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ORIGINAL ARTICLE

A real-world pharmacovigilance study of the FAERS database for fluvoxamine: perspectives from physicians and pharmacists

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Objective: Although fluvoxamine is a well-established treatment for depressive disorders, real-world safety data remain limited. This study analyzed adverse drug events associated with fluvoxamine in the U.S. Food and Drug Administration's Adverse Event Reporting System, a large-scale pharmacovigilance database, to assess the drug's safety profile.
Methods: The database was used to collect data on fluvoxamine-related adverse drug events from the first quarter of 2004 to the third quarter of 2024. Disproportionality analyses were performed using the reporting odds ratio, proportional reporting ratio, Bayesian confidence propagation neural network, and empirical Bayes geometric mean methods.
Results: A total of 355 fluvoxamine-related adverse drug event reports were identified, spanning 26 different system organ classes and 67 preferred terms. Psychiatric disorders were the most frequently reported adverse drug events. Notably, signals for reproductive system and breast disorders, cardiac disorders, and eye disorders were stronger but were unrelated to the pharmacological properties of fluvoxamine, thus warranting special clinical attention. Disinhibition had the highest signal strength and requires vigilance. A considerable number of drug interactions were noted, leading to increased antipsychotic drug levels and extrapyramidal symptoms, such as slow speech, drooling, and tardive dyskinesia. Self-harm and suicidal behavior require appropriate clinical risk management. Additionally, significant symptoms of serotonin syndrome were observed, including tics, clonus, mydriasis, and myoclonus. Our study also discovered adverse drug events not previously documented in product labels, such as Cushing's syndrome, papilledema, and increased intracranial pressure.
Conclusion: This study provides a real-world pharmacovigilance analysis of fluvoxamine, identifying several rare adverse drug events and clinically significant symptoms, particularly neuroleptic malignant syndrome and serotonin syndrome. Our study offers important insights for the clinical safety assessment of fluvoxamine.

Keywords: Fluvoxamine; FAERS; adverse drug events

Introduction

Depression is a major global public health challenge.[1] A cohort study using the Global Burden of Disease database to investigate depression incidence from 1990 to 2019 found that the incidence of depression was 290 million in 2019, a 59.3% increase compared to 1990.[2] Furthermore, a 2013 Global Burden of Disease study highlighted that depression had become the leading cause of disability-adjusted life years across all countries worldwide.[3] Depression severely affects quality of life, work, and social functioning.[4] Pharmacotherapy is considered the cornerstone of treatment.[5] One of the first selective serotonin reuptake inhibitors, fluvoxamine is now used in over 110 countries to treat depressive disorders.[6] Its antidepressant effects are due to inhibition of serotonin (5-hydroxytryptamine [5-HT]) reuptake in the presynaptic membrane, thereby increasing the concentration of serotonin in the synaptic cleft.[7]

In a double-blind, placebo-controlled study, patients treated with fluvoxamine for 4 to 6 weeks showed significant improvement in depressive symptoms; those with severe depression had a higher treatment response rate than those with mild or moderate depression.[8] Additionally, fluvoxamine has been approved for post-traumatic stress disorder,[9] autism spectrum disorder,[10]

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and as an adjunctive treatment for schizophrenia.[11] It has also led to improvement in insomnia and cognitive impairment.[12] Research has also indicated that, in high-risk patients with severe COVID-19 infection and underlying conditions such as diabetes, fluvoxamine can significantly reduce the risk of severe illness and mortality early in the infection.[13] This effect may be attributed to fluvoxamine's anti-inflammatory action, which is mediated through sigma-1 receptor agonism.[14]

Despite these emerging therapeutic benefits, concerns persist about fluvoxamine's safety profile. Common adverse drug events (ADEs) include gastrointestinal symptoms such as nausea, dry mouth, and constipation, central nervous system symptoms such as mild anxiety and sleep disturbances, and autonomic nervous system symptoms such as palpitations and tachycardia.[15] Serious adverse reactions include hyponatremia, bleeding disorders, and a potential risk of glaucoma.[16] Since no study has investigated the real-world adverse effects of fluvoxamine, we conducted this pharmacovigilance study using the U.S. Food and Drug Administration's Adverse Event Reporting System (FAERS) database. Through extensive monitoring and analysis of ADEs, we assessed the safety of fluvoxamine in real-world settings. We considered the perspective of physicians and pharmacists to reduce the risk of result bias,[17] focusing on ADEs from a professional viewpoint. Our study provides health care professionals with a comprehensive safety profile for fluvoxamine.

Methods

Data source

The FAERS database is designed to collect reports from patients, pharmaceutical manufacturers, health care professionals, and others worldwide to monitor drug-related ADE. These data files are made publicly available on a quarterly basis in seven sections: patient demographic information, drug information, ADE details, patient outcomes, report source, drug treatment dates, and drug indications. We selected all relevant data from the FAERS database from the first quarter of 2004 to the third quarter of 2024. The search strategy was based on the generic drug name ''fluvoxamine.'' Since the data files are de-identified, no ethics committee approval was required.

