Brazilian Journal of Psychiatry
bjp
Revista Brasileira de Psiquiatria

Braz J Psychiatry. 2025;47:e20243880
doi:10.47626/1516-4446-2024-3880
Brazilian Psychiatric Association

ORIGINAL ARTICLE

Signal mining and risk analysis of olanzapine adverse events in the FAERS database

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Objective: This study assessed the safety profile of olanzapine by analyzing adverse events reported in the U.S. Food and Drug Administration's Adverse Event Reporting System database, particularly focusing on newly identified risks.
Methods: The study involved olanzapine-related adverse events that occurred between January 1, 2004, and June 30, 2023. Four signal mining methods were used for a comprehensive analysis of the frequency and strength of adverse events, including the reporting odds ratio, proportional reporting ratio, Bayesian confidence propagation neural network, and empirical Bayesian geometric mean.
Results: A total of 43,664 reports with olanzapine as the primary suspect drug were collected, and 776 preferred terms signals involving 27 system organ classes were identified. The main affected groups were females and individuals between 18 and 45 years of age. Psychiatric disorders and nervous system disorders were the most common adverse reactions. The analysis also revealed some adverse reactions not recorded in the manual, including cardiovascular risk, such as pancreatitis, increased chylomicron, hyperchylomicronemia, and myocardial reperfusion injury, as well as rare but serious adverse reactions like neuroleptic malignant syndrome and anosognosia.
Conclusions: This study identified new cardiovascular risks associated with olanzapine, including pancreatitis and myocardial reperfusion injury, which require further investigation.

Keywords: Olanzapine; adverse reactions; FAERS database; drug safety; psychiatric disorders

Introduction

Olanzapine, a thienobenzodiazepine derivative originally developed from the molecular structure of clozapine, was introduced to the market in 1996. It is an atypical antipsychotic medication initially used to treat schizophrenia. However, over time, the clinical applications of olanzapine have expanded to include adjunctive treatment of a range of mental and neurological disorders such as bipolar disorder, Alzheimer's disease with associated psychiatric symptoms, behavioral disorders in children and adolescents, obsessive-compulsive disorder, and somatoform disorders.[1-3] While the widespread use of this drug has provided more treatment options for patients, it has also raised concerns about its safety and adverse reactions.

In practical application, many patients undergoing olanzapine therapy may experience a series of adverse reactions, including dry mouth, dizziness, increased appetite, etc. Therefore, before deciding to use olanzapine, doctors should conduct an accurate assessment of the patient and identify any contraindications to avoid adverse reactions that could affect treatment outcomes and prognosis. Common adverse reactions in non-schizophrenic patients treated with olanzapine include weight gain, somnolence, increased appetite, nausea, dry mouth, dizziness, and constipation. Studies have shown that the incidence of adverse reactions in patients taking olanzapine is high and, compared to other treatments, olanzapine may cause more discomfort.[4,5] The efficacy and common adverse reactions of olanzapine have been extensively studied in the literature, but there is a lack of in-depth analysis regarding its potential rare and serious adverse reactions. Many studies are limited to conventional clinical trials, which do not capture a broad range of real-world patient populations. Additionally, some adverse reactions may not have been sufficiently identified due to limited sample sizes. This highlights the need for further research involving larger, more diverse populations and real-world data to better detect and understand these rare but potentially serious adverse reactions. Therefore, it is crucial to conduct a comprehensive assessment of the potential risks of olanzapine to ensure that patients receiving this treatment achieve the maximum benefit and minimize the occurrence of adverse events (AEs).

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Submitted Aug 11 2024, accepted Oct 25 2024.

How to cite this article: Dong A, Shi L, Du Z, Zhou Q, Jiang Y, Zhu H, et al. Signal mining and risk analysis of olanzapine adverse events in the FAERS database. Braz J Psychiatry. 2025;47:e20243880. http://doi.org/10.47626/1516-4446-2024-3880

This study systematically assessed the potential risks of olanzapine through an AE signal mining analysis based on the U.S. Food and Drug Administration's (FDA) Adverse Event Reporting System (FAERS) database. This information will help healthcare professionals provide more comprehensive information about the safety of olanzapine. These insights will contribute to clinical decision-making and improvement, ensuring optimal treatment outcomes for patients receiving olanzapine while reducing the occurrence of AEs. Additionally, this study will provide a valuable reference for further drug safety assessments in the future.

Methods

Data source

The data used in this study come from the FAERS database, which is updated quarterly. The FAERS database gathers a large number of post-marketing AE reports, including details such as the number of reports, patient age, sex, and adverse reaction types.

Data processing

The database was searched using both the generic and brand names of the drug. The search terms were "OLANZAPINE," "OLANZAPINE PAMOATE," "ARKO LAMYL," "MIDAX," "OLANDIX," "OLANZAPIN," "REXA PIN," "ZYPADHERA," "ZYPINE," and "ZYPREXA." Data from the first quarter of 2004 to the second quarter of 2023 were extracted, selecting all reports in which olanzapine was the primary suspected drug. MySQL 8.0 was used for data processing, following FDA recommendations: when the CASEID is the same, select the latest FDA_DT; when both the CASEID and FDA_DT are the same, choose the higher PRIMARYID; finally, reports in the DELETE table were removed.

