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ORIGINAL RESEARCH

Drug-Induced Gynecomastia: Data Mining and Analysis of the FDA Adverse Event Reporting System Database

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Purpose: Drug-induced gynecomastia significantly affects patient health and quality of life. This study aimed to perform an exploratory analysis of gynecomastia reports and the most commonly associated medications within the FAERS database.

Patients and Methods: A comprehensive analysis of the FAERS from January 2004 to December 2023 was conducted. Disproportionality analysis and subsequent sensitivity analysis were performed to identify drugs potentially associated with gynecomastia, utilizing the reported odds ratio (ROR). Logistic regression analysis was employed to assess potential risk factors. The Weibull shape parameter (WSP) test was used to assess the time-to-onset characteristics of the top drugs associated with gynecomastia.

Results: The study identified 30,265 cases of gynecomastia, primarily associated with nervous system drugs, accounting for 85.50% of cases. Notably, risperidone accounted for 80.81% of the total cases. Among the 165 agents with ≥ 5 cases of gynecomastia, the strongest signals were exhibited by risperidone (ROR 602.38, 95% CI 585.07–620.20), dutasteride (ROR 17.18, 95% CI 15.55–18.89), spironolactone (ROR 15.8, 95% CI 13.99–17.83), and paliperidone (ROR 7.16, 95% CI 6.55–7.84). In the sensitivity analysis of disproportionality, unexpected associations were observed, such as montelukast (n = 21, ROR 1.94, 95% CI 1.26–2.98). The logistic regression analysis indicated that the risk of risperidone-induced gynecomastia was significantly lower in adults compared to pediatric patients (OR 0.12, 95% CI 0.09–0.15) and in patients with higher body weight than in those with lower body weight (OR 5.24, 95% CI 3.62–7.76). The WSP test showed that gynecomastia induced by most of the top 10 common agents tends to occur in an early failure mode.

Conclusion: The rankings and signal strengths of drugs associated with gynecomastia were extracted from the FAERS. The age distribution and time-to-onset distribution of the top 10 drugs linked to gynecomastia were investigated, which can facilitate accurate clinical recognition of drug-induced gynecomastia.

Keywords: drug-induced, gynecomastia, FAERS, risperidone, time-to-onset

Introduction

Gynecomastia, classified as a benign endocrine disorder, is distinguished by the proliferation of glandular breast tissue and the concomitant deposition of adipose tissue in males, culminating in a discernible alteration of breast morphology and dimensions.[1–3] An estimated 30 to 60% of men may experience gynecomastia at a certain stage in life.[4,5] Gynecomastia can occur at different stages of life, with a higher incidence among neonates, adolescents during puberty, and older adults.[2,6] Neonatal gynecomastia is a common condition in newborn males, affecting approximately 60%-90% of them. It is usually self-limited and is attributed to the transient increase in maternal estrogen levels that is either

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transplacental or transmitted through breast milk.[6] The occurrence of gynecomastia has been reported in 4%-70% of adolescent boys and up to 57%-65% of older men.[1,3,5,7]

Gynecomastia arises from a disruption in the equilibrium between estrogen and androgen activities within breast tissue.[2] Estrogens promote the growth of breast tissue, a process that is typically mitigated by androgens. An elevation in the estrogen-to-androgen ratio, whether caused by heightened estrogenic influences or diminished androgenic effects, precipitates the development of gynecomastia. This hormonal imbalance can result from various factors, including endocrine disorders, obesity, certain medications, and aging.[3]

Gynecomastia, generally not a serious condition in itself, may be an indication of underlying endocrine disorders and can have a significant impact on both the physical and psychological well-being of individuals.[8,9] Physical discomforts such as pain, tenderness, and in some cases, galactorrhea may occur. The psychological impact was equally profound, frequently leading to distress, embarrassment, and concerns about body image. Gynecomastia was shown to significantly lower self-esteem and quality of life, causing social withdrawal and heightened anxiety.[10] The etiology of gynecomastia was multifactorial, encompassing physiologic variations, disease-related factors such as tumors and endocrine disorders, and pharmacologic influences.[11] Nonmedication causes of gynecomastia encompass idiopathic cases, physiological conditions such as neonatal, adolescent, and elderly gynecomastia, as well as chronic diseases like cirrhosis, diabetes mellitus, heart failure, renal insufficiency, and tuberculosis.[3] Increases in estrogens or androgens, hypergonadotropic hypogonadism (eg, Klinefelter syndrome, testicular feminization syndrome), and hyperprolactinemia are also significant nonmedication causes. Given the varied etiologies of gynecomastia, a comprehensive differential diagnosis is essential.

Drug-induced gynecomastia accounted for approximately 9.3% to 25% of all reported cases.[12,13] The mechanism of drug-induced gynecomastia varied depending on the specific medication. It may involve androgen antagonism, estrogen receptor activation, or hormone synthesis alteration.[11] Although several drugs, including antiandrogens, antibiotics, proton pump inhibitors, and statins, have been identified as potential triggers of gynecomastia in men, it is crucial to conduct rigorous post-marketing surveillance to gain a more comprehensive understanding of the drugs associated with this adverse event (AE).[3,14] The US Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS) is a crucial component of pharmacovigilance.[15] It collects spontaneous AE reports from healthcare professionals, patients, and manufacturers, providing information on AEs, medication use, patient demographics, and other relevant details. This repository is a valuable resource for identifying and analyzing potential safety issues related to medical products. The FAERS database is frequently utilized in data mining and signal detection studies to identify adverse reactions that were not previously reported and to investigate known adverse reactions.[16,17] The objective of this study was to conduct an exploratory analysis of gynecomastia reports and the most frequently associated medications within the FAERS database.

Material and Methods

Data Source and Data Cleaning

FAERS has been issuing quarterly reports since 2004. The correlation between gynecomastia and drugs was investigated through a comprehensive search of the FAERS database spanning from January 2004 to December 2023. The FAERS database consists of seven datasets: DEMO (demographic and administrative information), DRUG (drug information), REAC (adverse reaction information), OUTC (clinical outcomes), RPSR (reporting sources), INDI (indications information), and THER (drug therapy dates). These datasets are interconnected via the PRIMARYID, which allows for the identification and linkage of AE reports across the various datasets.

