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Review Article

Sex differences in hepatic enzymes and transporters involved in pharmacokinetics

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ABSTRACT

Females experience adverse drug reactions at approximately twice the rate of males, contributing to drug-related morbidity and mortality in the United States. This disparity has been strongly associated with sex-based differences in pharmacokinetics. Hepatic drug-metabolizing enzymes and transporters, key regulators of pharmacokinetics, exhibit notable sex-based differences in expression and/or activity. However, findings on the sex-specific impacts of these enzymes and transporters are often scattered, highlighting the need for a comprehensive and up-to-date overview of knowledge in this area. This review compiles and analyzes existing data on sex differences in the expression and activity of clinically relevant hepatic drug-metabolizing enzymes and transporters across species, such as cytochrome P450s, UDP-glucuronosyltransferase, carboxylesterases, P-glycoprotein, breast cancer resistance protein, multidrug resistance-associated protein, organic anion-transporting polypeptides and organic cation transporters. It also summarizes how these differences influence clinical pharmacokinetics, adverse drug reactions, and drug dosing regimens. Furthermore, we explore potential underlying mechanisms, including the influence of sex hormones, sex chromosomes and lifestyle-related factors. Lastly, we discuss clinical implications and future directions in the field, highlighting the urgent need for more human-centered research to clarify the sex-specific impact on drug metabolism and transport in human. Such effort will support the development of sex-informed pharmacotherapy strategies that ultimately reduce adverse drug reactions and improve therapeutic outcomes for patients.

1. Introduction

Historically, females have been excluded from clinical trials due to concerns about fertility, fetal health, and the misconception that male subjects represented the “norm” in medical research. This male-dominated approach created substantial gaps in understanding sex-specific drug response and safety profiles, raising safety concerns in pharmacotherapy in females. In 1993, the National Institutes of Health (NIH) mandated the inclusion of sex-based analyses in clinical trials and later required the consideration of sex as a biological variable in preclinical studies.[1,2] Among the New Drug Applications that included a sex-based analysis, at least a 40% difference in pharmacokinetics (PK) parameters between males and females was reported.[3]

PK, encompassing absorption, distribution, metabolism, and excretion (ADME), plays a critical role in determining drug efficacy and safety.[4] PK parameters refer to the quantitative description of drug concentrations in the body over time, or what the body does to a drug.[4] Significant interindividual variability in PK often results in variations in pharmacodynamics (PD), leading to the variability in drug response.[5] Factors such as genetic variants, disease, age, sex, and drug-drug interactions contribute to this variability in PK and PD, which often leads to treatment failure or toxicity.[5] Among these, sex has increasingly been recognized as a critical factor influencing therapeutic outcomes and adverse drug reactions (ADRs).

ADRs are estimated to be the fourth leading cause of death in the United States, surpassing pre-pandemic pulmonary disease, diabetes, acquired immune deficiency syndrome (AIDS), pneumonia, and accidents.[6] Females are disproportionately affected, experiencing ADRs nearly twice as often as males, which presents a significant public health concern.[7] Data from the U.S. Centers for Disease Control and Prevention (CDC) indicate a 260% increase in

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fatal drug overdoses among women aged 30 to 64 from 1999 to 2017, with rates rising from 6.7 deaths per 100,000 population (4314 total deaths) in 1999 to 24.3 per 100,000 (18,110 total deaths) in 2017.[8] Furthermore, approximately 96% of drugs with a higher incidence of ADRs in females are associated with sex-biased PK.[7,9] Therefore, a comprehensive understanding of the impact of sex on PK is essential for explaining sex-based disparities in drug response and ADRs.[7]

Sex-based variability in PK is driven by multiple physiological factors, including gastric emptying time,[10] pH, total body water, blood volume, glomerular filtration rates (GFR) and hormone levels, all of which significantly affect drug disposition.[11] While weight-normalized dosing addresses some variability, it does not account for the sex-specific differences in hepatic drug-metabolizing enzymes and transporters (DMETs).[12] The liver, a major organ for drug metabolism, exhibits significant sex differences in DMET expression and function, which are key determinants of individual differences in drug PK and PD.[5] A deeper understanding of how sex influences DMET protein expression and activity is essential to addressing sex-based disparities in drug PK and PD, reducing the disproportionate burden of ADRs on females, and advancing personalized pharmacotherapy.

Over the past few decades, significant sex differences in certain DMETs have been reported.[13] However, a comprehensive and updated overview of the sex-based impact on DMETs remains lacking. This review summarizes the current research on sex-based differences in hepatic DMETs, explores the underlying mechanisms of these differences, and discusses the clinical implications. Additionally, it highlights key knowledge gaps and future research opportunities to advance understanding in this critical area.

2. Hepatic DMETs

Hepatic DMETs play a pivotal role in determining the PK of therapeutic agents and xenobiotics. The liver is the primary organ responsible for the metabolism and elimination of drugs, containing various DMETs including phase I and phase II metabolizing enzymes, as well as phase 0 and phase III transporters (Fig. 1).[14]

Drugs are often metabolized through sequential reactions involving phase I and II enzymes. In phase I, reactions like oxidation, reduction, and hydrolysis introduce reactive or polar groups (-OH, -COOH, -NH_2, -SH, etc.) to the drug molecules.[15] These modifications make the drug more polar, facilitating its excretion. Following this, in phase II, the modified drugs are conjugated with polar compounds in reactions catalyzed by a variety of transferase enzymes, such as uridine diphosphate (UDP)-glucuronosyltransferases (UGTs), sulfotransferases (SULTs), and glutathione S-transferases (GSTs).[15]

2.1. Phase I reactions

Among the enzymes involved in phase I metabolism, cytochrome P450 enzymes (CYPs) are of most interest in pharmacology research.[15] In humans, approximately 80% of oxidative metabolism and roughly 50% of the total elimination of common clinical drugs are mediated by 57 putatively functional CYP isoforms and from the CYP1, 2 and 3 families.[16] These CYP families share about 40% sequence homology; with 55% sequence identity shared between subfamilies.[17] In addition to CYPs, several other enzyme families contribute to phase I drug metabolism, complementing the role of CYPs and facilitating the efficient and varied metabolism of a wide range of xenobiotics. Flavin-containing monooxygenases (FMOs) are responsible for oxidizing nitrogen, sulfur, and phosphorus-containing compounds, adding an oxygen atom to substrates, typically forming N-oxides or S-oxides.[18] Aldehyde dehydrogenases (ALDHs) play a key role in oxidizing aldehydes to carboxylic acids, essential for the metabolism of substances like ethanol and certain chemotherapy agents.[18] Similarly, alcohol dehydrogenases (ADHs) oxidize alcohols to aldehydes or ketones, play a vital role for the metabolism of alcohol and methanol.[18] Monoamine oxidases (MAOs) metabolize neurotransmitters such as serotonin, dopamine, and norepinephrine by removing amine groups, impacting both drug metabolism and neurochemical regulation.[18] Peroxidases also contribute to drug oxidation, potentially forming reactive metabolite that cause oxidative stress and cytotoxicity.[18] Additionally, hydrolases, particularly esterases, are abundant in the liver, including carboxylesterases (CESs) and cholinesterases (acetylcholinesterase, AChE; and butyrylcholinesterase, BChE).[19] These enzymes catalyze the hydrolysis of ester and amide bonds, converting substrates into their corresponding alcohol and acid or amine metabolites.

2.2. Phase II reactions

Phase II metabolism enzymes catalyze conjugation reactions, where a polar functional group is attached to a drug or its phase I metabolite.[15] This conjugation increases the compound's polarity, enhancing its water solubility and thus facilitating its excretion through urine or bile. A key group of phase II enzymes are UGTs, which are predominantly found in the human liver.[20] UGTs catalyze glucuronidation by covalently linking a glucuronic acid molecule to various lipophilic compounds, significantly contributing to the hepatic clearance of approximately 90% of xenobiotic drugs.[21] The human UGT superfamily consists of four families: UGT1, UGT2, UGT3, and UGT8. UGT1 and UGT2 families are especially important in pharmacology and toxicology, influencing interindividual variability in drug metabolism and cancer susceptibility.[22] The functions of UGT3 and UGT8 enzymes have been more recently discovered, with distinct UDP-sugar preferences compared to UGT1 and UGT2. However, their activity in the liver is relatively low, limiting their contribution to drug metabolism.[22]

In addition to UGTs, SULTs are another key group of phase II metabolism enzymes. SULTs transfer a sulfonate group from the co-factor 3′-phosphoadenosine 5′-phosphosulfate (PAPS) to hydroxyl or amino groups on substrates, such as acetaminophen, opioids and non-steroidal anti-inflammatory drugs (NSAIDs).[23] GSTs catalyze the addition of glutathione to electrophilic compounds, aiding in the detoxification of substances like acetaminophen, cisplatin, and chlorambucil.[24] N-Acetyltransferases (NATs), NAT1 and NAT2, catalyze acetylation reactions by transferring an acetyl group to a drug substrate in humans.[25] NAT2 plays a key role in the acetylation of xenobiotics, while NAT1 is mainly involved in metabolizing endogenous compounds.[25] NAT2 activity has been used as a biomarker on the Food and Drug Administration (FDA) drug label for the combination therapy Rifater (rifampin, isoniazid, and pyrazinamide).[26] This label notes that individuals with certain *NAT2* genetic variants, classified as 'poor metabolizers' of isoniazid, are more likely to have elevated blood concentrations of the drug, increasing their risk of toxicity.[26]

2.3. Phase 0 and phase III transporters

Expanding from the classic phase I and II metabolism reactions, phase 0 and phase III reactions refer to uptake and efflux transport, respectively.[14] Phase 0 involves transporter-mediated uptake, where members of solute carrier (SLC) superfamily facilitate the transport of substrates from the blood or gut lumen into metabolizing cells.[14] The SLC superfamily consists of 52 families, many of which are involved in drug uptake, such as