The FAERS database uses the Medical Dictionary for Regulatory Activities, developed by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use, for coding.[6] Therefore, this study employed Medical Dictionary for Regulatory Activities' system organ class (SOC) and preferred terms from the Medical Dictionary for Regulatory Activities adverse drug reaction terminology set (version 25.1) for international standardization of AE description.

Data analysis

Four different statistical methods were used to explore potential adverse drug reaction signals, including the reporting odds ratio, proportional reporting ratio, Bayesian confidence propagation neural network, and empirical Bayesian geometric mean.[7-10] The reporting odds ratio calculates the difference in reporting rates of a specific AE between the target drug and other drugs. Its strengths lie in its simplicity, fast computation, and suitability for large-scale databases. However, its limitations include vulnerability to small sample sizes and the inability to account for covariates, which may lead to false-positive signals. The proportional reporting ratio measures the relative risk of an AE by comparing the reporting rate of the target drug with that of all other drugs. The proportional reporting ratio can quickly identify high-risk adverse reactions, but it relies on threshold settings and, like the reporting odds ratio, does not fully account for confounding factors. The Bayesian confidence propagation neural network is based on a Bayesian inference framework, using prior and posterior distributions to estimate the association between a drug and an AE. Compared to traditional methods, it handles uncertainty better, especially in smaller sample sizes. However, its complex algorithms and high computational costs may limit its real-time application in very large databases. The empirical Bayesian geometric mean adjusts frequency data to provide more accurate estimates of drug-AE associations. Its strength is in controlling errors and offering more reliable confidence intervals, making it suitable for complex datasets. However, its high computational complexity and need for significant computing resources can be a limitation. These methods are based on a 2×2 contingency table (Table 1), comparing the proportion of target events for the target drug with the proportion of target events for all other drugs to mine potential AE signals. The selected signals must meet the criteria of all four methods, indicating a potential association between the drug and the event (Table 2).

Results

Between January 1, 2004, and June 30, 2023, a total of 19,932,732 AE reports were collected. In 43,664 of these, olanzapine was identified as the primary suspected drug. Using the reporting odds ratio, proportional reporting ratio, Bayesian confidence propagation neural network, and empirical Bayesian geometric mean methods, 776 preferred term signals involving 27 SOCs were obtained.

Basic characteristics of adverse events reports

In these reports, there were slightly fewer females than males (42.46% and 47.95%, respectively). The reports covered patients of all age groups, but the most common was between 18 and 45 years old (30.92%). The number

Table 1 Four grid table

	Target AEs	Non-target AEs	Total
Olanzapine	a	b	a + b
Non-olanzapine	c	d	c + d
Total	a + c	b + d	n = a + b + c + d

AEs = adverse events.

Table 2 Reporting odds ratio, proportional reporting ratio, Bayesian confidence propagation neural network, and empirical Bayesian geometric mean methods, formulas, and thresholds

Method	Formula	Threshold
ROR	$\mathrm{ROR} = \frac{(a/c)}{(b/d)} = \frac{ad}{bc}$	a $\geqslant$ 3 and 95%CI (lower limit) $>$ 1
	$\mathrm{SE}(\ln\mathrm{ROR}) = \sqrt{\left(\frac{1}{a} + \frac{1}{b} + \frac{1}{c} + \frac{1}{d}\right)}$	
	$95\%\,\mathrm{CI} = e^{\ln(\mathrm{ROR}) \pm 1.96\sqrt{\left(\frac{1}{a} + \frac{1}{b} + \frac{1}{c} + \frac{1}{d}\right)}}$	
PRR	$\mathrm{PRR} = \frac{a/(a+b)}{c/(c+d)}$	a $\geqslant$ 3 and 95%CI (lower limit) $>$ 1
	$SE(\ln\mathrm{PRR}) = \sqrt{\frac{1}{a} - \frac{1}{a+b} + \frac{1}{c} - \frac{1}{c+d}}$	IC025 $>$ 0
	$95\%\,\mathrm{CI} = e^{\ln(\mathrm{PRR}) \pm 1.96\sqrt{\frac{1}{a} - \frac{1}{a+b} + \frac{1}{c} - \frac{1}{c+d}}}$	
BCPNN	$\mathrm{IC} = log_2 \frac{p(xy)}{p(x)p(y)} = log_2 \frac{a(a+b+c+d)}{(a+b)(a+c)}$	
	$\mathrm{E(IC)} = log_2 \frac{(a+\gamma 11)(a+b+c+d+\alpha)(a+b+c+d+\beta)}{(a+b+c+d+\gamma)(a+b+\alpha 1)(a+c+\beta 1)}$	
	$\mathrm{V(IC)} = \frac{1}{(ln2)^2}\left\{\left[\frac{(a+b+c+d)-a+\gamma-\gamma 11}{(a+\gamma 11)(1+a+b+c+d+\gamma)}\right] + \left[\frac{(a+b+c+d)-(a+b)+\alpha-\alpha 1}{(a+b+\alpha 1)(1+a+b+c+d+\alpha)}\right] + \left[\frac{(a+b+c+d)-(a+c)+\beta-\beta 1}{(a+c+\beta 1)(1+a+b+c+d+\beta)}\right]\right\}$	
	$\gamma = \gamma 11 \frac{(a+b+c+d+\alpha)(a+b+c+d+\beta)}{(a+b+\alpha 1)(a+c+\beta 1)}$	
EBGM	$IC - 2SD = E(IC) - 2\sqrt{V(IC)}$	EBGM05 $>$ 2
	$\mathrm{EBGM} = \frac{a(a+b+c+d)}{(a+c)(a+b)}$	
	$95\%\,\mathrm{CI} = e^{\ln(\mathrm{EBGM}) \pm 1.96\sqrt{\left(\frac{1}{a} + \frac{1}{b} + \frac{1}{c} + \frac{1}{d}\right)}}$	