Data extraction and analysis

To ensure the accuracy of the data, when duplicate reports were identified, we followed U.S. Food and Drug Administration guidelines by retaining only the most recent FDA_DT. Additionally, when both FDA_DT and CASEID were identical, we selected the report with the higher PRIMARYID. The Medical Dictionary for Regulatory Activities is one of the most commonly used medical coding dictionaries in clinical and post-market pharmacovigilance. We encoded the ADE reports obtained from the FAERS database and, based on the Medical Dictionary for Regulatory Activities' preferred terms, classified the ADEs into system organ classes. The selected fluvoxamine-related ADEs were further analyzed, including patient information such as sex, age, adverse event report timing, type, severity, and other relevant details.

Descriptive statistical analysis was employed in this study. Disproportionality analysis is the primary method for data mining in spontaneous reporting systems. In our study, disproportionality analysis was used to assess the association between fluvoxamine and ADEs, including the reporting odds ratio (ROR), proportional reporting ratio (PRR), Bayesian confidence propagation neural network, and empirical Bayes geometric mean (EBGM). Table 1 presents the 2 $\times$ 2 contingency table, the formulas for these algorithms, and the criteria for positive signal detection.[18] To minimize errors and improve sensitivity, this study combined four algorithms for comprehensive data analysis.

Statistical analysis

MySQL 8.0 and Microsoft Excel 2019 were used for statistical analysis, while R (version 4.3.1) was used for data visualization.

Results

Baseline information

From the first quarter of 2004 until the third quarter of 2024, a total of 355 fluvoxamine-related ADE reports were recorded in the FAERS database (Figure 1). Among patients whose sex was known, the incidence was slightly higher in women (48.7%) than men (40.8%). The highest proportion of patients was in the 18-64-year age group (53%), followed by the 65-85-year age group (10.1%). A significant proportion of missing weight data limited further analysis. Physicians accounted for 73% of the reports, more than twice the number filed by pharmacists (27%). The countries that filed the most reports were the United States (24.5%) and Japan (15.8%), and 39.29% of ADEs occurred within 30 days after beginning treatment. The highest proportion of serious outcomes was important medical events (39.7%), followed by hospitalization-initial or prolonged (32.4%), and death (9%). The number of reports showed a fluctuating upward trend each year, peaking in 2019 and subsequently declining (Supplementary Table S1).

System organ class signals

Fluvoxamine-related ADEs primarily involved 26 different SOCs (Table 2). The top three systems with the highest number of ADE reports were: psychiatric disorders (n=281, ROR 5.47, PRR 4.51, IC 2.17, EBGM 4.51), nervous system disorders (n=214, ROR 2.2, PRR 2, IC 1, EBGM 2), and general disorders and administration site conditions (n=166, ROR 0.81, PRR 0.83, IC -0.26, EBGM 0.83), which are consistent with the drug's mechanism of action. Notably, reproductive system and breast disorders (n=11, ROR 1.45, PRR 1.44, IC 0.53, EBGM 1.44), cardiac disorders (n=51, ROR 1.08, PRR 1.08, IC 0.11,

Table 1 A two-by-two contingency table and detailed formulas for disproportionality analysis

	Fluvoxamine-related ADEs	Other ADEs	Sums
Fluvoxamine	A	b	a + b
Other drugs	C	d	c + d
Sums	a + c	b + d	a + b+ c+ d

Algorithms	Calculation formulas	Threshold
ROR	$ROR = \frac{ad}{bc}$	a $\geqslant$ 3 and 95%CI (lower limit) $>$ 1
	$95\%CI = e^{\ln(ROR)\pm1.96\sqrt{\frac{1}{a}+\frac{1}{b}+\frac{1}{c}+\frac{1}{d}}}$	
PRR	$PRR = \frac{a(c+d)}{c(a+b)}$	PRR $\geqslant$ 2, a $\geqslant$ 3 and $\chi^2 \geqslant 4$
	$95\%CI = e^{\ln(PRR)\pm1.96\sqrt{\frac{1}{a}-\frac{1}{a+b}+\frac{1}{c}-\frac{1}{c+d}}}$	
	$\chi^2 = \frac{\left[(ad-bc)^2\right](a+b+c+d)}{[(a+b)(c+d)(a+c)(b+d)]}$	
BCPNN	$IC = \log_2 \frac{a(a+b+c+d)}{(a+c)(a+b)}$	IC025 $>$ 0
	$E(IC) = \log_2 \frac{(a+\gamma 11)(a+b+c+d+\alpha)(a+b+c+d+\beta)}{(a+b+c+d+\gamma)(a+b+\alpha 1)(a+c+\beta 1)}$	
	$V(IC) = \frac{1}{(ln2)^2}\left\{\left[\frac{(a+b+c+d)-a+\gamma-\gamma 11}{(a+\gamma 11)(1+a+b+c+d+\gamma)}\right]+\left[\frac{(a+b+c+d)-(a+b)+\alpha-\alpha 1}{(a+b+\alpha 1)(1+a+b+c+d+\alpha)}\right]+\left[\frac{(a+b+c+d)-(a+c)+\beta-\beta 1}{(a+c+\beta 1)(1+a+b+c+d+\beta)}\right]\right\}$	
	$95\%CI = IC025 = E(IC) - 2\sqrt{V(IC)}$	
	$\gamma = \gamma 11 \frac{(a+b+c+d+\alpha)(a+b+c+d+\beta)}{(a+b+\alpha 1)(a+c+\beta 1)}$	
MGPS	$EBGM = \frac{a(a+b+c+d)}{(a+c)(a+b)}$	EBGM05 $>$ 2
	$95\%CI = EBGM05 = e^{\ln(EBGM)\pm1.96\sqrt{\frac{1}{a}+\frac{1}{b}+\frac{1}{c}+\frac{1}{d}}}$	