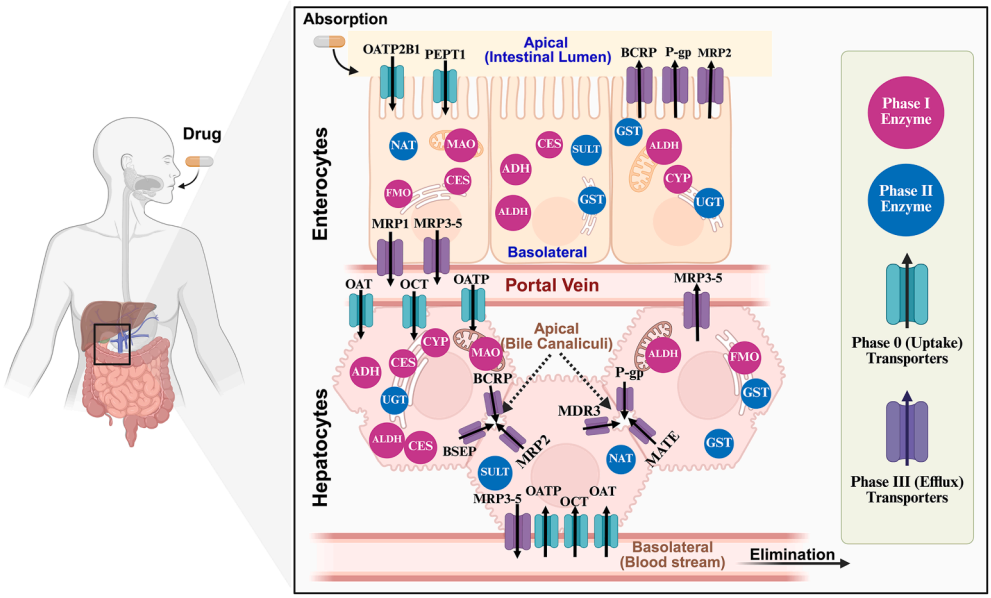

Fig. 1. Illustration of the coordinated roles of intestinal and hepatic drug-metabolizing enzymes and transporters in drug disposition. In the intestine, phase 0 uptake transporters (green) mediate the entry of drugs into enterocytes, where phase I enzymes (pink) initiate metabolism through oxidation or hydrolysis. Phase II enzymes (blue) then conjugate the metabolites to increase their solubility. Efflux transporters involved in phase III (purple) pump drugs or metabolites back into the intestinal lumen, limiting systemic absorption. In hepatocytes, a similar sequence occurs: uptake transporters facilitate drug entry, followed by sequential metabolism via phase I and phase II enzymes, and finally elimination via efflux transporters into bile or blood. Together, these processes in liver and intestine determine the extent of oral bioavailability and systemic clearance. Figure was created using BioRender. Abbreviations: ADH, alcohol dehydrogenase; ALDH, aldehyde dehydrogenase; BCRP, breast cancer resistance protein; BSEP, bile salt export pump; CES, carboxylesterase; CYP, cytochrome P450; FMO, flavin-containing monooxygenase; GST, glutathione S-transferase; MAO, monoamine oxidase; MATE, multidrug and toxin extrusion; MDR3, multidrug resistance protein 3; MRP, multidrug resistance-associated protein; NAT, N-acetyltransferase; OAT, organic anion transporter; OATP, organic anion-transporting polypeptide; OCT, organic cation transporter; PEPT1, peptide transporter 1; P-gp, P-glycoprotein; SULT, sulfotransferase; UGT, uridine diphosphate (UDP)-glucuronosyltransferase.

organic anion-transporting polypeptides (OATPs) and organic cation transporters (OCTs). However, an exception to this is the multidrug and toxin extrusion (MATE) family (SLC47A), including MATE1 and MATE2-K, which are not involved in phase 0 transport.[14] Phase 0 transporters often couple substrate movement with co-substrates, such as Na^+, H^+, and other electrolytes.[14]

In contrast, phase III transporters are responsible for drugs efflux, primarily relying on active transport through adenosine triphosphate (ATP)-binding cassette (ABC) transporters, which use ATP to move substrates across membranes.[14] The ABC transporters consist of seven families, with approximately 20 carriers involved in drug transport. In the liver, major ABC transporters, including P-glycoprotein (P-gp, also known as MDR1), breast cancer resistance protein (BCRP), and multidrug resistance-associated protein 2 (MRP2), are colocalized at the luminal domain of the plasma membrane and play a critical role in efflux transport.[14] In addition to ABC transporters, the SLC47A family (MATE1 and MATE2-K) are the only efflux transporters outside the ABC superfamily.[14]

2.4. Interindividual variability in hepatic DMETs

Interindividual variability in the expression and activity of DMETs in human liver plays a significant role in variations in drug PK, efficacy, and ADRs. This variability in DMETs activity caused by genetic variants has long been studied and widely acknowledged. Dozens of DMET genes, such as *CYP2C9*, *CYP2C19*, *CYP2D6*, *CYP3A4*, *CYP3A5*, *SLC19A1*, and *SLCO1B1*, carry genetic variants that significantly affect enzymes activity, leading to various metabolic phenotypes, including poor, intermediate, extensive, and ultrarapid metabolizer.[27] The variability in DMET expression has also been well documented. For instance, Yang *et al.*[28] (2013) analyzed the gene expression of 374 DMETs in 427 Caucasians human liver samples (234 males and 193 females) from Vanderbilt University (231), University of Pittsburgh (171), and Merck Research Laboratories (25), with average ages of 52, 51, and 46 years old, respectively. This study found that the standard deviation of individual expression for DMET genes was considerably higher than that for non-DMET genes, with many DMET genes showing large variability up to a 1000-fold difference between individuals.[28] Wang *et al.*[29] (2020) reported a coefficient of variation (CV) for CYPs ranging from 41.43% to 1009.95%, based on absolute protein expression levels of DMETs in 102 normal human liver samples. The donors ranged in age from 0.75 to 83 years and included 95 Caucasians, five African Americans, one Hispanic, and one classified as other. Of these samples, 46 were males and 56 were females. Rodríguez-Antona *et al.*[30] (2001) observed significant variations in the expression of 10 *CYP* genes across 12 human liver samples, including 40-fold, 50-fold, and over 500-fold differences in *CYP2C19*, *CYP3A4*, and *CYP2D6*, respectively. Further analyses of 261 DMET genes in primary hepatocytes from six individuals revealed the highest variation in *GSTM5* (166-fold), followed by *CYP26B1* (157-fold), and *SULT1C1* (58-fold).[30] Notably, Yang *et al.*[28] did not report liver tissue quality or donor exposure history, limiting the ability to account for confounding factors such as liver disease, environmental exposures, alcohol consumption, or medication use that may influence DMET expression. In contrast, Wang *et al.*[29] specifically used histologically confirmed normal liver tissues, although detailed donor exposure information was not provided. Rodríguez-Antona *et al.*[30] (2001) included additional donor data, such as smoking status, alcohol consumption, and medication use.

Genetic variants have been recognized as a major contributor to interindividual variability in drug response. To date, 609 drug-gene pairs are listed in the FDA "Pharmacogenomic Biomarkers

in Drug Labeling", with 33% of these involving DMET genes related to drug metabolism and transport.[31] While pharmacogenomics plays a crucial role in explaining a fraction of the variability in drug response, it accounts for only a small portion of the clinical variability observed. In addition to genetic factors, several other variables also contribute to differences in drug PK and PD.[28] Environmental factors such as diet, alcohol consumption, and exposure to pollutants can impact enzyme activity, while physiological factors like sex, body mass index, total body water, liver function, hormonal levels, age-related changes, and disease further contribute to variability in drug response.[7,28,32] Among these factors, sex-based differences have emerged as an increasingly important, yet an underexplored contributor to DMET variability. This review will focus on the growing body of evidence regarding sex differences in hepatic DMETs, highlighting current knowledge gaps and identifying future research opportunities in this area.

3. Sex differences in phase I drug metabolism

3.1. CYPs

Genes coding for the *CYP3A* subfamily, namely *CYP3A4*, *CYP3A5*, *CYP3A7*, and *CYP3A43*, are located on chromosome 7.[33] Among these, CYP3A4 is the most abundant CYP isoform in human liver and is the primary contributor to CYP3A-mediated drug metabolism, responsible for metabolizing approximately 30.2% of clinical drugs.[33] Sex-based differences in CYP3A4 expression and activity have been extensively reported. While most studies show higher CYP3A4 mRNA, protein expressions, and enzymatic activity in females,[34,35] some studies found no significant difference between the sexes.[36] For example, Wolbold *et al.*[34] demonstrated that female liver samples exhibited approximately twice the level of CYP3A4 protein and mRNA compared to males, along with a 50% increase in the *in vitro* metabolism of verapamil. In humanized mice models, Fashe *et al.*[37] demonstrated that female huPXR/CAR/CYP3A4/7 mice exhibited higher basal hepatic mRNA and protein concentrations of CYP3A4, as well as higher CYP3A4 activity on midazolam 1-hydroxylation in liver microsomes, compared with their male counterparts. *In vivo* human studies have also revealed higher clearance rates of CYP3A4 substrates, such as verapamil,[38] cyclosporine,[39] erythromycin,[40] nifedipine,[41] and steroids, in females.[42] While females generally exhibited faster clearance of CYP3A4 substrates administered intravenously (IV),[43] males showed faster verapamil clearance after oral administration. This may suggest sex-specific CYP3A4 differences might vary between intestinal and hepatic phases.[44] Moreover, the increased clearance of CYP3A4 substrates in females has been associated with lower activity of the efflux transporter P-gp, which may result in higher concentrations of CYP3A4 substrates in hepatic cells. While most literature supports CYP3A4 expression being higher in females than males, evidence regarding sexual dimorphism in its activity is inconclusive due to a lack of research in this area (Table 1).[23,34–36,45–74]

The second most prominent CYP enzyme for drug metabolism, CYP2D6, is responsible for metabolizing approximately 20% of clinically available medications.[33] Despite this, little to no literature exists to understand sex differences in mRNA and protein expression of CYP2D6, while data on sex differences in enzyme activity also produces inconsistent results (Table 1). Interestingly, notable sex differences in CYP2D6 activity emerge when considering individuals classified as extensive metabolizers (EMs), a term historically used, but now more accurately referred to as ultrarapid metabolizers (UMs) under current phenotype classifications, who possess certain *CYP2D6* alleles that enhance enzyme function. UMs metabolize CYP2D6 substrates more rapidly, often requiring higher medication doses to achieve therapeutic efficacy comparable to that found in normal metabolizers. Lopes *et al.*[45] (2020) demonstrated that female CYP2D6 UM patients demonstrate higher enzyme activity than their male counterparts while for normal metabolizers, some studies show females with higher enzyme activity and others demonstrate no significant sex difference (Table 1). Xie *et al.*[46] (1997) demonstrated a similar pattern for CYP2C19, an enzyme responsible for metabolizing 6.8% of clinically available drugs. Despite inconsistent results in normal metabolizers, CYP2C19 UM females had higher enzyme activity compared to CYP2C19 UM males. These findings demonstrate the importance of considering both sex and pharmacogenomics when determining drug dosing regimens.