BCPNN = Bayesian confidence propagation neural network; EBGM = empirical Bayesian geometric mean; IC = information component; PRR = proportional reporting ratio; ROR = reporting odds ratio.

of reports varied significantly between 2004 and 2023, with the highest number occurring in 2015, (14.47%). Consumers were the primary reporters, accounting for 37.23% of the total reports. Most reports originated from the United States (35.33%), followed by the United Kingdom (9.72%) and France (7.33%). The most common AE outcomes were hospitalization – initial or prolonged (40.96%) and death (11.12%) (Table 3).

Signal analysis

Table 4 ranks the SOCs based on the number of reports. Psychiatric disorders, nervous system disorders, investigations, general disorders and administration site conditions, and injury, poisoning, and procedural complications were frequent, consistent with the information in the product's manual.

The study results ranked preferred terms based on the number of reports and signal strength, presenting the top 30 in Tables 5 and 6. Table 5 includes common adverse reactions of psychiatric drugs that match those recorded in the olanzapine manual. Additionally, there were high frequencies of some preferred terms not mentioned in the manual, such as pancreatitis, neuroleptic malignant syndrome, suicide attempt, and completed suicide. Notably, neuroleptic malignant syndrome had a strong signal intensity, warranting further investigation and monitoring. As shown in Table 6, increased chylomicron and hyperchylomicronemia ranked in the top three for signal strength and are new potential adverse reactions. Furthermore, there were strong signal intensities for several AEs not mentioned in the manual, like psychogenic visual disorder, intravascular papillary endothelial hyperplasia, increased blood thrombin, myocardial reperfusion injury, lipomeningocele, decreased urine bilirubin, and anosognosia, indicating they are safety signals that warrant attention and further study.

Discussion

Olanzapine's antipsychotic efficacy mainly stems from its antagonistic activity on dopamine receptors. It also demonstrates high affinity for 5-hydroxytryptamine, muscarinic, and α1 adrenergic receptors.[11] This determines olanzapine's therapeutic effectiveness and tolerance. Olanzapine effectively reduces psychotic symptoms in schizophrenia patients and causes fewer extrapyramidal and tardive dyskinesia reactions. However, its action on

Table 3 Basic information on adverse events related to olanzapine

Factors	Events, n (%)
Sex	
Female	18,541 (42.46)
Male	20,939 (47.95)
Unknown	4,184 (9.58)
Age (years)	
< 18	1,861 (4.26)
18-45	13,500 (30.92)
45-65	9,773 (22.38)
65-75	2,843 (6.51)
⩾ 75	2,514 (5.76)
Unknown	13,173 (30.17)
Reporter	
Consumer	16,256 (37.23)
Pharmacist	5,703 (13.06)
Physician	13,229 (30.30)
Other health professionals	5,112 (11.71)
Unknown	1,130 (2.59)
Lawyer	2,234 (5.12)
Reported countries	
United States	15,426 (35.33)
United Kingdom	4,242 (9.72)
France	3,202 (7.33)
Italy	2,448 (5.61)
Germany	2,114 (4.84)
Report year	
2004	1,145 (2.62)
2005	2,092 (4.79)
2006	2,048 (4.69)
2007	2,910 (6.66)
2008	857 (1.96)
2009	1,392 (3.19)
2010	1,188 (2.72)
2011	1672 (3.83)
2012	1,347 (3.08)
2013	1,304 (2.99)
2014	1,642 (3.76)
2015	6,318 (14.47)
2016	1,828 (4.19)
2017	2,008 (4.60)
2018	2,965 (6.79)
2019	3,222 (7.38)
2020	2,664 (6.10)
2021	2,541 (5.82)
2022	3,086 (7.07)
2023	1,435 (3.29)
Serious outcomes	
Death	4,854 (11.12)
Disability	1,346 (3.08)
Hospitalization – Initial or prolonged	17,885 (40.96)
Life-threatening	3,266 (7.48)
Adverse event occurrence time – Medication date (days)	
0-30	6,762 (15.49)
31-60	737 (1.69)
61-90	426 (0.98)
91-120	349 (0.80)
121-150	229 (0.52)
151-180	214 (0.49)
181-360	945 (2.16)
> 360	3,453 (7.91)

muscarinic receptors and α1 adrenergic receptors can cause adverse reactions such as drowsiness, hypotension, and weight gain.[12]

In exploring the safety and effectiveness of olanzapine, this study provides new insights into the performance of this widely-used drug in real-world medical settings, based on an in-depth analysis of the FAERS database. Building on this, our discussion focuses on analyzing and interpreting adverse reaction signals related to olanzapine, especially potential risks not detailed in the medication manual. Through detailed exploration of these signals, this study aims to provide more precise guidance for doctors regarding olanzapine treatment, striving for the best balance between patient medication safety and effectiveness.

