROR), the Information Component (IC), and the Proportional Reporting Ratio (PRR) methodologies. Specifically, in older adults, the strongest IC signals included both psychiatric and non-psychiatric ADRs (e.g., inappropriate antidiuretic hormone secretion, orthostatic hypotension, hyponatremia, dementia, fall, arrhythmia, delirium, hallucination, decreased appetite, malaise, confusional state, and suicidal ideation) (Figure 4).

The PRR analysis identified a broader set of high-magnitude disproportional signals, reflecting differences in crude reporting frequency between age groups. In addition to neuropsychiatric events (e.g., panic attack, dementia, parkinsonism, delirium, suicidal ideation, balance disorder), PRR highlighted inappropriate antidiuretic hormone secretion, erectile dysfunction, lung neoplasm, respiratory complications such as pneumonia, aspiration, and decreased oxygen saturation, cardiovascular events (atrial fibrillation, arrhythmia, hypertensive crisis, decreased blood pressure), and renal and metabolic disturbances (acute kidney injury, hypokalemia, hyponatremia) (Figure 5).

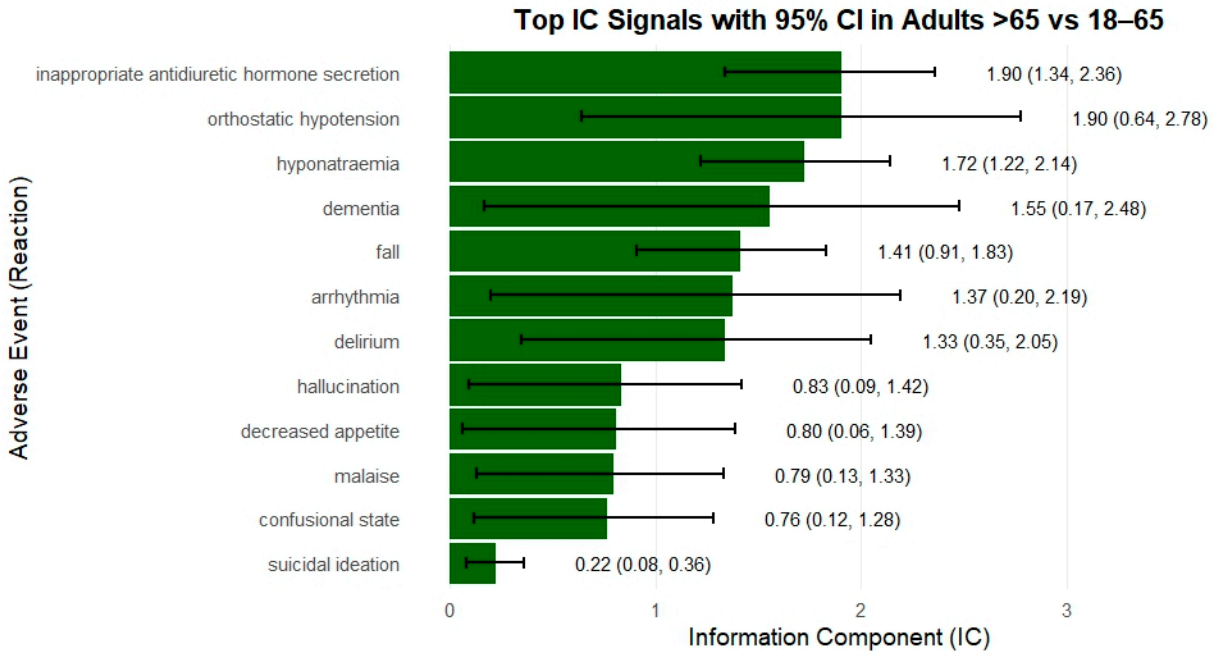


Figure 4. Top Information Component Signals.

