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Research article

Symptoms in Women, Severe Events in Men: Sex Differences in Adverse Event Reporting for Analgesic and Anti-Inflammatory Medicines Across 2,634,554 Reports

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Abstract: Sex differences in drug safety are usually studied one drug at a time, which cannot distinguish a class-specific effect from a general property of how adverse events are reported. We examined three analgesic and anti-inflammatory classes under a single design, against a baseline derived from four previously analysed classes. Case/non-case disproportionality analysis of the FDA Adverse Event Reporting System via openFDA database. All reports listing an NSAID, opioid agonist or corticosteroid 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 28 pre-specified Preferred Terms with Benjamini-Hochberg control of the false discovery rate. 2,634,554 reports were analysed. Male reports were more often serious in all three classes (all $p < 0.001$). The death ROR was 0.63, 0.70 and 0.61; pooled with four previously analysed classes it ranged 0.60 to 0.70 across seven unrelated classes (mean 0.637, SD 0.035). Against this baseline, women disproportionately reported symptomatic events and men structural ones: for NSAIDs, nausea (ROR 1.91) and abdominal pain (1.43) versus gastrointestinal haemorrhage (0.56) and myocardial infarction (0.54). Opioid outcomes separated by route of harm, with falls (1.69) in women and drug abuse (0.39) in men. Corticosteroid osteoporosis showed the largest female excess observed (2.16, 95% CI 2.04-2.28). A severity asymmetry invariant across seven classes underlies sex-stratified reporting and must be accounted for before class-specific signals are read. Opioids replicate a therapeutic-use versus misuse separation previously seen with benzodiazepines.

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Introduction

Analgesic and anti-inflammatory medicines are among the most widely used drug classes in the world, and all three considered here carry well-characterized serious risks: gastrointestinal and cardiovascular events with non-steroidal anti-inflammatory drugs (NSAIDs), dependence and respiratory depression with opioids, and metabolic, skeletal and ocular complications with corticosteroids [1, 2].

Whether these risks fall differently on women and men is usually investigated drug by drug. That approach has an inherent limitation [3]. Spontaneous reporting systems capture what is reported rather than what occurs, and if reports concerning men are systematically more severe than those concerning women for reasons unrelated to any particular drug, every sex-stratified estimate inherits that asymmetry. A single-class study cannot detect such a baseline, because it has nothing to compare against [4, 5].

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In two preceding analyses using an identical design, we observed the same pattern in four pharmacologically unrelated classes: statins, benzodiazepines, atypical antipsychotics and antiepileptic agents [6]. In each, male reports were more often serious, and the reporting odds ratio for death clustered near 0.6 [7]. We also observed, for benzodiazepines, that outcomes separated not by severity but by route of harm, with the complications of therapeutic use predominating in women and those of misuse predominating in men.

The present study extends that design to three analgesic and anti-inflammatory classes. It tests two specific predictions: that the death reporting baseline will recur in classes with no pharmacological relationship to those already examined, and that opioids, as the second class with substantial misuse potential, will reproduce the therapeutic-use versus misuse separation seen with benzodiazepines.

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 (20,692,690 reports). Reports were identified by the Established Pharmacologic Class terms 'Nonsteroidal Anti-inflammatory Drug', 'Opioid Agonist' and 'Corticosteroid' 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 symptomatic and severe organ-level outcomes. Death was included in all classes as a common comparator. Terms whose count fell below the retrievable frequency range in either sex stratum were excluded rather than estimated, since the public interface returns only a bounded value in that case.

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 were calculated with 95% confidence intervals from the standard error of the log odds ratio [6, 8]. An ROR above 1 indicates disproportionate reporting in women. Twenty-eight comparisons were made. The false discovery rate was controlled using the Benjamini-Hochberg procedure applied across all comparisons, and adjusted q values are reported [9]. Proportions were compared using the chi-squared test with continuity correction.

The severity baseline was characterised by comparing the proportion of reports flagged serious by sex within each class, and by pooling the death ROR across all seven classes analysed under this design to date. Analyses used Python 3 with SciPy. The study is reported in accordance with the STROBE statement [10].