ADE = adverse drug events; BCPNN = Bayesian confidence propagation neural network; EBGM05 = lower bound of the 95%CI of the empirical Bayes geometric mean; IC025 = lower bound of the 95%CI of the information component; MGPS = multi-item gamma Poisson shrinker; PRR = proportional reporting ratio; ROR = reporting odds ratio.

EBGM 1.08), and eye disorders (n=34, ROR 1.35, PRR 1.34, IC 0.43, EBGM 1.34), showed signals across the four algorithms and warrant special clinical attention. Additionally, some adverse reactions not mentioned in the drug's prescribing information were identified, such as respiratory, thoracic, and mediastinal disorders (n=28, ROR 0.39, PRR 0.41, IC -1.3, EBGM 0.41), vascular disorders (n=32, ROR 1.01, PRR 1.01, IC 0.02, EBGM 1.01), and ear and labyrinth disorders (n=6, ROR 1.25, PRR 1.25, IC 0.33, EBGM 1.25), which require further investigation.

Preferred term signals

This study identified 67 significant preferred terms related to fluvoxamine (Figure 2), which were ranked in descending order based on the strictest EBGM algorithm. The top thirty terms are listed in Table 3, of which the top three were disinhibition (n=5, ROR 112.57, PRR 112.14, IC 6.79, EBGM 111.04), antipsychotic drug level increased (n=7, ROR 60.06, PRR 59.74, IC 5.89, EBGM 59.43), and slow speech (n=3, ROR 56.1, PRR 55.98, IC 5.8, EBGM 55.7). The three ADEs with the highest number of reported cases were drug interaction (n=51, ROR 11.24, PRR 10.84, IC 3.44, EBGM 10.83), suicide attempt (n=33, ROR 17.65, PRR 17.2, IC 4.11, EBGM 17.21), and intentional overdose (n=24, ROR 13.4, PRR 13.17, IC 3.72, EBGM 13.16). Several extrapyramidal symptom (EPS) manifestations, such as drooling and tardive dyskinesia, were identified and require close clinical monitoring. We also found a notable proportion of serotonin syndrome manifestations, such as tics, clonus, and mydriasis, with myoclonus considered one of the core symptoms of serotonin syndrome. This study also uncovered some ADEs not listed in the drug's prescribing information, such as Cushing's syndrome, papilledema, and increased intracranial pressure. While these adverse effects are rare, their signal strengths were high and warrant further attention.