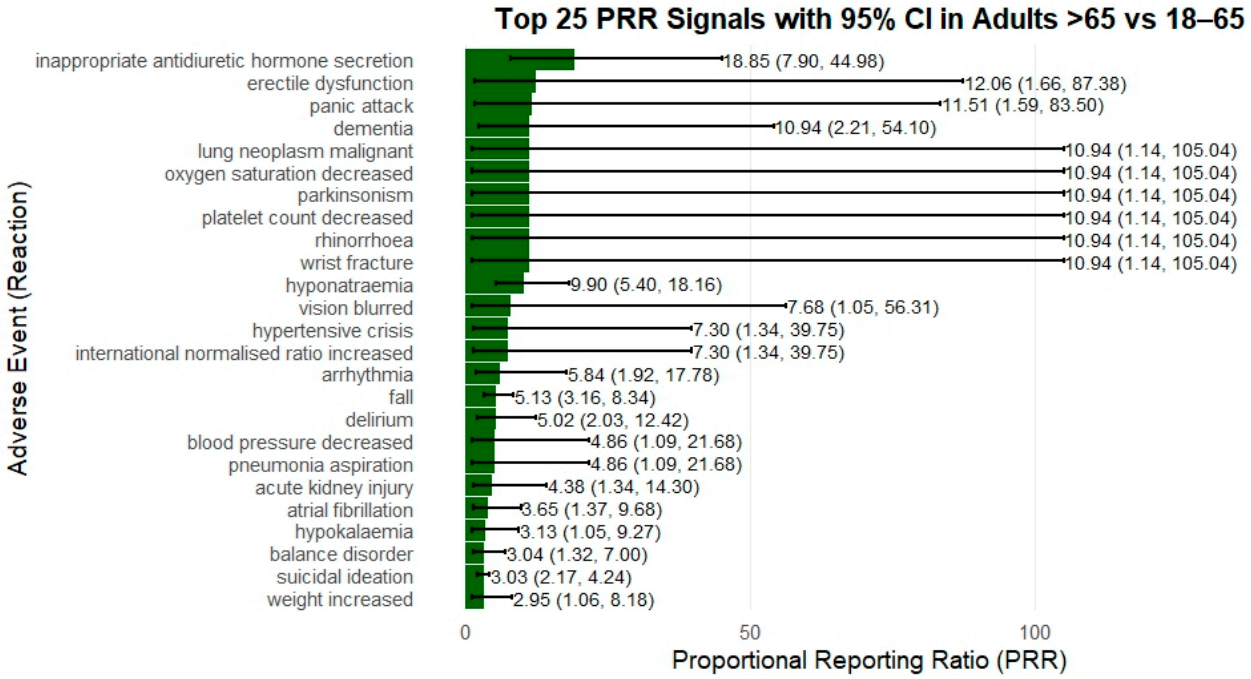


Figure 5. Top 25 Disproportionate Reactions in Adults > 65 vs. 18–65 (PRR).

The ROR analysis closely mirrored the PRR findings, confirming the consistency of the age-related disproportionality pattern. The same clusters of neuropsychiatric (panic attack, dementia, delirium, parkinsonism, suicidal ideation), cardiovascular (atrial fibrillation, hypertensive crisis, arrhythmia), metabolic/electrolyte (hypokalemia, hyponatremia), respiratory, and fall-related events were observed (Figure 6).

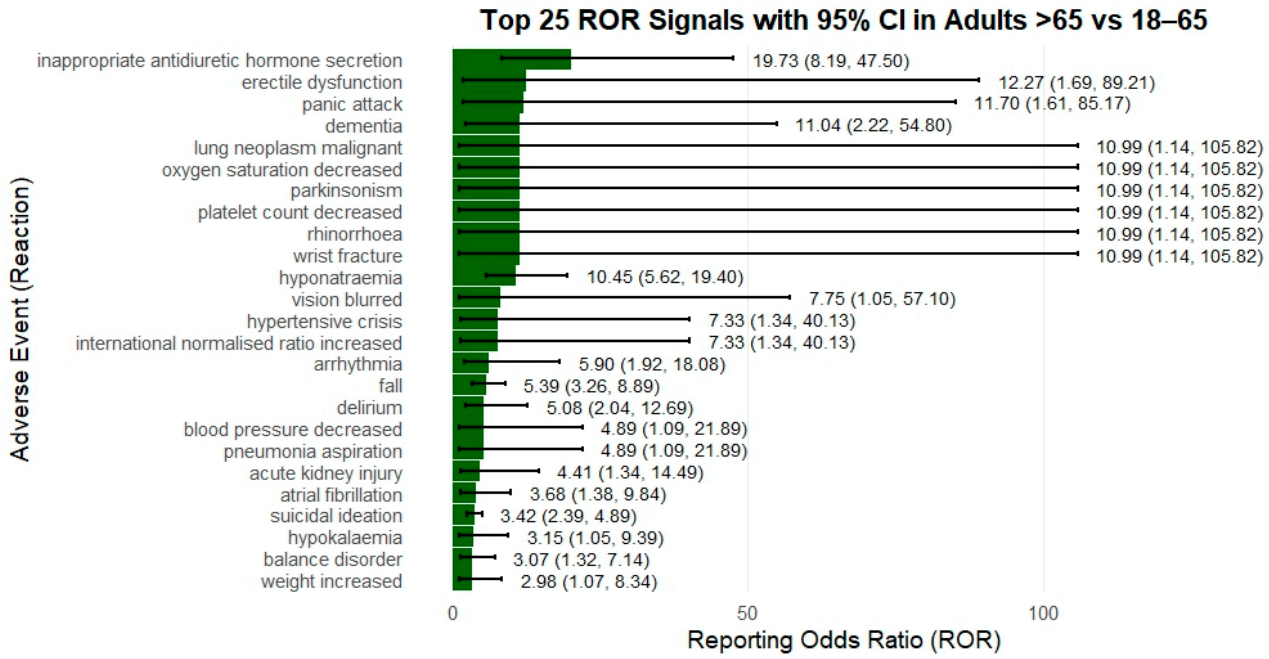


Figure 6. Top 25 Disproportionate Reactions in Adults > 65 vs. 18–65 (ROR).

2.2. Vortioxetine vs. Other Antidepressants

Ranking the 25 AE terms with the highest IC for vortioxetine vs. other antidepressants, the highest IC terms were dominated by genital/uterine hemorrhage, abnormal weight, and depressive symptoms, e.g., abulia, feelings of worthlessness, feeling guilty, and suicide threat. Product use issues (e.g., circumstances or information capable of leading to medication error, product use issue, wrong technique in product use process) were also reported (Figure 7).