Report dynamics and patient characteristic analysis

In analyzing AE reports for olanzapine, this study found slightly fewer reports for females than males, which may reflect sex differences regarding sensitivity to drug reactions or disease. The largest concentration of reports was in the 18 to 45 age group, which aligns with the typical age range for the onset of schizophrenia and other mental disorders. Notably, the number of reports fluctuated between 2004 and 2023, particularly in 2015, which may have been related to changes in drug usage rates, increased public awareness, or reporting system improvements. The fact that consumers were the primary reporters highlights the crucial role of the public in drug safety monitoring. The reports were mainly from the United States, the United Kingdom, and France, which reflects specific drug use and regulatory conditions in these countries. Clinical outcomes mainly involved hospitalization and death, indicating the risks associated with olanzapine are serious. These observations provide key information for safety monitoring and clinical application of olanzapine.

Known adverse reactions

This study indicates that the primary safety warning signals for olanzapine are concentrated in AEs related to psychiatric disorders, which are closely linked to its extensive pharmacological activity across multiple receptor systems. Olanzapine's blockade of dopamine D2 receptors in the central nervous system's nigrostriatal and tuberoinfundibular pathways can cause side effects such as extrapyramidal reactions, increased prolactin levels, and impaired thermoregulation. Its antagonistic effects on 5-HT2A receptors, muscarinic M1 receptors, and histamine H1 receptors are also associated with AEs like increased weight, diabetes mellitus, somnolence, overdose, confusional state, agitation, sedation, and type 2 diabetes mellitus.[13,14] These findings highlight the balance between the therapeutic benefits of olanzapine and its potential for a wide range of adverse reactions, emphasizing the need for comprehensive risk assessment and patient monitoring during use.

Table 4 The signal strength of adverse events of olanzapine at the SOC level

SOC	SOC code	Case reports	ROR (95% CI)	PRR (95%CI)	$\chi 2$	IC (IC025)	EBGM (EBGM05)
Psychiatric disorders	10037175	27,274	3.03 (2.99-3.07)	2.72 (2.69-2.75)	31111.70	1.43 (1.41)	2.70 (2.67)
Nervous system disorders	10029205	27,078	1.92 (1.89-1.94)	1.78 (1.76-1.80)	9980.41	0.82 (0.81)	1.77 (1.75)
Investigations	10022891	20,246	1.96 (1.93-1.98)	1.85 (1.82-1.87)	8314.01	0.88 (0.86)	1.84 (1.81)
General disorders and administration site conditions	10018065	18,523	0.55 (0.55-0.56)	0.60 (0.59-0.61)	5945.92	-0.73 (-0.76)	0.60 (0.59)
Injury, poisoning, and procedural complications	10022117	15,264	0.86 (0.84-0.87)	0.87 (0.86-0.88)	324.50	-0.20 (-0.22)	0.87 (0.86)
Metabolism and nutrition disorders	10027433	13,842	3.83 (3.76-3.90)	3.61 (3.55-3.67)	26322.23	1.84 (1.81)	3.57 (3.51)
Gastrointestinal disorders	10017947	8,756	0.56 (0.54-0.57)	0.58 (0.57-0.59)	2959.54	-0.79 (-0.82)	0.58 (0.57)
Cardiac disorders	10007541	6,628	1.40 (1.36-1.43)	1.38 (1.35-1.41)	710.80	0.46 (0.43)	1.38 (1.35)
Respiratory, thoracic, and mediastinal disorders	10038738	5,460	0.64 (0.62-0.66)	0.65 (0.64-0.67)	1055.09	-0.61 (-0.65)	0.65 (0.64)
Vascular disorders	10047065	4,382	1.14 (1.11-1.18)	1.14 (1.11-1.17)	75.62	0.19 (0.14)	1.14 (1.10)
Infections and infestations	10021881	4,041	0.43 (0.41-0.44)	0.44 (0.43-0.45)	3037.80	-1.18 (-1.23)	0.44 (0.43)
Musculoskeletal and connective tissue disorders	10028395	3,954	0.41 (0.40-0.43)	0.43 (0.41-0.44)	3201.21	-1.22 (-1.27)	0.43 (0.41)
Blood and lymphatic system disorders	10005329	3,450	1.17 (1.13-1.21)	1.16 (1.13-1.20)	80.30	0.22 (0.17)	1.16 (1.12)
Renal and urinary disorders	10038359	2,910	0.84 (0.81-0.87)	0.84 (0.81-0.87)	87.79	-0.25 (-0.30)	0.84 (0.81)
Skin and subcutaneous tissue disorders	10040785	2,694	0.27 (0.26-0.28)	0.28 (0.27-0.29)	5191.74	-1.82 (-1.88)	0.28 (0.27)
Eye disorders	10015919	2,683	0.76 (0.74-0.79)	0.77 (0.74-0.80)	192.32	-0.38 (-0.44)	0.77 (0.74)
Hepatobiliary disorders	10019805	1,951	1.21 (1.15-1.26)	1.20 (1.15-1.26)	67.24	0.27 (0.20)	1.20 (1.15)
Reproductive system and breast disorders	10038604	1,668	1.02 (0.97-1.07)	1.02 (0.97-1.07)	0.62	0.03 (-0.04)	1.02 (0.97)
Surgical and medical procedures	10042613	1,140	0.49 (0.46-0.52)	0.50 (0.47-0.52)	593.02	-1.01 (-1.10)	0.50 (0.47)
Congenital, familial, and genetic disorders	10010331	787	1.43 (1.34-1.54)	1.43 (1.33-1.53)	101.85	0.51 (0.41)	1.43 (1.33)

