

Drugs with Sex-Linked Risk of ADRs

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1 Introduction



2 Methods

1 paragraph summary outlining steps of method without details

identify drug-ADR pairs with disproportionately high ADR incidence in males or females. Get crowdsourced severity ranking.

2.1 Identifying Drugs with Disproportionate Sex Associations

AEOLUS, a standardized, de-duplicated version of the public US Food and Drug Administration Adverse Event Reporting System, was used to identify drugs with sex risks of ADRs. [1] Records with missing or nonsensical sex information were removed from AEOLUS.

We isolated drug-ADR pairs with significantly elevated incidence of the adverse event for either sex. After conducting tests on 264023 drug-ADR pairs in AEOLUS and applying a Bonferroni adjustment, 615 significant drug-ADR pairs ($p < 0.05$) remained. After dropping ADRs that were sex-exclusive (pregnancy, menopausal, prostate) or irrelevant (gunshot wound or homicide), 5914 drug-ADR pairs remained. ~~Sex at risk and sample size were determined from ADR frequencies.~~

2.2 Quantifying Sex Risk of Drug-ADR Pairs

For a given drug, the risk of ADRs to any population is influenced by two key features: the probability of occurrence of the ADR or the frequency and the extent of physiological harm caused by the ADR, or the severity.

Determining Severity Gottlieb et al. used Internet-based crowdsourcing to rank the severity of adverse events. [5] Ranging from 0 to 1, the rankings were positively related to the severity of the ADR. While ADRs in the severity resource were defined using MedDRA terminology, ADRs in AEOLUS were defined using SNOMED CT terminology. A public MedDRA-SNOMED mapping was used to retrieve the majority of ADR severity ranks. [2] The remaining were manually mapped. *put mapping list in supplementary?*

Determining Frequency Since drug prescription data was unavailable, ADR incidence could not be compared to drug usage across sexes. Instead for the population on a given drug, the sex ratio of a target ADR was compared to that of all other ADR. A 2×2 contingency table for each drug-ADR pair was created as follows:

	Target ADR Present	Target ADR Absent
Target Sex	a	b
Not Target Sex	c	d

The target sex was the sex with a higher incidence of the adverse event in the drug-ADR pair. For some subpopulation of AEOLUS on drug X, if some ADR Y was observed more often in Males then: a was number of Males that experienced Y; b was Males that experienced any ADR except Y; c was Females that experienced Y; d was Females that experienced any ADR except Y.

From this contingency table, various measures of frequency were calculated. The Reporting Odds Ratio (ROR) uses effect size to determine the association between sex and adverse event and has been used previously to identify sex-associations in drug ADR population data. [10] In most cases, this ratio of odds (ROR) acceptably approximates the ratio of risks or Relative Risk (RR). However, as probabilities become large, small changes in probabilities create significant deviations between ROR and RR. [7] In some cases, RR is considered more conservative and tends to yield accurate estimation of population risks. [3, 7] Another frequency measure, Likelihood Ratios (LR) combines sensitivity and specificity to calculate risk probabilities detached from the prevalence of the ADR. All three measures captured the frequency associated risk in a slightly different manner and were calculated using Equation 1.

$$ROR = \frac{a/c}{b/d} ; \quad LR = \frac{\frac{a}{a+c}}{\frac{b}{b+d}} ; \quad RR = \frac{\frac{a}{a+b}}{\frac{c}{c+d}} \quad (1)$$

During calculations, the sex ~~and risk~~ of the ADR was selected as the target sex in the contingency table. As a result, the magnitude of the frequency measures was always greater than 1 and directly related to the frequency associated sex risk of ADR. After calculating frequency measures for the 5914 ADR-pairs, their values were normalized to between 0 and 1 to yield three more frequency measures: normalized Reporting Odds Ratio (RORn), normalized Likelihood Ratio (LRn) and normalized Relative Risk (RRn). Ultimately the frequency-associated sex risk was quantified by 6 factors: ROR, RORn, LR, LRn, RR and RRn.