Additionally, enzymes including CYP2C11, CYP2C13, CYP2C23, CYP3A11, CYP3A18 and CYP4A2 have demonstrated higher mRNA expression in males compared to females, while CYP1A1, CYP1A2, CYP2B10, CYP2C12, CYP2E1, CYP3A9, CYP4A1, CYP4F1, CYP4F4 and CYP7A1 show female predominant mRNA expression (Table 1). Beyond gene expression, sex effect on enzymatic activity has also been reported for some CYPs. For instance, Gerges and El-Kadi[47] (2023) demonstrate that CYP2B1 shows male-dominant expression and activity in rats, while various studies have demonstrated female-dominant expression and activity in humans for CYP2A6, CYP2B6, and CYP3A4 (Table 1).

Despite these general trends, sex-related differences in drug disposition are complex and influenced by additional factors such as hormonal and genetic regulation, as well as interactions with other DMETs. Ultimately, a more comprehensive understanding of their impact on drug metabolism requires integrating data across multiple levels of regulation. Although sex differences in CYP mRNA expression have been well characterized, this dimorphism in relation to enzymatic activity remains less explored. While mRNA expression levels are a commonly used indicator of gene transcription, providing insight into potential protein production, they do not always directly correlate with the amount of functional protein present or its subsequent enzymatic activity due to the complexity of post-transcriptional and post-translational modifications that occur as mRNA is converted into protein. As a result, relying solely on mRNA expression data to understand sex differences may result in misinterpretations and ultimately suboptimal clinical decision making. To enhance the precision of pharmacotherapy, it is critical to complement this knowledge of sex differences in mRNA expression with data on whether similar trends are observed in protein expression and ultimately enzyme activity as these parameters are of more direct clinical relevance in determining drug safety and efficacy.

3.2. Other phase I enzymes

In addition to CYP enzymes, CES, FMO, and ADH enzymes also play a critical role in phase I drug metabolism, albeit to a lesser extent than CYP enzymes. Collectively, these enzymes facilitate key oxidative, reductive, and hydrolytic reactions required for the biotransformation of drug and xenobiotic compounds.

CESs, particularly CES1 and CES2, are crucial to the hydrolysis of esters and amides, catalyzing the activation or deactivation of numerous clinically important medications. CES1 is the most abundant DMET in the human liver, and the sex differences in its activity have been highlighted in two independent studies examining the hydrolysis of its substrate drugs, oseltamivir and dabigatran. It was demonstrated that female livers exhibited higher CES1 activity in the activation of both dabigatran and oseltamivir compared to male livers.[75] The FMO family contributes to the oxidation of nitrogen, sulfur and phosphorous containing xenobiotics. Of this family, FMO1,

Table 1
Summary of sex differences in cytochrome P450 (CYP) enzyme expression and activity.

CYP enzyme	Parameter	Experimental model	Sex difference	Reference
CYP1A1	mRNA expression via RT-PCR	Rat heart	Female > male (3x)	47
	mRNA expression via RT-PCR	Mice	Female > male (16–256x)	49
CYP1A2	Enzyme activity	Human	Male > female	50
	Enzyme activity	Human	Male > female	51
	mRNA expression via RT-PCR	Rat heart	Female > male (3x)	47
	mRNA expression via RT-PCR	Rat liver	Female > male (2.5x)	47
	Enzyme activity	Human	Male > female	52
	Enzyme activity	Human	Male > female	53
	Enzyme activity	Human liver	Male > female	54
	Enzyme activity	Minipig liver microsome	Female > male	55
	Enzyme activity	Mouse liver	Female > male	56
	Enzyme activity	Human liver	No significant difference	57
	Expression	Human liver	No significant difference	36
CYP1B1	RNA expression	Human circulating leukocytes	Female > male	58
	Protein expression	Human circulating leukocytes	No significant difference	58
	N/A	Rat liver	Male > female	47
	N/A	Rat kidney	Male > female	47
	N/A	Rat heart	No significant difference	47
	N/A	Human liver	Female > male (1.13x)	48
CYP2A6	Gene expression	Human liver	Female > male (1.49x)	48
	mRNA expression	Human liver	Female > male	59
	Protein expression	Human liver	Female > male	59
	Enzyme activity	Human liver	Female > male	59
	Enzyme activity	Human liver	Female > male	60
	Enzyme activity	Human liver	No significant difference	57
CYP2A7	Gene expression	Human liver	Female > male (1.46x)	48
CYP2A13	Gene expression	Human liver	Female > male (1.43x)	48
CYP2B1	mRNA expression	Rat	Male > female	47
	Protein expression	Rat	Male > female	47
	Enzyme activity	Rat	Male > female	47
CYP2B6	mRNA expression via RT-PCR	Human liver	Female > male	61
	Protein expression via Western blot	Human liver	Female > male	61
	Enzyme activity	Human liver	Female > male	61
	mRNA expression	Human liver	Female > male (1.6x)	62
	Protein expression	Human liver	No significant difference	62
	Enzyme activity	Human liver	No significant difference	62
	Gene expression	Human liver	Female > male (1.33x)	48
	Enzyme activity	Human liver	No significant difference	57
	Enzyme activity	N/A	Female > male	51
	mRNA expression	Human liver	Female > male (3.9x)	61
	Protein expression	Human liver	Female > male (1.7x)	61
	Enzyme activity	Human liver	Female > male (1.6x)	61
	mRNA expression via RT-qPCR	Human liver	No significant difference	63
	Enzyme activity	Human liver	No significant difference	63
CYP2B10	mRNA expression	Mouse liver	Female > male	56
CYP2C8	mRNA expression	Human liver	No significant difference	64
	Protein expression	Human liver	No significant difference	64
CYP2C9	Enzyme activity	Human	No significant difference	52
	mRNA expression via RT-PCR	Human	No significant difference	65
CYP2C11	mRNA expression via RT-PCR	Rat liver	Male > female (1700x)	47
CYP2C12	mRNA expression via RT-PCR	Rat liver	Female > male (200x)	47
CYP2C13	mRNA expression via RT-PCR	Rat liver	Male > female (1300x)	47
CYP2C19	Enzyme activity	N/A	Male > female	66
	Enzyme activity	Human (extensive metabolizers)	Female > male	46
	Enzyme activity	Human	No significant difference	67
CYP2C23	mRNA expression via RT-PCR	Rat heart	Male > female	47
	mRNA expression via RT-PCR	Rat liver	Male > female	47
CYP2D6	Enzyme activity	Human (extensive metabolizers)	Female > male	45
	Enzyme activity	Human	No significant difference	68
	Enzyme activity	Human	Female > male	67
	Enzyme activity	Human liver	No significant difference	57
CYP2E1	mRNA expression via RT-PCR	Rat heart	Female > male (4x)	47
	mRNA expression via RT-PCR	Rat liver	Female > male	47
	mRNA expression via RT-PCR	Mouse	Female > male	49
	Enzyme activity	Human	Male > female	52
	Enzyme activity	Minipig liver microsome	Female > male (4x)	55
	Enzyme activity	Pig liver microsome	Female > male (2x)	55
	Enzyme activity	Human liver	No significant difference	57
	Expression	Human liver	No significant difference	23
CYP2J2	Gene expression	Human liver	Female > male (1.19x)	48
CYP3A4	Gene expression	Human liver	Female > male (1.73x)	48
	Enzyme activity	Human	Female > male	69
	Enzyme activity	Human	Female > male	70

(*continued on next page*)

Table 1 (*continued*)

CYP enzyme	Parameter	Experimental model	Sex difference	Reference
	mRNA expression	Human liver	Female > male	35
	Protein expression	Human liver	Female > male	35
	Enzyme activity	Human liver	No significant difference	57
	Protein expression	Human liver	No significant difference	36
	mRNA expression via RT-PCR	Human liver	No significant difference	71
	mRNA expression via RT-PCR	Human liver	Female > male (1.91x)	34
CYP3A5	Gene expression	Human liver	Female > male (1.27x)	48
	Enzyme activity	Hepatocyte culture	Female > male (~2x)	72
CYP3A7	Gene expression	Human liver	Female > male (2x)	48
CYP3A9	mRNA expression via RT-PCR	Rat liver	Female > male (10x)	47
	mRNA expression via RT-qPCR	Rat liver	Female > male (128x)	73
CYP3A11	mRNA expression	Mouse liver	Male > female	56
CYP3A18	mRNA expression via RT-PCR	Rat liver	Male > female (25x)	47
CYP4A1	mRNA expression via RT-PCR	Rat heart	Female > male (3x)	47
	mRNA expression via RT-PCR	Rat liver	Female > male (2.9x)	47
CYP4A2	mRNA expression via RT-PCR	Rat heart	No significant difference	47
	mRNA expression via RT-PCR	Rat liver	Male > female (3000x)	47
CYP4A3	mRNA expression via RT-PCR	Rat heart	No significant difference	47
CYP4F1	mRNA expression via RT-PCR	Rat heart	Female > male (3x)	47
CYP4F4	mRNA expression via RT-PCR	Rat heart	Female > male (3x)	47
CYP4F5	mRNA expression via RT-PCR	Rat heart	No significant difference	47
CYP4Z1	Gene expression	Human liver	Female > male (1.16x)	48
CYP7A1	Gene expression	Human liver	Female > male (2.1x)	48
	mRNA expression	Mice	Female > male	74

Abbreviations: N/A, not applicable; RT-PCR, reverse transcription-polymerase chain reaction.