Continued on next page

Table 4 (*Continued*)

SOC	SOC code	Case reports	ROR (95% CI)	PRR (95%CI)	$\chi 2$	IC (IC025)	EBGM (EBGM05)
Social circumstances	10041244	774	0.94 (0.88-1.01)	0.94 (0.88-1.01)	2.57	-0.08 (-0.19)	0.94 (0.88)
Endocrine disorders	10014698	768	1.76 (1.64-1.89)	1.75 (1.63-1.88)	247.89	0.81 (0.70)	1.75 (1.63)
Pregnancy, puerperium, and perinatal conditions	10036585	759	0.97 (0.90-1.04)	0.97 (0.90-1.04)	0.78	-0.05 (-0.15)	0.97 (0.90)
Neoplasms benign, malignant, and unspecified (including cysts and polyps)	10029104	758	0.15 (0.14-0.16)	0.16 (0.15-0.17)	3538.81	-2.67 (-2.77)	0.16 (0.15)
Product issues	10077536	461	0.17 (0.15-0.18)	0.17 (0.15-0.18)	1929.68	-2.57 (-2.70)	0.17 (0.15)
Ear and labyrinth disorders	10013993	378	0.49 (0.44-0.54)	0.49 (0.44-0.54)	203.43	-1.03 (-1.18)	0.49 (0.44)
Immune system disorders	10021428	375	0.19 (0.17-0.21)	0.19 (0.18-0.21)	1271.10	-2.36 (-2.51)	0.19 (0.18)

EBGM = empirical Bayesian geometric mean; IC = information component; PRR = proportional reporting ratio; ROR = reporting odds ratio; SOC = system organ class.

Potential adverse reactions and possible mechanisms

Particularly noteworthy in this analysis are the adverse reactions not mentioned in the manual that occurred frequently or with strong signal intensity. These findings offer new perspectives on safety assessment for olanzapine, necessitating attention and caution from healthcare professionals.

Cardiovascular risk

Olanzapine may increase the risk of pancreatitis, increased chylomicron, and hyperchylomicronemia by affecting lipid metabolism and directly impacting pancreatic cells.[15,16] During olanzapine treatment, doctors should closely monitor their patients' lipid metabolism and pancreatic function to promptly identify and address these potential adverse reactions. Additionally, a potential risk of myocardial reperfusion injury was noted. Though its direct link to olanzapine requires further research, it may involve drug effects on the cardiovascular system, including endothelial cell function and altered myocardial metabolism.[17]

Rare but serious adverse reactions

This study particularly focused on rare but potentially severe adverse reactions, such as neuroleptic malignant syndrome and anosognosia. Neuroleptic malignant syndrome is an emergency medical condition, most commonly theorized to result from blockade of dopamine receptors, particularly in the nigrostriatal pathway of the central nervous system. Dopamine regulates neurological functions, including muscle movement and temperature regulation. Drug-induced blockade of dopamine D2 receptors may disrupt these functions, leading to typical symptoms of neuroleptic malignant syndrome, like muscle rigidity and hyperthermia.[18,19] Anosognosia, a condition in which individuals lack awareness or deny their disease or deficit, is common in neurological diseases, such as stroke or neurodegenerative diseases.[20] Olanzapine's action on multiple neurotransmitter systems, including dopamine and serotonin, can affect the brain's information processing capabilities, impacting patients' awareness of their health condition.[21,22] In olanzapine users, especially those with severe mental disorders, regular assessments of cognitive function and disease awareness should be conducted to ensure the overall effectiveness of the medication regimen.

Vascular and coagulation-related adverse reactions

Intravascular papillary endothelial hyperplasia is an abnormal proliferation of endothelial cells, while thrombin plays a key role in the activation of endothelial cells and blood coagulation. Olanzapine may indirectly cause endothelial cell activation and proliferation, leading to intravascular papillary endothelial hyperplasia by impacting endothelial cell function or promoting inflammatory responses.[23,24] However, it should be noted that these potential mechanisms are mainly based on theoretical speculation and lack direct clinical evidence. In patients

Table 5 The top 30 signal strength of adverse events of olanzapine ranked by case reports

