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REVIEW

Sex-Related Differences in Pharmacokinetics and Pharmacodynamics of Frequently Prescribed Drugs: A Review of the Literature

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ABSTRACT

While there is considerable evidence about sex-related differences between men and women in drug metabolism, efficacy and safety of frequently prescribed drugs such as analgesics, tranquillizers, statins and beta-blockers, clinicians' awareness of the implications on dosing and adverse event monitoring in routine practice is inadequate. Some drugs are more effective in men than women (e.g. ibuprofen) or vice versa (e.g. opioids, benzodiazepine), typically owing to pharmacodynamic causes. The 5-hydroxytryptamine (5-HT) receptor 3 antagonist alosetron is approved for women only since it largely lacks efficacy in men. For statins, equal efficacy was demonstrated in secondary prevention of cardiovascular events, but primary prevention is still under debate. For some drugs (e.g. paracetamol, metoprolol), women are at significantly higher risk of adverse effects. Therefore, considering sex-specific features in clinical trials and therapeutic guidelines is warranted to ensure efficacy and safety of medicines.

Keywords: CYP; Gender differences; Pharmacodynamics; Pharmacokinetics; Sex differences

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Key Summary Points

There is considerable evidence about sex-related differences in drug metabolism, efficacy and safety of frequently prescribed drugs such as analgesics, tranquillizers, statins and beta-blockers.

Some drugs are more effective in men than women (e.g. ibuprofen) or vice versa (e.g. opioids, benzodiazepine).

With other drugs (e.g. paracetamol, metoprolol), women are at significantly higher risk of adverse effects.

In the era of personalized medicine, all healthcare professionals should be concerned about the most effective use of medicines to ensure high-quality healthcare and should hence always bear in mind potential sex-related differences in efficacy and safety.

INTRODUCTION

Men and women are different in terms of physiology and pathophysiology. These differences are highly relevant in medicine as they can account for sex-specific clinical manifestations. An example is coronary heart disease: In the event of myocardial infarction, men typically display left-sided chest pain while the predominant symptoms in women are shortness of breath, abdominal pain and nausea. Coronary artery disease (CAD) differs phenotypically between men and women. Women typically display a later onset of coronary heart disease than men owing to the protective effects of oestrogen [1, 2]. Women more commonly suffer non-obstructive CAD, spontaneous coronary artery dissection, coronary microvascular dysfunction, stress-induced cardiomyopathy, just to name a few [3–6]. Risk factors for CAD, such as diabetes mellitus or smoking, may have different relative impact in men and women [4]. Importantly, there are also significant differences between men and women in terms of bioavailability, distribution, metabolism and elimination of drugs. This can differentially affect their efficacy and safety—certain drugs may work much better in women than men or vice versa. This is of particular relevance for long-term medication.

Underlying reasons for sex-related differences in pharmacokinetics and pharmacodynamics include obvious differences in physiology such as body fat content and hormonal control. Additionally, there are significant differences with respect to the physiology of organs such as the stomach, liver, lung and kidneys. The pH of the gastric juice in women is on average 0.5 units higher than in men, and the speed of gastric passage is inversely related to the level of oestrogen [7–10]. Liver mass and organ perfusion are lower in women than in men [11, 12].

Lung volume and functional lung capacity are also lower in women. Men have longer airways than women, causing greater specific resistance in the respiratory tract [13]. The glomerular filtration rate (GFR) is on average about 10% lower in women, and further, all other tubular processes are reduced in women [11, 14]. Moreover, there are sex differences in effects that correlate with differences in the plasma protein binding of drugs [15]. Finally, men and women also display differences with respect to drug metabolism e.g. the pre-systemic elimination of drugs can take divergent courses [7–17]. These sex-related differences in drug metabolism are described in more detail below.

In the past, women tended to be under-represented in clinical trials [18–20]. Following tragedies such as the congenital malformation of babies in women who had taken thalidomide during pregnancy [21, 22], drug testing on women, particularly those of child-bearing age, was not recommended by the US Food and Drug Administration (FDA) until the early 1990s [23, 24]. Thus, clinical trials for new medicines focused on middle-aged men for years, and the results of these trials still form the basis of current treatment guidelines [25, 26]. Sex-differentiated dosage data are lacking for most drugs [18, 19]. Importantly, there is evidence that

bioequivalence studies of generic versus reference drugs are carried out mostly in adult young men, neglecting to test for bioequivalence of active as well as inactive ingredients in women [27]. In theory it should not matter whether bioequivalence studies are conducted in men or in women, because each individual acts as their own control and differences between two tested formulations, if they exist, would be apparent whether one studies either male or female individuals. This may, however, not always be the case. There is evidence from several drug studies that intra-individual variability may be different between men and women [28]. Sex-related differences have been demonstrated for several substances [29–31] and awareness is rising. More recently, sex-specific approaches have been described e.g. for carboplatin dosing [32] or cardiovascular medications in the elderly [33].