FMO3 and FMO5 are the most relevant to human drug metabolism. While findings on sex differences in FMO1 and FMO3 protein expression are conflicting, FMO5 consistently shows no significant protein expression difference between the two sexes in murine models (Table 2).[75–81] ADH enzymes catalyze the oxidation of alcohol functional groups to aldehydes and play a crucial role in the metabolism of ethanol and other hydroxylated drug compounds. Most studies on sex differences in ADH have focused on understanding enzyme activity. No significant sex differences have been observed for class III and IV ADH enzymes, which are encoded by the *ADH5* and *ADH7* genes, respectively (Table 2). Given that different drugs are substrates for specific enzyme subclasses, the findings highlight that understanding these distinctions on a case-by-case basis is crucial to accurately predict drug metabolism, optimize dosing strategies and minimize adverse effects.

Sex-based differences in the expression and activity of phase I DMETs may have clinically relevant implications, especially for drugs that are substrates for these enzymes and rely on these enzymes for metabolism and elimination. Further research is necessary to understand the full extent of sex-based differences in these phase I enzymes to optimize drug therapy based on individual metabolic profiles.

4. Sex differences in phase II drug metabolism

4.1. UGTs

UGTs are key phase II enzymes in human liver that play a critical role in drug disposition and are classified into 5 families and 6 subfamilies.[21] UGT enzymes catalyze glucuronidation reactions where a glucuronic acid group is conjugated to the drug substrate.[21] This reaction enhances the solubility of lipophilic compounds, facilitating their excretion through urine or bile. Glucuronidation serves as a key mechanism for clearance and detoxification of xenobiotics, environmental pollutants and low molecular weight endogenous compounds like bilirubin. Given their significant role in drug metabolism, UGTs have been well characterized in humans and UGTs 1A1, 1A3, 1A4, 1A6, 1A9, 2B7

Table 2
Summary of sex differences in other phase I enzyme expression and activity.

Phase I enzyme	Parameter	Experimental model	Sex difference	Reference
Class I ADH (ADH1A, ADH1B, ADH1C)	Enzyme activity	Human liver	Male > female	76
Class II ADH (ADH4)	Enzyme activity	Human liver	Male > female	76
Class III ADH (ADH5)	Enzyme activity	Human liver	No significant difference	76
Class IV ADH (ADH7)	Enzyme activity	Human liver	No significant difference	77
CES1	Protein expression	Human liver	Female > male (17.3%)	75
	Enzyme activity	Human liver	Female > male	78
FMO1	Protein expression via immunoblot	Mouse liver	Female > male (2–3x)	79
	Protein expression via Western blot	Mouse liver	Female > male (2–3x)	80
	Protein expression via Western blot	Rat liver	Male > female	80
	Protein expression via Western blot	Human liver	Undetectable	80
FMO3	FMO3 levels via methionine S-oxidase activity and immunoblotting	Mouse liver	Female > male	81
	Protein expression via immunoblot	Mouse liver	Female only	79
	Protein expression via Western blot	Rat liver	No significant difference	80
	Protein expression via Western blot	Human liver	No significant difference	80
FMO5	Protein expression via immunoblot	Mouse liver	No significant difference	79
	Protein expression via Western blot	Mouse liver	No significant difference	80
	Protein expression via Western blot	Rat liver	No significant difference	80

Abbreviations: ADH, alcohol dehydrogenase; CES1, carboxylesterase 1; FMO, flavin-containing monooxygenase.

and 2B15 have been established as the most clinically relevant UGTs present in the liver.[21] These UGT isoforms are responsible for the metabolism of a wide range of endogenous and exogenous compounds including β-estradiol, paracetamol and morphine.[21] The diversity of UGT substrates highlights their broad metabolic impact, as they regulate the biotransformation of various therapeutic agents.

Sex differences in UGT mRNA expression have been most extensively studied compared to their protein or enzymatic activity. Using murine models, UGT2B1 and UGT2B3 were shown to mainly exhibit male-dominant mRNA expression while UGT1A1, UGT1A2, UGT1A5, UGT1A9 and UGT2B34 showed female-dominant mRNA expression (Table 3).[48,56,82–92] Human liver samples showed male-dominant UGT2B17 expression and female-dominant UGT2A3, UGT2B10 and UGT2B28 mRNA expression (Table 3). Despite the importance of UGTs in human drug disposition, very few studies focused on potential sexual dimorphism in UGT enzyme activity. In 2004 and 2010, Court *et al.*[87,92] performed studies using human liver samples and determined UGT2B15 demonstrated greater enzyme activity in males. Further research is essential to fully understand the regulation of UGT by sex, which could support the development of more precise, sex-based therapeutic strategies to improve drug safety and efficacy for all patients.

4.2. SULTs

SULT enzymes are also involved in phase II metabolism reactions, catalyzing the transfer of a sulfo group to make the drug substrate more hydrophilic. The SULT family of enzymes primarily plays a critical role metabolizing endogenous compounds like steroid hormones and neurotransmitters and plays a comparatively smaller role metabolizing xenobiotic compounds. Notably, understanding sex differences in SULT expression and activity holds clinical relevance as these endogenous substrates can modulate drug metabolism, efficacy and toxicity. For instance, sulfation mediated by SULTs may regulate the availability of sex steroid hormones, which in turn can influence the metabolism of certain therapeutic compounds.[93] Most existing studies focused primarily on mRNA expression levels of various SULT enzymes in murine models. While SULT1C1 and SULT1C2 demonstrate male-predominant mRNA expression in murine and human models respectively, SULT1A1, SULT1D1, SULT2A1, SULT2A2, SULT3A1 and SULT4A1 had higher mRNA expression in females compared to males (Table 3). However, no studies have evaluated whether these sex differences in mRNA expression extend to protein expression or enzyme activity, representing a significant literature gap that needs to be further explored.

Table 3
Summary of sex differences in phase II enzyme expression and activity.

Phase II enzyme	Parameter	Experimental model	Sex difference	Reference
UGT1A1	mRNA expression	Mouse liver	Female > male	83
	Enzyme activity	Rat liver	Female > male	84
	mRNA expression	Mouse liver	Female > male	56
UGT1A2	mRNA expression	Mouse kidney	Female > male	83
UGT1A5	mRNA expression	Mouse liver	Female > male	83
	mRNA expression	Mouse liver	Female > male	56
UGT1A9	mRNA expression	Mouse liver	Female > male	56
UGT2A3	Gene expression	Human liver	Female > male (1.24x)	48
UGT2B1	mRNA expression	C57BL/6 mouse liver	Male > female	83
	mRNA expression via RT-PCR	Rat liver	Female > male	85
	mRNA expression	Mouse liver	Male > female	56
	mRNA expression via Northern blot	Rat liver	Male > female	86
UGT2B3	mRNA expression via Northern blot	Rat liver	Male > female	86
UGT2B10	Gene expression	Human liver	Female > male (1.2x)	48
UGT2B15	Enzyme activity	Human liver	Male > female	87
	Enzyme activity	Human liver	Male > female	92
UGT2B17	Gene expression	Human liver	Male > female (1.59x)	48
	mRNA expression via RT-PCR	Human liver	Male > female (4x)	88
UGT2B28	Gene expression	Human liver	Female > male (1.25x)	48
UGT2B34	mRNA expression	Mouse liver	Female > male	56
UGT2B35	mRNA expression	Mouse liver	Male > female	56
UGT2B38	mRNA expression	Mouse liver	Male > female	83
	mRNA expression	Mouse kidney	Male > female	83
SULT1A1	mRNA expression	Mouse liver	Female > male	89
	mRNA expression	Mouse liver	Female > male	56
	mRNA expression	Rat liver	Male > female (2x)	90
SULT1C1	mRNA expression	Mouse liver	Male > female	89
	mRNA expression	Rat liver	Male > female (10x)	90
SULT1C2	Gene expression	Human liver	Male > female (1.15x)	48
SULT1D1	mRNA expression	Mouse liver	Female > male	89
SULT2A1	mRNA expression	Mouse liver	Female > male	89
SULT2A2	mRNA expression	Mouse liver	Female > male	89
SULT3A1	mRNA expression	Mouse liver	Female > male	89
	mRNA expression	Mouse liver	Female > male	56
SULT4A1	mRNA expression	Mouse brain	Female > male	89
GSTA1	Gene expression	Human liver	Female > male (1.82x)	48
GSTA2	Gene expression	Human liver	Female > male (1.69x)	48
GSTA5	Gene expression	Human liver	Female > male (1.43x)	48
NAT1	N/A	F344 rat	No significant difference	91
NAT2	N/A	F344 rat	No significant difference	91
NAT3	N/A	F344 rat	No significant difference	91

Abbreviations: GST, glutathione S-transferase; N/A, not applicable; NAT, N-acetyltransferase; RT-PCR, reverse transcription-polymerase chain reaction; SULT, sulfotransferase; UGT, UDP-glucuronosyltransferase.

4.3. GSTs

GST enzymes are another type of phase II metabolizing enzymes that are responsible for catalyzing the reduced form of glutathione (GSH) to xenobiotics to detoxify them. Although their role in drug metabolism is limited compared to other DMETs, GSTs have a significant influence in the pathogenesis of various liver diseases including nonalcoholic fatty liver disease and hepatocellular carcinoma due to their involvement in oxidative stress and detoxification pathways.[94] Despite their biological significance, sex differences in mRNA, protein expression and activity data have not been widely studied for this family of enzymes. Human liver samples show GSTA1, GSTA2 and GSTA3 all having higher gene expression in females compared to males, while expression and activity trends for other key GST subfamilies have not been studied (Table 3). Given the role of GSTs in detoxification pathways and liver disease pathogenesis, understanding whether sex-specific variations influence enzymatic efficiency may have important clinical implications.

4.4. NATs

NATs are a family of enzymes that are also involved in drug metabolism to a limited extent. These enzymes chemically modify the amine group in xenobiotics to an acetyl group, increasing their hydrophilicity thus facilitating their excretion.[95] No studies using human liver samples have been conducted to study sexual dimorphism in mRNA and protein expression and activity (Table 3). Future studies are needed to fill this gap by evaluating sex differences in hepatic NAT expression and activity, ensuring a thorough understanding of sex impact on their role in drug metabolism and personalized medicine.