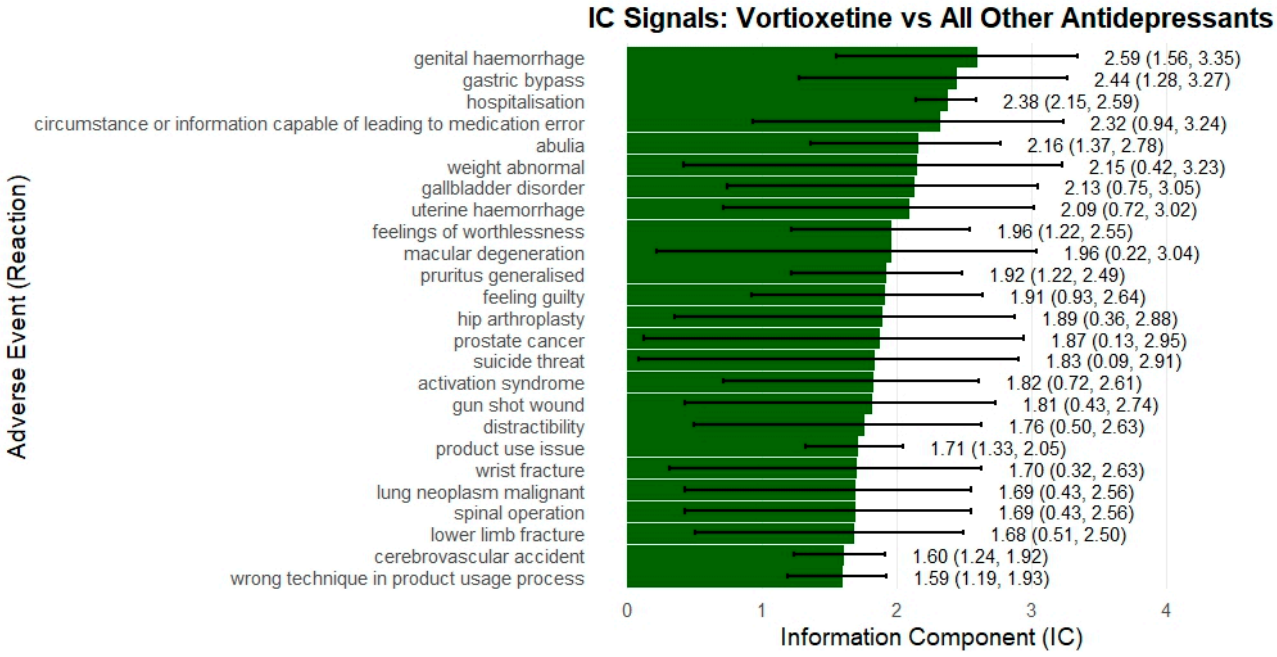


Figure 7. Top 25 IC signals: Vortioxetine vs. Other ADs.

Similarly, the list for the PRR was notable for dysphoria, several severe clinical syndromes (e.g., metabolic acidosis, status epilepticus, respiratory depression/distress, hy-

poxia), and errors in product use (e.g., intentional product misuse and circumstances or information capable of leading to medication error) (Figure 8). Moreover, here some cardiac (e.g., sinus tachycardia, ventricular fibrillation, and *torsade de pointes*) and respiratory ADRs (respiratory depression, hypoxia, pulmonary edema, asphyxia) were recorded.

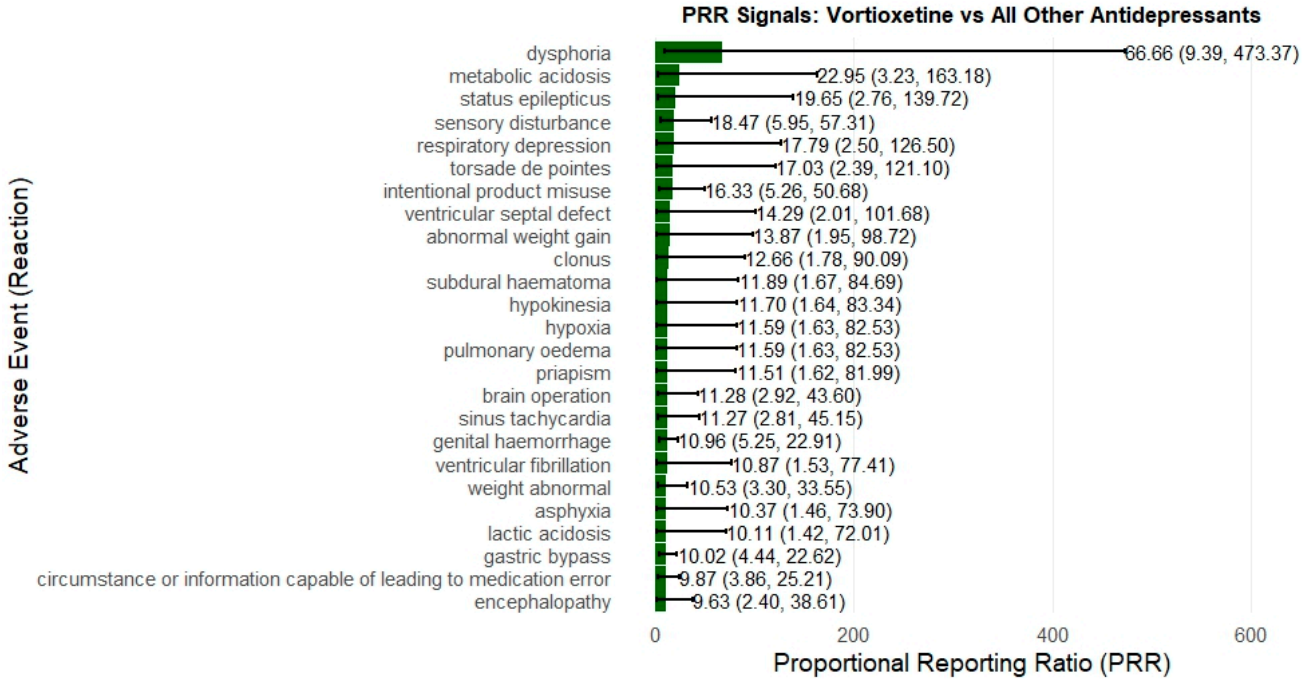


Figure 8. Top 25 PRR signals: Vortioxetine vs. Other ADs.