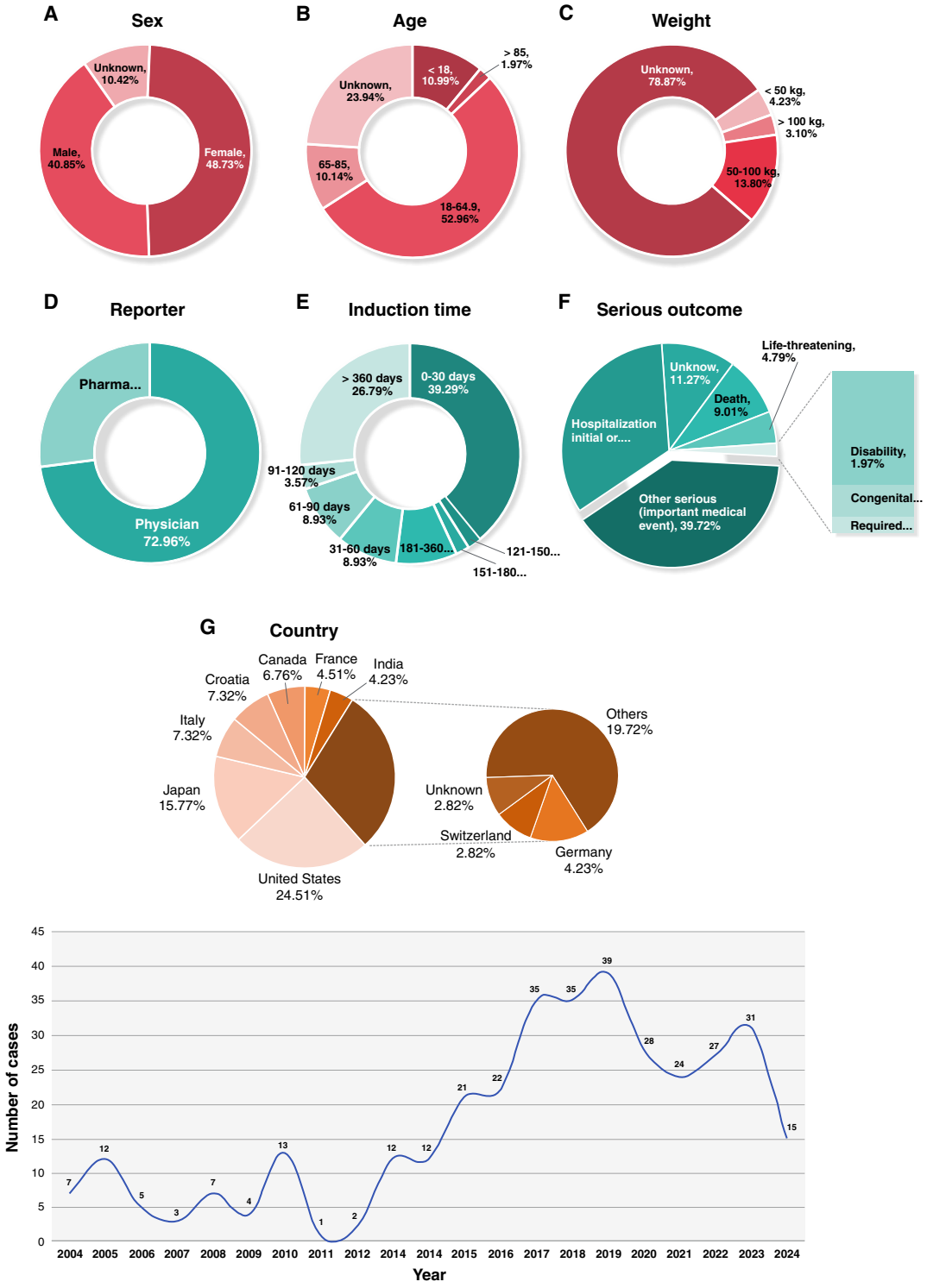

Figure 1 Basic information on adverse drug event reports for fluvoxamine by (A) patient sex distribution, (B) age distribution, (C) weight distribution, (D) reporter distribution, (E) induction time distribution, (F) serious outcome distribution, (G) reported countries distribution, as well as number of cases per year.

Discussion

Fluvoxamine is a selective serotonin reuptake inhibitor approved by the U.S. Food and Drug Administration for the treatment of depression and obsessive-compulsive disorder.[19] In addition to its classic 5-HT reuptake inhibition and 5-HT receptor desensitization effects,[20] it also alleviates depression-related insomnia by modulating

Table 2 Signal strength of ADE reports for fluvoxamine at the SOC level in the FAERS database

SOC	Case reports	ROR (95%CI)	PRR (95%CI)	χ^2	IC (IC025)	EBGM (EBGM05)
Psychiatric disorders	281	5.47 (4.80 to 6.25)	4.51 (4.41 to 4.62)	806.25	2.17 (1.98)	4.51 (4.04)
Nervous system disorders	214	2.20 (1.90 to 2.54)	2.00 (1.88 to 2.12)	116.65	1.00 (0.79)	2.00 (1.77)
General disorders and administration site conditions	166	0.81 (0.69 to 0.95)	0.83 (0.69 to 0.98)	6.44	-0.26 (-0.50)	0.83 (0.73)
Injury, poisoning, and procedural complications	122	1.10 (0.91 to 1.33)	1.09 (0.92 to 1.26)	1.05	0.13 (-0.14)	1.09 (0.93)
Investigations	100	1.09 (0.89 to 1.34)	1.08 (0.90 to 1.27)	0.70	0.12 (-0.18)	1.08 (0.91)
Gastrointestinal disorders	62	0.55 (0.42 to 0.70)	0.57 (0.32 to 0.81)	22.38	-0.82 (-1.19)	0.57 (0.46)
Cardiac disorders	51	1.08 (0.82 to 1.43)	1.08 (0.81 to 1.35)	0.29	0.11 (-0.30)	1.08 (0.85)
Metabolism and nutrition disorders	37	1.09 (0.79 to 1.52)	1.09 (0.77 to 1.41)	0.29	0.13 (-0.35)	1.09 (0.83)
Skin and subcutaneous tissue disorders	34	0.48 (0.34 to 0.67)	0.49 (0.16 to 0.82)	19.10	-1.03 (-1.52)	0.49 (0.37)
Eye disorders	34	1.35 (0.96 to 1.90)	1.34 (1.01 to 1.67)	3.03	0.43 (-0.07)	1.34 (1.01)
Vascular disorders	32	1.01 (0.71 to 1.44)	1.01 (0.67 to 1.35)	0.01	0.02 (-0.49)	1.01 (0.75)
Musculoskeletal and connective tissue disorders	29	0.45 (0.31 to 0.65)	0.46 (0.10 to 0.82)	19.29	-1.12 (-1.65)	0.46 (0.34)
Respiratory, thoracic, and mediastinal disorders	28	0.39 (0.27 to 0.57)	0.41 (0.04 to 0.77)	25.48	-1.30 (-1.84)	0.41 (0.30)
Hepatobiliary disorders	19	1.01 (0.64 to 1.58)	1.01 (0.56 to 1.45)	0.00	0.01 (-0.64)	1.01 (0.69)
Renal and urinary disorders	13	0.49 (0.28 to 0.85)	0.50 (-0.04 to 1.04)	6.78	-1.01 (-1.79)	0.50 (0.31)
Infections and infestations	12	0.15 (0.08 to 0.26)	0.16 (-0.41 to 0.72)	58.52	-2.69 (-3.49)	0.16 (0.10)
Product issues	11	0.66 (0.37 to 1.20)	0.66 (0.08 to 1.25)	1.90	-0.59 (-1.43)	0.66 (0.40)
Reproductive system and breast disorders	11	1.45 (0.80 to 2.62)	1.44 (0.85 to 2.03)	1.50	0.53 (-0.31)	1.44 (0.88)
Blood and lymphatic system disorders	10	0.26 (0.14 to 0.48)	0.26 (-0.35 to 0.88)	21.12	-1.92 (-2.79)	0.26 (0.16)
Neoplasms benign, malignant, and unspecified (including cysts and polyps)	8	0.18 (0.09 to 0.36)	0.18 (-0.51 to 0.87)	29.96	-2.44 (-3.41)	0.18 (0.10)
Surgical and medical procedures	7	0.44 (0.21 to 0.93)	0.44 (-0.30 to 1.18)	4.95	-1.17 (-2.20)	0.44 (0.24)
Endocrine disorders	6	1.34 (0.60 to 2.98)	1.33 (0.54 to 2.13)	0.50	0.42 (-0.68)	1.33 (0.68)
Ear and labyrinth disorders	6	1.25 (0.56 to 2.80)	1.25 (0.46 to 2.05)	0.31	0.33 (-0.77)	1.25 (0.64)
Immune system disorders	6	0.34 (0.15 to 0.76)	0.34 (-0.45 to 1.14)	7.63	-1.54 (-2.64)	0.34 (0.18)
Congenital, familial, and genetic disorders	4	0.91 (0.34 to 2.44)	0.91 (-0.06 to 1.89)	0.03	-0.13 (-1.42)	0.91 (0.40)
Pregnancy, puerperium, and perinatal conditions	3	0.46 (0.15 to 1.43)	0.46 (-0.67 to 1.59)	1.90	-1.12 (-2.56)	0.46 (0.18)