Adjusting for Sex Bias of Adverse Events The aforementioned frequency factors were calculated from disproportionality within drug consuming subpopulations. To isolate the sex-risk posed by a drug, we correct the drug-ADR frequency factors by the sex-risk posed by the adverse event. We identify adverse events with significant sex associations using χ^2 tests to compare the observed sex ratio of a target ADR to the expected sex ratio of all other ADRs in AEOLUS.

For significantly sex-biased adverse events (Bonferroni $p < 0.05$), all 6 frequency measures were computed with the universe as the complete AEOLUS population rather than a drug-specific subpopulation. The individual drug-ADR frequency factors were adjusted by their respective adverse event frequency factors to reflect the frequency sex-risk posed by the drug.

Data for the 5914 drug-ADR pairs, including adjusted frequency measures, severity ranking and sex at risk, is available in Table 5 of the Supplementary Materials.

2.3 Deriving Composite Drug Risk Scores

Linear combination was used to condense the frequency and severity information of thousands of individual drug-ADR pairs into composite sex-risks for 385 drugs. Each drug had 6 composite risks, one for each of the frequency measures, which were calculated using Equation 2.

$$\begin{aligned} \text{Individual Drug-Sex Risk} &= \text{Adjusted Frequency Measure} \times \text{Severity Rank} \\ \text{Composite Drug Risk} &= \log \left(\frac{\sum \text{Individual Male Risks}}{\sum \text{Individual Female Risks}} \right) \end{aligned} \quad (2)$$

For each drug, the composite risk score captures the increased risk of adverse events to either sex. Its magnitude communicates the difference in risk posed to males and females. Since we applied log transformation to make risks symmetric, a negative value indicates a female risk while a positive value indicates a male risk.

Figure 1 demonstrates that for a given drug, the composite risk scores critically account for the divergence between risk to males and females. Sertaline and Duloxetine's large, negative composite risks are explained by their high female propensity (i.e. more female ADR nodes than male). In contrast, Bupropion and Citalopram's smaller, positive female risks are illustrated in the more balanced distribution of pink and blue nodes. In this manner, the composite risk score for a drug provides a comparative, elevated risk for that sex rather than the absolute risk to that sex.

To eliminate statistical bias, six composite risk scores were derived from the six frequency measures for each of the 385 drugs. We established consistency across risk scores for a given drug by verifying that all scores proposed a risk to the same sex, that is, they were either all positive (male risk) or all negative (female risk). For the 322 drugs that were consistent, risk data is presented in Table 1 of Supplementary Materials.

2.4 Validation of Sex Risks

Statistical Significance We conducted permutation analysis to determine the statistical significance of these composite drug risks. For the 5914 drug-ADR pairs, frequency measure and severity rank values were shuffled and composite risks were computed. The number of drugs with consistent risks was determined. After 10000 randomized runs, 52% drugs had consistent risk scores on average in contrast with the 84% consistent drugs in our results.

Scientific Literature Drugs with known sex-linked ADR risks were identified from a manual PubMed review. Many findings in literature were too narrow because they were specific drug-ADR pairs with sex-risks and would be unfair comparisons since our method calculates a global, general drug level risk. Nevertheless, 12 drugs (all posing female risks) were identified in literature reviews that were suitable to corroborate our results. Drugs identified for corroboration generally consisted of cardiac, nervous system and HIV medication due to the extensive clinical research conducted regarding the effects of these drugs.