This review describes important examples of commonly prescribed drugs, including some over-the-counter (OTC) drugs, with significant and clinically relevant sex-related differences in terms of pharmacokinetics and pharmacodynamics as well as the consequences for prescription and use of these drugs. PubMed (incl. PubMed Central and Medline) and an Austrian data source (Austria Codex) were searched using the following search terms and their combinations: "gender", "differences", "pharmacokinetics", "pharmacodynamics", "adverse reaction" and "drugs". Additionally, reference lists of identified articles and key systematic reviews were searched manually. Relevant articles in English and German published between January 1979 and December 2019 were considered. This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

SEX-DEPENDENT DIFFERENCES IN DRUG METABOLISM

There are remarkable differences between the sexes regarding the activity of drug metabolizing enzymes, both in phase I (drug modification) and phase II (conjugation).

Phase I of drug metabolism involves a variety of enzymes, of which cytochrome P450 (CYP) enzymes are particularly relevant [34–36]. Some of these CYP enzymes display significant sex-dependent differences in activity. For instance, the enzyme CYP3A4 is known to be up to 50% more active in adult Caucasian women than men [14, 17, 29, 30, 37].

While the normal menstrual cycle has no clinically relevant effect on enzyme activity, enzyme performance is increased during pregnancy [17]. Sex-related differences of CYP enzymes are summarised in Table 1, along with the effects of oral contraceptives and pregnancy and examples of drugs that are substrates of the respective enzymes.

Other phase I enzymes also show sex-related differences. The gastric enzymes alcohol dehydrogenase and aldehyde dehydrogenase, which are among the microsomal phase I enzymes and are involved in oxidative degradation, are significantly more active in men than women. This results in a much higher bioavailability of ethanol in women and represents the underlying pharmacokinetic reason why men tend to cope better with alcohol than women [14, 29, 30].

Or phase II conjugation enzymes, glucuronidating enzymes, for instance, display a lower activity in women than men. The most relevant sex-dependent differences of phase II enzymes are summarised in Table 2.

Further, some efflux transporters like P-glycoprotein (Pgp, also known as ATP-dependent translocase ABCB1) and the breast cancer resistance protein (BCRP, also known as broad substrate specificity ATP-binding cassette transporter ABCG2) are more active in men than in women [14, 29, 30]. Also, many transmembrane transport processes take place in which the sex hormones are directly or indirectly involved, most importantly oestrogen (primarily as oestradiol) in women and androgens (primarily testosterone) in men [16]. All these features contribute to relevant sex-related differences in metabolism and, as a consequence, in efficacy and safety of certain drugs as described below.

Table 1 Phase I metabolism: CYP450 enzymes and their sex-dependent activity [14, 17, 29, 30, 34–37]

CYP enzyme	Enzyme activity in men (M) vs. women (W)	Example drugs	Other characteristics
1A2	M > W	Clozapine, olanzapine	Suppressed activity during pregnancy or concomitant use of oral contraceptives
2A6	W > M	Nicotine, coumarin	Increased activity upon concomitant use of oral contraceptives
2B6	W > M	Bupropion, tamoxifen	Activity higher in Hispanic women than in Caucasian or African-American women
2C9	M = W	Imipramine, phenytoin	Increased activity during pregnancy
2C19	M = W	Imipramine, topiramate	Decreased activity during pregnancy or use of oral contraceptives
2D6	W > M	Codeine, fluoxetine, haloperidol	Exhibits extensive genetic polymorphism, increased activity during pregnancy
3A4	W > M	Cyclosporine, nimodipine, cortisol, zolpidem	Increased activity during pregnancy Expression is generally higher in Caucasian women than in Asian women Testosterone stimulates the activity level

Table 2 Phase II metabolism: enzymes and their sex-dependent activity [14, 17, 29, 30, 34–37]