5. Sex differences in transporters

5.1. ABC transporters

The ABC transporters consist of 12 subfamilies of enzymes that are highly involved in drug disposition, primarily by mediating drug efflux through an ATP-dependent mechanism.[96] Among these, P-gp, encoded by the *ABCB1* gene holds the most clinical relevance and as such, is the most extensively studied ABC transporter with regards to sex-specific expression and activity. As an efflux transporter, P-gp is responsible for removing a wide range of drug substrates out of cells, including immunosuppressants, steroids, cardiac medications and more, thus facilitating the clearance of these drug substrates.[97] Both Bebawy and Chetty[98] (2009) and Schuetz *et al.*[99] (1995) showed male-dominant P-gp mRNA expression in human liver samples while Salphati and Benet[100] (1998) demonstrated female-dominant mRNA expression in rat liver samples.[98–100] These discrepancies suggest species-specific regulatory mechanisms, hormonal influences and metabolic pathways contributing to variations in transporter expression, which highlights the need for more studies using human liver models to better characterize the role of P-gp in drug transport. Male-dominant mRNA expression was also shown for BCRP by numerous research teams across various murine models. Although none of MDR1, MRP2, MRP3 and MRP4 have been studied using human models, murine models have demonstrated female-dominant mRNA and protein expression (Tables 4 and 5).[56,98–124] No significant expression difference has been observed for either MRP5 or MRP6. No publications are available for assessing the sex effect on enzyme activity of ABC transporters, representing a large knowledge gap in this field.

Conflicting results have been reported for the sex-specific effect on MRP3 expression when tested with different animal species. Rost *et al.*[101] (2005) found that females had greater hepatic MRP3 protein expression in the rat, whereas Rohrer *et al.*[114] (2014) showed that males had greater hepatic MRP3 protein expression in the mouse. This variability across species emphasizes the need for further studies using human liver models to clarify the role of sex differences in DMET expression and activity. In addition to species, discrepancies in the sex effect on DMETs have also been observed across various tissues. For instance, the MRP3 protein is expressed across multiple organs, but its sex-specific expression can vary by tissue. Rohrer *et al.*[114] (2014) reported male-dominant protein expression of MRP3 in the mouse liver, whereas Maher *et al.*[115] (2006) observed female-dominant mRNA and protein expression in the mouse kidney (Table 5). These findings suggest that sex-specific differences in DMETs may be species- and organ-specific.[114,115] Thus, findings regarding the impact of sex on DMETs may not be appropriate for extrapolation across species or from one tissue type to another without thorough validation.

5.2. SLC transporters

SLC transporters are a large family of molecules involved in phase III metabolism by mediating the efflux of substrates through key transporters like OATs, OATPs and OCTs.[116] Similar to phase II enzymes, research on sex differences in SLC transporters are largely limited to murine models, with few data available in humans. Among OATs, OAT1 exhibits male dominance in mRNA expression, while OAT2 shows no significant difference, and findings for OAT3 are inconsistent. For OATPs, mRNA expressions indicate that OATP1A1 is more highly expressed in males, whereas OATP1A4 is higher in females (Table 4). Expression patterns for OCTs are also variable, with reports showing inconsistent findings for OCT1, male-dominant expression for OCT2, and no significant difference for OCT3 (Table 4). Notably, the influence of sex on enzymatic activity of SLC transporters remains largely unexplored, representing a critical knowledge gap that warrants further investigation.

6. Mechanisms underlying sex differences

Sex chromosomes and hormones are central to the development of sex-specific phenotypes,[125] including drug metabolism and transport.[126] Estrogen influences PK by modulating the activity of key DMETs and altering transporter expression.[127,128] Genome-wide association studies have also identified sex-differentiated genetic effects on drug-metabolizing enzyme regulation,[82] suggesting contributions from both sex chromosomes and hormones. These influences on drug metabolism and transport can alter efficacy and toxicity, increasing the risk of therapeutic failure or severe ADRs.[3]

6.1. Hormonal regulation

The composition and levels of sex hormones are considered as key factors contributing to the sex-specific variations in drug metabolism and transport. Testosterone and other androgens are the main sex hormones for biological males while estrogen and progesterone are the primary sex hormones for biological females.[129] Previous research has demonstrated that sex hormones play a pivotal role in driving the sex-specific differences observed in hepatic DMET expression and activity in phase I CYP enzymes (Table 6),[60,67,130–147] other phase I enzymes (Table 7),[148–151] phase II enzymes (Table 8),[83,86,89,137,145,152–154] phase 0 transporters (Table 9),[83,112,121,155] and phase III transporters (Table 10).[124,156–162]

Table 4
Summary of sex differences in phase 0 SLC transporter expression and activity.

SLC transporter	Parameter	Experimental model	Sex difference	Reference
OATP1	mRNA expression	Rat liver	No significant difference	102
	mRNA expression	Rat kidney	Male > female	102
OATP1A1	Protein expression	Rat liver	No significant difference	101
	Total RNA expression	Mouse liver	Male > female	103
	mRNA expression	Mouse liver	Male > female	56
	mRNA expression	Mouse liver	Male > female	104
OATP1A2	Protein expression via Western blot	Human liver	Female > male	105
OATP1A4	Protein expression	Rat liver	Male > female	101
	Total RNA expression	Mouse liver	Female > male	103
	mRNA expression	Mouse liver	Female > male	56
	mRNA expression	Mouse liver	Female > male	104
OATP1B1	Transporter activity	Human	Female > male	106
OATP1B2	Protein expression	Rat liver	No significant difference	101
	mRNA expression	Mouse liver	No significant difference	56
OATP2	mRNA expression	Rat liver	No significant difference	102
OATP2B1	Protein expression via Western blot	Human liver	Female > male	105
OATP3	mRNA expression	Rat liver	No significant difference	102
OATP4	mRNA expression	Rat liver	No significant difference	102
OATP5	mRNA expression	Rat liver	No significant difference	102
OAT1	mRNA expression	Mouse kidney	Male > female	107
	mRNA expression	Rat liver	No significant difference	108
OAT2 (SLC22A7)	mRNA expression	Mouse kidney	No significant difference	107
OAT3 (SLC22A8)	mRNA expression	Mouse liver	Male > female	107
	mRNA expression	129J mouse kidney	Female > male	107
OCT1	mRNA expression	Mouse kidney	Male > female	109
	mRNA expression	Rat kidney	Male > female	109
	Protein expression	Mouse kidney	Male > female	109
	Protein expression	Rat kidney	Male > female	109
	mRNA expression via RT-PCR	Human liver	No significant difference	110
	Protein expression via Western blot	Human liver	No significant difference	110
	mRNA expression	Rat kidney	No significant difference	111
OCT2	mRNA expression	Rat kidney	Male > female	111
	Protein expression	Rat kidney	Male > female	111
OCT3	mRNA expression	Rat kidney	No significant difference	111
NTCP (SLC10A1)	mRNA expression	Mouse liver	Female > male	112
	Protein expression	Mouse liver	Female > male	112
	Transporter activity	Rat hepatocyte	Male > female	113

Abbreviations: NTCP, sodium taurocholate cotransporting polypeptide; OAT, organic anion transporter; OATP, organic anion-transporting polypeptide; OCT, organic cation transporter; RT-PCR, reverse transcription-polymerase chain reaction; SLC, solute carrier.

A synergistic effect can be seen with regards to enzymes such as CYP2B6 and CYP3A4, where most research has shown higher mRNA and protein expression and activity in females compared to males, which aligns with the findings that female sex hormones induce the expression and activity of both CYP2B6 and CYP3A4. Additionally, the regulation of drug metabolizing enzymes by sex hormones has also shown a concentration-dependent manner. Choi *et al.*[130] reported a concentration-dependent regulation on CYP2A6, CYP2B6, CYP2C8, CYP3A4 and CYP3A5 mRNA expressions by estradiol and/or progesterone as quantified by quantitative reverse transcription-polymerase chain reaction (qRT-PCR). Evangelista *et al.*[131] reported that estradiol showed a concentration-dependent induction effect in CYP2J2 mRNA levels. However, this consistency was not observed across all hepatic DMETs. For instance, CYP1A1 demonstrated higher mRNA expression in females, but both its enzyme activity and mRNA expression levels were shown to be reduced by female sex hormones. Although P-gp demonstrated higher mRNA and protein expression in males, testosterone was shown to have a negative effect on protein expression levels. Similarly, MRP4 expression was shown to be higher in females compared to males, yet progesterone exhibited a negative effect on enzyme activity. These cases demonstrate the complexities associated with sex-hormone mediated regulation of hepatic DMETs and highlight the need for further research to fully understand the potential role of sex hormones in explaining sex-specific differences in hepatic DMETs.

Moreover, significant interspecies differences in sex hormones regulation of DMETs have been observed. For example, Choi *et al.*[132] showed that estradiol increased the mRNA and protein expression, as well as the enzyme activity of CYP1A2 in rats, while having no significant effect on mRNA expression in human hepatocytes.[130] This inconsistency emphasizes the need for cautious interpretation when extrapolating animal data to human drug metabolism and interpreting differences between *in vitro* and *in vivo* findings. In addition, many studies demonstrate that sex-dependent growth hormone (GH) secretion is also an important contributor to the sex-specific differences in hepatic DMET expression and activity.[163] GH secretion from the pituitary gland is pulsatile in males but continuous in females, which may further regulate the expression of hepatic DMETs beyond the influence of sex hormones alone.[164] Collectively, these findings highlight the large influence that endocrine regulation has on drug disposition, emphasizing the need to consider multiple hormonal factors when examining sex-based differences in drug metabolism.

The complex role of hormonal influences on drug disposition has profound implications and significant clinical relevance, particularly for patients with hormonal imbalances due to pre-existing conditions including but not limited to polycystic ovarian syndrome (PCOS) or those undergoing hormonal therapy.[165] Additionally, significant fluctuations in female sex hormone levels throughout the menstrual cycle and pregnancy may also modulate the expression and activity of key hepatic DMETs, introducing an additional layer of complexity that warrants

Table 5
Summary of sex differences in phase III ABC transporter expression and activity.