ADE = adverse drug events; EBGM = empirical Bayes geometric mean; FAERS = U.S. Food and Drug Administration Adverse Event Reporting System; IC = information component; PRR = proportional reporting ratio; ROR = reporting odds ratio; SOC = system organ classes.

glutamate release through activation of the σ1 receptor and reducing the degradation of melatonin.[21] Although fluvoxamine has shown impressive clinical efficacy in patients with depressive disorder,[22] current research has also raised concerns regarding its adverse effects.[23] With the increasing global depression prevalence, ADE monitoring for antidepressants in clinical practice is crucial. Routine pharmacovigilance studies include the entire population, which makes it difficult to avoid outcome bias due to reports from non-medical professionals.[17] Therefore, based on the perspectives of physicians and pharmacists, we utilized the FAERS database to analyze real-world ADEs of fluvoxamine, providing evidence for drug safety monitoring and clinical practice.

According to our results, significantly more reports were filed for female patients than male patients, which might be attributed to physiological and hormonal differences that affect drug metabolism and response in the body.[24] This difference may also be related to a greater help-seeking behavior among women.[25] The fact that the highest proportion of patients was in the 18-64 year age group could be due to a higher prevalence of antidepressant use in this age group.[26] Further research is needed to obtain accurate age group data. The highest proportion of reports came from the United States, which could be due to the fact that the FAERS database was established in the United States, the country's level of development, and its emphasis on ADE monitoring. Further investigation is needed to rule out cultural or regional biases. Although, most ADEs occurred within 30 days of beginning the medication, nearly a quarter occurred 1 year after beginning the medication, highlighting the importance of long-term clinical monitoring. Most of the severe adverse events involved hospitalization and other serious events. There was a fluctuating upward trend in annual reports of fluvoxamine-related ADEs, which might have been influenced by expanded reporting channels, improved monitoring systems, and increased awareness of the need to identify and report ADEs in the population.[27]

According to the proportional analysis, the most common signals for fluvoxamine at the system organ class level were psychiatric disorders, nervous system disorders, and general disorders and administration site

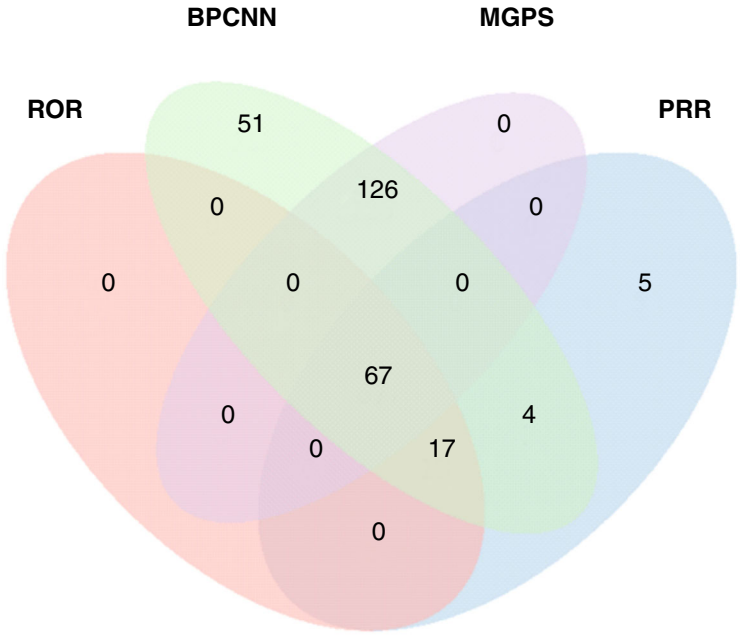

Figure 2 Venn diagram of four different methods: among the 484 signal combinations, the ROR method identified 84 related signals, the PRR method identified 93, the MGPS method identified 193, and the BCPNN method identified 265 valid signals. BCPNN = Bayesian confidence propagation neural network; MGPS = multi-item gamma Poisson shrinker; PRR = proportional reporting ratio; ROR = reporting odds ratio.