Similarly, the leading ROR signals again included dysphoria, status epilepticus, and respiratory compromise terms (Figure 9).

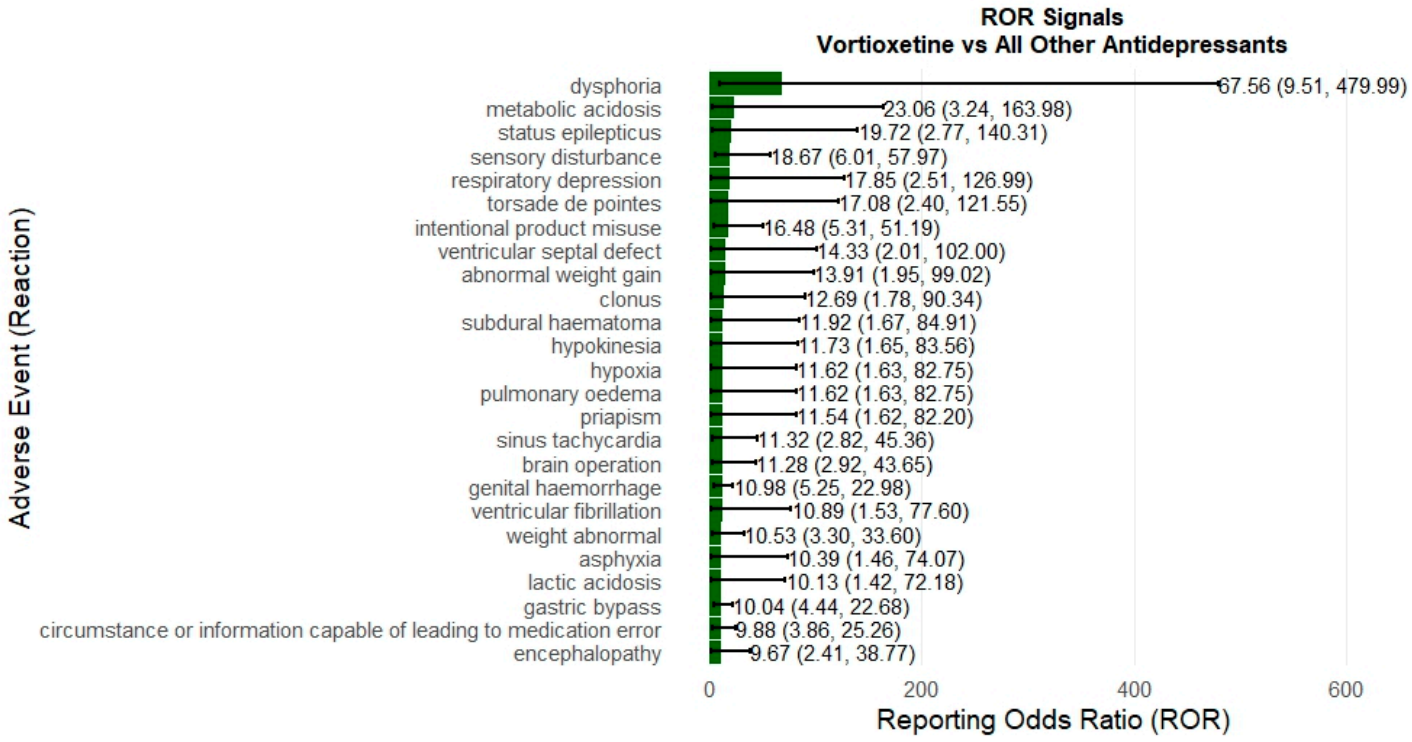


Figure 9. Top 25 ROR Reactions: Vortioxetine vs. Other ADs.

3. Discussion

The present study includes the first disproportionality analysis conducted using three complementary pharmacovigilance metrics, e.g., PRR, ROR, and IC, where vortioxetine was listed as the primary suspect drug, and comparing different age groups. A point of strength was a comparator design (vortioxetine vs. other antidepressants) with primary suspect restriction, which helps reduce (though not eliminate) confounding by concomitant suspect products. Moreover, age-stratified disproportionality identifies clinically meaningful vulnerability patterns in older adults that may be diluted in pooled analyses. Finally, triangulation across PRR, ROR, and IC increases robustness; concordance across metrics supports signal stability and strengthens the validity of findings [12,13].

3.1. Summary of the Main Findings

According to FAERS cases reported from January 2014 up to February 2025, vortioxetine accounted for a small proportion of primary suspect antidepressant reports compared with the aggregate of other antidepressants. The temporal pattern (increase after launch, peak around 2018, then plateau/decline) is compatible with evolving utilization and reporting dynamics rather than a simple monotonic accumulation of risk. Importantly, the age-stratified disproportionality analyses suggest that, among vortioxetine reports, older adults (>65 years) showed a distinct enrichment of neuropsychiatric (e.g., delirium/confusional state, hallucinations), fall/trauma, cardiovascular rhythm, and electrolyte/metabolic events relative to adults aged 18–65 years.