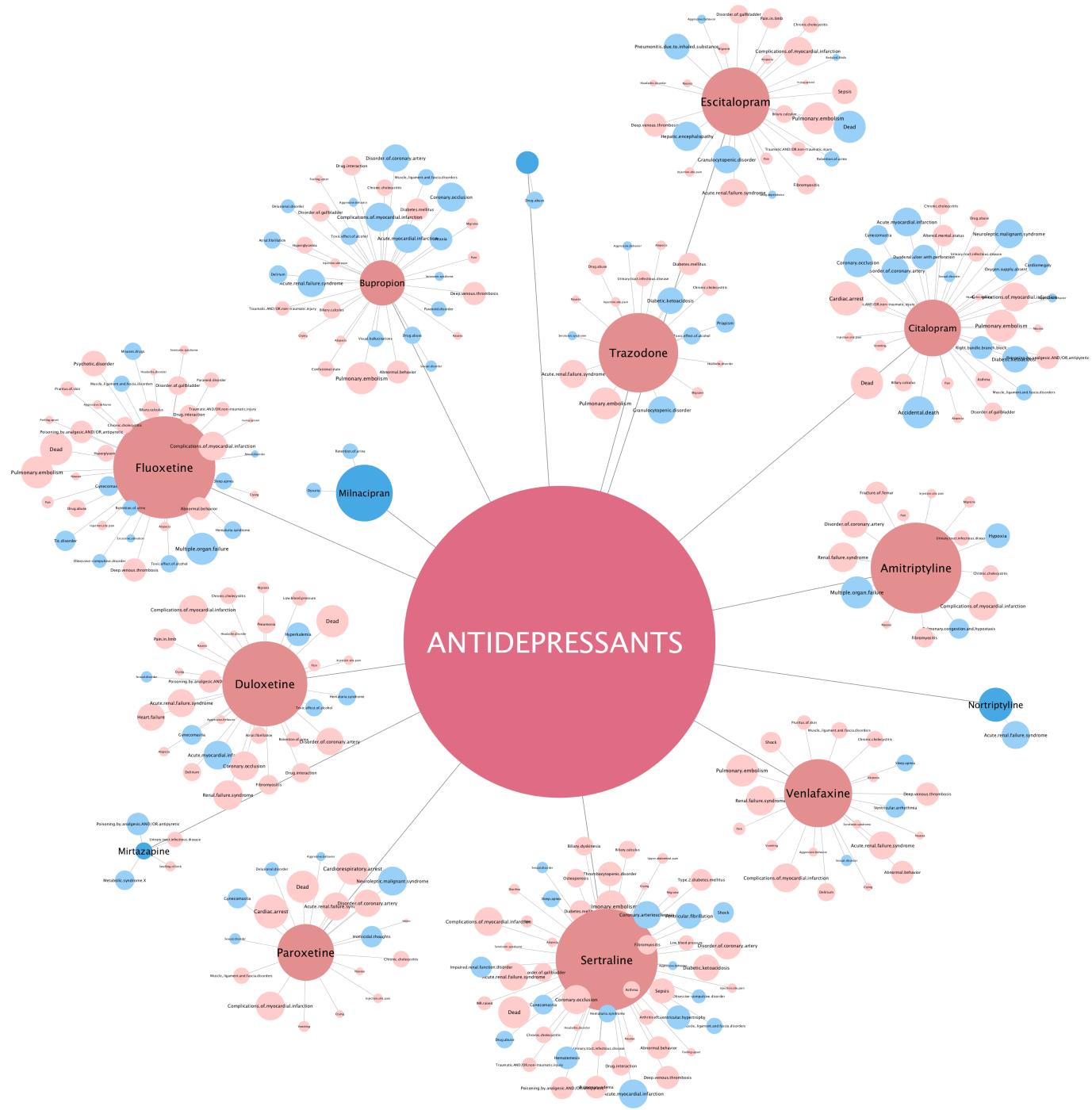


Figure 1: Antidepressant network illustration of individual drug-ADR risks converging into composite drug risks. Drug nodes are colored by sex at risk (pink for females, blue for males) and sized to scale by composite risks. Drugs are linked to adverse event nodes with significant sex bias. Adverse Event nodes are colored by sex at risk and sized by severity rank.

3 Results

Of 1506 drugs in AEOLUS, 322 drugs (21.4%) are found to have a sex-linked risk of ADRs. The majority (70.2%) of these drugs pose an increased risk to women. Although six independent risk scores were calculated, for convenience and clarity the mean of risk by RRn and risk by LRn is used as a proxy for the various scores.

According to our results, 10 of these drugs pose a female risk (agreeing with literature) while 2 drugs pose a male risk (disagreeing with literature). **For example, Digoxin – women (general cardiovascular??)... then explain HIV story** [] development for men and now widely found to have more effects in women Further details of individual drug validation can be found in Table 3.