conditions, which might be attributed to the drug's mechanism of action. Notably, reproductive system and breast disorders also showed strong signals, which could be related to fluvoxamine's potential impact on hypothalamic function, interfering with normal hormonal fluctuations.[28] Respiratory, thoracic, and mediastinal disorders, vascular disorders, and ear and labyrinth disorders, which were not listed in the drug's package insert, exhibited correlations in our results. This may be linked to the progression of the patient's underlying disease, genetic factors, or individual differences,[29,30] which warrants further attention.

At the preferred terms level, significant ADEs primarily included disinhibition, antipsychotic drug level increased, and slow speech. The most frequently reported ADEs were drug interactions, suicide attempts, and intentional overdoses. The drug interaction results indicate that fluvoxamine has a high potential for interaction with other medications, which resulted in significant ADEs, such as increased antipsychotic drug levels. EPS, like slow speech, drooling, tardive dyskinesia, and salivary hypersecretion, were also observed. We also found several manifestations of serotonin syndrome, such as tics, clonus, myoclonus, and mydriasis. Importantly, serotonin syndrome is difficult to distinguish from neuroleptic malignant syndrome (NMS), as both are life-threatening emergencies with different management approaches. Clinicians should closely monitor for core symptom differences. In addition to common symptoms listed in the package insert, such as galactorrhea, orthostatic hypotension, and suicide attempt, rare and unlisted ADEs like Cushing's syndrome, papilledema, increased intracranial pressure, and acidosis also had strong signals and should be closely monitored in clinical practice.

Disinhibition, a state in which an individual's internal behavioral restraints are lifted, primarily manifests as a reduced ability to control impulses. This may involve neural circuit changes, particularly in the prefrontal cortex, basal ganglia, and thalamus.[31] In our study, disinhibition had the highest signal strength. Although the precise mechanism is not yet clear, a potential mechanism involves alterations in serotonin (5-HT) levels mediated by fluvoxamine. Changes in 5-HT levels can lead to fluctuations in neurotransmitter homeostasis, subsequently affecting an individual's responsiveness to external stimuli.[32] Further research is needed to clarify this mechanism.

Antipsychotic drug levels increased and drug interaction had high signal strength and was the most frequently reported ADE, consistent with the drug interactions indicated in fluvoxamine's prescribing information. Fluvoxamine is primarily metabolized by CYP2D6,[33] with additional minor involvement of CYP1A2.[34] Variability in the CYP2D6 genotype (e.g., poor metabolizers) can lead to elevated fluvoxamine plasma concentrations and increased risk of adverse reactions.[35] Fluvoxamine is also a potent inhibitor of CYP1A2,[34] CYP2C19,[36] and to a lesser extent CYP3A4[37] and CYP2D6,[33] which can substantially affect the pharmacokinetics of co-administered drugs such as clozapine, alprazolam, propranolol,

Table 3 The top 30 signal strengths of ADEs reported for fluvoxamine at the PT level

