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SEX-BASED PHARMACOLOGY: Understanding Differences in Drug Response for Safer, More Individualized Treatment

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Abstract

Sex-based pharmacology examines how biological sex can influence the way medicines are absorbed, distributed, metabolized, eliminated, and experienced by the body. Differences in body composition, hormones, organ function, gene expression, transport proteins, and immune responses may alter drug exposure, therapeutic benefit, or the risk of adverse effects. These differences are not universal: the direction and clinical importance depend on the medicine, dose, age, health status, and individual patient. Gender-related factors—including access to care, communication, social roles, and patterns of medicine use—can also shape real-world outcomes, but they should not be confused with biological mechanisms. This narrative review summarizes key concepts in sex-based pharmacology, explains the relevance of pharmacokinetics and pharmacodynamics, and discusses examples such as zolpidem, cardiovascular medicines, analgesics, and medicines used during pregnancy. It also highlights limitations in the evidence, including historical underrepresentation of women and insufficient sex-stratified reporting. The central clinical message is that sex should inform research and assessment, but should not replace individualized prescribing. Clinicians should follow current product information, consider organ function and interacting medicines, monitor response, and discuss uncertainty with patients. A more inclusive evidence base can improve both medicine safety and effectiveness.

Keywords: sex-based pharmacology; sex differences; gender; pharmacokinetics; pharmacodynamics; adverse drug reactions; precision medicine; individualized treatment.

1. Introduction

Medicines are often introduced with a standard dose, yet patients do not respond identically. One person may obtain the intended benefit, while another experiences little improvement or develops an adverse reaction. Age, body size, genetics, kidney

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and liver function, other medicines, diet, and adherence are familiar sources of variability. Biological sex is another factor that can matter, although it is frequently oversimplified or overlooked. Research reviews describe sex-related differences in drug exposure and response across several therapeutic areas, while also emphasizing that evidence is incomplete for many individual medicines [1–3].

In this article, "sex" refers mainly to biological characteristics, including chromosomes, reproductive physiology, hormones, body composition, and related organ-level differences. "Gender" refers to social and behavioral factors that can influence healthcare experiences, such as expectations about symptoms, medicine use, caregiving responsibilities, and access to treatment. These concepts interact but are not interchangeable. Neither category can be inferred perfectly from appearance or treated as a complete description of an individual. The purpose of sex-based pharmacology is not to assume that every woman or every man needs a different dose; it is to recognize relevant variation and use evidence to make treatment safer and more effective.

2. Biological foundations of differences in drug response

Sex-linked differences arise through multiple pathways. Sex chromosomes can affect gene expression, while hormones such as estrogen, progesterone, and testosterone influence tissues and metabolic systems. Body composition also matters: on average, women and men may differ in total body water, fat proportion, plasma volume, and muscle mass. These are population-level tendencies, not rules for every individual. The effect on a medicine depends on its chemical properties and the clinical situation. For example, a drug that distributes mainly in body water may behave differently from a highly lipid-soluble drug when body composition differs.

Liver enzymes and drug transporters contribute to metabolism and movement of medicines through the body. Some enzyme activities differ on average by sex, but the pattern is medicine-specific and may be modified by age, pregnancy, menopause, genetics, smoking, diet, and other medicines. Kidney filtration and tubular transport, plasma protein binding, gastrointestinal transit, and immune function may also influence exposure or response. Hormonal changes across the menstrual cycle, pregnancy, postpartum period, and menopause can alter physiology; however, clinically meaningful effects should be established for the particular drug rather than presumed.

3. Pharmacokinetics: what the body does to a drug

Pharmacokinetics is commonly summarized as ADME: absorption, distribution, metabolism, and excretion. A sex-related difference at any stage may change the

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concentration of a medicine over time. The result may be a stronger effect, a longer-lasting effect, a reduced effect, or no clinically important difference.

ADME stage	Potential contributors	Clinical meaning
Absorption	Gastrointestinal motility, pH, transporters, formulation and route	May alter how quickly or how much drug reaches circulation.
Distribution	Body water, fat mass, blood volume, protein binding	May influence apparent distribution volume and concentration.
Metabolism	Liver enzyme activity, hormones, genetics, interacting drugs	May change the rate at which a medicine is converted or inactivated.
Excretion	Kidney function, renal blood flow, transport processes	May change drug or metabolite clearance and duration of exposure.