To further investigate the reliability of risk scores derived using this method, we analyze the distribution of drugs by considering the number of ADRs that contribute to risk score calculation and the average sample size of patients experiencing side effects from the drug. Figure 2A shows that the two drugs conflicting with literature have a low sample size (less than 100) and low ADR count (less than 5). On the other hand, drugs agreeing with literature are evenly distributed across sample size and ADR count. This suggests that one risks to exclude or deem unreliable are those with both, ADR count less than 5 and sample size less than 100.

Figure 2B shows separate reliability distributions of male and female risks colored by the magnitude of risk posed. The most reliable drugs seem to pose female low-to-medium female risks. In comparison to evenly distributed female risks, male risks appear to be clustered in the bottom left corner with low sample size and low ADR count. Nevertheless, most drugs with identified male risks do not meet the exclusion criteria and have an ADR count greater than 5 or average sample size greater than 100. Thus, most of the novel sex-risks presented in Table 1 seem to be reliable even if there is no supporting clinical evidence to our knowledge. **Which risks are "reliable and interesting"???** Be specific

To assess patterns in sex-risk posed by drugs with similar mechanisms of action, drugs are grouped according to the Anatomical Therapeutic Chemical (ATC) Classification System. Figure 3 shows the number drugs in each ATC 1 class that pose a risk to either gender as a percentage of the total number of drugs in that ATC 1 class.

The dominance of female risk drugs could stem from the fact that the majority of drug risks found in this paper are female. Nevertheless, this prevalence of female risks is also cataloged in literature. In particular, anti-infectives for systemic use, muscolo-skeletal system and nervous system drugs have been generally shown to have a greater likelihood of causing ADRs in women than men. [9] Furthermore, cardiovascular system drugs have been consistently reported to pose greater risk of ADRs to females. [4, 6, 8]

However, the ATC distribution in Figure 3 goes beyond merely confirming clinical knowledge from a population perspective to reveal that drugs with similar mechanisms of action can pose widely varying risks the sexes. Some drugs within an ATC class have increased likelihood of causing ADRs in females whereas other drugs within the same class pose an increased risk to males. This is further illustrated at the ATC 3 level in Figure 4. For example, 29.4% of all antidepressants pose an increased risk to women while another 11.8% of antidepressants pose a risk to men.