3.2. Age-Related Signals for Vortioxetine

Across all three disproportionality metrics, a convergent signal pattern emerged, with older adults showing a disproportionate reporting of delirium, cognitive impairment, falls, cardiovascular instability, electrolyte disturbances, and serious systemic events. IC analysis provided conservative confirmation of key signals, while PRR and ROR captured a wider spectrum of high-risk reactions [14–16]. The convergence of IC/PRR/ROR in identifying acute neuropsychiatric syndromes in older adults is clinically plausible. Older patients are intrinsically more vulnerable to delirium and cognitive fluctuations due to multimorbidity, polypharmacy, and reduced physiological reserve. Most clinical trials on antidepressants often underrepresent older adults, leading to a paucity of age-specific data that clinicians can rely on for decision-making. Moreover, the heterogeneity within the elderly population, including varying degrees of frailty, comorbidity burden, and concomitant medication use, necessitates tailored insights into antidepressant tolerability. In voluntary reporting, such outcomes may reflect (i) true susceptibility to serotonergic modulation under frailty conditions, (ii) drug–drug interactions (e.g., sedatives, anticholinergics), or (iii) confounding by indication and disease severity (e.g., depression with prodromal cognitive decline). The enrichment of falls and trauma-related terms (including fracture outcomes) in older vortioxetine reports is consistent with the broader literature linking antidepressant exposure to increased fall risk in older adults [17]. Falls likely represent a downstream phenotype integrating multiple proximal contributors highlighted in the figures—delirium/confusion, dizziness, orthostatic hypotension, and possibly hyponatremia. Systematic evidence supports an association between antidepressant use and falls, while orthostatic hypotension itself is also associated with falls in older people, providing a mechanistic bridge that fits the signal "cluster" (falls/orthostatic hypotension/trauma) [18]. Hyponatremia and Syndrome of Inappropriate Antidiuretic Hormone Secretion (SIADH) signals in older adults are particularly relevant because antidepressant-associated hyponatremia is a recognized class effect (especially in older patients), with clinically meaningful morbidity (delirium, gait instability, falls, arrhythmia susceptibility) [18]. Hyponatremia risk varies across antidepressant

classes and compounds but remains an important safety consideration overall [19]. In this context, the repeated appearance of hyponatremia/SIADH in multiple disproportionality metrics suggests a potentially actionable signal in older vortioxetine users—at least supporting closer electrolyte monitoring in high-risk individuals (advanced age, diuretics, low baseline sodium, frailty). Signals such as atrial fibrillation and arrhythmia may reflect a mix of true ADRs, event "unmasking" in comorbid patients, and confounding by age-related cardiovascular disease burden. Notably, clinical trial and pooled safety data for vortioxetine generally suggest no clinically relevant effects on Electrocardiographic QT interval or blood pressure in trial populations—highlighting the classic pharmacovigilance gap between selected RCT populations and real-world older adults with multimorbidity [20]. Indeed, two recent decade-long pharmacovigilance studies, similarly based on the FAERS database evaluating the post-marketing safety profile of vortioxetine, identified, among all patients, unexpected signals like blurred vision, bruxism, disturbance in attention, akathisia, restless legs syndrome, urinary retention, and prolonged electrocardiogram QT [21,22]. The results obtained also diverge from those of a non-interventional post-authorization safety study, which utilized longitudinal administrative claims/medical records data from 10,358 patients newly prescribed vortioxetine in Finland, Spain, and the Netherlands [23]. Therefore, these rhythm signals in FAERS may be better interpreted as real-world vulnerability signals (drug exposure within a high-risk milieu) rather than direct electrophysiological toxicity per se, and they warrant hypothesis-driven evaluation in denominator-based data sources.

Importantly, several of the disproportionately reported adverse events identified in the present analysis are already reflected in the currently approved Summary of Product Characteristics (SmPC) for vortioxetine, including hyponatremia/SIADH (particularly in older patients), dizziness, falls and fractures, serotonin syndrome, and the recommendation for caution in patients with risk factors for bleeding or when used concomitantly with other centrally acting or serotonergic medicines [24]. Thus, the observed pharmacovigilance signals are not necessarily indicative of previously unrecognized adverse drug reactions but rather reinforce the clinical relevance of established safety information in routine practice, particularly among frail older adults with multimorbidity and polypharmacy. Conversely, signals such as atrial fibrillation, broader cardiovascular instability, and certain serious systemic events are not specifically characterized in the SmPC and therefore should be interpreted as hypothesis-generating observations requiring confirmation in studies with appropriate denominators and adjustment for confounding. It should also be emphasized that disproportionality analyses are designed for signal detection rather than causal inference; they cannot establish a causal relationship between drug exposure and adverse events, nor can they estimate the incidence or magnitude of risk. Instead, they identify adverse events that are reported more frequently than expected within a voluntary reporting system, providing useful clinical context and helping to prioritize safety signals for further investigation [25,26].

Together, these findings suggest that vortioxetine-associated ADRs in the elderly are characterized not only by psychiatric symptoms but also by multisystem medical complications, highlighting the importance of age-specific risk assessment and monitoring in clinical practice. From a clinical point of view, the association of an antidepressant medication with adverse effects can lead to poor medication adherence, discontinuation of therapy, and worsening of depressive symptoms, thereby undermining treatment outcomes. In the context of treating late-life depression, the tolerability profiles of antidepressants remain a critical consideration. The Vortioxetine in the Elderly vs. Selective Serotonin Reuptake Inhibitors: a Pragmatic Assessment (VESPA) trial aimed to assess whether newer agents offered advantages in this regard. Contrary to initial expectations, the study found no clear tolerability benefit for vortioxetine over SSRIs. At six months, treatment discontinuation