ABC transporter	Parameter	Experimental model	Sex difference	Reference
P-glycoprotein (ABCB1)	mRNA expression	Human liver	Male > female (2.4x)	98
	Protein expression	Human liver	Male > female (2.4x)	98
	mRNA expression	Rat liver	Female > male	100
	mRNA expression	Human liver	Male > female (2x)	99
MDR1	Protein expression	Mouse kidney	Female > male (1.5x)	117
	mRNA expression	Mouse kidney	Female > male	118
	Protein expression	Mouse kidney	Female > male	118
	mRNA expression	Mouse lungs	Female > male	118
	mRNA expression	Mouse liver	Female > male	119
	mRNA expression	Mouse kidney	Female > male	119
MRP2 (ABCC2)	Protein expression	Rat liver	Female > male	120
MRP3 (ABCC3)	mRNA expression	Mouse kidney	Female > male	115
	Protein expression	Mouse kidney	Female > male	115
	Protein expression	Mouse liver	Male > female	114
	Protein expression	Rat liver	Female > male	101
	mRNA expression	Mouse liver	Female > male	56
	mRNA expression	Mouse kidney	Female > male	119
	mRNA expression	Rat liver	No significant difference	121
MRP4 (ABCC4)	mRNA expression	Mouse kidney	Female > male	115
	Protein expression	Mouse kidney	Female > male	115
	Protein expression	Mouse liver	No significant difference	114
	mRNA expression	Mouse liver	Female > male	119
	mRNA expression	Mouse kidney	Female > male	119
	mRNA expression	Mouse liver	Female > male	56
	mRNA expression	Mouse kidney	No significant difference	119
MRP6 (ABCC6)	mRNA expression	Mouse kidney	No significant difference	119
BCRP (ABCG2)	mRNA expression	Mouse liver	Male > female	122
	mRNA expression via LC-MS/MS	Rat kidney	Male > female (2x)	123
	mRNA expression	Mouse liver	Male > female	56
	mRNA expression	Rat kidney	Male > female	124
	mRNA expression	Mouse liver	Male > female	124
BSEP (ABCB11)	mRNA expression	Mouse liver	No significant difference	112
	mRNA expression	Human liver	No significant difference	112

Abbreviations: ABC, ATP-binding cassette; BCRP, breast cancer resistance protein; BSEP, bile salt export pump; LC-MS/MS, liquid chromatography-tandem mass spectrometry; MDR1, multidrug resistance 1; MRP, multidrug resistance-associated protein.

further investigation. Interestingly, the interaction between sex hormones and hepatic DMETs exhibits bidirectionality: while sex hormones influence the expression and activity of these DMETs, DMETs themselves are also responsible for metabolizing and regulating the level of sex hormones. A comprehensive understanding of the interaction between sex hormones and hepatic DMETs is critical for optimizing dosing, maximizing drug efficacy and minimizing adverse events, especially in patients with hormonal imbalances or substantial fluctuations.

6.2. Sex chromosome regulation

Biological males and females differ not only in hormonal composition but also in their genetic makeup, with males having XY chromosomes and females having XX chromosomes. Although most hepatic DMETs are encoded on autosomal chromosomes, growing evidence suggests that sex chromosomes may indirectly contribute to observed sex differences in their expression and activity. Prior research has shown that drug responses can be altered when epigenetic dysregulation occurs on the sex chromosome, or there is loss of the entire Y chromosome, which are increasingly observed in aging male populations.[166,167] Similarly, impairment in X inactivation, an essential biological process in females, has been shown to alter drug response.[168] Moreover, many genes that the X chromosome codes for regulate immune function and inflammation, and inflammation has been shown to be associated with DMETs expression and function.[169,170] While the regulation mechanism remains inclusive, the evidence suggests direct or indirect regulation of DMETs through sex chromosomes, and more research is required to better understand whether sex chromosome-linked regulatory mechanisms contribute to the sexual dimorphism observed in hepatic DMETs.

6.3. Environmental and lifestyle influences

Aside from biological factors directly related to DMETs differences between sexes, environmental and lifestyle factors could play a role to the sex-specific variation as well. Alcohol consumption and smoking are prevalent around the world despite the widely accepted and scientifically proven notion of these lifestyle choices being harmful to human health.[32] In general, women smoke less and have lower alcohol consumption compared to men both in prevalence and quantity.[171] Given the impact of alcohol and smoking on DMETs, these lifestyle differences may also contribute to the sex-based variability in drug metabolism and transport. Gaither *et al.*[32] demonstrated that alcohol and smoking can have significant impacts on drug metabolism due to changes in hepatic DMET protein levels and complex drug interactions that may occur. For instance, CYP2E1 and UGT1A6 protein levels were upregulated by 1.7 and 1.4-fold in heavy drinkers compared to non-drinker controls, while the protein levels of CYP1A1, CYP1A2, CYP4A11, CUP4F2, UGT1A3, UGT2B7, UGT2B15 and FMO5 were downregulated in heavy drinkers.[32] Furthermore, CYP1A2, CYP4F22, FMO1 and FMO5 protein levels were upregulated in smokers compared to non-smokers.[32] Furthermore, recent findings have suggested that the gut microbiome may also contribute to the observed sex difference in DMETs. Before arriving at the liver for metabolism, orally consumed drugs pass through the intestine where they are exposed to the gut microbiome, a large collection of microorganisms that help with digestion and the regulation of

Table 6
Summary of hormonal regulation in cytochrome P450 (CYP) enzyme expression and activity.

CYP enzyme	Hormone	Parameter	Regulation	Experimental model	Reference
CYP1A1	Estradiol	mRNA expression	Decrease	Human endometrial ECC-1 cells	133
	Estradiol	Enzyme activity	Decrease	Human endometrial ECC-1 cells	133
CYP1A2	Oral contraceptives	CYP1A2 index	Decrease (33% reduction)	Human	134
	Estradiol (E2)	mRNA expression	Increase	Rat	132
	Estradiol (E2)	Protein expression	Increase	Rat	132
	Estradiol (E2)	Enzyme activity	Increase	Rat	132
	Estradiol	mRNA expression via RT-PCR	Increase	Human hepatocytes	130
CYP1B1	Estradiol	mRNA expression via RT-PCR	Increase	Estrogen receptor (ER) positive MCF-7 cells	135
CYP2A6	Oral contraceptives	CYP2A6 markers	Increase	Human	60
	Estradiol	mRNA expression	Increase (2.9x)	Estrogen receptor (ER) positive MCF-7 cells	136
	Estradiol	mRNA expression	Increase (1.3x)	HepG2 cells	136
	Estradiol	mRNA expression	Decrease	Estrogen receptor (ER) negative MDA-MB-435 cells	136
	Estradiol	mRNA expression	Increase (1.2–1.5x)	Human hepatocytes	136
	Estradiol	mRNA expression via RT-qPCR	Increase (5.9–23.4x and concentration dependent)	Human hepatocytes	130
	Estradiol	Enzyme activity	Increase (1.5–60.8x)	Human hepatocytes	130
	Progesterone	mRNA expression via RT-qPCR	Increase (1.7–3.4x and concentration dependent)	Human hepatocytes	130
	Progesterone	Enzyme activity	Increase	Human hepatocytes	130
	Estradiol	mRNA expression	Increase (7.2x)	Human hepatocytes	137
CYP2A7	Estradiol	mRNA expression	Increase (6.85x)	Human hepatocytes	137
CYP2A13	Estradiol	mRNA expression	Increase (1.66x)	Human hepatocytes	137
CYP2B6	Estradiol	mRNA expression via RT-qPCR	Increase (1.4–4.8x and concentration dependent)	Human hepatocytes	130
	Estradiol	Enzyme expression	Increase (1.5–4.9x)	Human hepatocytes	130
	Progesterone	Enzyme expression	Increase (1.8–7.6x and concentration dependent)	Human hepatocytes	130
	Progesterone	Enzyme activity	Increase	Human hepatocytes	130
	Estradiol	mRNA expression via RT-qPCR	Increase (4.98x)	Primary human hepatocytes	137
	Estradiol	Enzyme activity	Increase	Primary human hepatocytes	137
CYP2B9	Beta-Estradiol	mRNA expression	Increase	C57BL/6 mouse liver (male)	138
	Testosterone	mRNA expression	Decrease	C57BL/6 mouse liver (female)	138
	Testosterone	mRNA expression	Decrease	C57BL/6 mouse liver (female)	138
CYP2C6	Estradiol (E2)	mRNA expression	Decrease	Rat	132
	Estradiol (E2)	Protein expression	Decrease	Rat	132
	Estradiol (E2)	Enzyme activity	Decrease	Rat	132
CYP2C7	Estradiol (E2)	mRNA expression	Decrease	Rat	132
	Estradiol (E2)	Protein expression	Decrease	Rat	132
	Estradiol (E2)	Enzyme activity	Decrease	Rat	132
	Estradiol (E2)	Expression	Increase (to female rat level)	Ovariectomized female rat	139
	Estradiol (E2)	Expression	Increase	Male rat	139
	Testosterone	Expression	No significant effect	Female rat	139
	Testosterone	Expression	Decrease (to normal levels)	Neonatally castrated males treated during adulthood	139
CYP2C8	Estradiol	mRNA expression via RT-qPCR	No significant effect	Human hepatocytes	130
	Estradiol	mRNA expression via RT-qPCR	Increase (1.4–2.9x and concentration dependent)	Human hepatocytes	130
CYP2C9	Estradiol	mRNA expression via RT-qPCR	No significant effect	Human hepatocytes	130
	Estradiol	Protein expression	No significant effect	Human hepatocytes	130
	Estradiol	Enzyme activity	Increase (1.3–2.0x)	Human hepatocytes	130
	Oral contraceptives	Metabolism via oxidation of losartan	Decrease (metabolism rate reduced from 0.86 to 1.70)	Human hepatocytes	140
CYP2C12	Estradiol (E2)	mRNA expression	Increase	Rat	132
	Estradiol (E2)	Protein expression	Increase	Rat	132
	Estradiol (E2)	Enzyme activity	Increase	Rat	132
	Estradiol	mRNA expression	Increase	Rat	141
CYP2C19	Estradiol	mRNA expression via RT-qPCR	No significant effect	Human hepatocytes	130
	Oral contraceptives	Enzyme activity	Decrease	Human	142
	Oral contraceptives	Enzyme activity	Decrease	Human	67
CYP2D6	Estradiol	mRNA expression via RT-qPCR	No significant effect	Human hepatocytes	130
	Testosterone	Catalytic function	No significant effect	HepG2 cells	143
CYP2E1	Estradiol	mRNA expression via RT-qPCR	No significant effect	Human hepatocytes	130
	Estradiol	Protein expression	No significant effect	Human hepatocytes	130
	Estradiol	Enzyme activity	Increase (1.7–2.1x)	Human hepatocytes	130
	17β-Estradiol	mRNA expression	Increase	Wild-type and CYP2E1-humanized mice, established by insertion of the human CYP2E1 transgene into Cyp2e1-null	144