SOC	PTs	Case reports	ROR (95%CI)	PRR (95%CI)	$\chi 2$	IC (IC025)	EBGM (EBGM05)
Investigations	Weight increased	4,000	6.51 (6.31-6.72)	6.38 (6.19-6.58)	17819.22	2.64 (2.60)	6.26 (6.07)
Metabolism and nutrition disorders	Diabetes mellitus	3,410	15.67 (15.13-16.22)	15.38 (14.87-15.92)	43514.64	3.87 (3.81)	14.63 (14.13)
Nervous system disorders	Somnolence	2,035	3.52 (3.37-3.68)	3.49 (3.34-3.65)	3588.01	1.79 (1.73)	3.46 (3.31)
Injury, poisoning, and procedural complications	Overdose	1,833	2.88 (2.75-3.01)	2.86 (2.73-2.99)	2196.21	1.50 (1.43)	2.84 (2.71)
Psychiatric disorders	Confusional state	1,629	3.45 (3.28-3.62)	3.43 (3.26-3.60)	2773.13	1.76 (1.69)	3.40 (3.23)
Vascular disorders	Hypertension	1,552	2.56 (2.44-2.70)	2.55 (2.43-2.68)	1454.67	1.34 (1.27)	2.54 (2.41)
Injury, poisoning, and procedural complications	Toxicity to various agents	1,525	2.92 (2.78-3.08)	2.91 (2.77-3.06)	1894.54	1.53 (1.45)	2.89 (2.75)
Psychiatric disorders	Agitation	1,450	6.56 (6.22-6.91)	6.51 (6.18-6.86)	6617.14	2.67 (2.59)	6.38 (6.06)
Nervous system disorders	Sedation	1,377	21.43 (20.28-22.64)	21.27 (20.14-22.46)	24716.45	4.29 (4.21)	19.83 (18.77)
Gastrointestinal disorders	Pancreatitis	1,226	8.08 (7.63-8.56)	8.03 (7.59-8.50)	7343.42	2.96 (2.88)	7.84 (7.40)
Nervous system disorders	Neuroleptic malignant syndrome	1,223	39.92 (37.59-42.39)	39.65 (37.35-42.09)	40332.77	5.08 (4.99)	34.83 (32.79)
General disorders and administration site conditions	Drug interaction	1,204	2.61 (2.46-2.76)	2.60 (2.45-2.75)	1174.01	1.37 (1.28)	2.58 (2.44)
Metabolism and nutrition disorders	Type 2 diabetes mellitus	1,103	11.32 (10.65-12.02)	11.25 (10.60-11.95)	9907.57	3.43 (3.34)	10.85 (10.22)
Injury, poisoning, and procedural complications	Prescribed overdose	1,101	21.68 (20.38-23.05)	21.55 (20.27-22.91)	20027.15	4.30 (4.21)	20.07 (18.87)
Injury, poisoning, and procedural complications	Intentional overdose	1,059	5.81 (5.47-6.18)	5.78 (5.44-6.15)	4109.59	2.50 (2.41)	5.69 (5.35)
Cardiac disorders	Tachycardia	1,034	4.04 (3.80-4.30)	4.03 (3.79-4.28)	2322.70	1.99 (1.90)	3.98 (3.75)
Metabolism and nutrition disorders	Hyperglycemia	1,025	9.79 (9.20-10.42)	9.74 (9.15-10.36)	7771.32	3.23 (3.14)	9.44 (8.87)
Psychiatric disorders	Psychotic disorder	1,022	12.18 (11.44-12.97)	12.11 (11.38-12.89)	9989.96	3.53 (3.43)	11.65 (10.94)
General disorders and administration site conditions	General physical health deterioration	961	3.21 (3.02-3.43)	3.20 (3.01-3.41)	1441.33	1.66 (1.57)	3.18 (2.98)
Psychiatric disorders	Suicide attempt	940	5.40 (5.06-5.76)	5.37 (5.04-5.73)	3285.42	2.40 (2.30)	5.29 (4.96)

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Table 5 (*Continued*)

SOC	PTs	Case reports	ROR (95%CI)	PRR (95%CI)	$\chi 2$	IC (IC025)	EBGM (EBGM05)
Nervous system disorders	Dysarthria	895	8.19 (7.66-8.76)	8.15 (7.63-8.71)	5461.71	2.98 (2.88)	7.95 (7.44)
Investigations	Blood triglycerides increased	892	17.49 (16.34-18.72)	17.41 (16.27-18.62)	12984.30	4.01 (3.91)	16.44 (15.36)
Psychiatric disorders	Drug abuse	891	3.64 (3.41-3.89)	3.63 (3.40-3.88)	1676.68	1.84 (1.74)	3.59 (3.36)
Psychiatric disorders	Aggression	818	5.40 (5.04-5.79)	5.38 (5.02-5.77)	2866.65	2.40 (2.30)	5.30 (4.95)
Psychiatric disorders	Completed suicide	816	3.17 (2.96-3.39)	3.16 (2.95-3.38)	1191.51	1.64 (1.54)	3.13 (2.92)
Investigations	Electrocardiogram QT prolonged	797	7.82 (7.29-8.39)	7.79 (7.26-8.35)	4589.10	2.91 (2.81)	7.60 (7.08)
Metabolism and nutrition disorders	Metabolic disorder	783	54.18 (50.18-58.50)	53.94 (49.98-58.23)	34079.22	5.42 (5.31)	45.34 (41.99)
Nervous system disorders	Coma	782	5.64 (5.26-6.06)	5.62 (5.24-6.03)	2914.27	2.46 (2.35)	5.53 (5.15)
Metabolism and nutrition disorders	Diabetic ketoacidosis	780	11.54 (10.74-12.40)	11.49 (10.70-12.34)	7176.91	3.45 (3.35)	11.07 (10.31)
Investigations	Blood cholesterol increased	750	5.75 (5.35-6.19)	5.73 (5.33-6.16)	2873.62	2.49 (2.38)	5.64 (5.24)

EBGM = empirical Bayesian geometric mean; IC = information component; PRR = proportional reporting ratio; PT = preferred terms; ROR = reporting odds ratio; SOC = system organ class.

using olanzapine, potential vascular and coagulation-related adverse reactions should be closely monitored, with prompt assessment and intervention upon the appearance of related symptoms.