Results

Cohort

2,634,554 reports with recorded sex were analysed: 1,183,527 NSAID reports (698,719 women, 484,808 men), 308,390 opioid agonist reports (168,930 women, 139,460 men) and 1,142,637 corticosteroid reports (651,361 women, 491,276 men).

Table 1. Severity baseline across seven drug classes analyzed under one design.

Drug class	Reports, women	Reports, men	Serious, women	Serious, men	ROR, death
NSAID	698,719	484,808	68.9%	75.1%	0.63
Opioid agonist	168,930	139,460	70.8%	77.9%	0.70
Corticosteroid	651,361	491,276	75.5%	82.0%	0.61
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 $p < 0.001$. ROR, reporting odds ratio for death, women versus men, within class. *Analysed previously under the same design and reproduced here for comparison. Across all seven classes the death ROR ranges 0.60 to 0.70 (mean 0.637, SD 0.035).

The severity baseline recurs

Male reports were more often flagged serious in all three classes: 75.1% versus 68.9% for NSAIDs, 77.9% versus 70.8% for opioids, and 82.0% versus 75.5% for corticosteroids (all $p < 0.001$). The ROR for death was 0.63 for NSAIDs, 0.70 for opioids and 0.61 for corticosteroids.

Pooled with the four classes analysed previously, the death ROR across seven pharmacologically unrelated classes ranged from 0.60 to 0.70, with a mean of 0.637 and a standard deviation of 0.035 **(Figure 2A)**. Male reports were more often serious in all seven **(Figure 2B)**. A quantity that varies this little across classes with no shared mechanism, indication or patient population is a property of reporting rather than of pharmacology, and is treated here as the baseline against which class-specific estimates are read.

NSAIDs

NSAID outcomes divided sharply by whether the event was symptomatic or structural **(Figure 1, Table 2)**. Women disproportionately reported nausea (ROR 1.91, 95% CI 1.88-1.94), rash (1.72, 1.68-1.75), hypertension (1.46, 1.42-1.50), abdominal pain (1.43, 1.40-1.47) and anaphylactic reaction (1.28, 1.22-1.35). Men disproportionately reported myocardial infarction (0.54, 0.52-0.55), gastrointestinal haemorrhage (0.56, 0.55-0.58), acute kidney injury (0.69, 0.67-0.70) and anaemia (0.83, 0.81-0.86).

