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Research article

Sex differences in adverse event reporting for psychotropic medicines: a disproportionality analysis of benzodiazepines, atypical antipsychotics and antiepileptic agents in 1,231,335 reports

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Abstract: Sex differences in psychotropic drug safety are clinically important but have been studied drug by drug, without a common comparator. Whether reported differences reflect class-specific pharmacology or a general asymmetry in how adverse events are reported for women and men has not been established. Case/non-case disproportionality analysis of the FDA Adverse Event Reporting System (FAERS) via openFDA database. All reports listing a benzodiazepine, atypical antipsychotic or antiepileptic agent with a recorded patient sex were included. Comparisons were made within each class, holding drug exposure constant. Reporting odds ratios (RORs) for women versus men were calculated for 32 pre-specified Preferred Terms, with Benjamini-Hochberg control of the false discovery rate across all comparisons. 1,231,335 reports were analysed. Male reports were more often serious in every class (79.8% vs 70.9%, 80.8% vs 78.5%, 80.2% vs 73.4%; all $p < 0.001$), and the ROR for death was near-invariant (0.60, 0.66, 0.65). Against this baseline, women disproportionately reported memory impairment (ROR 1.46, 95% CI 1.40-1.52) and falls (1.38) with benzodiazepines; QT prolongation (1.44, 1.36-1.52) and tardive dyskinesia (1.40) with antipsychotics; and cutaneous reactions with antiepileptics, including Stevens-Johnson syndrome (1.17, 1.08-1.25). Men disproportionately reported drug abuse (0.42, 0.41-0.44) and dependence (0.51), and hyperprolactinaemia (0.44) and galactorrhoea (0.48). A general severity asymmetry underlies sex-stratified FAERS analyses and must be accounted for before class-specific signals are interpreted. Once it is, benzodiazepine harms separate into therapeutic-use effects in women and misuse-related outcomes in men, and two recognised sex effects in antipsychotic safety are reproduced.

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Introduction

Psychotropic medicines are prescribed to women more often than to men in most high-income health systems, and sex differences in their effects are well recognised in specific instances. Women are more susceptible to drug-induced QT interval prolongation, and tardive dyskinesia is more frequent in women, particularly older women (Drici and Clement, 2001). Severe cutaneous adverse reactions to antiepileptic drugs

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show a female predominance. Each of these observations has been established separately, for a single drug or a single outcome (Evans et al., 2001).

What has not been established is whether such findings sit on a level playing field. Spontaneous reporting systems record what is reported, not what occurs, and if reports concerning men are systematically more severe than those concerning women for reasons unrelated to any particular drug, then every sex-stratified disproportionality estimate inherits that asymmetry. A reporting odds ratio below 1 for a serious outcome would then be expected by default, and interpreting it as a drug-specific signal would be an error (Hazell and Shakir, 2006). We therefore analysed three pharmacologically unrelated psychotropic classes together, using an identical within-class design, and examined whether a common baseline could be detected across them. Because exposure to the class is shared by both arms of each comparison, this design removes the prescribing-prevalence confounding that affects naive comparisons of which drugs generate reports for which sex.

Material and Methods

Data source and cohort

The FDA Adverse Event Reporting System (FAERS) was accessed through the public openFDA application programming interface, using the database (20,692,690 reports). Reports were identified by the Established Pharmacologic Class terms 'Benzodiazepine', 'Atypical Antipsychotic' and 'Anti-epileptic Agent' applied to any listed drug, irrespective of suspect status, and were included where patient sex was recorded as male or female.No ethical approval was required; FAERS is a public, de-identified database.

Outcome selection

For each class we pre-specified Preferred Terms spanning its recognised adverse effect profile, chosen to include both severe and non-severe outcomes and both established and unexamined sex associations. Death was included in all three classes as a common comparator. One term was excluded after inspection. 'Foetal exposure during pregnancy' appeared in 1,361 male-coded and 956 female-coded antiepileptic reports. A male-coded report of transplacental exposure indicates that the sex field refers to the exposed offspring rather than to the person who took the drug, so the field does not denote the drug recipient in this report type and the term is not analysable under this design.

Statistical analysis

Analyses were conducted within each class, so that drug exposure was held constant and sex was the exposure of interest. For each Preferred Term a 2 x 2 table compared reports containing that term against all other reports of the same class, separately by sex. Reporting odds ratios (RORs) were calculated with 95% confidence intervals from the standard error of the log odds ratio. An ROR above 1 indicates disproportionate reporting in women.