Data cleaning was a critical preliminary step to ensure the integrity and accuracy of our analysis. Deduplication was rigorously performed in accordance with the FDA's guidelines.[18] This involved selecting the most recent FDA_DT (FDA date) for identical CASE IDs (case identification numbers). In cases where both CASE IDs and FDA_DT were identical, we chose the higher PRIMARYID. This methodological approach ensured that each (AE report was represented only once, avoiding duplication of data that could skew the analysis. The drugs identified as the primary suspect (PS) role code in reports associated with gynecomastia were selected for further analysis. To ensure data quality, records that contained anomalies suggestive of data entry errors were carefully removed from the dataset. Examples of anomalies in the data included individuals with an age over 150 years, which is biologically implausible, and cases of gender

misclassification as female, which were inconsistent with the clinical presentation of gynecomastia. The preferred terms "gynecomastia" and "breast enlargement" were used to identify AEs of interest.

To further conduct the time-to-onset analysis, the interval between the date of the adverse event occurrence (EVENT_DT) and the initiation date of the target medication (START_DT) was calculated and designated as the time-to-onset. Data entries with incomplete dating information, absent dates, or dates formatted incorrectly were excluded.

Statistical Analysis

A descriptive statistical analysis was conducted on the target cases, focusing on variables such as age, reporter occupation, outcomes, and report origin countries. Each target medication was categorized according to the Anatomical Therapeutic Chemical (ATC) classification system, as endorsed by the World Health Organization (WHO) Collaborating Centre (accessible at https://atcddd.fhi.no/atc_ddd_index/).

Disproportionality analyses were conducted on the top 45 drugs ranked by the number of drug-related gynecomastia cases in the FAERS database, utilizing the reported odds ratio (ROR). ROR demonstrates exceptional proficiency in identifying risk signals, characterized by its high reliability and sensitivity.[19] The ROR was calculated using a two-by-two contingency table, which compared the incidence of the drug of interest to that of other medications.[20] The ROR formula and its corresponding 95% confidence interval (CI) are detailed in Supplementary Table S1. The ROR values indicate the strength of association between a specific drug and an AE. A positive signal is present when the lower bound of the ROR's 95% CI is greater than 1, provided there are at least three reported AE cases. For drugs that received approval prior to the first quarter of 2004, the comparator background drugs were selected from the first quarter of 2004 to the fourth quarter of 2023. Conversely, for drugs approved after the first quarter of 2004, the background drug selection spanned from the quarter of approval until the fourth quarter of 2023. In addition, given that the proportion of cases for the top-ranked drug (risperidone) was excessively large, which might mask positive signals for other agents, a sensitivity analysis was performed.[21] In the sensitivity analysis, the background drug cases, both those with and without gynecomastia, were adjusted by subtracting the cases of gynecomastia and non-gynecomastia associated with risperidone during the corresponding period. Furthermore, logistic regression analysis was used to examine the relationship between age, body weight, and the risk of developing risperidone-induced gynecomastia.

The time-to-onset characteristics of the top 10 drugs associated with gynecomastia were assessed using median, interquartile range (IQR), and Weibull shape parameter (WSP) tests. The non-constant incidence of AEs over time of onset can be statistically analyzed using the WSP test.[22,23] The Weibull distribution is defined by two parameters: the scale parameter (α) and the shape parameter (β). The scale parameter determines the scale or width of the distribution, while the shape parameter determines the shape of the distribution curve. The hazard of AEs over time was predicted using the shape parameter in the analysis of time-to-onset, categorizing outcomes into early, random, or wear-out failure. A shape parameter and its 95% CI both under 1 indicate diminishing risk (early failure), values near 1 with a CI including 1 suggest stable risk (random failure), and values over 1 with a CI above 1 imply escalating risk (wear-out failure).

All data cleaning, mining, statistical analyses, and graph generation were conducted using R software version 4.3.2 and Microsoft Excel 2019.

Results

Descriptive Analysis

The FAERS database encompassed a total of 20,629,811 AE reports (Supplementary Figure S1) submitted from the first quarter of 2004 to the fourth quarter of 2023. Of these reports, 30,265 cases related to gynecomastia were included in our analysis, representing 0.17% of all reports. The basic characteristics of gynecomastia cases were shown in Table 1. The median age of the patients was 20 years, with an IQR of 12 to 48 years. The incidence of serious outcomes was relatively infrequent, with 153 (0.51%) deaths and 119 (0.39%) life-threatening cases documented. The majority of reports were submitted by consumers with 23,136 (76.4%) cases, followed by lawyers with 2559 (8.5%) cases. The United States was

Table 1 Characteristics of Cases Associated with Gynecomastia

Characteristics	Value
Number of total cases	30,265
Age, years (the number of patients with available data)	(n=10,506)
Median (IQR)	20 (12–48)
Reporter's Occupation, n (%)	
Consumer	23,136 (76.4%)
Lawyer	2559 (8.5%)
Other health-professional	2246 (7.4%)
Physician	1675 (5.5%)
Pharmacist	294 (1.0%)
Registered nurse	1 (0.0%)
Unknown	354 (1.2%)
Outcomes, n (%)	
Death	153 (0.51%)
Life-threatening	119 (0.39%)
Hospitalization	1085 (3.58%)
Disability	283 (0.94%)
Congenital Anomaly	3 (0.01%)
Required intervention	62 (0.20%)
Other Serious	6908 (22.83%)
Unknown	21,653 (71.54%)
Top 10 Report Countries, n (%)	
USA	27,594 (91.17%)
Britain	456 (1.51%)
France	297 (0.98%)
Canada	257 (0.85%)
Germany	188 (0.62%)
Japan	154 (0.51%)
Spain	128 (0.42%)
Netherlands	94 (0.31%)
Australia	85 (0.28%)
Italy	63 (0.21%)

Abbreviation: IQR, Interquartile range.

the primary source of these reports, with a substantial 27,594 cases, representing 91.7% of the total cases analyzed. Throughout the 20-year span of the FAERS database, there was a notable escalation in the annual number of reported cases after 2014, peaking in 2017 with a total of 10,300 cases (34.0%) (Supplementary Figure S2).