(*continued on next page*)

Table 6 (*continued*)

CYP enzyme	Hormone	Parameter	Regulation	Experimental model	Reference
				mice on the C57BL/6J background	
	17β-Estradiol	Enzyme activity	Decrease	Wild-type and CYP2E1-humanized mice, established by insertion of the human CYP2E1 transgene into Cyp2e1-null mice on the C57BL/6J background	144
	Progesterone	mRNA expression	Increase	Wild-type and CYP2E1-humanized mice, established by insertion of the human CYP2E1 transgene into Cyp2e1-null mice on the C57BL/6J background	144
	Progesterone	Enzyme activity	Increase	Wild-type and CYP2E1-humanized mice, established by insertion of the human CYP2E1 transgene into Cyp2e1-null mice on the C57BL/6J background	144
CYP2J2	Estradiol	mRNA expression	Increase (concentration dependent)	Adult-derived human primary cardiac cell line	131
	Testosterone	mRNA expression	Decrease	Adult-derived human primary cardiac cell line	131
CYP3A1	Estradiol (E2)	mRNA expression	Decrease	Rat	132
	Estradiol (E2)	Protein expression	Decrease	Rat	132
	Estradiol (E2)	Enzyme activity	Decrease	Rat	132
	Estrogen	Enzyme activity	Decrease	N/A	145
CYP3A4	Estradiol	mRNA expression via RT-qPCR	Increase (1.5–6.8x and concentration dependent)	Human hepatocytes	130
	Estradiol	Enzyme activity	Increase (0.9–2.7x)	Human hepatocytes	130
	Progesterone	mRNA expression	Increase (1.4–12.0x and concentration dependent)	Human hepatocytes	130
	Progesterone	Enzyme activity	Increase	Human hepatocytes	130
	Ovral (50 microg etinyloestradiol/500 microg norgestrel)	Enzyme activity	No significant effect	Human	146
CYP3A5	Estradiol	mRNA expression via RT-qPCR	No significant effect	Human hepatocytes	130
	Progesterone	mRNA expression via RT-qPCR	Increase (1.4–6.7x and concentration dependent)	Human hepatocytes	130
CYP3A9	Estradiol (E2)	mRNA expression	Increase	Rat	132
	Estradiol (E2)	Protein expression	Increase	Rat	132
	Estradiol (E2)	Enzyme activity	Increase	Rat	132
	Estrogen	Gene expression	Increase	Rat	147
CYP3A11	Estrogen	Enzyme activity	Decrease	N/A	145
CYP7A1	Estrogen	Enzyme activity	Increase	N/A	145
CYP8B1	Estrogen	Enzyme activity	Increase	N/A	145

Abbreviations: N/A, not applicable; RT-PCR, reverse transcription-polymerase chain reaction.

the immune system. Alterations in the gut microbiome between males and females may influence expression of hepatic DMETs, which ultimately can influence drug disposition.[172]

7. Clinical implications of sex differences in hepatic drug metabolism and transport

7.1. Sex differences in pharmacokinetics

Over 88% of FDA-approved drugs examined in a systematic review exhibited significant differences in PK parameters between males and females.[7] These sex-based variations in PK parameters including area under the curve (AUC), peak concentrations (C_{max}), half-life ($t_{1/2}$), clearance (CL), and volume of distribution (V_d), could not be explained solely by body weight differences between sexes.[7] An updated analysis in 2023 further identified five additional drugs with significantly higher plasma concentrations and lower CL in women compared to men.[173] These sex-based PK differences span multiple therapeutic areas and drug classes, highlighting the importance of sex-specific considerations in drug dosing and therapeutic outcomes.

Central nervous system (CNS) drugs,[174] such as benzodiazepines,[175–178] atypical antipsychotics,[179] selective serotonin reuptake inhibitors (SSRIs),[180–182] tricyclic amines,[180] antidepressants,[183] anticonvulsants,[184,185] anti-Parkinson's drugs,[174,186] and opioids,[187] consistently show sex-based differences in PK parameters. Females generally exhibit higher C_{max}, greater AUC, and/or slower CL compared to men.[174] Specifically, in benzodiazepines, females demonstrated a 66.3% longer elimination $t_{1/2}$ for chlordiazepoxide,[175] a 30.9% higher C_{max} for midazolam,[176] and a 36.6% longer $t_{1/2}$ and 24.4% lower CL in females for temazepam. Zolpidem showed a 61.6% longer $t_{1/2}$ and 45% higher AUC and C_{max} in females. In atypical antipsychotics, olanzapine concentrations were consistently higher in females over exposed time, with an 84.9% relative increase beyond eight weeks treatment.[174] In SSRIs, females had higher plasma concentrations of citalopram (17.6%) and its metabolite desmethylcitalopram (25%),[180] and a 60% increase in AUC and C_{max} of fluvoxamine.[181] Paroxetine exhibited a 24.9% lower V_d and 75.0% higher plasma concentrations in females.[182] For tricyclic amines, females had significantly higher average plasma concentrations of clomipramine and nortriptyline, with increases of 309 nmol/L and 81.0%, respectively.[180] In other antidepressants,

Table 7
Summary of hormonal regulation in other phase I enzymes.

Phase I enzyme	Hormone	Parameter	Regulation	Experimental model	Reference
ADH (overall)	Estradiol	Hepatic enzyme activity	Increase	Female rat	148
	Testosterone	Hepatic enzyme activity	Decrease (but not significant)	Female rat	148
	Estradiol	Hepatic enzyme activity	Increase	Mature male rat	149
CES1	17β-Estradiol	mRNA expression	Decrease (29%–39%)	Human liver	150
	17β-Estradiol	Protein expression	Decrease (45%)	Human liver	150
	17β-Estradiol	mRNA expression	Decrease	Mouse liver	150
	17β-Estradiol	Protein expression	Decrease	Mouse liver	150
CES2	17β-Estradiol	mRNA expression	Decrease (28%–55%)	Human liver	150
	17β-Estradiol	Protein expression	Decrease (47%)	Human liver	150
	17β-Estradiol	mRNA expression	Decrease	Mouse liver	150
	17β-Estradiol	Protein expression	Decrease	Mouse liver	150
FMO1	17β-Estradiol	Protein expression	Increase	Male CD-1 mouse	151
FMO3	Testosterone	Enzyme activity	Decrease	Male and female CD-1 mouse	151
FMO5	Estrogen	Enzyme activity	No significant effect	CD-1 mouse	151
FMO (overall)	Testosterone	Enzyme activity	Decrease	Female (ovariectomized or control mice)	151
	Hormone replacement therapy	Enzyme activity	No significant effect	Female	151

Abbreviations: ADH, alcohol dehydrogenase; CES, carboxylesterase; FMO, flavin-containing monooxygenase.

Table 8
Summary of hormonal regulation in phase II enzymes.

Phase II enzyme	Hormone	Parameter	Regulation	Experimental model	Reference
UGT1A1	Androgen	Protein expression	Increase	Female rat renal microsome	152
	Androgen	Enzyme activity	Increase	Female rat renal microsome	152
	Progesterone	Enzyme activity	Increase	HepG2 cells	153
	Estrogen	Enzyme activity	Increase	HepG2 cells	153
UGT1A2	Testosterone	mRNA expression	Decrease	Mouse kidney	83
UGT2B1	Testosterone	Enzyme activity	Increase	Rat liver	86
	Testosterone	mRNA expression	Increase (29%)	Rat hepatocytes	154
UGT2B3	Testosterone	Enzyme activity	Increase	Rat liver	86
	Testosterone	mRNA expression	Increase	Rat hepatocytes	154
UGT2B7	Estrogen	Enzyme activity	No significant effect	HepG2 cells	153
	Progesterone	Enzyme activity	No significant effect	HepG2 cells	153
UGT2B15	Estradiol	mRNA expression	Increase (1.56x)	Human hepatocytes	137
UGT2B38	Testosterone	mRNA expression	Increase	Mouse kidney	83
SULT1A1	Androgen	mRNA expression	Decrease	Mouse liver	89
SULT1C1	Androgen	mRNA expression	Increase	Mouse liver	89
	Estrogen	mRNA expression	No significant effect	Mouse liver	89
SULT2A1	Estradiol (E2)	mRNA expression	Increase (2.42x)	Human hepatocytes	137
	Androgen	mRNA expression	Decrease	Mouse liver	89
	Estrogen	Enzyme activity	Decrease	N/A	145
SULT2A2	Androgen	mRNA expression	Decrease	Mouse liver	89
SULT3A1	Androgen	mRNA expression	Decrease	Mouse liver	89
	Estrogen	mRNA expression	Increase	Mouse liver	89
GSTA3	Estradiol (E2)	mRNA expression	Increase (1.92x)	Human hepatocytes	137

Abbreviations: GSTA3, glutathione S-transferase A3; N/A, not applicable; SULT, sulfotransferase; UGT, UDP-glucuronosyltransferase.

single-dose bupropion resulted in 27.2% higher AUC, 26.5% higher C_{max}, and 43.8% longer $t_{1/2}$ in females, while mirtazapine concentrations were 30.4% higher.[183] In anticonvulsants, females had a 58.1% higher AUC and significantly lower CL for valproic acid,[185] and a significantly lower CL for felbamate.[184] For anti-Parkinson's drug levodopa, females had an 81.5% higher AUC and 57.7% higher C_{max}.[186] Opioids, such as buprenorphine, showed a 39.4% higher AUC and 35.3% higher C_{max} in females.[187]

Sex-based PK differences are also evident in anticancer agents. A review of 99 anticancer drugs found that 14 drugs with significantly lower CL in females,[188] including 5-fluorouracil (26%),[189,190] carboplatin (31%),[191] doxorubicin (50%),[192] pegylated liposomal doxorubicin (43%),[193] epirubicin (23%),[194] paclitaxel (20%),[195] temozolomide (22%),[196,197] topotecan (33%),[198,199] axitinib (35%),[200] cabozantinib (22%),[201] imatinib (25%),[202–204] regorafenib (27% for parent compound, 25% for active metabolite),[205] sunitinib (35% for active metabolite),[206] atezolizumab (20%),[207] and panitumumab (23%).[208]

Additionally, several other commonly prescribed medications show significant sex-based differences in PK profiles.[209] For example, acebutolol and aspirin demonstrated a significantly larger AUC in females.[12,210] Similarly, lower CL in females was observed for metoprolol,[211] propranolol,[212,213] ciprofloxacin,[214] ofloxacin,[215] and verapamil.[209,216]

These findings emphasize the importance of considering sex when evaluating drug metabolism and transport. Sex-specific PK differences can lead to variations in drug response. Understanding these differences is essential for optimizing drug regimens, minimizing ADRs, and improving patient outcomes.