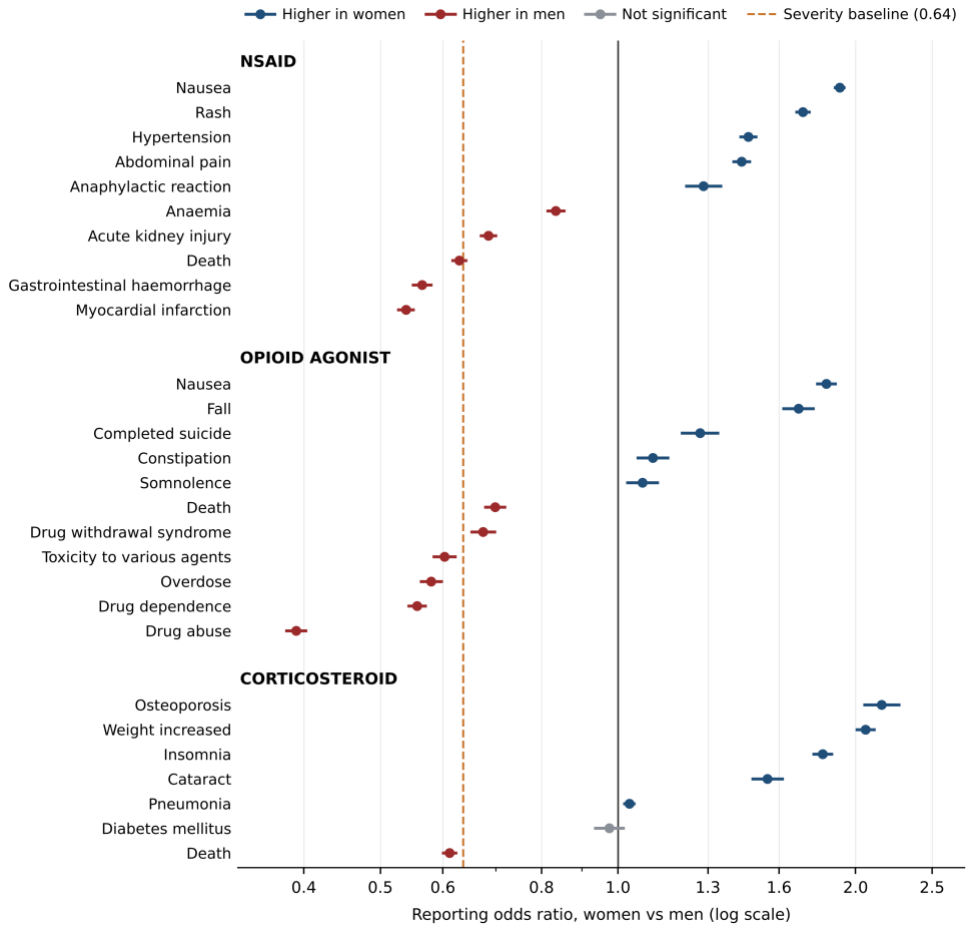


Figure 1. Reporting odds ratios for women versus men across three drug classes.
Points are reporting odds ratios with 95% confidence intervals, on a logarithmic scale. Values to the right of the solid line are reported disproportionately in women; values to the left, in men. The dashed line marks the severity baseline of 0.64 derived from seven drug classes **(Table 1, Figure 2)**. Terms are ordered by effect size within each class.

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

MedDRA Preferred Term	Women, n	Men, n	ROR (95% CI)	q
NSAID				
Nausea	50,056	18,837	1.91 (1.88–1.94)	$< 10^{-300}$
Rash	27,036	11,116	1.72 (1.68–1.75)	$< 10^{-300}$
Hypertension	17,559	8,399	1.46 (1.42–1.50)	2.0×10^{-178}
Abdominal pain	16,061	7,828	1.43 (1.40–1.47)	5.8×10^{-149}
Anaphylactic reaction	3,767	2,039	1.28 (1.22–1.35)	1.5×10^{-19}
Anaemia	11,382	9,437	0.83 (0.81–0.86)	4.6×10^{-38}
Acute kidney injury	11,937	11,995	0.69 (0.67–0.70)	8.0×10^{-186}
Death	13,732	14,967	0.63 (0.61–0.64)	$< 10^{-300}$
Gastrointestinal haemorrhage	7,862	9,577	0.56 (0.55–0.58)	2.5×10^{-311}
Myocardial infarction	10,573	13,448	0.54 (0.52–0.55)	$< 10^{-300}$
OPIOID AGONIST				
Nausea	13,971	6,524	1.84 (1.78–1.89)	$< 10^{-300}$
Fall	5,247	2,592	1.69 (1.61–1.78)	4.6×10^{-106}
Completed suicide	3,138	2,048	1.27 (1.20–1.34)	8.0×10^{-17}
Constipation	4,021	3,005	1.11 (1.06–1.16)	3.5×10^{-5}
Somnolence	3,869	2,979	1.07 (1.02–1.13)	0.0041
Death	7,222	8,380	0.70 (0.68–0.72)	9.9×10^{-106}
Drug withdrawal syndrome	5,156	6,217	0.67 (0.65–0.70)	3.3×10^{-94}
Toxicity to various agents	5,667	7,593	0.60 (0.58–0.62)	5.2×10^{-178}
Overdose	6,163	8,548	0.58 (0.56–0.60)	1.2×10^{-226}
Drug dependence	8,682	12,373	0.56 (0.54–0.57)	$< 10^{-300}$
Drug abuse	5,841	11,702	0.39 (0.38–0.40)	$< 10^{-300}$
CORTICOSTEROID				
Osteoporosis	5,057	1,775	2.16 (2.04–2.28)	3.9×10^{-178}
Weight increased	17,130	6,362	2.06 (2.00–2.12)	$< 10^{-300}$
Insomnia	14,098	5,910	1.82 (1.76–1.87)	$< 10^{-300}$
Cataract	5,273	2,579	1.55 (1.48–1.62)	4.9×10^{-74}
Pneumonia	28,549	20,863	1.03 (1.01–1.05)	4.3×10^{-4}
Diabetes mellitus	4,432	3,428	0.97 (0.93–1.02)	0.27
Death	13,950	16,971	0.61 (0.60–0.63)	$< 10^{-300}$