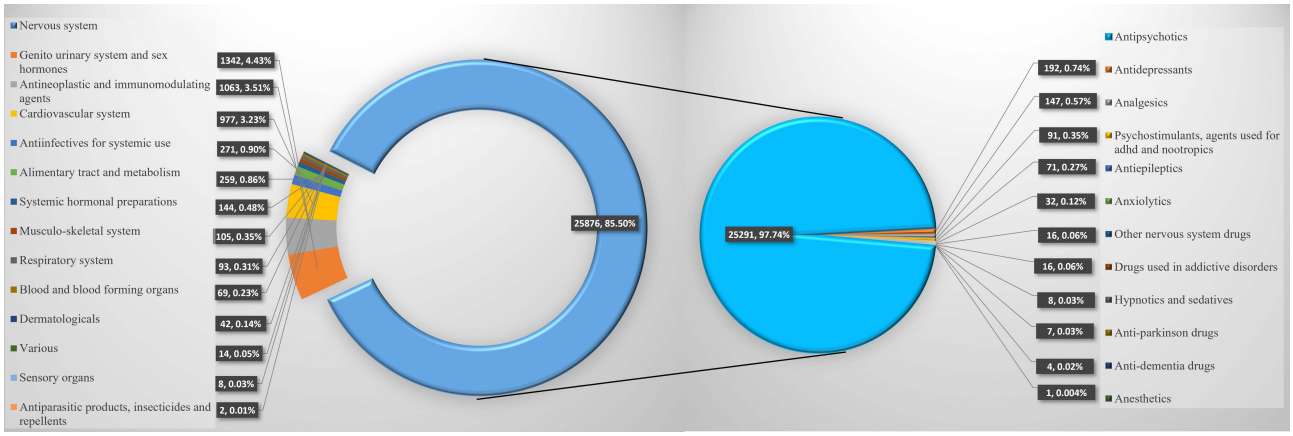

Figure 1 Number of Drug-induced Gynecomastia Cases Classified by the Anatomical Therapeutic Chemical (ATC).

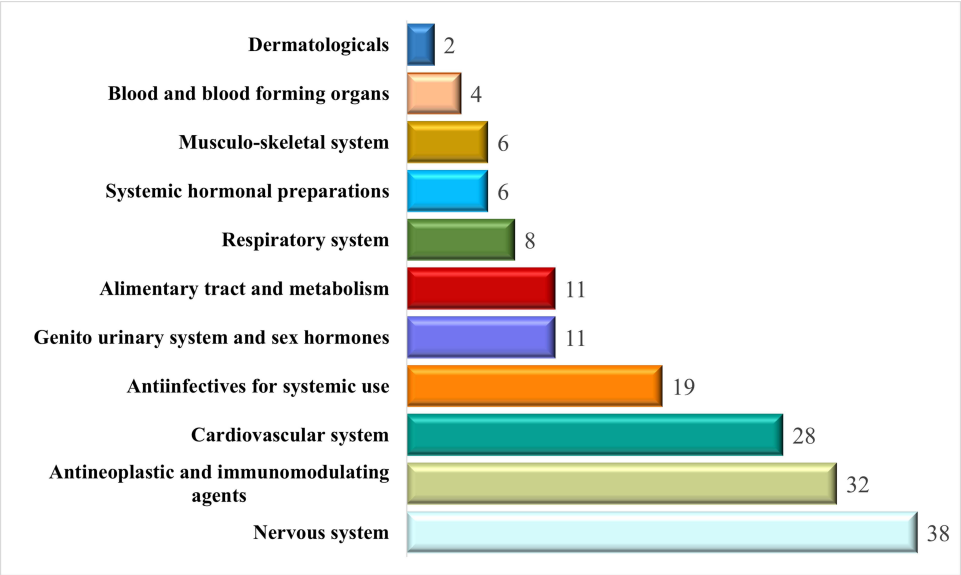

Figure 2 Number of drugs causing ≥ 5 cases of Gynecomastia Classified by the Anatomical Therapeutic Chemical (ATC).

The frequencies of AE reports, categorized based on the ATC system, showed that nervous system drugs were predominantly associated with gynecomastia, comprising 85.50% of the cases (Figure 1). This was followed by genito urinary system and sex hormones drugs, which accounted for 4.43% of the cases. Among the subset of cases related to nervous system drugs, the majority (97.74%) involved antipsychotic agents. A total of 165 drugs were found to have more than 5 reported cases of gynecomastia. The number of cases and rankings for these drugs were listed in Supplementary Table S2. Among these drugs, 38 (23.0%) belonged to the category of nervous system agents, 32 (19.4%) were classified as antineoplastic and immunomodulating agents, and 28 (17.0%) were related to the cardiovascular system (Figure 2). Of all the agents obtained, risperidone, an antipsychotic, was implicated in the greatest number of gynecomastia cases, amounting to 24,457 cases, which constitutes 80.81% of the total cases reported. (Supplementary Table S2). In addition to risperidone, nine other drugs caused more than 100 cases, such as finasteride (552 cases, 1.82%), paliperidone (486 cases, 1.61%), dutasteride (403 cases, 1.33%), leuprorelin (317 cases, 1.05%), and spironolactone (271 cases, 0.90%).

The analysis of age distribution among patients with gynecomastia showed that 1989 cases (18.9%) were aged ≤ 10 years, 2755 cases (26.2%) were in the 11 to 17 age group, 4310 cases (41.0%) were aged between 18 to 64 years, and

Table 2 Age Distribution of Patients with Gynecomastia for Top 10 Drugs

Drugs	≤10 Years n (%)	11–17 Years n (%)	18–64 Years n (%)	≥65 Years n (%)	Total n (%)	Media (IQR), year
Overall	1989 (18.9%)	2755 (26.2%)	4310 (41.0%)	1452 (13.8%)	10,506 (100.0%)	20.0 (12.0–48.0)
Risperidone	1921 (27.8%)	2553 (36.9%)	2422 (35.0%)	20 (0.3%)	6916 (100.0%)	14.0 (10.0–22.0)
Finasteride	0	2 (0.9%)	144 (62.3%)	83 (36.2%)	229 (100.0%)	43.0 (29.0–71.0)
Paliperidone	5 (2.7%)	20 (10.8%)	159 (85.4%)	2 (1.1%)	186 (100.0%)	27.5 (21.0–36.0)
Dutasteride	0	0	51 (19.9%)	205 (80.1%)	256 (100.0%)	73.0 (66.0–80.0)
Leuprorelin	0	1 (0.6%)	33 (20.5%)	127 (78.9%)	161 (100.0%)	72.0 (66.0–78.0)
Spironolactone	1 (0.5%)	0	112 (53.8%)	99 (46.9%)	212 (100.0%)	64.0 (56.0–73.0)
Testosterone	2 (2.2%)	1 (1.1%)	53 (57.0%)	37 (39.8%)	93 (100.0%)	60.0 (47–69.0)
Enzalutamide	0	0	18 (23.4%)	59 (76.6%)	77 (100.0%)	69.0 (65–74.0)
Olanzapine	0	7 (9.7%)	64 (88.9%)	1 (1.4%)	72 (100.0%)	36.0 (24.5–45.0)
Atorvastatin	0	0	32 (36.0%)	57 (64.0%)	89 (100.0%)	66.0 (60.0–71.0)