These mechanisms should not be interpreted as a checklist that automatically leads to different doses. A pharmacokinetic difference matters clinically when it is large enough to alter benefit or harm, and when reliable evidence supports a change in prescribing. For medicines with a narrow therapeutic index, even a modest change in exposure may require closer monitoring. For other medicines, body weight, kidney function, age, or interacting drugs may be more informative than sex alone.

4. Pharmacodynamics: what the drug does to the body

Pharmacodynamics describes the relationship between drug concentration and its effects, including receptor binding, signal pathways, and changes in organ function. Two patients with similar blood concentrations can respond differently if receptor sensitivity, disease mechanisms, or physiological reserves differ. Hormones and sex-linked gene expression may influence these pathways, but the clinical evidence varies substantially between drug classes. Differences in pain perception, immune activity, cardiovascular physiology, and central nervous system function may also contribute to observed response patterns.

Importantly, pharmacodynamic differences cannot always be separated neatly from pharmacokinetic ones. A stronger effect may reflect higher drug exposure, greater sensitivity at the target, or both. Good studies therefore measure outcomes carefully

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and, when possible, examine exposure as well as response. Findings should be replicated and assessed for clinical importance before being translated into routine dosing recommendations.

5. Clinical examples and lessons

5.1 Zolpidem and next-morning impairment

Zolpidem is a well-known example of a sex-related prescribing change. The US Food and Drug Administration required lower recommended doses for women using certain zolpidem products because the medicine may be eliminated more slowly, leaving blood concentrations high enough the next morning to impair alertness and activities such as driving. A lower dose should also be considered for men in relevant circumstances, and patients should follow the specific product label and prescriber's advice [4]. This example demonstrates how pharmacokinetic evidence can lead to a concrete safety action.

5.2 Cardiovascular medicines

Cardiovascular diseases may present differently across populations, and sex can influence body size, hormonal environment, disease mechanisms, drug exposure, and adverse-effect patterns. However, the evidence is not uniform across all beta-blockers, statins, antihypertensives, or antithrombotic medicines. Prescribers should use established indications, measured blood pressure and heart rate, kidney and liver function, comorbidities, and current guidelines rather than applying a broad "female dose" or "male dose." Where evidence supports monitoring for a particular adverse effect, it should be incorporated into follow-up.

5.3 Analgesics and central nervous system medicines

Studies of analgesics, sedatives, and other centrally acting medicines have reported differences in efficacy, metabolism, and adverse reactions. Yet pain is affected by many factors, including the cause of pain, prior treatment, sleep, mental health, expectations, and social context. A sex-based average cannot predict an individual's pain experience. Clinicians should assess the patient's response and adverse effects directly, avoid stereotyping symptoms, and adjust treatment according to evidence and the patient's clinical needs [2,3].

5.4 Pregnancy, postpartum changes, and menopause

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Pregnancy can alter plasma volume, renal filtration, enzyme activity, gastrointestinal function, and protein binding. These changes may affect the exposure of some medicines and can change across pregnancy. At the same time, a medicine may cross the placenta or affect fetal development, so treatment decisions must consider both maternal benefit and fetal risk. Postpartum physiology does not immediately return to a single baseline, and lactation introduces additional considerations. Menopause and hormone therapy may also affect drug metabolism or symptoms that influence treatment. Decisions should be medicine-specific and guided by current prescribing information and specialist advice when needed.