Thirty-two comparisons were made. The false discovery rate was controlled using the Benjamini-Hochberg procedure applied across all comparisons in the study rather than within each class, and adjusted q values are reported. Proportions were compared using the chi-squared test with continuity correction and are given with Wilson score intervals. To characterise the baseline against which class-specific signals should be read, the proportion of reports flagged serious was compared by sex within each class, and the ROR for death was compared across classes. Statin reports, analysed separately under the same design, are included in that comparison as an external non-psychotropic reference. Analyses used Python 3 with SciPy.

Reporting

The study is reported in accordance with the STROBE statement (van Puijenbroek et al., 2002).

Results

Cohort

1,231,335 reports with recorded sex were analysed: 637,716 benzodiazepine reports (407,673 women, 230,043 men), 401,704 atypical antipsychotic reports (200,589 women, 201,115 men) and 191,915 antiepileptic reports (118,132 women, 73,783 men).

A common severity baseline

In every class, reports concerning men were more often flagged serious than those concerning women: 79.8% versus 70.9% for benzodiazepines, 80.8% versus 78.5% for antipsychotics, and 80.2% versus 73.4% for antiepileptics (all $p < 0.001$). The same direction and a similar magnitude were present in statin reports analysed under the same design (75.6% versus 68.7%).

The ROR for death was correspondingly stable across all four classes, at 0.60 for benzodiazepines, 0.66 for atypical antipsychotics, 0.65 for antiepileptics and 0.61 for statins. That a single value should recur across four pharmacologically unrelated classes indicates that it reflects a property of reporting rather than of any drug. It is therefore treated here as the baseline against which class-specific estimates are read: an ROR near 0.6 for a fatal outcome is the expected value, not a signal, and only departures from this baseline warrant pharmacological interpretation. Baseline data are given in **Table 1**.

Table 1. Severity baseline by drug class and patient sex.

Drug class	Reports, women	Reports, men	Serious, women	Serious, men	ROR, death
Benzodiazepine	407,673	230,043	70.9%	79.8%	0.60
Atypical antipsychotic	200,589	201,115	78.5%	80.8%	0.66
Antiepileptic agent	118,132	73,783	73.4%	80.2%	0.65
HMG-CoA reductase inhibitor*	180,392	168,464	68.7%	75.6%	0.61

All sex differences in the proportion of reports flagged serious are significant at $p < 0.001$ (chi-squared with continuity correction). ROR, reporting odds ratio for death, women versus men, within class. *Non-psychotropic external reference, analysed separately under the same design. The near-invariance of the death ROR across four pharmacologically unrelated classes identifies it as a property of reporting rather than of any drug.

Benzodiazepines

Benzodiazepine outcomes separated sharply by mechanism of harm rather than by severity **(Table 2)**. Women disproportionately reported harms arising from therapeutic use: memory impairment (ROR 1.46, 95% CI 1.40-1.52) and falls (1.38, 1.34-1.42). Men disproportionately reported harms arising from misuse: drug abuse (0.42, 0.41-0.44), drug dependence (0.51, 0.49-0.53) and overdose (0.69, 0.67-0.71). The separation is not explained by the severity baseline. Drug abuse at 0.42 and dependence at 0.51 lie well below the 0.60 baseline, while memory impairment and falls lie far above it. Completed suicide (0.97, 0.94-1.00) and intentional overdose (1.07, 1.02-1.11), by contrast, sat close to parity, distinguishing deliberate self-harm from the misuse pattern.

Atypical antipsychotics

Two recognised sex effects were reproduced. QT interval prolongation was reported disproportionately in women (ROR 1.44, 95% CI 1.36-1.52), as was tardive dyskinesia (1.40, 1.32-1.48). Weight increase (1.21, 1.17-1.25) and somnolence (1.18, 1.14-1.23) were also female-predominant, while extrapyramidal disorder was male-predominant (0.76, 0.71-0.80). An unexpected finding concerned prolactin-related effects. Hyperprolactinaemia (0.44, 0.41-0.47) and galactorrhoea (0.48, 0.45-0.53) were both reported substantially more often in men, despite galactorrhoea being clinically associated with women. Both estimates fall below the severity baseline and so cannot be attributed to it.