7.2. Impact on drug efficacy and safety

ADRs remain a major public health concern, disproportionately affecting females compared to males, with this disparity being largely linked to sex-based differences in PK.[7] Studies have documented that many medications exhibit consistent sex-based

Table 9
Summary of hormonal regulation in phase 0 SLC transporter expression and activity.

SLC transporter	Hormone	Parameter	Regulation	Experimental model	Reference
OATP1A1	Ethinylestradiol	mRNA expression	Decrease	Rat	155
	Ethinylestradiol	Protein expression	Decrease	Rat	155
	Androgen	mRNA expression	Increase	Mouse liver	83
OATP1A4	Ethinylestradiol	mRNA expression	Decrease	Rat	155
	Ethinylestradiol	Protein expression	Decrease	Rat	155
OATP1B2	Ethinylestradiol	mRNA expression	Decrease	Rat	155
	Ethinylestradiol	Protein expression	Decrease	Rat	155
NTCP (SLC10A1)	Sex hormones	mRNA expression	No significant effect	Mouse liver	112
	Estrogen	mRNA expression	Decrease	Male rat liver	121

Abbreviations: NTCP, sodium taurocholate cotransporting polypeptide; OATP, organic anion-transporting polypeptide; SLC, solute carrier.

Table 10
Summary of hormonal regulation in phase III ABC transporter expression and activity.

ABC transporter	Hormone	Parameter	Regulation	Experimental model	Reference
P-glycoprotein (ABCB1)	Testosterone	Protein expression	Decrease (reduce to male levels)	Female rat	156
	Ethinylestradiol	Protein expression	No significant difference	Female rat	156
MRP2 (ABCC2)	Ethinylestradiol	Protein expression	Decrease (by 41%)	Rat	157
	Ethinylestradiol	mRNA expression via RT-PCR	Increase (4x)	Rat	158
	Estrogen	mRNA expression	Increase	Male rat	159
	Estrogen	Protein expression	Increase	Male rat	159
	Testosterone	mRNA expression	Decrease	Male rat	159
	Testosterone	Protein expression	Decrease	Male rat	159
	Testosterone	Protein expression	Decrease (reduce to male levels)	Female rat	156
	Ethinylestradiol	mRNA expression	No significant difference	Rat liver	160
	Ethinylestradiol	Protein expression	Decrease	Rat liver	160
MRP3 (ABCC3)	Ethinylestradiol	mRNA expression	Increase (321% of control)	Rat liver	161
	Ethinylestradiol	Protein expression	Increase (200%)	Rat	157
MRP4 (ABCC4)	Progesterone	Transporter activity via cyclic nucleotide efflux	Decrease	HEK293 cells	162
MRP5 (ABCC5)	Progesterone	Transporter activity via cyclic nucleotide efflux	Decrease	HEK293 cells	162
BCRP (ABCG2)	Estradiol	mRNA expression	Decrease	Rat kidney	124
	Testosterone	mRNA expression	Increase	Mouse liver	124

Abbreviations: ABC, ATP-binding cassette; BCRP, breast cancer resistance protein; MRP, multidrug resistance-associated protein; RT-PCR, reverse transcription-polymerase chain reaction.

differences in PK and adverse effect profiles, often resulting in increased drug sensitivity and toxicity in females.

Many CNS medications and pain medications exhibit notable sex-biased PK profiles associated with higher ADRs in females. For example, tramadol has elevated treatment discontinuation rates in females due to adverse effects such as dizziness and nausea.[217] Similarly, females experience a higher risk of electroencephalogram (EEG) abnormalities and seizures when using bupropion, an atypical antidepressant.[218] Methylphenidate, commonly prescribed for attention-deficit hyperactivity disorder (ADHD), is associated with a higher incidence of anxiety disorders in females.[219] Benzodiazepines like diazepam pose increased risks of prolonged sedation and toxicity for female patients.[220] Zolpidem use is linked to a higher occurrence of cognitive impairments and driving-related issues in women.[221,222] Additionally, females experience higher risk of prolonged respiratory depression when using morphine,[223] a critical consideration for postoperative pain management.

Cardiovascular and anticoagulant drugs also show significant sex-based differences in their effects. Anticoagulants such as warfarin and heparin are associated with higher rates of bleeding and blood disorders in females.[224] Similarly, clopidogrel use leads to increased bleeding and fracture rates in females than males.[225] Digoxin demonstrates higher mortality rates in females compared to males.[226,227]

Respiratory drugs and anti-infectives further illustrate sex differences in drug responses. Terfenadine and fexofenadine pose increased risks of Torsades de Pointes arrhythmias and neurocognitive impairments like attention deficits in females. Fluoroquinolones such as levofloxacin exhibit higher exposure levels and toxicity in female patients.[228,229] Monoclonal antibodies like infliximab are associated with more frequent allergic reactions and discontinuations in females compared to males.[230]

These findings highlight the need for sex-specific dosing protocols and therapeutic monitoring. Integrating sex-based PK/PD analysis into clinical practice will help reduce ADR-related hospitalizations while optimizing therapeutic outcomes. By addressing these differences, healthcare providers can enhance treatment effectiveness while minimizing adverse effects, particularly for women.

7.3. Sex-specific dosing considerations

Despite growing evidence of sex-related differences in PK and drug responses, sex-specific dosing recommendations remain absent for most drugs. To address this gap, the FDA recently issued draft guidance on January 29, 2025, titled “Study of Sex Differences in the Clinical Evaluation of Medical Products.” This guidance encourages increased enrollment of females in clinical trials and emphasizes the analysis of sex-specific data. The FDA aims to ensure that the benefits and risks of medical products are adequately evaluated for both sexes, including potential differences in dosing requirements.[231]

To date, zolpidem remains the hallmark example of sex-specific dosing approved by the FDA. This nonbenzodiazepine “Z-drug” used for insomnia displays slower metabolic clearance in females, increasing their likelihood of experiencing ADRs such as cognitive and driving impairments. To mitigate these risks, the FDA-approved labeling for zolpidem products recommends a lower starting dosage in females. Specifically, the prescribing

information for Ambien, in which zolpidem is the active ingredient, recommends "an initial dose is a single dose of 5 mg for women and a single dose of 5 mg or 10 mg for men".[232] To date, zolpidem remains the sole drug to have sex-based dosing recommended by the FDA.[233]

Studies have shown that females using zolpidem experience higher blood concentrations and decreased clearance of the medication.[233] Specifically, females have a 35% reduction in zolpidem clearance compared to males, along with plasma levels that are 40%–70% higher.[233,234] Many drugs exhibit similar pharmacokinetic differences between sexes as seen with zolpidem, yet few include FDA-recommended dosage adjustments for females. Two FDA analyses revealed that, between 1977 and 1995, only 26 pharmaceutical studies submitted to the agency examined sex-based pharmacokinetic differences. In 87% of the datasets provided by these studies, C_{max} was greater in women, and in 71% of them, AUC was also higher in women.[9] These differences are often observed in clinical practice, as seen with rocuronium, a neuromuscular blocking agent. One study found that females were 30% more sensitive to rocuronium doses, even when accounting for weight-based dosing.[235] These findings, both from research trials and clinical settings, highlight the critical need for further investigation into sex-based differences in PK.

While zolpidem is the first and only drug with FDA approved sex-specific dosing guidelines to date, it emphasizes the need for more research into sex differences in drug metabolism and response. Clinical studies specifically designed to examine these differences are crucial to understanding how sex influences PK and PD and are instrumental in developing tailored dosing regimens that can maximize drug efficacy while minimizing toxicity for both sexes.

8. Conclusions and future perspectives

Sex differences are increasingly recognized as a key contributor to variability in drug response. Numerous DMETs, such as CYPs, CESs, FMOs, ADHs, ALDHs, MAOs, UGTs, SULTs, GSTs, ABC and SLC transporters, exhibit sex-specific differences in expression and/or activity, affecting the PK of many clinically used drugs.[13] Moreover, females often experience higher systemic drug concentrations and slower elimination rates, contributing to a greater incidence of ADRs.[7] These differences are influenced by sex-related hormonal, genetic, and environmental factors, though the underlying mechanisms remain incompletely understood.[28]

Despite growing awareness of sex-based differences in drug disposition, findings are often inconsistent, and critical knowledge gaps persist, particularly regarding human DMET protein expression, activity, and the underlying mechanisms. To date, most research has relied on murine models. While these studies have provided valuable insights, significant species differences limit the translation to humans.[2] This underscores the need for more studies using human tissues and *in vivo* clinical investigations to clarify the role of sex differences in DMET expression and activity. Additionally, further exploration of the underlying mechanisms is essential to fully understand sex-related variability in drug disposition. Advancing this understanding will enable the development of sex-informed dosing strategies, enhancing therapeutic outcomes, and promoting equitable pharmacotherapy for both sexes.

Authors' contributions

Mehak Behal: Writing – review & editing, Writing – original draft. **Zachary McCalla:** Writing – original draft, Writing – review & editing. **Xinwen Wang:** Writing – review & editing, Writing – original draft, Conceptualization, Supervision.

Declaration of competing interest

The authors declare that there is no conflicts of interest.

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