SOC	PTs	Case reports	ROR (95%CI)	PRR (95%CI)	χ^2	IC (IC025)	EBGM (EBGM05)
Psychiatric disorders	Disinhibition	5	112.57 (46.57-272.09)	112.14 (111.26-113.02)	545.30	6.79 (5.61)	111.04 (53.06)
Investigations	Antipsychotic drug level increased	7	60.06 (28.52-126.47)	59.74 (59.00-60.48)	402.18	5.89 (4.87)	59.43 (31.87)
Nervous system disorders	Slow speech	3	56.10 (18.02-174.67)	55.98 (54.84-57.11)	161.18	5.80 (4.35)	55.70 (21.54)
Psychiatric disorders	Enuresis	4	50.21 (18.78-134.28)	50.06 (49.08-51.04)	191.48	5.64 (4.34)	49.84 (21.89)
Psychiatric disorders	Tic	5	46.02 (19.09-110.95)	45.85 (44.97-46.72)	218.46	5.51 (4.33)	45.66 (21.87)
Nervous system disorders	Psychomotor skills impaired	3	35.98 (11.57-111.92)	35.90 (34.77-37.04)	101.48	5.16 (3.71)	35.79 (13.85)
Reproductive system and breast disorders	Galactorrhea	4	34.96 (13.08-93.42)	34.85 (33.87-35.83)	131.13	5.12 (3.82)	34.75 (15.27)
Nervous system disorders	Clonus	3	33.48 (10.77-104.13)	33.41 (32.28-34.54)	94.04	5.06 (3.61)	33.31 (12.89)
Endocrine disorders	Cushing's syndrome	3	25.96 (8.35-80.69)	25.90 (24.77-27.03)	71.65	4.69 (3.24)	25.84 (10.00)
Psychiatric disorders	Obsessive-compulsive disorder	3	23.25 (7.48-72.28)	23.20 (22.07-24.33)	63.61	4.53 (3.09)	23.16 (8.96)
Investigations	Drug level increased	11	22.83 (12.60-41.34)	22.64 (22.05-23.23)	227.17	4.50 (3.66)	22.60 (13.75)
Nervous system disorders	Drooling	3	22.42 (7.21-69.68)	22.37 (21.24-23.50)	61.12	4.48 (3.03)	22.33 (8.64)
Vascular disorders	Orthostatic hypotension	12	19.98 (11.31-35.28)	19.80 (19.24-20.36)	213.94	4.31 (3.50)	19.77 (12.28)
Eye disorders	Papilledema	3	19.03 (6.12-59.13)	18.99 (17.85-20.12)	51.03	4.24 (2.80)	18.95 (7.34)
Nervous system disorders	Serotonin syndrome	11	18.85 (10.41-34.15)	18.70 (18.12-19.29)	184.11	4.22 (3.39)	18.67 (11.36)
Nervous system disorders	Tardive dyskinesia	5	17.86 (7.42-43.02)	17.80 (16.92-18.68)	79.17	4.15 (2.97)	17.77 (8.52)
Psychiatric disorders	Suicide attempt	33	17.65 (12.49-24.95)	17.20 (16.90-17.57)	504.57	4.11 (3.60)	17.21 (12.88)
Psychiatric disorders	Intentional self-injury	9	17.57 (9.12-33.86)	17.40 (16.80-18.11)	139.45	4.12 (3.21)	17.43 (10.07)
Nervous system disorders	Myoclonus	7	17.54 (8.34-36.90)	17.46 (16.72-18.19)	108.45	4.12 (3.10)	17.43 (9.36)
Psychiatric disorders	Apathy	4	17.30 (6.48-46.20)	17.25 (16.27-18.23)	61.16	4.11 (2.81)	17.23 (7.57)
Nervous system disorders	Sedation	12	16.83 (9.53-29.73)	16.69 (16.12-17.25)	176.78	4.06 (3.25)	16.66 (10.35)
Nervous system disorders	Intracranial pressure increased	3	16.57 (5.33-51.48)	16.53 (15.40-17.66)	43.72	4.05 (2.60)	16.51 (6.39)
Nervous system disorders	Extrapyramidal disorder	7	16.47 (7.83-34.64)	16.39 (15.65-17.13)	101.05	4.03 (3.01)	16.37 (8.79)
Injury, poisoning, and procedural complications	Labelled drug-drug interaction medication error	5	16.32 (6.78-39.30)	16.26 (15.39-17.14)	71.53	4.02 (2.84)	16.24 (7.78)
Nervous system disorders	Neuroleptic malignant syndrome	6	13.62 (6.10-30.39)	13.56 (12.76-14.36)	69.76	3.76 (2.67)	13.55 (6.92)
Injury, poisoning, and procedural complications	Intentional overdose	24	13.40 (8.95-20.08)	13.17 (12.78-13.57)	270.08	3.72 (3.14)	13.16 (9.39)
Eye disorders	Mydriasis	4	12.91 (4.83-34.46)	12.87 (11.89-13.85)	43.76	3.68 (2.39)	12.86 (5.65)
Gastrointestinal disorders	Salivary hypersecretion	3	12.25 (3.94-38.04)	12.22 (11.09-13.35)	30.88	3.61 (2.16)	12.21 (4.73)
General disorders and administration site conditions	Drug interaction	51	11.24 (8.49-14.88)	10.84 (10.57-11.11)	456.81	3.44 (3.03)	10.83 (8.57)
Metabolism and nutrition disorders	Acidosis	3	10.75 (3.46-33.4)	10.73 (9.60-11.86)	26.45	3.42 (1.98)7	(4.15)

ADE = adverse drug events; EBGM = empirical Bayes geometric mean; IC = information component; PRR = proportional reporting ratio; PT = preferred term; ROR = reporting odds ratio; SOC = system organ classes.

and theophylline.[38] Additionally, fluvoxamine can interact with monoamine oxidase inhibitors[39] and drugs like terfenadine, astemizole, and carbamazepine.[40] Clinicians must be vigilant regarding these interactions. There was a high frequency of reported suicide attempts, which aligns with the risk warnings in the prescribing information, ie, that fluvoxamine may increase the risk of suicide, particularly during the early stages of treatment (especially in the first month).[41] It is important to note that the risk of suicide-related events may not improve after the first few weeks of treatment or beyond.[42] Therefore, both health care providers and family members should closely monitor changes in the patient's mood and behavior, especially during the early phases of treatment or following dosage adjustments.