Table 2. Reporting odds ratios for women versus men, by drug class.

MedDRA Preferred Term	Women, n	Men, n	ROR (95% CI)	q
BENZODIAZEPINE				
Memory impairment	7,179	2,792	1.46 (1.40–1.52)	1.2×10^{-63}
Fall	17,293	7,149	1.38 (1.34–1.42)	9.3×10^{-113}
Intentional overdose	5,997	3,176	1.07 (1.02–1.11)	0.0041
Completed suicide	11,453	6,690	0.97 (0.94–1.00)	0.024
Somnolence	13,216	7,944	0.94 (0.91–0.96)	8.2×10^{-6}
Confusional state	9,656	5,831	0.93 (0.90–0.96)	4.6×10^{-5}
Drug withdrawal syndrome	4,021	2,563	0.88 (0.84–0.93)	2.0×10^{-6}
Sedation	2,902	1,881	0.87 (0.82–0.92)	3.8×10^{-6}
Overdose	7,906	6,427	0.69 (0.67–0.71)	1.5×10^{-107}
Death	10,951	10,177	0.60 (0.58–0.61)	$< 10^{-300}$
Drug dependence	4,113	4,510	0.51 (0.49–0.53)	6.2×10^{-218}
Drug abuse	9,432	12,178	0.42 (0.41–0.44)	$< 10^{-300}$
ATYPICAL ANTIPSYCHOTIC				
Electrocardiogram QT prolonged	2,919	2,046	1.44 (1.36–1.52)	1.0×10^{-35}
Tardive dyskinesia	2,795	2,009	1.40 (1.32–1.48)	3.3×10^{-30}
Weight increased	8,730	7,290	1.21 (1.17–1.25)	1.2×10^{-31}
Somnolence	6,890	5,865	1.18 (1.14–1.23)	1.4×10^{-20}
Akathisia	2,566	2,305	1.12 (1.06–1.18)	1.5×10^{-4}
Diabetes mellitus	2,019	1,933	1.05 (0.98–1.12)	0.15
Extrapyramidal disorder	2,088	2,761	0.76 (0.71–0.80)	1.3×10^{-21}
Death	7,399	10,986	0.66 (0.64–0.68)	2.2×10^{-158}
Galactorrhoea	800	1,649	0.48 (0.45–0.53)	3.2×10^{-65}
Hyperprolactinaemia	1,044	2,364	0.44 (0.41–0.47)	1.7×10^{-112}
ANTIEPILEPTIC AGENT				
Dizziness	5,223	2,032	1.63 (1.55–1.72)	8.1×10^{-77}
Rash	6,435	2,576	1.59 (1.52–1.67)	9.7×10^{-86}
Suicidal ideation	2,260	1,124	1.26 (1.17–1.36)	5.3×10^{-10}
DRESS	1,914	996	1.20 (1.11–1.30)	3.8×10^{-6}
Toxic epidermal necrolysis	1,027	549	1.17 (1.05–1.30)	0.0038
Stevens-Johnson syndrome	2,087	1,121	1.17 (1.08–1.25)	5.2×10^{-5}
Somnolence	3,880	2,567	0.94 (0.90–0.99)	0.024
Hyponatraemia	880	720	0.76 (0.69–0.84)	1.2×10^{-7}
Death	1,795	1,713	0.65 (0.61–0.69)	8.9×10^{-37}
Ataxia	752	768	0.61 (0.55–0.67)	6.4×10^{-22}

ROR, reporting odds ratio; values above 1 indicate disproportionate reporting in women. Denominators are the class totals in Table 1. DRESS, drug reaction with eosinophilia and systemic symptoms. q values are Benjamini-Hochberg adjusted across all 32 comparisons in the study; all are significant at $q < 0.05$ except diabetes mellitus. Terms are ordered by ROR within each class.

Antiepileptic agents

Cutaneous reactions were consistently female-predominant: rash (ROR 1.59, 95% CI 1.52-1.67), drug reaction with eosinophilia and systemic symptoms (1.20, 1.11-1.30), toxic epidermal necrolysis (1.17, 1.05-1.30) and Stevens-Johnson syndrome (1.17, 1.08-1.25), reproducing the established female predominance in severe cutaneous adverse reactions. Dizziness (1.63, 1.55-1.72) and suicidal ideation (1.26, 1.17-1.36) were also female-predominant. Ataxia (0.61, 0.55-0.67) and hyponatraemia (0.76, 0.69-0.84) were male-predominant; the ataxia estimate is indistinguishable from the severity baseline and should not be read as a sex-specific pharmacological signal.