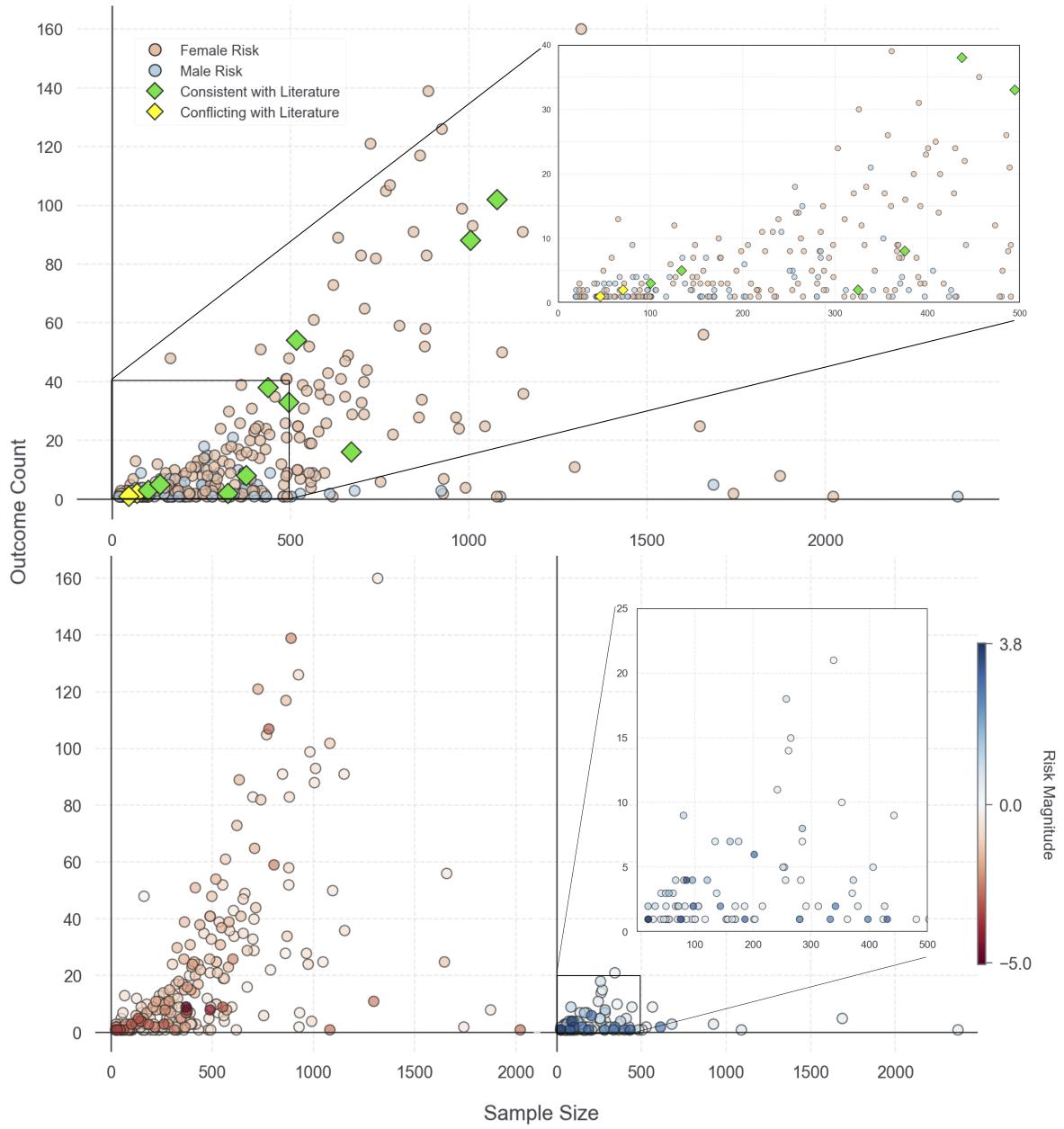


Figure 2: Reliability of Drug Risk Scores 2A. Comparing distribution of manually validated drug risks to all drug risks. 2B. Most reliable novel findings are drugs with medium-to-low female risk.

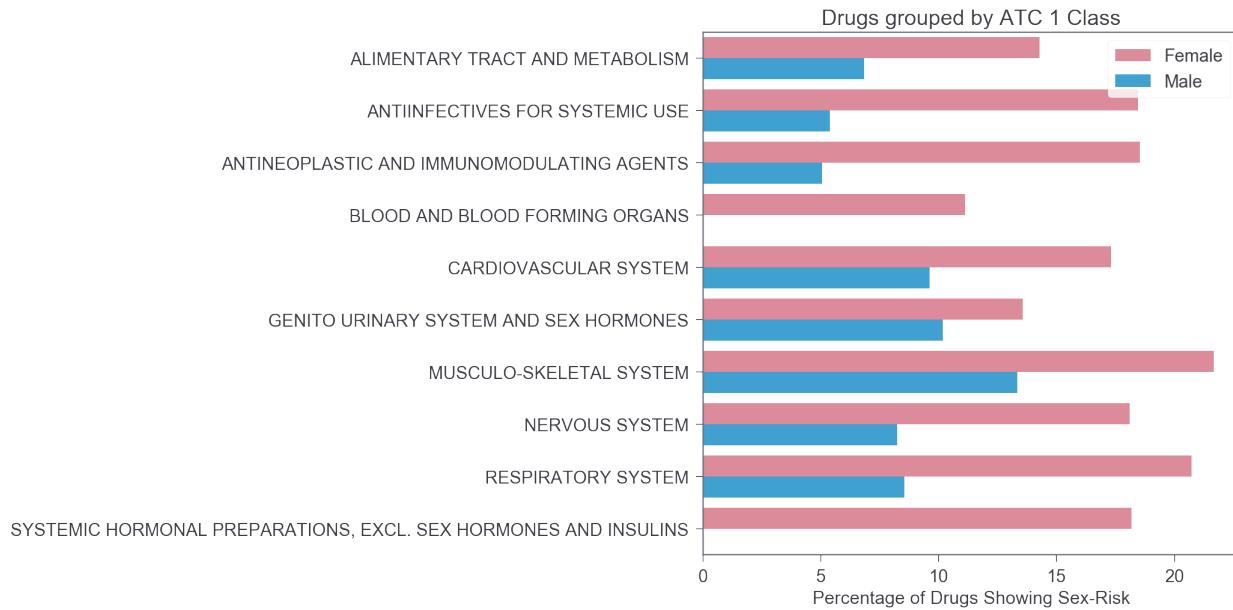


Figure 3: The number drugs that pose a risk to either gender as a percentage of the total number of drugs in each ATC 1 group.