Table 3 Top 10 Drugs Causing Gynecomastia in Children and Adolescents (Age < 18)

Rank	Drugs	n (%)
1	Risperidone	4474 (94.31%)
2	Methylphenidate	35 (0.74%)
3	Growth hormone	32 (0.67%)
4	Paliperidone	25 (0.53%)
5	Aripiprazole	16 (0.34%)
6	Atomoxetine	12 (0.25%)
7	Quetiapine	11 (0.23%)
8	Sertraline	11 (0.23%)
9	Stavudine	9 (0.19%)
10	Montelukast	8 (0.17%)
10	Isotretinoin	8 (0.17%)

1452 cases (13.8%) were ≥ 65 years old (Table 2). Among the top 10 drugs causing gynecomastia, except risperidone and paliperidone, the incidence of patients under 18 years of age was notably low for the remaining drugs. This may be due to the specific indications of these agents and their targeted treatment populations. Among the 4744 cases of gynecomastia in patients under the age of 18 years that were identified, the top 10 contributing drugs were detailed in Table 3. Risperidone was the most frequently reported drug with 4474 cases, followed by methylphenidate with 35 cases, growth hormone with 32 cases, paliperidone with 25 cases, and aripiprazole with 16 cases.

Disproportionality Analysis and Sensitivity Analysis

The disproportionality analysis of the top 45 drugs causing gynecomastia showed that only 11 of them exhibited a positive signal (Figure 3). The strongest signals were exhibited by risperidone (ROR 602.38, 95% CI 585.07–620.20), followed by dutasteride (ROR 17.18, 95% CI 15.55–18.89), spironolactone (ROR 15.8, 95% CI 13.99–17.83), paliperidone (ROR 7.16, 95% CI 6.55–7.84), and finasteride (ROR 5.33, 95% CI 4.90–5.81).

A sensitivity analysis was conducted for the top 2–45 drugs causing gynecomastia by removing both cases and non-cases of risperidone from the background comparison. This analysis revealed an additional 24 drugs with positive signals, such as ziprasidone, tamsulosin, testosterone, rosuvastatin, olanzapine, ramipril, and atorvastatin (Figure 4). Including the initial 11 drugs identified as positive in the disproportionality analysis, the total count of drugs with a positive signal increased to 35.

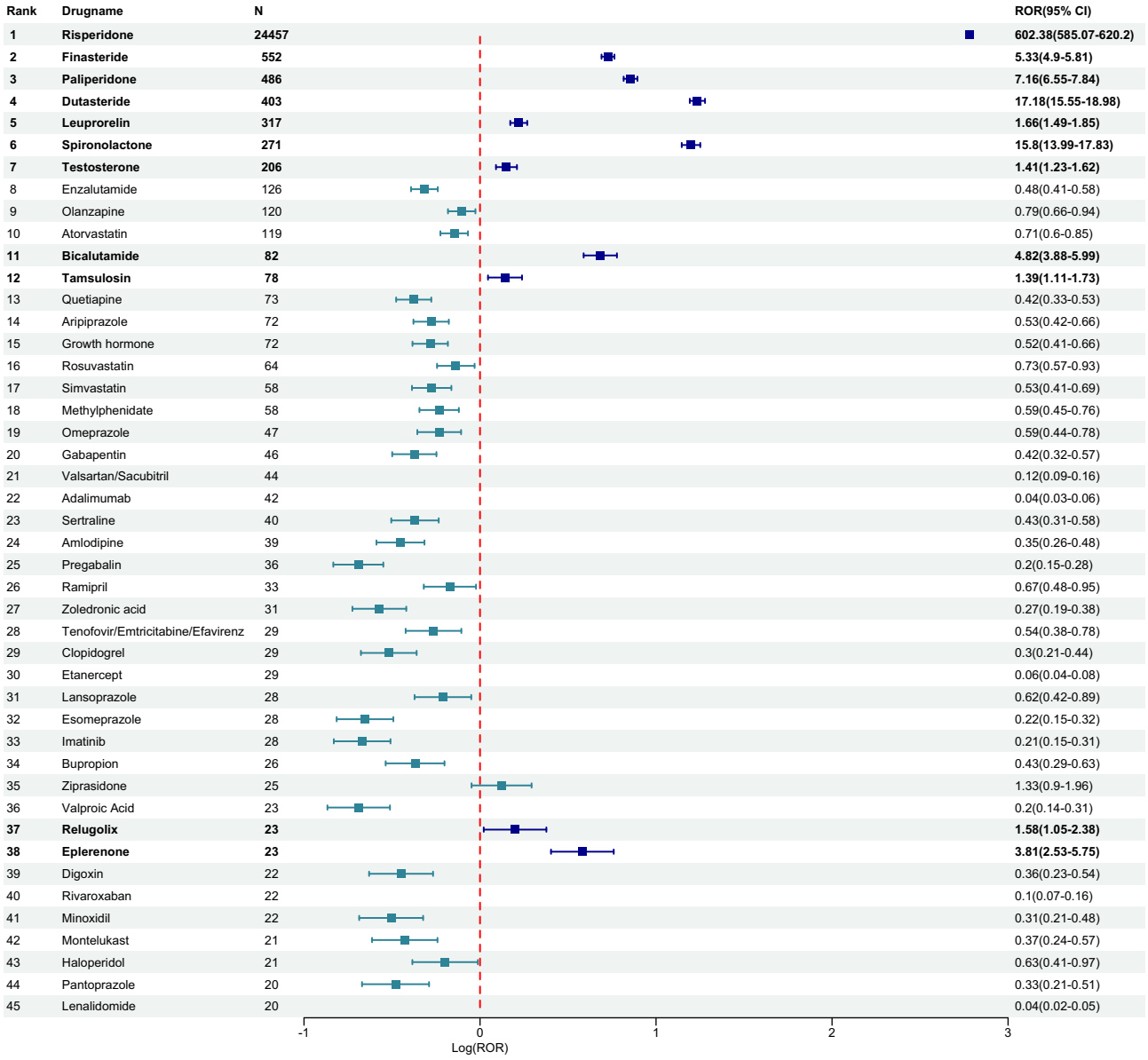

Figure 3 Forest plot of Reporting Odds Ratios for the Top 45 Drugs Causing Gynecomastia.
Notes: Bold text indicates statistically significant associations (lower limit of ROR 95% CI > 1 and at least three reported cases), suggesting a potential signal of gynecomastia with the respective medication.