due to adverse events occurred in 44% of participants receiving vortioxetine (78 out of 179) and 33% of those receiving SSRIs (59 out of 178), with an odds ratio of 1.56 (95% CI: 1.01–2.39) for vortioxetine relative to SSRIs [11]. These findings highlight the complexity of pharmacological treatment in older adults, a population often underrepresented in clinical trials and characterized by increased medical comorbidity, polypharmacy, and age-related pharmacokinetic changes [27]. Such factors may influence both the incidence of adverse events and treatment adherence, underscoring the need for cautious interpretation and individualized prescribing decisions. Existing literature on antidepressant effects in this age group remains heterogeneous, with many studies limited by short follow-up periods, selective inclusion criteria, and a lack of head-to-head comparison—challenges that the VESPA trial attempted to address through its pragmatic design. Consistent with this, in a meta-analysis assessing the safety and tolerability of vortioxetine compared to SSRIs in late-life depression (patients aged 60 years or older), Rodrigues Alessi et al. [28] found no statistically significant differences between the vortioxetine group and the SSRI group for several common gastrointestinal and other AEs, suggesting that vortioxetine is safe for the treatment of late-life depression, with no significant increase in adverse effects compared to serotonin reuptake inhibitors.

3.3. Vortioxetine vs. Other Antidepressants

The comparative analysis between vortioxetine and the pooled group of other antidepressants produced a signal pattern that differed from the age-stratified analysis. Whereas the comparison between older and younger vortioxetine users highlighted clinically coherent clusters involving delirium, falls, cardiovascular instability, and electrolyte disturbances, the drug-versus-drug analysis was more strongly influenced by typical mood ADRs (both strictly depressive terms and dysphoria), but also medical syndromes and medication error ADRs. This distinction is important, because disproportionality rankings may be driven by differences in how a medicine is prescribed, monitored, and reported, particularly for a relatively newer antidepressant with a smaller cumulative exposure base.

The presence of high PRR and ROR values for rare serious events, including status epilepticus and respiratory-compromise syndromes, warrants attention but does not by itself establish a specific vortioxetine safety liability. In voluntary-reporting databases, large disproportionality estimates may arise from very small numerators, sparse comparator counts, selective reporting of severe cases, co-exposure to other psychotropic or centrally acting medicines, overdose, underlying medical illness, or confounding by indication.

Overall, the comparative findings do not identify a single, internally consistent organ-system toxicity pattern that clearly differentiates vortioxetine from the other antidepressants included in the analysis. Instead, they suggest a heterogeneous reporting profile in which non-classical and context-dependent terms contribute substantially to the strongest signals. This is broadly compatible with the interpretation that the observed differences reflect, at least in part, reporting structure and medicine-use context rather than a direct measure of comparative risk [29]. Confirmation in denominator-based pharmacoepidemiological studies, with adjustment for age, indication, comorbidity, polypharmacy, treatment duration, and exposure prevalence, is required before any comparative clinical conclusion can be drawn.

From a clinical perspective, these findings should not be used to infer that vortioxetine is either safer or less safe than comparator antidepressants. They instead identify specific report clusters that merit targeted review at case level and, where appropriate, further evaluation using electronic health records, claims databases, registries, or prospective post-authorization studies.

3.4. Limitations

Data from the FAERS dataset are inherently subject to reporting biases, including notoriety bias, stimulated reporting following regulatory actions or increased media attention, under-reporting, and the lack of denominator data, which precludes exposure-adjusted incidence estimates. Furthermore, integration with clinical or epidemiological datasets was beyond the scope of the present study and was not feasible with the available data. Indeed, observed disproportionality reflects reporting patterns rather than true risk. The findings are further limited by under-reporting, variable report quality, missing clinical context, and duplicate submissions, all of which can bias both the magnitude and direction of detected signals. In addition, confounding by indication and channeling bias—such as age-, frailty-, or comorbidity-driven prescribing patterns—may partially account for the observed age-related profile. Signal rankings may also be distorted by Medical Dictionary for Regulatory Activities (MedDRA) coding artifacts and the prominence of non-clinical terms (e.g., medication errors, product quality issues, or procedures), which should be analytically managed according to the study objective. Finally, temporal changes in reporting driven by public awareness, regulatory actions, litigation, or media attention can produce apparent peaks or declines that are unrelated to the underlying pharmacology.

4. Materials and Methods

4.1. Study Design

A retrospective pharmacovigilance disproportionality analysis was conducted using individual case safety reports submitted to FAERS. Two principal signal-detection analyses were performed. First, among reports in which vortioxetine was designated as the primary suspect drug, adverse-event reporting in adults aged >65 years was compared with reporting in adults aged 18–65 years. Second, vortioxetine reports were compared with reports involving other antidepressants, using both a pooled antidepressant comparator and class-specific comparator groups.

The primary signal-detection analyses were conducted using the clinically filtered PT list described below. All disproportionality analyses were intended to identify signals of disproportionate reporting and were not designed to estimate adverse-event incidence, relative risk, and comparative safety.

4.2. Data Extraction and Preparation

Cohort flow diagrams for each comparative analysis are shown in Figure 10 and are described below.

Quarterly FAERS data files were downloaded from the U.S. Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS) repository from database inception through February 2025, including the final quarterly release from 2024. Demographic, drug, indication, reaction, and outcome files were merged using the unique FAERS case identifier. When multiple versions of the same case were present, only the most recent case version was retained to minimize duplicate reporting.