Multidimensional consideration of drug safety

Safety assessment of olanzapine should go beyond traditional monitoring of drug side effects and delve into how the drug impacts the patient's overall health at different levels. Olanzapine use involves not only its direct pharmacological effects but also includes long-term and short-term side effects, individual variations, drug interactions, and its impact on specific patient groups. Long-term side effects like metabolic syndrome, increased cardiovascular disease risk, and potential long-term neurological changes threaten the patient's sustained health. Short-term side effects, such as nausea, drowsiness, and impaired cognitive function, can significantly affect the patient's quality of life and treatment adherence. Individual differences, including genetic factors, comorbid conditions, and lifestyle factors, also significantly impact the drug's efficacy and safety.

The study is primarily based on data from the FAERS database, which relies on spontaneous reporting and may be subject to reporting biases. Thus, there are potential reporting biases in the system, such as the likelihood that severe adverse reactions are reported more frequently than mild ones, and that reports from consumers may differ from those submitted by healthcare professionals. Additionally, sex differences and age distribution may result in the underestimation or overestimation of adverse reactions in certain populations. For example, women and older patients may have different risks of adverse reactions due to physiological differences, but because of lower reporting rates, the analysis might be skewed toward more common or more heavily reported groups. Secondly, since the database data is observational, we cannot establish a direct causal relationship between olanzapine use and the observed adverse reactions. Additionally, the study did not fully consider individual differences among patients, such as genetic background, lifestyle, or other drug use, which could all impact the safety of olanzapine.

In conclusion, this study thoroughly explores olanzapine therapy for mental illnesses and the range of adverse reactions associated with it. While olanzapine has shown significant efficacy for certain mental disorders, we have also identified various potential adverse reactions, including cardiovascular risks, rare but serious adverse reactions, and vascular and coagulation-related issues. Cardiovascular risks, such as pancreatitis and myocardial reperfusion injury, as well as serious adverse reactions caused by neurotransmitter imbalances like malignant neuroleptic syndrome and anosognosia, pose especially significant risks to olanzapine users. These findings will help guide clinical decision-making, optimize patient treatment plans, and ensure that the overall health of patients is maximally protected while treating mental disorders. In the future, electronic health records and other real-world data could be integrated to validate the

Table 6 The top 30 adverse events of olanzapine with the greatest signal strength ranked by EBGM at the PT level

SOC	PTs	Case reports	ROR (95%CI)	PRR (95%CI)	$\chi 2$	IC (IC025)	EBGM (EBGM05)
Nervous system disorders	Post-injection delirium sedation syndrome	695	4,974.64 (3,603.06-6,868.35)	4,955.11 (3,589.16-6,840.93)	182910.30	7.58 (7.43)	264.23 (191.38)
Investigations	Chylomicron increased	3	834.18 (86.77-8,019.83)	834.17 (86.77-8,019.62)	624.13	1.97 (0.04)	209.29 (21.77)
Metabolism and nutrition disorders	Hyperchylomicronemia	6	208.55 (72.36-601.07)	208.54 (72.36-601.04)	708.16	2.73 (1.41)	119.60 (41.50)
Surgical and medical procedures	Anxiolytic therapy	8	202.23 (81.34-502.78)	202.22 (81.34-502.75)	927.37	3.07 (1.91)	117.50 (47.26)
Metabolism and nutrition disorders	Hyperinsulinism	41	193.27 (129.74-287.90)	193.23 (129.72-287.82)	4625.89	4.95 (4.42)	114.41 (76.81)
Psychiatric disorders	Psychogenic visual disorder	6	185.38 (65.98-520.83)	185.37 (65.98-520.80)	660.16	2.73 (1.42)	111.62 (39.73)
Surgical and medical procedures	Drug therapy enhancement	8	171.12 (70.92-412.86)	171.11 (70.92-412.83)	837.54	3.06 (1.92)	106.31 (44.06)
Investigations	Electrocardiogram J wave abnormal	4	158.89 (46.51-542.80)	158.89 (46.51-542.78)	399.37	2.26 (0.73)	101.48 (29.70)
Nervous system disorders	Pharyngeal dystonia	7	139.03 (56.11-344.48)	139.03 (56.11-344.46)	639.50	2.89 (1.70)	93.02 (37.54)
Investigations	Blood triglycerides	20	118.34 (70.12-199.70)	118.32 (70.12-199.67)	1632.10	4.08 (3.36)	83.30 (49.36)
Metabolism and nutrition disorders	Ketosis-prone diabetes mellitus	9	113.76 (52.38-247.06)	113.75 (52.38-247.04)	713.82	3.17 (2.12)	81.02 (37.30)
Neoplasms benign, malignant, and unspecified (including cysts and polyps)	Intravascular papillary endothelial hyperplasia	7	108.14 (45.17-258.91)	108.13 (45.17-258.89)	534.96	2.87 (1.70)	78.14 (32.63)
Investigations	Glucocorticoids increased	5	106.95 (38.13-300.00)	106.94 (38.13-299.98)	379.00	2.49 (1.14)	77.52 (27.63)
Investigations	Blood thrombin increased	9	104.28 (48.47-224.34)	104.27 (48.47-224.32)	669.48	3.16 (2.12)	76.11 (35.38)
Gastrointestinal disorders	Obstructive defecation	11	89.97 (45.58-177.56)	89.96 (45.58-177.54)	731.13	3.36 (2.43)	68.21 (34.56)
Cardiac disorders	Myocardial reperfusion injury	8	88.98 (40.14-197.28)	88.98 (40.14-197.26)	527.21	3.00 (1.92)	67.65 (30.51)
Metabolism and nutrition disorders	Acetonemia	44	85.58 (61.04-119.98)	85.56 (61.03-119.95)	2811.82	4.75 (4.27)	65.66 (46.83)
Musculoskeletal and connective tissue disorders	Camptocormia	47	83.80 (60.47-116.11)	83.77 (60.46-116.07)	2953.96	4.79 (4.33)	64.61 (46.63)