Logistic Regression Analysis of Risperidone

The results of the multivariable logistic regression analysis indicated that adult patients who were treated with risperidone had a significantly lower risk of developing gynecomastia compared to pediatric patients under the age of 18 (odds ratio [OR] 0.12, 95% CI 0.09–0.15; p<0.001) (Table 4). Additionally, the analysis revealed that the risk of gynecomastia induced by risperidone was significantly higher in patients weighing ≥ 50 kg than in those weighing < 50 kg (OR 5.24, 95% CI 3.62–7.76; p<0.001).

Time-to-Onset Analysis

The results of the time-to-onset analysis were presented in Figure 5 and Table 5. Following the exclusion of reports with incomplete date information, the analysis comprised a total of 2235 reports, which revealed a median onset time of 427.0 days (IQR 110.5–1721.5) overall. Among the top 10 drugs associated with gynecomastia, risperidone demonstrated the

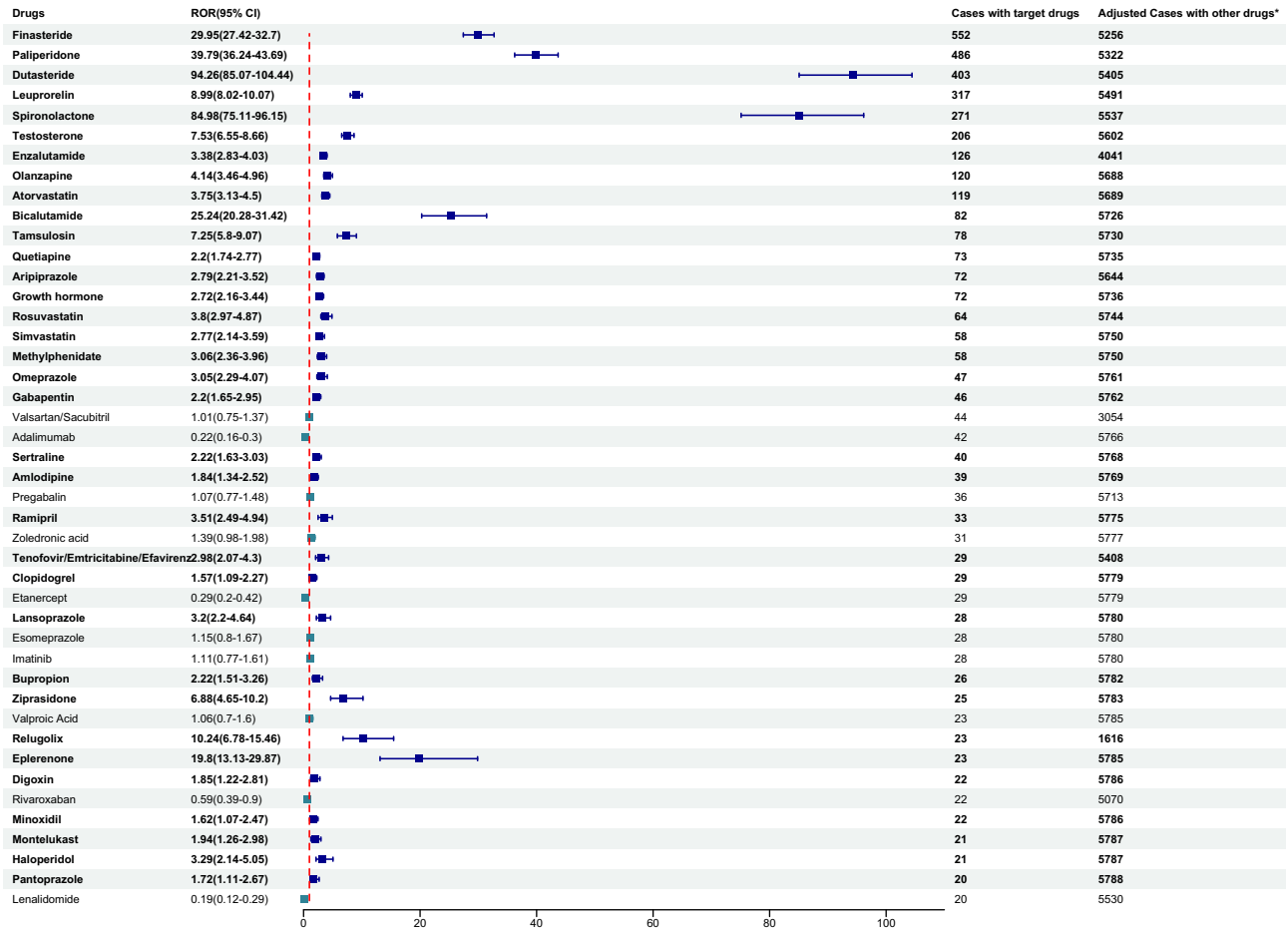

Figure 4 Forest plot of Sensitivity Analysis of Reporting Odds Ratios for the Top 2–45 Drugs Causing Gynecomastia.
Notes: Bold text indicates statistically significant associations (lower limit of ROR 95% CI > 1 and at least three reported cases), suggesting a potential signal of gynecomastia with the respective medication. * The total number of cases of other drugs in a given time period minus the number of cases caused by risperidone.

longest median time-to-onset of 1296.0 days (IQR: 348.5–2776.0), followed by finasteride with a median time-to-onset of 465.0 days (IQR: 123.5–1163.0). Conversely, enzalutamide exhibited the shortest median time-to-onset of 45.0 days (IQR: 25.0–228.0). The WSP test revealed that the 95% CIs for the shape parameter β of values for risperidone, finasteride, paliperidone, leuprolide, spironolactone, atorvastatin, and the overall cases were less than 1. This suggests

Table 4 Logistic Regression Analysis of Risperidone-Associated Gynecomastia

Variable	Cases without Gynecomastia (n)	Cases with Gynecomastia (n)	Univariable			Multivariable		
			OR	95% CI	p	OR	95% CI	p
Age (y)								
<18	2499	4474	Reference			Reference		
≥18	11,011	2442	0.12	0.11–0.13	p<0.001	0.12	0.09–0.15	p<0.001
Weight (kg)								
<50	682	70	Reference			Reference		
≥50	4610	680	1.44	1.12–1.88	p=0.006	5.24	3.62–7.76,	p<0.001

Abbreviation: OR, odds ratio.

