Data-driven identification of drugs that pose increased risk of adverse reactions to women.

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According to the FDA, adverse drug reactions (ADRs) are the fourth leading cause of death in the US although up to half are preventable.1 The variation of ADRs across demographic groups is not comprehensively understood. Many population specific ADRs remain unidentified because clinical trials have historically focused on evaluating safety and efficacy in homogenous patient populations (ie. white males). Until 1993, the FDA classified women as a special ‘subgroup’ and medications were approved without sufficient awareness of potential sex differences. For example, women often take longer to metabolically clear medications and report significantly more side effects than men.2 These differences are not widely known or used in clinical decision making.

We present a novel pharmacovigilance algorithm that quantifies the sex-risks posed by individual drugs and drug classes. To ensure that sex-specific drug prescription is not driving sex risks, we require minimum sample sizes and exclude sex-specific conditions. A minimum of 100 males and 100 females are required for each drug evaluated. Sex-specific conditions such as ‘prostate cancer’ or ‘miscarriage’ are excluded using the list of MedDRA gender-specific conditions. We use propensity score matching to correct for confounding factors. Propensity scores are calculated using out-of-bag scores from a random forest model, that is trained to predict a patient’s sex from input features age and co-medication. For each drug, a sex-balanced sub-population is derived by matching on propensity scores. Within this balanced drug-consuming cohort, the sex disproportionalility of each ADR is tested using Chi Squared tests. Drug-ADR pairs posing significant sex differences (adjusted $P < 0.01$) are retained. For each significant drug-ADR pair, the sex-specific risk is quantified using log(ROR). A positive score indicates female risk and negative indicates male risk. For each drug, the drug-ADR pairs posing significant sex-specific risks are summed to derive comprehensive sex risk scores for the drug(s). By mining the FDA Adverse Event Reporting System, we have developed a comprehensive database of drugs that pose an increased risk of ADRs to either sex.

Of the 1501 drugs evaluated, 379 signal sex-specific risks with 74.9% of these indicating female risks. To validate, we curated a set of 39 drugs with clinically established sex-differences — all of which demonstrated greater risk towards females. Our algorithm predicts 28 drugs to have sex differences, 23 of which are comprehensively identified as female risk (sensitivity=71.8%, positive predictive value=82.1%).

We noted significant sex differences in ADR risks of proton pump inhibitors (PPI). While PPI exposure has been associated with an increase in cardiovascular mortality (HR = 2.00; 95% CI 1.07–3.78; $P = 0.031$)3, no sex differences were noted. We replicate their survival analysis in the CUIMC EHR and stratify the adjusted Cox Proportional Hazards Model by sex, we discover that women (HR = 1.94; 95% CI 1.80-2.09; $P < 0.005$) are 26% more likely than men (HR = 1.68; 95% CI 1.59-1.77; $P<0.005$) to experience a fatal cardiovascular event after exposure to PPIs. In our results, when adverse reactions of PPIs are grouped by ICD 10 cardiovascular conditions their sex-risks become noisy. Thus, we have not be able to corroborate the general female risk found in our results with the cardio-specific risk in the EHR.

In conclusion, we provide a method to quantify sex-differences in ADR risk from post-marketing surveillance data and a comprehensive database of these risks. Although novel risks suggested here require further validation before modifying clinical practice, there is an opportunity to minimize adverse events by tailoring prescription to sex.

References