Drug names were standardized using the Medi-Span® Drug Database (Medi-Span, Inc. now part of Wolters Kluwer/UpToDate, Inc., Indianapolis, Indiana, United States of America). Generic and brand names were mapped to a common generic drug name to identify reports involving antidepressants of interest. Antidepressants included vortioxetine; the selective serotonin reuptake inhibitors (SSRIs) sertraline, citalopram, escitalopram, paroxetine, fluoxetine, and fluvoxamine; the serotonin and norepinephrine reuptake inhibitors (SNRIs) duloxetine, venlafaxine, and desvenlafaxine; the tricyclic antidepressants (TCAs) amitriptyline and nortriptyline; trazodone and mirtazapine; and an "other" category consisting of bupropion and antidepressants not otherwise classified into the preceding

drug classes. To reduce confounding by concomitant exposure, analyses were restricted to reports in which a study drug was designated as the primary suspect (PS) medication.

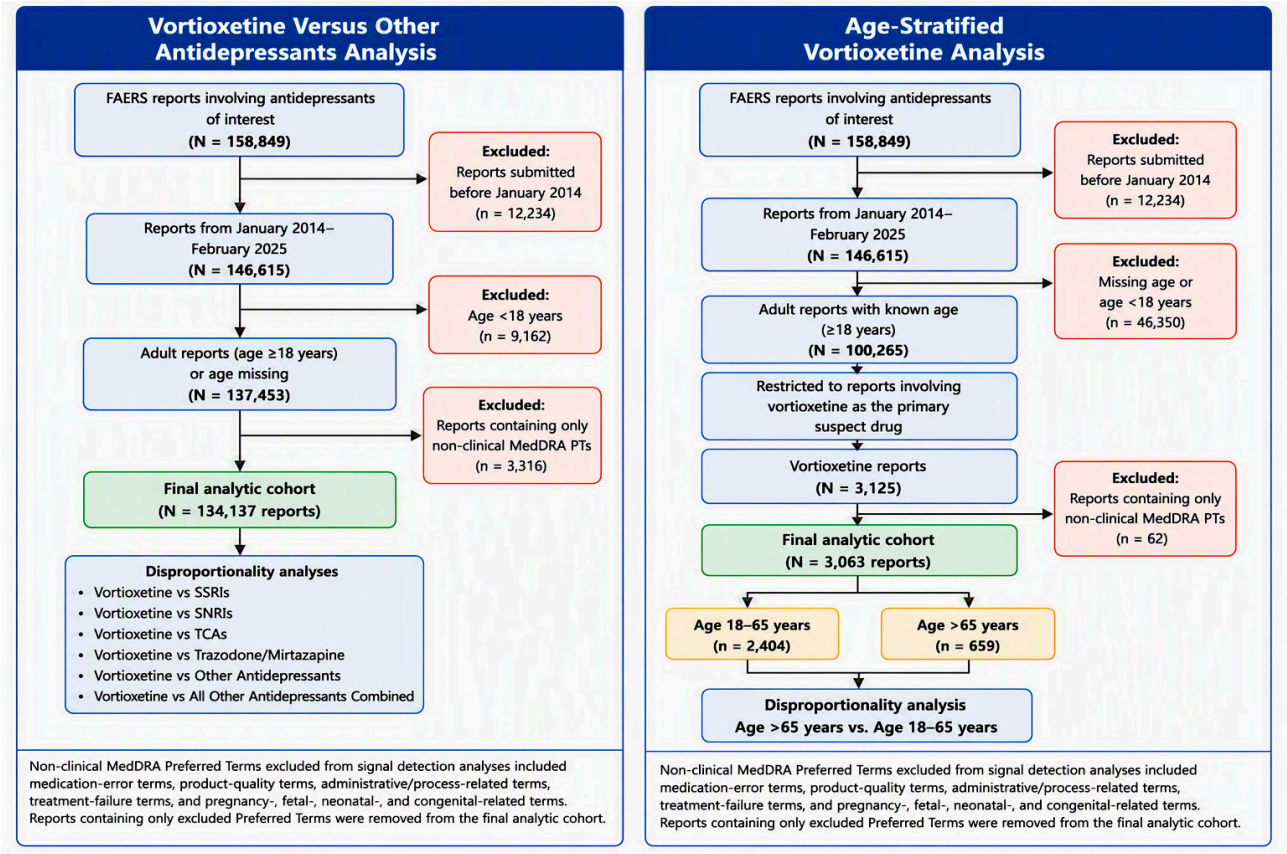


Figure 10. Cohort flow diagrams for each comparative analysis.

Since vortioxetine received FDA approval in the US in late 2013, reports submitted prior to 1 January 2014 were excluded. Age values reported in hours, days, weeks, months, or years were standardized to years using FDA age-unit coding conventions. For analyses comparing vortioxetine with other antidepressants, reports involving individuals younger than 18 years were excluded, whereas reports with missing age were retained. For analyses examining age-related reporting patterns among vortioxetine users, reports with missing age were excluded, and only adults aged 18 years or older were retained.