ROR, reporting odds ratio; values above 1 indicate disproportionate reporting in women. Denominators are the class totals in Table 1. q values are Benjamini-Hochberg adjusted across all 28 comparisons; all significant at q < 0.05 except diabetes mellitus. Terms are ordered by ROR within each class.

The juxtaposition of abdominal pain and gastrointestinal haemorrhage is notable. Women reported the symptom 1.43 times as often and the structural lesion 0.56 times as often, a 2.6-fold divergence between two outcomes of the same organ system. Myocardial infarction and gastrointestinal haemorrhage both lie below the 0.637 baseline and so are not explained by it; anaemia at 0.83 lies above it.

Opioid agonists

The prediction that opioids would reproduce the benzodiazepine pattern was confirmed. Outcomes separated by route of harm rather than by severity. Women disproportionately reported the complications of therapeutic use: nausea (ROR 1.84, 95% CI 1.78-1.89), falls (1.69, 1.61-1.78), constipation (1.11, 1.06-1.16) and somnolence (1.07, 1.02-1.13). Men disproportionately reported the complications of misuse: drug abuse (0.39, 0.38-0.40), drug dependence (0.56, 0.54-0.57), overdose (0.58, 0.56-0.60), toxicity to various agents (0.60, 0.58-0.62) and drug withdrawal syndrome (0.67, 0.65-0.70).

Drug abuse at 0.39 is the most extreme male-predominant estimate in this study and lies far below the severity baseline. Completed suicide, by contrast, was female-predominant (1.27, 1.20-1.34), distinguishing deliberate self-harm from the misuse pattern, as was also observed for benzodiazepines.