6. Figure: a practical framework for understanding drug response

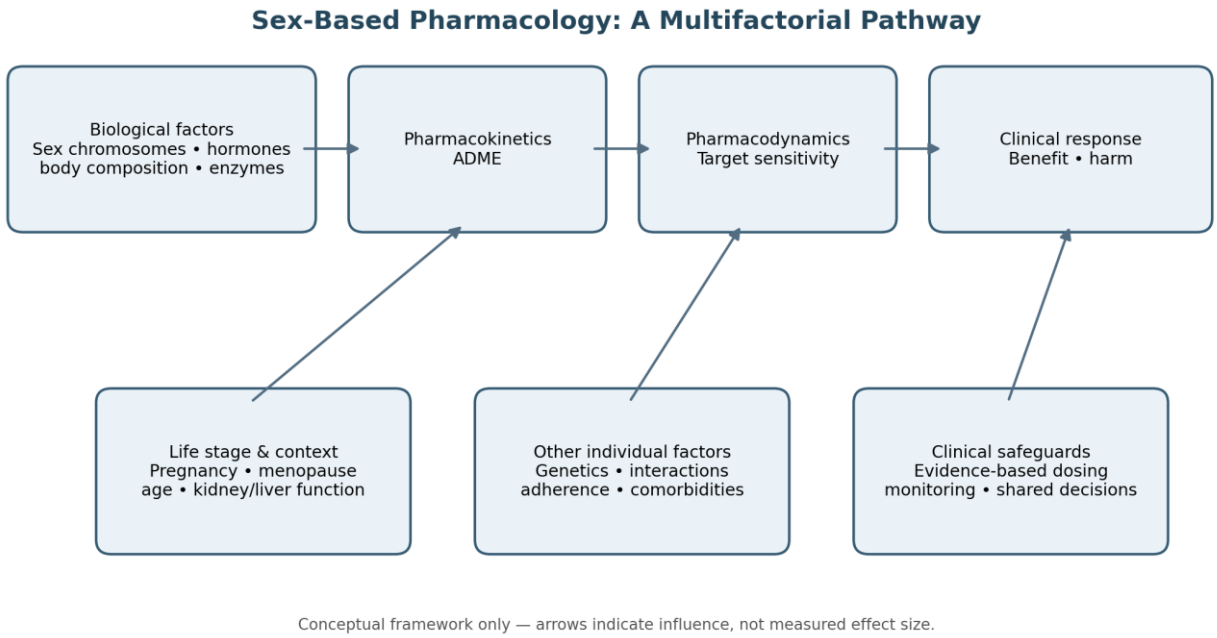


Figure 1. Conceptual framework showing how biological, life-stage, and individual factors can influence pharmacokinetics, pharmacodynamics, and clinical outcomes. The figure is illustrative and does not represent measured effect sizes.

7. Summary table: applying the evidence in practice

Clinical question	Useful action	Avoid
Could sex affect this medicine?	Check current product information and evidence for the specific drug.	Assuming all medicines work differently by sex.

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Could exposure be altered?	Review weight, kidney/liver function, age, pregnancy status where relevant, and interacting medicines.	Using sex as a substitute for clinical assessment.
Is the medicine causing harm or not working?	Ask about response, adverse effects, adherence, and timing; monitor when indicated.	Dismissing symptoms or relying on population averages.
Is evidence incomplete?	Explain uncertainty, document the rationale, and follow the patient.	Treating absence of evidence as proof of no difference.

8. Limitations and research priorities

Sex-based pharmacology is an evolving field. Many studies have not been designed or powered to detect differences between groups, and results may be reported without sex-stratified analyses. Women, pregnant people, older adults, and people with multiple health conditions have not always been adequately represented in drug-development research. Even when a difference is statistically significant, it may be too small to change treatment. Conversely, a meaningful difference can be missed when sample sizes are limited. Differences between studies may reflect population characteristics, dose, disease severity, study design, or measurement methods rather than sex alone.

Future research should recruit participants of different sexes across the life course, prespecify sex-stratified analyses when scientifically justified, and report both absolute and relative effects. Researchers should distinguish biological sex from gender-related influences and include diverse populations rather than treating women and men as internally uniform groups. Post-marketing surveillance and real-world data can help identify adverse effects that were too rare to appear in clinical trials. Ultimately, research should translate into clear clinical guidance rather than adding complexity without a demonstrated benefit.

9. Conclusion

Sex-based pharmacology helps explain why the same medicine and dose may not produce identical outcomes in every patient. Biological sex can influence drug absorption, distribution, metabolism, elimination, and response at the target site. Hormonal life stages and gender-related experiences may add further complexity. The

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strongest practical lesson is not to prescribe according to sex alone, but to recognize where evidence identifies a meaningful difference and combine it with the patient's age, body size, organ function, genetics when relevant, other medicines, and observed response. More inclusive research and careful reporting are essential to close evidence gaps. When clinicians use current guidance, monitor benefits and harms, and make decisions with patients, sex-aware pharmacology can support safer and more equitable care.

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