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Sex and gender in drug utilization: insights from the the Janusmed Sex and Gender database

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Background

The database Janusmed Sex and Gender, available in English and Swedish at www. https://janusinfo.se/, covers recommended medicines, focusing on clinically important differences in drug utilization for men, women, boys, and girls.

To the best of our knowledge, it is the first of its kind worldwide. It was projected by Karin Schenck-Gustafsson in 2014 with funding provided by the Region Stockholm (Stockholm County Council). Collaborations were established with the FDA in the US as well as the Swedish Medical Product Agency. Presently, our database is an integral part of routine activities within the Stockholm region, staffed with employed pharmacists, pharmacologists, consultants, and others professionals. Additionally, it is utilized in other regions of Sweden. To date, three doctoral dissertations have originated from our database. The background and how we built up the database have been described elsewhere.[1-4] In a recent update,[5] we summarized the results from 400 recommended medications, including the newest registrations. Approximately 4,000 individuals per month in Sweden, predominantly from the healthcare sector, consult our database, with an additional 2,000 users from other countries.

Analysing sex differences in drug utilization

However, pivotal clinical studies seldom include sex analyses concerning effects and adverse drug reactions. Power calculations to achieve statistical significance are often missing. Instead, sex analyses are tipically conducted post-hoc, often as a supplement or in a new publication. Women are often included as a subgroup alongside variables such as diabetes, age, ethnicity, and socioeconomic status. The absence of sex analysis was more prevalent among older medications. Sometimes, pharmacokinetic analyses remain unpublished. The absence of MeSH-terms often makes literature searching difficult. Sometimes, biological differences are described as gender differences or vice versa. Few studies prioritize sex differences as a primary outcome. Sometimes, a well-executed large observational study with sex analysis may be superior to a clinical trial lacking an analysis of sex differences.[6,7] Our group, working with the database, meets regularly. We also upgrade the database promptly upon receiving new information, otherwise on a regular basis, such as monthly.

Substances with clinically relevant sex differences exist across almost all therapeutical areas. Here are some examples:

- digoxin is recommended to be administered in lower doses for women due to lower renal function at older ages. Serum concentration is crucial;
- ACE-inhibitors (enalapril and ramipril) induce more coughing in women than men. ARB is recommended instead;
- citalopram prolongs QT time on ECG, increasing the risk of dangerous cardiac arrhythmias (Torsade de Pointes ventricular tachycardia);
- levodopa should be administered in lower doses to women because they have a higher risk of dyskinesias.

Pharmacokinetic differences between sexes might be more important than previously considered

Uptake, metabolization, and elimination of drugs, especially those eliminated renally, might vary between men and women, carrying clinical implications. Examples include digoxin, pregabalin, and ganciclovir. Older substances often lack pharmacokinetic data. Also, while most pharmacokinetic studies employ weight corrections, the majority of medical drugs are administered in standard doses. It is clearly easier to detect pharmacokinetic differences between men and women when adjusting for weight.

Classical pharmacodynamic sex differences are evident in inflammatory modifying antibodies, receptor sensitivity, and concentration-effect connection. However, the clinical relevance of these differences remains unclear.

Adverse side effects and sex differences

Women experience and report more adverse side effects of drugs. They are also prescribed more drugs, and polypharmacy is more common among women. Consequently, drug interactions are more common among women. Women typically weigh less than men and have

lower renal elimination rates, resulting in greater exposure to drugs. Moreover, unexpected adverse side effects are more frequent among women, probably due to stronger autoimmunity and influence of sex hormones.

Women also face a higher risk of dangerous drug-induced Torsade de Pointes ventricular tachycardia because they more frequently exhibit QT prolongation on their ECG compared to men. Testosterone reduces the QT-interval, potentially explaining why men are less affected.

Concerning statin use, a large register-based cohort study[8] showed that the risk of moderate to serious myopathy was higher in men than in women for lipophilic statins such as simvastatin and atorvastatin. However, for hydrophilic statins like rosuvastatin and pravastatin, there were no sex differences in the risk of moderate to serious myopathy. The adjusted hazard ratio for atorvastatin-induced myopathy was 6.7 in men compared to 2.9 in women.

Reproduction

Sex hormones can influence the effects and metabolism of drugs during the menstrual cycle, pregnancy, and menopause. For example, estrogen might increase the plasma concentrations of angiotensin II. During pregnancy, the plasma concentrations of lamotrigine and topiramate will decrease, potentially resulting in epileptic seizures if doses are not adjusted, highlighting the importance of monitoring drug concentrations. Carbamazepine and phenytoin might adversely affect natural sex hormones in both men and women, leading to changes in sexual health and menstruation. Some medications might reduce the concentration of synthetic hormones like estrogen and progesterone. Cancer drugs like capecitabine and fluorouracil can impact the sex cells in both men and women, which is crucial to consider when assessing the effectiveness of contraceptives.

Results from the first 400 analysed drugs

In our analysis of the first 400 recommended medicines,[5] we found that in 22% of the studies no adequate sex analysis was performed, even for drugs targeting diseases equally prevalent in men and women. In 20% of cases, we found significant sex differences. While these percentage may appear small, they are undoubtedly very significant.

Conclusions

With this tool, we aim to foster a better understanding of the importance of analyzing study results in both women and men, a practice already recommended by many research councils for clinical studies as well as animal and cell studies. Our goal is to ensure the administration of the correct medication at the appropriate dose, for the right indication, based on evidence that includes sex analyses.

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Conflicts of interest statement. Karin Schenck-Gustafsson is chair and founder of www.Janusinfo.se/sex and gender.

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