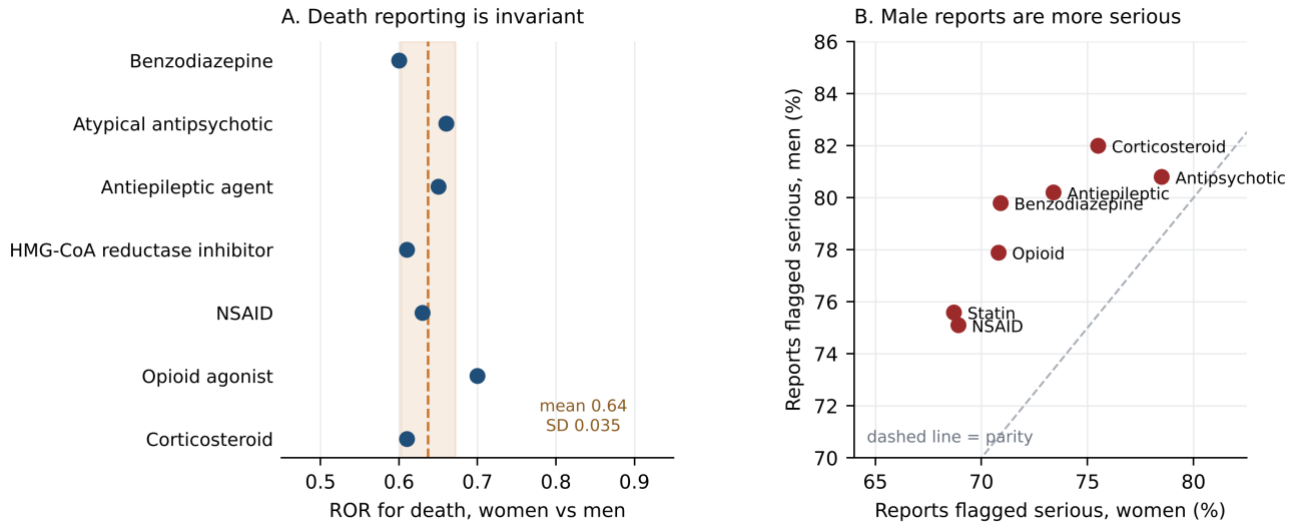


Figure 2. The severity baseline across seven drug classes. **(A)** Reporting odds ratio for death, women versus men, within each of the seven drug classes analysed under this design. The shaded band spans one standard deviation about the mean of 0.637. **(B)** Proportion of reports flagged serious, men against women, for the same seven classes; every class lies above the line of parity, indicating that male reports are more often serious irrespective of drug class.

Corticosteroids

Corticosteroid outcomes were strongly female-predominant across the recognised toxicity profile. Osteoporosis showed the largest female excess observed anywhere in this programme (ROR 2.16, 95% CI 2.04-2.28), followed by weight increase (2.06, 2.00-2.12), insomnia (1.82, 1.76-1.87) and cataract (1.55, 1.48-1.62). Pneumonia was marginally female-predominant (1.03, 1.01-1.05) and diabetes mellitus showed no sex difference (0.97, 0.93-1.02; q = 0.27), the only non-significant comparison in the study. Death was male-predominant at 0.61, indistinguishable from the baseline.

Discussion

Across 2,634,554 reports for three analgesic and anti-inflammatory classes, both predictions were confirmed. The death reporting baseline recurred, extending to seven the number of unrelated classes in which it has now been observed, with a standard deviation of 0.035 around a mean of 0.637. And opioids reproduced the therapeutic-use versus misuse separation previously seen with benzodiazepines, in the same direction and with comparable effect sizes.

The replication matters because it was predicted in advance rather than found by inspection. Two classes with substantial misuse potential, sharing no pharmacology beyond that, produced the same split: falls and nausea predominating in women, abuse and dependence predominating in men [11, 12]. The most parsimonious reading is that these classes are used differently by women and men rather than tolerated differently, and that spontaneous reporting is capturing a difference in the pattern of use [4].

The NSAID findings extend a pattern first observed with statins, where women reported muscle symptoms and men reported muscle destruction. Here the same divergence appears in the gastrointestinal tract: women reported abdominal pain disproportionately and gastrointestinal haemorrhage disproportionately less, a 2.6-fold divergence between symptom and lesion within one organ system. That this structure recurs across unrelated classes and organ systems suggests something general about how symptomatic and structural events reach reporting systems differently for women and men [7].

The corticosteroid results are the most readily explained pharmacologically. The female excess in reported osteoporosis, the largest in the programme at 2.16, is consistent with postmenopausal bone loss compounding glucocorticoid-induced loss, and the cataract finding is consistent with the higher background prevalence of cataract in women. These are plausibly real differences in occurrence rather than reporting artefacts, and they illustrate that the baseline does not render all estimates uninterpretable, only those close to it [3].

The practical implication is methodological and applies to any sex-stratified disproportionality analysis.

An ROR near 0.64 for a severe outcome is what this database returns by default. Studies reporting such a value as evidence of greater male susceptibility may be reporting the baseline. Estimates that depart from it materially, such as drug abuse at 0.39 or osteoporosis at 2.16, are the ones that warrant pharmacological or behavioural interpretation.