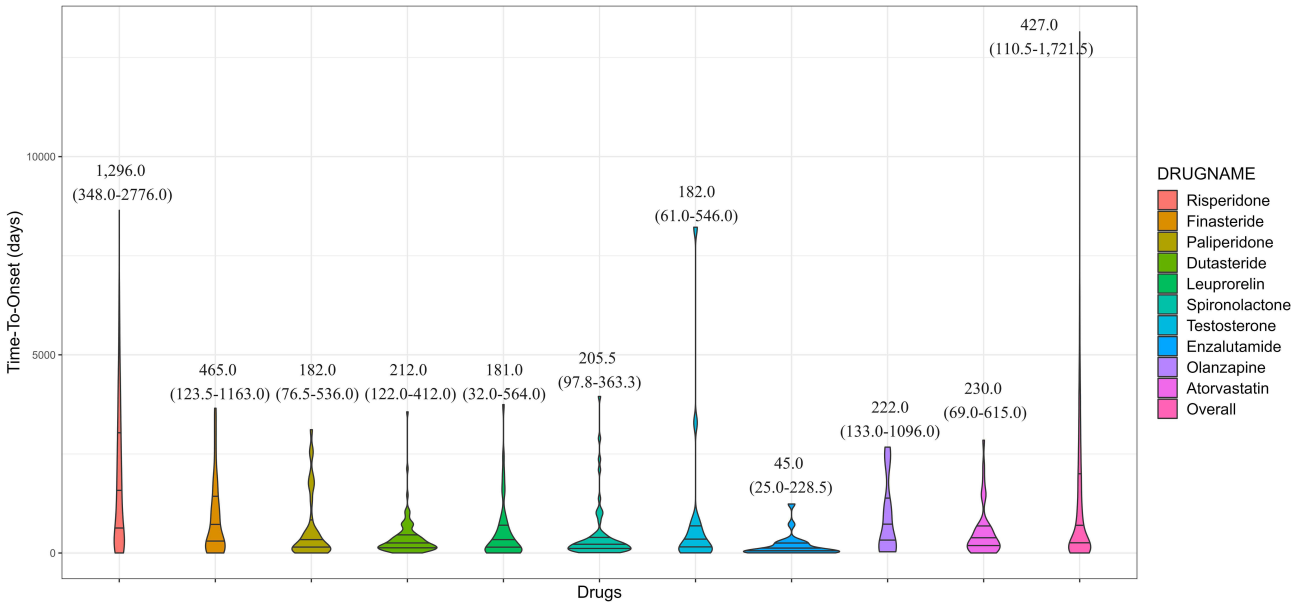

Figure 5 Violin plots of Time-to-Onset for Top 10 Drugs Causing Gynecomastia.

that the onset time of gynecomastia induced by these medications followed an early failure mode. Dutasteride was identified as an exception with a random failure pattern.

Discussion

Gynecomastia is the abnormal development of large breasts in males. This condition can lead to a range of significant psychological and social implications for affected individuals, including depression, anxiety, eating disorders, body image dissatisfaction, and diminished self-esteem.[24] The etiology of gynecomastia is complex, with both endogenous and exogenous factors contributing to its development.[1,11] Certain drugs, especially those with estrogenic or anti-androgenic properties, have been found to have the potential to cause gynecomastia.[14,25] Understanding the correlation between gynecomastia and various medications is therefore critical for both healthcare providers and patients.

This study performed a comprehensive analysis of drug-induced gynecomastia using data from the FAERS database, spanning the period from the first quarter of 2004 to the fourth quarter of 2023. The analysis revealed that drug-induced

Table 5 Fitted Weibull Distribution and Failure Patterns of Time-to-Onset for Top 10 Drugs

Drugs	Available Cases	Time-to-Onset (Days)	Weibull Distribution		Failure Patterns
	(n)	Median (IQR)	α (95%)	β (95%)	
Risperidone	1069	1296.0 (348.0–2776.0)	1678.36 (1557.76–1798.96)	0.87 (0.83–0.92)	Early failure
Finasteride	111	465.0 (123.5–1163.0)	732.53 (547.05–918.01)	0.77 (0.66–0.89)	Early failure
Paliperidone	39	182.0 (76.5–536.0)	435.06 (211.12–659.00)	0.64 (0.48–0.80)	Early failure
Dutasteride	101	212.0 (122.0–412.0)	353.18 (277.27–429.09)	0.96 (0.82–1.09)	Random failure
Leuprorelin	52	181.0 (32.0–564.0)	343.97 (191.60–496.34)	0.65 (0.51–0.79)	Early failure
Spironolactone	66	205.5 (97.8–363.3)	357.91 (242.42–473.39)	0.79 (0.66–0.93)	Early failure
Testosterone*	17	182.0 (61.0–546.0)	-	-	-
Enzalutamide*	23	45.0 (25.0–228.5)	-	-	-
Olanzapine*	20	222.0 (133.0–1096.0)	-	-	-
Atorvastatin	43	230.0 (69.0–615.0)	432.11 (255.58–608.64)	0.77 (0.59–0.95)	Early failure
Overall	2235	427.0 (110.5–1721.5)	863.00 (807.02–920.98)	0.66 (0.64–0.68)	Early failure

Notes: *The number of cases was relatively small, and Weibull distribution analysis was not performed.
Abbreviation: IQR, interquartile range.

gynecomastia represented only 0.17% of all adverse event reports, emphasizing its rarity in clinical practice. Moreover, the incidence of serious outcomes, such as fatal and life-threatening incidents, was strikingly low, with rates of 0.51% and 0.39% respectively among the cases analyzed. While gynecomastia is generally regarded as a benign condition that often resolves without treatment, recent research has implicated an association between gynecomastia and an increased risk of all-cause mortality (hazard ratio [HR] 1.37; 95% CI 1.31–1.43).[26] The observed elevation in mortality risk was predominantly attributed to underlying malignant neoplasms as well as circulatory, pulmonary, and gastrointestinal diseases.