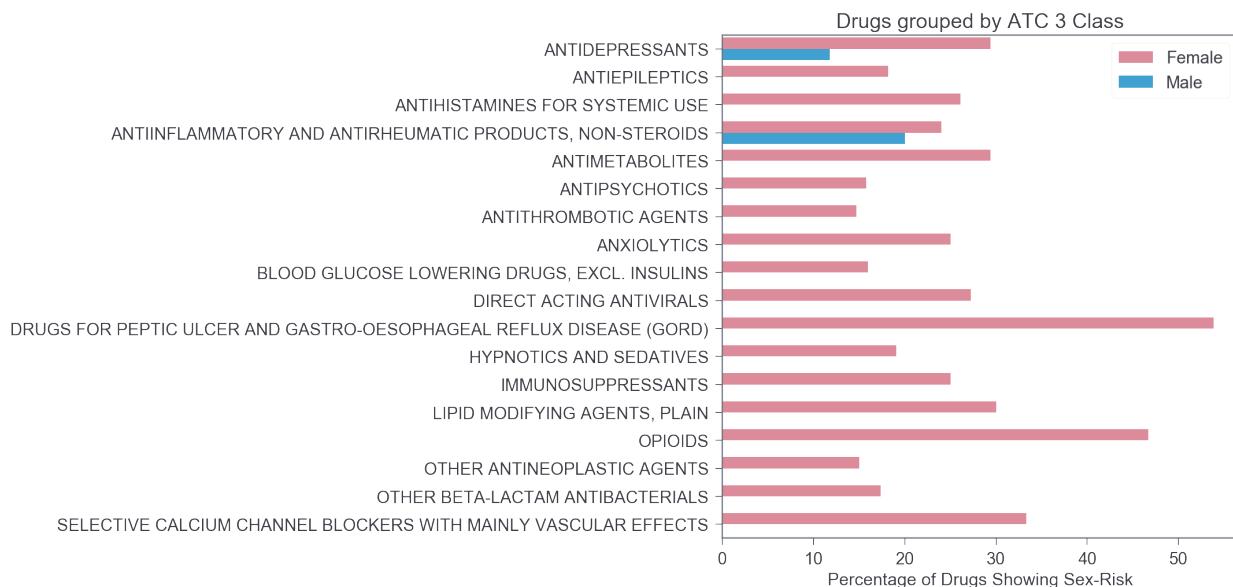


Figure 4: The number drugs that pose a risk to either gender as a percentage of the total number of drugs in each ATC 3 group.

4 Discussion

- 1) The results contain many novel drug risks that were previously unknown (to our knowledge) which seem reliable. There is potential to minimize ADRs by avoiding high-risk drugs for certain gender groups. The numerical, global risk score could be provided during decision making. (UpToDate).
- 2) Been widely cataloged that women have different pharmacology, dose response and tolerance to drugs. Thus groups of drugs (ATC classes) are expected to behave differently in men and women on the whole. Drugs with the same mechanism consistently behave differently in men and women. Drug behavior is expected to vary across ATC classes but not within. But this paper results suggest that same MOA drugs have different ADR risk in Males and Females. This is a novel suggestion that needs to be corroborated in multiple ways including but not limited to pharmacological lab evidence in vitro, EHR validation, and running the study on other population data.
- 3) Method provided can achieve composite risk for any demographic factor – age, ethnicity, expanded to apply. However, (a limitation) these factors are known to be covariates for each other.
- 4) A limitation of this study is also that our method needs to be corrected to account for covariates in order for the relationships found need to be established as causal. In particular, women are known to take more medications concomitantly and to be older... all of which could explain the increased female risks found by this study.

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