Study limitations: Spontaneous reporting yields no denominator of exposed patients, so no incidence, risk or rate can be calculated, and a reporting odds ratio measures disproportionate reporting rather than relative risk.[1,2] 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, duration or concomitant medication. Age is a particular concern for the corticosteroid and opioid findings, since osteoporosis, cataract and falls are strongly age-related and the treated populations differ in age structure by sex; the female excess in these outcomes may partly reflect an older female treated population. Indication is a concern for NSAIDs, where the cardiovascular findings may reflect a higher burden of pre-existing cardiovascular disease among male users. The severity baseline is characterised but not explained. It may arise from differences in who reports, in healthcare contact, in the threshold of severity that prompts a report, or in the underlying distribution of events. A decomposition would require simultaneous stratification by sex, class and reporter qualification, which the public interface cannot perform because it rejects queries combining three field restrictions. Replication using the downloadable quarterly FAERS files, which permit arbitrary stratification, would allow it.

Conclusion

In 2,634,554 reports for NSAIDs, opioid agonists and corticosteroids, male reports were more often serious and the reporting odds ratio for death fell within the narrow range now observed across seven unrelated drug classes. Sex-stratified disproportionality estimates should be interpreted against that baseline rather than against unity. Once this is done, NSAID outcomes divide between symptomatic events predominating in women and structural events predominating in men, opioid outcomes reproduce a previously predicted separation between therapeutic use and misuse, and corticosteroid osteoporosis emerges as the largest sex difference yet observed under this design.

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References

1. Evans, S.J.W., Waller, P.C., and Davis, S. Use of proportional reporting ratios (PRRs) for signal generation from spontaneous adverse drug reaction reports. Pharmacoepidemiology and Drug Safety. **2001**. 10(6): 483–486 10.1002/pds.677.
2. Fulcher, J., O'Connell, R., et al. Efficacy and safety of LDL-lowering therapy among men and women: meta-analysis of individual data from 174,000 participants in 27 randomised trials. The Lancet. **2015**. 385(9976): 1397–1405 10.1016/S0140-6736(14)61368-4.
3. Food, U.S. and Drug, A. openFDA: Drug Adverse Event API. **2025**.
4. Mockenhaupt, M., Viboud, C., et al. Stevens-Johnson syndrome and toxic epidermal necrolysis: assessment of medication risks with emphasis on recently marketed drugs. The EuroSCAR-study. Journal of Investigative Dermatology. **2008**. 128(1): 35–44 10.1038/sj.jid.5701033.
5. Montastruc, J.L., Sommet, A., et al. Benefits and strengths of the disproportionality analysis for identification of adverse drug reactions in a pharmacovigilance database. British Journal of Clinical Pharmacology. **2011**. 72(6): 905–908 10.1111/j.1365-2125.2011.04037.x.
6. van Puijenbroek, E.P., Bate, A., et al. A comparison of measures of disproportionality for signal detection in spontaneous reporting systems for adverse drug reactions. Pharmacoepidemiology and Drug Safety. **2002**. 11(1): 3–10 10.1002/pds.668.
7. Watson, S., Caster, O., et al. Reported adverse drug

reactions in women and men: aggregated evidence from globally collected individual case reports during half a century. EClinicalMedicine. **2019**. 17: 100188 10.1016/j.eclinm.2019.10.001.

8. Rothman, K.J., Lanes, S., and Sacks, S.T. The reporting odds ratio and its advantages over the proportional reporting ratio. Pharmacoepidemiology and Drug Safety. **2004**. 13(8): 519–523 10.1002/pds.1001.
9. Benjamini, Y. and Hochberg, Y. Controlling the false discovery rate: a practical and powerful approach to multiple testing. Journal of the Royal Statistical Society: Series B (Statistical Methodology). **1995**. 57(1): 289–300 10.1111/j.2517-6161.1995.tb02031.x.
10. von Elm, E., Altman, D.G., et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. The Lancet. **2007**. 370(9596): 1453–1457 10.1016/S0140-6736(07)61602-X.
11. Wood, F.A., Howard, J.P., et al. N-of-1 trial of a statin, placebo, or no treatment to assess side effects. New England Journal of Medicine. **2020**. 383(22): 2182–2184 10.1056/NEJMc2031173.
12. Zucker, I. and Prendergast, B.J. Sex differences in pharmacokinetics predict adverse drug reactions in women. Biology of Sex Differences. **2020**. 11: 32 10.1186/s13293-020-00308-5.

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