Discussion

Analysing three unrelated psychotropic classes under a single design revealed a feature that no single-class study could detect: a severity asymmetry in reporting that is common to all of them. Male reports were more often serious in every class, and the reporting odds ratio for death clustered between 0.60 and 0.66 across four classes with no shared pharmacology. The most economical explanation is that this reflects how adverse events involving men and women reach the reporting system, not how the drugs behave.

The practical consequence is methodological (Rushovich et al., 2023; Thompson et al., 2016). A sex-stratified ROR of around 0.6 for a severe outcome is what this database returns by default. Published disproportionality analyses that interpret such a value as evidence of greater male susceptibility may be reporting the baseline rather than a signal. Conversely, estimates that depart from it, in either direction, are the ones that merit pharmacological attention. Read against that baseline, the benzodiazepine findings are the most clinically striking (Rushovich et al., 2023). The split is not between mild and severe outcomes but between two different routes to harm. Falls and memory impairment are the characteristic complications of benzodiazepines taken as prescribed, particularly in older patients, and both were substantially female-predominant. Drug abuse, dependence and overdose are the complications of misuse, and all three were strongly male-predominant, well below the severity baseline. That intentional overdose and completed suicide sat near parity reinforces the distinction, since deliberate self-harm belongs to neither pattern.

The antipsychotic results provide reassurance about method and one genuine surprise (Food and Drug, 2025; van Puijenbroek et al., 2002). QT prolongation and tardive dyskinesia, both independently established as more frequent in women, emerged with closely similar effect sizes, which supports the validity of the design. The prolactin findings run the other way: hyperprolactinaemia and galactorrhoea were roughly twice as likely to be reported in men. We do not interpret this as a higher incidence in men. A more plausible explanation is reporting salience: galactorrhoea in a man is anomalous and prompts investigation and reporting, whereas in a woman it may be attributed to other causes or considered unremarkable. If so, it is a clear demonstration that spontaneous reporting measures the detection of events as much as their occurrence (Montastruc et al., 2011). The antiepileptic findings reproduce the known female predominance of severe cutaneous adverse reactions across four related terms, which again supports the method, and add a female excess of reported suicidal ideation that merits examination in data with a denominator.

Study limitations: Spontaneous reporting cannot yield incidence, risk or rate, and a reporting odds ratio measures disproportionate reporting rather than relative risk (Benjamini and Hochberg, 1995; Rothman et al., 2004). Reporting is voluntary and incomplete, causality is not established for individual reports, and a drug listed in a report is not necessarily the cause of the event. We could not adjust for age, indication, dose, treatment duration or concomitant medication. Age is a particular concern for the benzodiazepine findings, since falls and memory impairment are strongly age-related and the age distribution of benzodiazepine use differs by sex; the female predominance of these outcomes may partly reflect an older female treated population rather than a sex effect as such. The severity baseline is characterised rather than explained. It may arise from differences in who reports, from differences in healthcare contact, from differences in the severity of events that prompt reporting, or from a combination. We identified it but cannot decompose it here, and a formal analysis stratified simultaneously by sex, class and reporter qualification is not possible through the public interface, which rejects queries combining three field restrictions. Replication using the downloadable quarterly FAERS files, which permit arbitrary stratification, would allow that decomposition. Counts for terms falling outside the retrievable frequency range of a stratum are bounded rather than exact; such terms were excluded rather than estimated.

Conclusions

Across 1,231,335 reports for three unrelated psychotropic classes, a consistent severity asymmetry was found in which male reports were more often serious and the reporting odds ratio for death was near-invariant at approximately 0.6. Sex-stratified disproportionality estimates should be interpreted against that baseline rather than against unity. Once this is done, benzodiazepine harms separate cleanly into therapeutic-use effects predominating in women and misuse-related outcomes predominating in men, recognised sex effects in antipsychotic and antiepileptic safety are reproduced, and a counterintuitive male excess of reported

prolactin-related effects emerges that is best explained by differential detection rather than differential occurrence.

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