Enzymes	Enzyme activity in men (M) vs. women (W)	Example drugs
UDP-glucuronosyltransferases (UGTs)	M > W	Oxazepam, acetaminophen, statins
Sulfotransferases	M > W	Acetaminophen
N-Acetyltransferases	M < W	Isoniazid, hydralazine
Methyltransferases	M > W	L-Dopa, azathioprine

SEX-RELATED DIFFERENCES OF FREQUENTLY PRESCRIBED DRUGS

In the era of personalized medicine consideration of sex and gender differences in the evaluation of drugs as well as in their post-marketing use and surveillance is of paramount importance [38]. Sex and gender differences have been demonstrated in a broad variety of diseases and drugs ([27, 38, 39] and references therein), although methodological limitations compromise the available evidence for most indications [39]. There is, however, high-quality evidence available in cardiovascular disease [39], e.g. for angiotensin-converting enzyme inhibitors (ACE inhibitors), angiotensin II receptor blockers (ARBs), newer antiplatelet agents, oral antithrombotic medications and the aldosterone blocker eplerenone, which have been reviewed and evaluated elsewhere [27, 39–41]. Evidence is also abundant for analgesics (ibuprofen, opioids, paracetamol, acetylsalicylic acid), tranquillisers (e.g. benzodiazepines), statins and beta-blockers, which are

the focus of this review. Further, an example of a medicine with sex-specific marketing authorisation is presented (alosetron).

Ibuprofen

Ibuprofen is a very commonly used non-steroidal anti-inflammatory drug (NSAID). Its absorption is rapid and complete when taken orally [42]. The area under the plasma concentration–time curve (AUC) of ibuprofen is dose-dependent, with extensive binding to plasma albumin in a concentration-dependent manner [43].

In an experimental pain model, ibuprofen resulted in significantly better pain reduction in men than in women [42]. In other studies, however, the pain-lowering effect of ibuprofen was comparable in men and women [44]. The disparity between the study results can be explained by differences in nociceptive mechanisms in the experimental pain models [45] and various factors influencing pain perception in clinical practice [46]. The potential sex difference in nociception might be connected to oestrogenic effects on the activity of the nervous system, resulting in improved transmission of pain impulses [42, 43, 47].

Opioids

In contrast to ibuprofen, opioids appear to work better in women; however, the desired stronger analgesic effects also correlate with an increased risk of adverse drug reactions (ADRs) [48, 49].

The pharmacological basis for these observations are differences in the affinity and density of the opioid receptors as well as different signal transduction pathways. Men are more responsive to opioids that bind to the μ-receptor, e.g. morphine and methadone [50]. In contrast, women benefit more from opioids that interact with the κ-receptor, e.g. nalbuphine and pentazocine [51]. This observation could be advantageously utilized e.g. when employing opioids after surgery.

Paracetamol (Acetaminophen, APAP)

Paracetamol is another commonly used analgesic. After oral administration paracetamol is rapidly absorbed from the gastrointestinal tract. The speed of absorption is dependent on the rate of gastric emptying [52]. Subsequently the drug is biotransformed predominantly in the liver to its major metabolites, sulfate and glucuronide conjugates. Additionally, a small proportion of the drug is transformed by CYP to a reactive intermediate which is detoxified by conjugation with glutathione [53]. Bioactivation and detoxification of paracetamol is controlled by a circadian rhythm coupled to nutritional suppression and food intake [54]. Research indicates that toxicity correlates with liver glutathione levels that rise and fall with the daily phases of eating and fasting, regardless of the food type [54, 55]. Moreover, various animal models showed that after meal consumption glutathione levels rise and correlate with liver protection, whereas low glutathione levels after fasting correlate with susceptibility [56, 57]. It also has been proposed that ketones generated during fasting increase the levels of cytochrome P450 enzymes, such as CYP2E1 [58, 59]. CYP2E1 is widely accepted as the most important form of cytochrome P450 responsible for upturn in APAP hepatotoxicity [54]. In humans, food typically delayed absorption and the maximum serum concentration of common analgesics such as aspirin, diclofenac, ibuprofen and paracetamol analgesics [60]. The known hepatotoxicity of paracetamol thus seems to be due to pharmacokinetic effects [52, 53, 61].

On average, women have a lower volume of distribution and a reduced metabolic clearance rate, resulting in higher plasma levels of paracetamol compared to men. This effect, coupled with the tendency of women to consume more tranquillisers than men, increases the risk of acute and chronic liver failure [62]. Also, cases of hepatic encephalopathy are more common in women.