Continued on next page

Table 6 (*Continued*)

SOC	PTs	Case reports	ROR (95%CI)	PRR (95%CI)	$\chi 2$	IC (IC025)	EBGM (EBGM05)
Social circumstances	Ex-drug abuser	6	79.45 (32.07-196.84)	79.44 (32.07-196.83)	361.47	2.67 (1.45)	62.01 (25.03)
Psychiatric disorders	Mixed delusion	4	79.45 (26.15-241.36)	79.44 (26.15-241.35)	240.98	2.23 (0.78)	62.01 (20.41)
Congenital, familial, and genetic disorders	Lipomeningocele	4	74.15 (24.61-223.42)	74.15 (24.61-223.41)	227.88	2.22 (0.78)	58.75 (19.50)
Surgical and medical procedures	Patient restraint	14	70.78 (39.37-127.28)	70.78 (39.36-127.26)	767.68	3.58 (2.76)	56.62 (31.49)
Surgical and medical procedures	Bladder catheter permanent	4	69.52 (23.24-207.94)	69.51 (23.24-207.93)	216.09	2.22 (0.78)	55.81 (18.66)
Nervous system disorders	Synesthesia	4	61.79 (20.91-182.58)	61.79 (20.91-182.58)	195.73	2.21 (0.78)	50.74 (17.17)
Psychiatric disorders	Secondary tic	5	60.45 (22.98-159.01)	60.45 (22.98-159.00)	240.12	2.44 (1.15)	49.83 (18.94)
Investigations	Urine bilirubin decreased	3	55.61 (16.10-192.10)	55.61 (16.10-192.10)	134.07	1.90 (0.32)	46.51 (13.46)
Investigations	Psychiatric evaluation abnormal	3	55.61 (16.10-192.10)	55.61 (16.10-192.10)	134.07	1.90 (0.32)	46.51 (13.46)
Nervous system disorders	Anosognosia	102	54.68 (44.22-67.61)	54.65 (44.20-67.57)	4489.58	5.00 (4.69)	45.84 (37.07)
Metabolism and nutrition disorders	Metabolic disorder	783	54.18 (50.18-58.50)	53.94 (49.98-58.23)	34079.22	5.42 (5.31)	45.34 (41.99)
Nervous system disorders	Diabetic coma	416	54.03 (48.64-60.01)	53.90 (48.53-59.86)	18092.46	5.36 (5.20)	45.31 (40.79)

EBGM = empirical Bayesian geometric mean; IC = information component; PRR = proportional reporting ratio; PTs = preferred terms; ROR = reporting odds ratio; SOC = system organ class.

signals identified in the FAERS database. Such studies would provide more representative patient data, helping identify potential unreported or underestimated adverse reactions, especially in the context of long-term treatment risk assessment. This approach would enhance the robustness of safety evaluations and provide a more comprehensive understanding of the risks associated with medications in real-world clinical practice.

Acknowledgements

This study was supported by the Natural Science Foundation of the Jiangsu Higher Education Institutions of China (no. 22KJD360003), Wuxi Municipal Health Commission (no. Q202101 and ZH202110). This study was performed using the U.S. Food and Drug Administration's Adverse Event Reporting System, which was provided by the Food and Drug Administration. The information, results, and interpretations of the current study do not represent the opinion of the Food and Drug Administration.

Disclosure

The authors report no conflicts of interest.

Data availability statement

The dataset generated during and analyzed during the current study is available from the corresponding author on reasonable request.

Author contributions

AD: Conceptualization, Investigation, Methodology, Supervision, Validation, Writing – original draft.
LS: Data curation, Formal analysis, Software, Supervision.
ZD: Formal analysis, Investigation, Methodology.
QZ: Investigation, Methodology, Validation, Visualization.
YJ: Conceptualization, Data curation, Formal analysis, Project administration, Software, Supervision, Writing – original draft, Writing – review & editing.
HZ: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Supervision, Writing – original draft, Writing – review & editing.
AZ: Supervision, Funding acquisition, Writing – review & editing.
All authors have read and approved of the final version to be published.

Handling Editor: Giselli Scaini

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