Reaction terms were coded using MedDRA PTs. To improve clinical interpretability and reduce the influence of non-clinical reporting artifacts, several categories of PTs were excluded prior to signal detection. Excluded terms included medication-error and dosing-related PTs (underdose, prescribed underdose, incorrect dose administered, product administered to patient of inappropriate age), product-quality and product-substitution PTs (product quality issue, product substitution issue), administrative and process-related PTs (hospitalization, therapy interrupted, circumstance or information capable of leading to medical error), treatment-failure and disease-progression PTs (drug ineffective, condition aggravated), and other non-clinical reporting categories (no adverse event). In addition, PTs describing product reactions or non-specific toxicities (reaction to excipient, toxicity to various agents), withdrawal-related events (drug withdrawal syndrome), procedures or surgeries (surgery, shoulder operation, knee operation, shoulder arthroplasty), and malignancy-related terms (neoplasm malignant, brain neoplasm) were excluded. Pregnancy-, fetal-, neonatal-, and congenital-related PTs (fetal exposure during pregnancy, premature baby, neonatal distress respiratory syndrome, atrial septal defect)

were also excluded because they were not relevant to the study objective of evaluating adverse-event reporting patterns in older adult populations. Additional excluded PTs included death, drug eruption, and product use in an unapproved indication. Reports containing only excluded PTs were removed from the final analytic cohort, whereas reports containing both excluded and non-excluded PTs were retained and analyzed using the remaining clinically relevant PTs. This clinically filtered PT dataset constituted the analytic dataset for the disproportionality analyses described herein. Consequently, excluded PTs were not eligible for identification as signals in the analyses.

Missing demographic and clinical variables were not imputed. Analyses were conducted using all available information, and missing values were reported where applicable.

4.3. Analysis of Age-Related Reporting Patterns Among Vortioxetine Users

To evaluate age-related differences in adverse-event reporting, analyses were restricted to reports in which vortioxetine was designated as the primary suspect drug. Adults aged 18–65 years were compared with adults older than 65 years. Reports with missing age information were excluded.

Descriptive analyses summarized year of report, age group, sex, reporting country, indication, and outcome. The ten most frequently represented reporting countries and indications were identified overall, and frequencies for those same categories were subsequently reported within each age group.

Disproportionality analyses were conducted using the R package 'pvda' (version 0.0.4). For these analyses, age group served as the exposure variable, with adults aged 18–65 years serving as the reference group. Reporting odds ratios (RORs), proportional reporting ratios (PRRs), and information components (ICs), together with corresponding 95% confidence intervals, were calculated for all eligible adverse-event terms. Signals were defined as adverse events reported disproportionately more frequently among adults older than 65 years compared with adults aged 18–65 years. To reduce instability arising from sparse data, only adverse events meeting the package default minimum reporting threshold of three reports were evaluated. Signal detection criteria were defined a priori as an IC lower 95% confidence limit greater than zero, a PRR lower 95% confidence limit greater than one, or an ROR lower 95% confidence limit greater than one. Adverse events meeting at least one of these criteria were classified as signals. The 25 strongest signals according to each disproportionality metric (IC, PRR, and ROR) were displayed graphically, and complete signal tables were generated for all events meeting at least one signal criterion.

4.4. Comparative Analysis of Vortioxetine and Other Antidepressants

To compare adverse-event reporting patterns between vortioxetine and other antidepressants, reports involving vortioxetine were compared with reports involving SSRIs, SNRIs, TCAs, trazodone, mirtazapine, and other antidepressants of interest. Reports in which vortioxetine and another antidepressant of interest were co-reported were excluded to ensure mutually exclusive exposure groups.

Descriptive analyses summarized age, sex, reporting country, indication, and outcome overall and by exposure group (vortioxetine versus comparator antidepressants). The ten most frequently represented reporting countries and indications were identified overall and subsequently characterized within each exposure group.

Disproportionality analyses were performed using the R package 'pvda' (version 0.0.4). RORs, PRRs, and ICs, with corresponding 95% confidence intervals, were calculated for all eligible adverse-event terms. Signals were defined as adverse events reported disproportionately more frequently in vortioxetine reports than in comparator antidepressant reports. Comparator analyses were conducted separately for SSRIs, SNRIs, TCAs, trazodone/mir-

tazapine, and other antidepressants, as well as for a pooled comparator group consisting of all non-vortioxetine antidepressants. As in the age-stratified analysis, only events meeting the minimum reporting threshold of three reports were evaluated, and the 25 strongest signals according to each disproportionality metric were reported. Signal detection criteria were defined a priori as an IC lower 95% confidence limit greater than zero, a PRR lower 95% confidence limit greater than one, or an ROR lower 95% confidence limit greater than one. Adverse events meeting at least one of these criteria were classified as signals. The 25 strongest signals according to each disproportionality metric (IC, PRR, and ROR) were displayed graphically, and complete signal tables were generated for all events meeting at least one signal criterion.

4.5. Reporting Guideline

This study was reported in accordance with the Reporting of A Disproportionality Analysis for Drug Safety Signal Detection Using Individual Case Safety Reports in Pharmacovigilance (READUS-PV) recommendations. A completed READUS-PV checklist is provided in the Supplementary Materials.

5. Conclusions

The consistent identification of certain AEs across all three disproportionality analyses underscores their importance as potential safety signals for vortioxetine in older adults. These findings suggest that older patients may be particularly vulnerable to central nervous system effects, metabolic disturbances, cardiovascular issues, and drug–drug interactions, necessitating careful monitoring and consideration of age-related physiological changes when prescribing vortioxetine. The observed associations represent potential pharmacovigilance signals requiring further confirmation through pharmacoepidemiological studies and clinical investigations, rather than evidence of increased clinical risk in older adults treated with vortioxetine. Identified signals may support pharmacovigilance awareness and targeted monitoring. Further clinical investigation into these specific disproportionate reactions in the elderly population is warranted to better understand their clinical significance and to develop appropriate risk mitigation strategies. Complementary methods such as clinical trials, cohort studies, and other pharmacovigilance tools are often needed to corroborate findings and provide a more comprehensive assessment of drug safety.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/ph19111855/s1, The READUS-PV checklist.

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