Another aspect to consider when prescribing paracetamol is the narrow therapeutic index of the drug. Hence, women and in particular infants and children are at increased risk of overdose. This risk is further increased by the

common off-label use of paracetamol in primary care. Hence, paracetamol is often overdosed in the youngest children and conversely dosed at subtherapeutic levels in adolescents [63]. Hence, healthcare professionals should specifically inquire about the details of paracetamol administration when discussing antipyresis with parents.

Acetylsalicylic Acid (ASA, Aspirin)

Acetylsalicylic acid (ASA) is an NSAID that is widely used as an analgesic, but also—at lower doses—to prevent severe cardiovascular events. Strikingly, ASA reduces the risk of first myocardial infarction in men, but only the risk of second infarction in women [64, 65]. Another relevant sex-related difference is that ASA protects women far better from ischemic stroke than men [66]. However, these experiences from clinical practice cannot be accurately confirmed using pharmacokinetic models, because the absorption rate for ASA varies greatly between individuals and depends, among other factors, on the filling state of the stomach and on the gastric pH, with better absorption at low pH [67]. Since women have a slightly higher pH in the stomach, a lower absorption would be expected. On the other hand, since the activity of the glucuronidating enzymes in women is lower, the excretion of absorbed ASA is slowed by 30–40%. Women taking ASA regularly, especially at higher doses, are therefore at an increased risk of gastrointestinal complications [33].

Benzodiazepines and Nonbenzodiazepine Drugs (Z-Drugs)

Benzodiazepines are a group of tranquillisers. In the late 1970s, studies on the metabolic rate of one such drug, diazepam, showed longer elimination half-lives in young women than young men, in particular because of lower liver mass and lower enzyme activity [68]. As a consequence, dose reductions were encouraged.

Similarly, women display a slower overall metabolic clearance rate of the nonbenzodiazepine drug ("Z-drug") zolpidem and are hence more likely to experience ADRs [69]. For this reason, the FDA has requested that for women, the single dose be reduced from 10 to 5 mg for immediate-release formulations and from 12.5 to 6.25 mg for extended-release formulations. Initial absorption and systemic exposure from sublingual formulations are particularly high compared to normal characteristic tablets [70]. In the USA, zolpidem is also available in an low-dose sublingual form (3.5 mg) for patients who wake up in the middle of the night [71]. The reduced dose recommendation for women has not been implemented in Europe after a European risk assessment procedure, in which additional pharmacodynamic studies were considered. The lower maximum daily dose (5 mg) is recommended only for elderly people and patients with hepatic dysfunction, but no distinction between the sexes is made [72, 73].

For triazolam, clearance is generally comparable in both sexes. However, triazolam is significantly more potent in women taking progesterone or oral contraceptives [74]. It is believed that progesterone-containing oral contraceptives enhance the receptor binding of benzodiazepines. Other studies have shown that in general, the metabolism of oxidized benzodiazepines such as triazolam and alprazolam is inhibited by oral contraceptives at low doses while that of conjugated benzodiazepines such as lorazepam and temazepam is accelerated [75].

Statins

The regulation of cholesterol in the human body is interrelated with the hormonal system. Numbers of low-density lipoprotein (LDL) receptors and 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) reductase activity are closely connected with the level of endogenous oestrogen. After menopause, the LDL cholesterol (LDL-C)-lowering effects of statins were found to be attenuated [76]. Women's body composition and organ size initially lead to 15–20% higher serum levels, but differences in plasma adipokine levels and higher CYP3A4 expression subsequently induce faster and more extensive statin metabolism with a net effect of reduced

statin activity in women [76, 77]. Apart from the lipid-lowering effect of statins, other pleiotropic effects are known, such as a reduction of oxidative stress and the increment of antioxidant defences, effects to which women seem to be more responsive [78]. Therefore, there is an ongoing debate whether these sex-related differences in absorption and metabolism of statins result in a difference in clinical efficacy in cardiovascular prevention. Equal efficacy between sexes has to date only been established for secondary prevention of cardiovascular events [79].

Although not the focus of this publication, it needs to be noted that—aside from the sex-differences described above—research has shown substantial differences in the gender aspects of statin treatment, which describe the sociocultural differences [80]. In daily practice women requiring statin therapy were being offered statins less frequently and often not at the required intensity, while declining and discontinuing treatment more frequently [80, 81].