EPS and serotonin syndrome showed strong signals in our study. Slow speech may be related to EPS,[43] with other ADEs, such as drooling and tardive dyskinesia, also indicating an association between fluvoxamine and EPS. This may be partly related to pharmacokinetic interactions. In clinical practice, fluvoxamine is often used in combination with atypical antipsychotics as an augmentation therapy for depression. Fluvoxamine's inhibition of liver enzymes[33,34] can increase the concentration of certain antipsychotics like clozapine and olanzapine, thereby increasing the risk of EPS.[44] This interaction also increases the risk of NMS. NMS is a life-threatening complication characterized by altered mental status, muscle rigidity, hyperthermia, and autonomic dysfunction, typically occurring after taking antipsychotic medications.[45] Reports of fluvoxamine interacting with quetiapine to trigger NMS have been documented,[46] which is likely related to imbalance between the dopamine and serotonin systems.[47] Our study also confirmed this ADE. Serotonin syndrome is a life-threatening clinical condition caused by excessive 5-HT activity, presenting with autonomic dysfunction, neuromuscular hyperactivity, and altered mental status.[48] Our study identified core symptoms of serotonin syndrome, including tics, clonus, myoclonus, and mydriasis.[49] Although both serotonin syndrome and NMS are life-threatening conditions, their management strategies differ. Moreover, their symptoms overlap to some extent, with the key distinction being the presence of myoclonus.[50] This underscores the need for close clinical attention to differentiate between these two potentially fatal syndromes and apply appropriate treatment strategies. Hunter's criteria, a widely used diagnostic tool for serotonin syndrome, emphasizes specific clinical features – including inducible clonus and hyperreflexia – to aid in diagnosis.[51]

Importantly, our study also identified some rare safety concerns at the preferred terms level, such as Cushing's syndrome, increased intracranial pressure, and papilledema. Cushing's syndrome is a group of serious systemic abnormalities caused by elevated cortisol levels, which lead to various clinical manifestations and complications, significantly increasing cardiovascular risk.[52] While this signal may be related to fluvoxamine's potential effect on adrenocorticotropic hormone and cortisol levels,[53] it should be interpreted with caution. Further investigation is needed to clarify this potential association. Increased intracranial pressure refers to elevated pressure inside the skull, which can lead to acute or chronic physiological disturbances and pathological changes. If untreated, it can rapidly escalate into a clinical catastrophe.[54] We observed a signal between fluvoxamine and this serious event; however, given the spontaneous nature of the data, this finding should be considered exploratory rather than conclusive. Further research is required to clarify the underlying mechanisms. Papilledema, often associated with increased intracranial pressure, is the swelling of the optic disc due to elevated pressure within the skull. When intracranial pressure exceeds intraocular pressure, the optic disc swells, resulting in optic disc edema.[55] Although a previous clinical study reported rare cases of increased intracranial pressure and papilledema potentially associated with fluvoxamine,[56] the underlying mechanisms remain unclear. One proposed explanation involves fluvoxamine's effect on cerebral blood flow, which could contribute to hypoxia and subsequent brain edema.[57,58] These rare ADEs indicate the need for vigilant monitoring, particularly in high-risk patients, as well as for further research to elucidate the mechanisms behind these serious outcomes.

Although this study analyzed real-world ADE data for fluvoxamine, identified multiple signals of concern, and explored its potential mechanisms, providing valuable insights for clinical application, it nevertheless has some limitations. First, as a spontaneous reporting system, the FAERS database is a subject to underreporting, reporting bias, and variable data quality. Moreover, causality between fluvoxamine and the reported ADEs cannot be established. Second, subgroup analyses by age, sex, or polypharmacy status were not performed, which could reduce the generalizability of the findings across diverse populations. Third, due to the lack of detailed clinical information in the data, we were unable to further analyze factors, such as patient history, comorbidities, and drug interactions, which could affect the accuracy of adverse reaction assessments, especially for fluvoxamine, a drug with numerous interactions. Future research should integrate multi-center prospective studies and include subgroup analyses to further explore fluvoxamine's safety.

In conclusion, this study provided a comprehensive investigation of real-world ADEs associated with fluvoxamine, offering new insights into the drug's safety profile. Disinhibition and drug interactions are ADEs with significant signals that require special clinical attention. EPS, such as slow speech, drooling, tardive dyskinesia, and serotonin syndrome (including tics, clonus, myoclonus, and mydriasis), were prevalent in our study and warrant caution in clinical practice. Additionally, NMS was identified, which requires heightened clinical awareness. Appropriate risk management is needed for symptoms of self-harm and suicidal behavior. Rare and unlisted ADEs, such as Cushing's syndrome, papilledema, and increased intracranial pressure, were also identified and require further exploration to clarify the underlying mechanisms. Despite certain limitations, this study provides strong evidence in support of clinical adverse reaction warnings for fluvoxamine and serves as a reference for future drug safety monitoring and the development of personalized

treatment strategies. Future studies should incorporate prospective designs, detailed clinical data, and pharmacogenomics analysis to better characterize risk factors and validate these findings in diverse patient populations.

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Disclosure

The authors report no conflicts of interest.

Data availability statement

The original contributions presented in this study are included in the article material; further inquiries can be directed to the corresponding authors.

Author contributions

WX: Conceptualization, Investigation, Writing – original draft.
NL: Conceptualization, Methodology.
JG: Data curation, Formal analysis.
FW: Funding acquisition.
LL: Resources, Software.
JW: Investigation, Writing – review & editing.
HW: Writing – review & editing.
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