In our study, nervous system drugs were identified as the primary contributors to drug-induced gynecomastia. Furthermore, among the 165 drugs that induced more than 5 cases of gynecomastia, nervous system agents were the most prevalent, with a total of 38 drugs (23.0%). This result was inconsistent with previous studies. An analysis of the French national pharmacovigilance database (FPVD) from January 1, 2008, to December 31, 2015, has revealed that antiretrovirals were the most common drug class associated with gynecomastia, accounting for 23.5% of reported cases.[27] Additionally, a meta-analysis incorporating 30 randomized controlled trials (RCTs) indicated that antiandrogen-induced gynecomastia was the most frequently observed case.[28]

In terms of individual drugs, risperidone, a widely prescribed second-generation antipsychotic, was associated with the highest number of cases of gynecomastia, reaching up to 24,457 (80.81%). A nested case-control study among men aged 40 to 85 years revealed that the use of risperidone significantly increased the risk of developing gynecomastia (rate ratio [RR] 1.69, 95% CI 1.05–2.72).[29] The occurrence of gynecomastia in patients receiving risperidone was frequently associated with high doses. It can be exacerbated by the concurrent use of fluoxetine, which inhibits risperidone metabolism through cytochrome P450 inhibition.[14,30] Additionally, our findings revealed that several other antipsychotics resulted in five or more cases of gynecomastia including paliperidone (486 cases), olanzapine (120 cases), quetiapine (73 cases), aripiprazole (72 cases), ziprasidone (25 cases), haloperidol (21 cases), clozapine (9 cases), lurasidone (5 cases), fluphenazine (5 cases) and brexpiprazole (5 cases). The development of antipsychotic-induced gynecomastia is primarily considered a symptom of hyperprolactinemia, a condition triggered by antipsychotics blocking pituitary dopamine D2 receptors. This blockade inhibits prolactin suppression and may reduce GnRH secretion by the hypothalamus, potentially leading to hypogonadism.[14,31] Additionally, the presence of prolactin receptors in male breast tissue suggests a direct role in the pathogenesis of this condition. A majority of first-generation antipsychotics, as well as specific second-generation drugs such as risperidone and paliperidone, were known to elevate prolactin levels. These findings underscore the importance of considering the risk of gynecomastia when prescribing antipsychotic medications, particularly risperidone.

We performed a disproportionality analysis on the top 45 drugs associated with gynecomastia, which identified only nine drugs with a positive signal. The disproportionality method was widely used in quantitative signal detection and pharmacovigilance based on spontaneous reporting databases.[32] However, various factors can affect the accuracy and obscure the detection signals, including the high background frequency of drugs or AEs, the overall safety profile of the drug, and the quality of the reported information.[21,32,33] It's worth noting that the results of disproportionality between different drugs or AEs are interdependent: an increase in disproportionate results for one AE leads to a decrease in other AEs, similar to a seesaw equilibrium. If many drugs have been reported with a particular AE in large numbers, this may mask the potential AE of a new drug. In some cases, it may be necessary to exclude certain reports from the observed data to improve the accuracy of the analysis and reduce bias, such as sensitivity analyses that exclude known strong signals from the background. In our disproportionality analysis, the high prevalence of risperidone-induced gynecomastia reported in the FAERS appeared to mask many potentially significant signals associated with other agents. Thus, a sensitivity analysis was conducted by subtracting risperidone-related cases from the controlled background data.

Upon integrating the initial disproportionality analysis with a subsequent sensitivity analysis, positive signals were detected for 35 out of the 45 agents most frequently associated with cases of gynecomastia. In the sensitivity analysis, dutasteride and finasteride, both being 5-α reductase inhibitors, were ranked first and fourth, respectively, based on the ROR values. 5-α reductase inhibitors effectively block the conversion of testosterone to dihydrotestosterone by inhibiting the enzyme 5-α reductase. Consequently, serum testosterone levels rise, leading to increased aromatization to estrogen in the liver. This process alters the estrogen/androgen ratio in the body, triggering a hormonal cascade that ultimately heightens the risk of gynecomastia.[12,25] Several studies have reported increases in the risk of gynecomastia with the use

of 5-alpha reductase inhibitors. Gerald et al[34] discovered a higher incidence of gynecomastia in the dutasteride arm compared to the placebo arm (1.9% [76 of 4105 men] versus. 1.0% [43 of 4126 men], P = 0.002). The Prostate Cancer Prevention Trial also showed that gynecomastia was more common in finasteride-treated patients than in the placebo group (4.5% versus. 2.8%, P<0.001).[35] A cohort study with nested case–control analyses utilizing the UK Clinical Practice Research Datalink demonstrated that the risk associated with dutasteride was higher (adjusted OR=5.40, 95% CI 3.64–8.00) in comparison to finasteride (adjusted OR=2.92, 95% CI 2.31–3.68), which was consistent with our findings.[36]

Spironolactone, a nonselective aldosterone antagonist, demonstrated the second most significant signal with an ROR of 84.98 (95% CI 75.11–96.15) in the sensitivity analysis of disproportionality. The mechanism of spironolactone causing gynecomastia was multifaceted, including potential reductions in blood testosterone levels and elevated estrogen levels due to long-term or high-dose therapy, as well as the exhibition of its anti-androgenic properties.[37,38] Another aldosterone antagonist, eplerenone, also exhibited a positive signal in our analysis (n = 23, ROR 19.80, 95% CI 13.13–29.87). Eplerenone exhibited selective aldosterone receptor blockade with negligible effects on other steroid receptors, thereby reducing the hormonal AEs commonly associated with spironolactone.[39] The incidence of gynecomastia in patients receiving eplerenone therapy was significantly lower compared to spironolactone.[40] Therefore, eplerenone should be used in patients who were intolerant to spironolactone and especially in those who experienced anti-androgenic symptoms such as breast tenderness, gynecomastia, mastodynia, or sexual dysfunction.[41,42] Nevertheless, the ROR for eplerenone in our sensitivity analysis of disproportionality ranked 6th out of 44 drugs, suggesting that gynecomastia remains a significant AE associated with eplerenone that warrants attention.