Beta-Blockers

Sex-related differences are also prominent for some frequently employed beta-blockers. One example is metoprolol, which is primarily decomposed via CYP2D6 [82]. Women build up metoprolol plasma levels which are about 40% higher than in men when standardised daily doses are given as a result of various reasons such as differences body weight, sex hormones, and other physiological and biochemical differences [65, 83]. This finding is significant as the plasma concentration of metoprolol rises by up to another 50% in women taking oral contraceptives, owing to effects on metabolizing enzymes [84]. It is therefore not surprising that ADRs are much more common in women undergoing treatment with metoprolol [85]. Further, metoprolol displays high hepatic extraction, equivalent to a high first-pass effect [84]. Hence, the extent of bioavailability correlates with the blood flow through the liver, which has a lower mass in women [85]. Limitations of liver perfusion may lead to (undesirable) increased bioavailability. The subsequent inactivation and excretion depend on the metabolic capacity of the liver parenchyma and the activity of CYP2D6.

Dose equivalency studies showed that the standard doses in young men, geriatric men and geriatric women (50 mg, 25 mg and 15 mg, respectively) result in largely consistent plasma level curves [86]. However, these findings have not yet found their way into the summary of product characteristics/prescription information, where dose reductions are recommended only in cases of severe liver dysfunction.

There are no significant sex-related differences in beta-blockers with CYP2D6-independent metabolism.

The beta-blocker sotalol, which is a class III antiarrhythmic, does not interact with CYP enzymes, but has a considerable potential of prolonging the QT interval [87, 88]. When using sotalol, women under the age of 45 develop disproportionately more torsade de pointes tachycardias than men of this age group [88]. It is known for ibutilide, another class III antiarrhythmic, that the female physiological sex hormones in the first half of the cycle are relevant for facilitating QT prolongation [89]. When prescribing drugs for which QT prolongation is a known ADR, special attention must be paid to the sex-dependent differences as women are at greater risk of drug-induced arrhythmias [87].

It should be noted that irrespective of sex-related differences, the dosage of beta-blockers should always be determined on an individual basis dependent on the pulse rate and the treatment response.

Gabapentin and Pregabalin

Gabapentin and pregabalin are both drugs used to treat epilepsy. Their plasma levels obtained at the usual doses (within the approved daily maximum dose) may differ depending on age, gender and co-medication by up to more than a hundredfold [90].

Of note, the concentration–dose ratio of pregabalin is on average up to 42% higher in women than in men. Hence, the dosage in women should be adjusted accordingly from

the beginning; under no circumstances should the maximum daily dose be applied without due consideration.

There is an increase in the number of cases of pregabalin abuse, in particular in combination with alcohol, methadone or benzodiazepines [91].

Alosetron

Alosetron, a 5-hydroxytryptamine (5-HT) receptor 3 antagonist, is an example of a drug that is effective in women but almost ineffective in men. The drug has a slightly lower metabolic clearance rate in women, but this pharmacokinetic difference cannot fully explain why men basically do not respond to the drug [92]. At identical plasma concentrations, the active ingredient develops pharmacodynamic effects in women only, a sex difference attributed to different serotonergic receptors in the intestine [93]. Alosetron was withdrawn from the market in 2000 owing to serious adverse effects and was reintroduced in 2002 under restricted conditions in the USA only and only for treatment of women with severe irritable bowel syndrome with the leading symptom of diarrhoea.

Similarly, the selective high affinity 5-HT_4 receptor agonist prucalopride was approved for women but not men suffering from chronic obstipation or opioid-induced constipation after unsuccessful treatment with other laxatives. The reason for the sex-specific approval was an insufficient number of men in clinical trials and hence a lack of clear evidence for efficacy in male patients. The missing studies in men have been supplied in the meantime, leading to approval of the drug for men as well [94].

CONCLUDING REMARKS AND OUTLOOK

There is considerable knowledge about differences between the sexes regarding the course of diseases and differential effects of some drugs. Yet, this knowledge has not fully made its way into clinical practice, where inadequate dosing is common. In order to make drug therapy more evidence-based and safer, the sex-specific features should be better presented and highlighted in clinical trials, marketing authorisation statements and therapeutic guidelines. Given the complexity of the topic with biological (sex) and psychosocial and cultural (gender) ramifications, rules to improve clinical research for integrating sex and gender aspects into clinical trials have been proposed [38].

In the era of personalized medicine, all healthcare professionals should be concerned about the most effective use of medicines to ensure high-quality healthcare and should hence always bear in mind potential sex-related differences in efficacy and safety.

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