In the sensitivity analysis for disproportionality, in addition to the known antipsychotics, antiandrogen agents, proton pump inhibitors, antiviral agents, statins, hormonal agents, calcium channel blocking agents (CCB), angiotensin-converting enzyme inhibitors (ACEI), bisphosphonates, digoxin, and others, the unanticipated occurrence of montelukast (n = 21, ROR 1.94, 95% CI 1.26–2.98) in relation to gynecomastia was identified. Analyzing 21 cases of montelukast-related gynecomastia from the FAERS, we found that 13 cases involved the concomitant use of glucocorticoids (fluticasone, mometasone) or antihistamines (cetirizine), which have previously been reported associated with the development of gynecomastia.[14] Therefore, the contribution of these co-administered drugs should be considered. On the other hand, the remaining 8 cases were reported with montelukast as the only medication, suggesting the necessity for further investigation into the potential of montelukast to cause gynecomastia.

Consistent with previous research,[12,43] the present study indicated that drug-induced gynecomastia was more prevalent among adults. An analysis of 10,506 cases with available age data revealed that children and adolescents accounted for 45.2% of cases. Additionally, after excluding cases related to risperidone, the percentage of adult cases increased significantly to 92.5%. The average age among patients with drug-induced gynecomastia was found to be 58.1 years, with almost 70% being above 50 years old in the FPDV.[27] However, the median age of all patients in our study was 20 years, with an interquartile range of 12 to 48 years. Among the 10 most commonly reported drugs associated with gynecomastia, risperidone stands out as an exception due to the median age of affected patients being below 18 years. In contrast, for the remaining nine drugs, the median age of patients reporting gynecomastia exceeded 18 years. This difference likely reflects the varying therapeutic indications of these drugs. However, it highlighted the fact that drug-induced gynecomastia was a potential risk for all age groups.

Clarifying the time-to-onset of AEs enhanced the ability of healthcare professionals to anticipate and identify AEs.[44] In our study, the median onset times for gynecomastia associated with risperidone, finasteride, and atorvastatin were 1296.0 days (IQR, 348.0–2776.0), 465.0 days (IQR, 123.5–1163.0), and 230.0 days (IQR, 69.0–615.0), respectively. These durations were longer than previously reported, where the onset of gynecomastia associated with risperidone has ranged from 3 months to 3 years, with finasteride from 2 weeks to 2.5 years, and atorvastatin from 2 months to 6 months.[12,14] The Weibull shape parameter can be used to predict trends in the probability of AEs over time.[45] Our WSP test demonstrated that the risk of developing gynecomastia associated with risperidone, finasteride, paliperidone, leuprolide, spironolactone, and atorvastatin exhibited an early failure profile. This suggests that the risk of gynecomastia associated with these agents decreases over time. In contrast, dutasteride was identified as having a random failure

pattern, suggesting that the risk of dutasteride-associated gynecomastia remains constant and does not change with the duration of treatment.

There are inevitably some limitations in our study. Firstly, the FAERS database, which can capture drug-induced AEs globally, is a spontaneous reporting system for adverse drug reactions, which introduces inherent biases. The accuracy and robustness of the results may be compromised due to the database's lack of requirement for comprehensive patient case information and potential data omissions, such as age, gender, and dosage. This could lead to under- or overestimation of specific AEs. Additionally, the risperidone-associated gynecomastia signal was so strong that it inadvertently masked many other potential signals. A sensitivity analysis was conducted to exclude risperidone-associated cases from the background used for comparison. This allowed for a more precise assessment of the association between other drugs and gynecomastia. Thirdly, it is important to note that the statistical method of disproportionality analysis is only applicable to hypothesis generation and not hypothesis testing. Therefore, it can help to identify potential drug safety signals but cannot clarify the causal relationship between drugs and adverse events. To improve the precision of identifying adverse events, disproportionality analysis can be complemented with data from drug labels, literature, clinical practice guidelines, and insights from authoritative databases. Additionally, patient-specific factors such as age, gender, underlying conditions, and genetic predispositions, along with nuances of drug administration such as dosage, duration, and concomitant medication, must be taken into account. By integrating multifaceted analysis, we can achieve a more nuanced and accurate assessment of drug-induced adverse events, providing solid evidence for clinical decision-making.

Conclusion

In a comprehensive review of the FAERS database for the period January 2004 through December 2023, we found that nervous system medications were the primary category associated with gynecomastia. Of the medications within this category, risperidone was associated with the highest number of cases. A total of 165 drugs were associated with over five reported cases of gynecomastia. Risperidone, spironolactone, dutasteride, paliperidone, and finasteride exhibited the strongest associations. Our findings also revealed unexpected associations, such as montelukast with gynecomastia. The time-to-onset analysis revealed diverse patterns among the top implicated drugs, with the majority demonstrating early onset of adverse effects. This suggests that healthcare providers should be particularly vigilant in the early stages following the initiation of administration, as this is when the risk of gynecomastia is seemingly the highest. The logistic regression analysis showed that pediatric and adolescent patients have a higher risk of developing risperidone-induced gynecomastia compared to adults. Additionally, patients with a higher body weight exhibited a higher risk of risperidone-associated gynecomastia than those with a lower body weight. This may be related to the fact that hormonal balance is more easily disturbed in children and obese patients.[3,46] Overall, the findings of this study contribute to a more comprehensive understanding of the correlation between different medications and gynecomastia. The development of specific monitoring, assessment, and follow-up strategies can facilitate the management of drug-induced gynecomastia in clinical practice by addressing the risk profiles of different drugs.

Data Sharing Statement

The data presented in this study are available on request from the corresponding author.

Ethics Approval and Informed Consent

The current study, which involved the analysis of anonymised data from the publicly available FAERS database, was determined to be exempt from institutional ethics approval. This exemption is in accordance with Article 32 of China's "Notice on the Issuance of Measures for the Ethical Review of Human Life Science and Medical Research" (2023), which allows for the waiver of ethical review for research using public, anonymised information data that does not harm human beings or involve sensitive personal information or commercial interests. The Ethics Committee of Zhejiang Provincial People's Hospital reviewed the research protocol and data handling procedures and confirmed that the study complied with the above regulations and was exempt from ethical review.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas. Took part in drafting, revising or critically reviewing the article, gave final approval of the version to be published, have agreed on the journal to which the article has been submitted, and agree to be accountable for all aspects of the work.

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Disclosure

Jiangfeng Wang is affiliated with Ipharmacare Ltd. The authors report no other conflicts of interest in this work.

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