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Sex Differences in Drug Development

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Abstract: The premise of individualized or personalized medicine is that the intervention is tailored to the individual. Individualized therapy will accommodate differences in body size, differences in metabolism and elimination, as well as differences in response. One appropriate starting point for individualized therapy is to focus on sex differences. Men and women differ in critical molecular, genetic, cellular, and physiological aspects. One important consequence of these differences is how sex influences drug disposition and impact. While, historically, women were excluded from most clinical studies, more recently there have been attempts to include them as subjects in all aspects of drug development. Additionally, more attention is being directed to sex-appropriate diagnosis and treatment of disease as a component of individualized medicine. Despite this

increased attention to sex differences, there remain substantial gaps in our understanding of sex differences in drug development, the focus of this review. This review was adapted from a talk presented at the Second International Congress of Gender Medicine in Vienna in 2007.

Kurzfassung: Die Voraussetzung für individualisierte oder personalisierte Medizin ist der Zuschnitt der Behandlung auf das Individuum. Individualisierte Therapie berücksichtigt Unterschiede bei Körpergröße, Metabolismus und Medikamentenausscheidung sowie unterschiedliches Ansprechen. Ein geeigneter Ansatzpunkt für individualisierte Therapie ist der Fokus auf Geschlechtsunterschiede. Männer und Frauen unterscheiden sich kritisch in molekularer, genetischer, zellulärer und physiologischer Sicht. Eine wichtige Konse-

quenz dieser Unterschiede ist, wie das Geschlecht die Anwendung von Medikamenten und deren Wirkung beeinflusst. In der Vergangenheit waren Frauen von den meisten klinischen Studien ausgeschlossen, in den vergangenen Jahren wurden Versuche unternommen, sie in Medikamentenentwicklungsstudien einzuschließen. Zusätzlich wird mehr Aufmerksamkeit auf geschlechtsangepasste Diagnose und Behandlung als Teil der individualisierten Medizin gelegt. Trotz der steigenden Beachtung von Geschlechtsunterschieden bleiben weitreichende Diskrepanzen in unserem Verständnis von Geschlechtsunterschieden in der Entwicklung neuer Medikamente, worauf diese Übersicht eingehen wird. Diese Übersichtsarbeit ist die Fortführung einer Präsentation am Second International Congress of Gender Medicine, der im Juni 2007 in Wien stattfand. **Blickpunkt DER MANN 2008; 6 (1): 21–5.**

■ Introduction

Determining sex differences in efficacy and safety of drugs is fundamental for developing appropriate individualized strategies [1–3]. Due to differences in pharmacokinetic (pk) and pharmacodynamic (pd) responses between men and women it is important to understand the principles of clinical pharmacology as they apply to the disease, drug, and sex of the patient [4]. In this review, sex is defined as the classification of living organisms as male or female based on reproductive organs and chromosomal complement [5]. Gender refers to a person's self representation as male or female [5]. Sex differences are biologically based, with gender differences social and culturally centered [5]. In 1932, sex differences in pharmacology were first noted in animal studies [6–9]. Female rats required half the dose of barbiturates, compared to males, to induce sleep, and the duration of sleep was substantially longer in females given the same dose as males. Since that time, pharmacological and toxicological differences have been observed in many animal models, including rat, mouse, rhesus, beagle, cat, rabbit, hamster, goat, cattle, trout, and humans [2, 6, 10–12].

Before 1993, women of childbearing potential were intentionally excluded from phase-I and phase-II clinical trials by the United States Food and Drug Administration (FDA). The concerns leading to their exclusion focused on two factors: hormonal variations across the ovarian cycle which might alter pk or pd and the potential for pregnancy which might produce concerns about placental or fetal safety [13]. In 1988, the FDA published a guideline calling for the analysis of data to iden-

tify variation in response to drugs, including sex-based differences among different populations. Subsequently, in 1992, the General Accounting Office (GAO) analyzed sex, race, and age distribution of subjects in all new drug applications approved from 1988 through 1991. Females were found to be present but substantially under-represented in most of the clinical trials. The pharmaceutical companies were asked if they were ever advised by the FDA to include women in their trials and over half reported that the FDA had not requested information on dosing, safety or efficacy based on sex. The GAO highlighted the fact that even though the number one cause of death for women is cardiovascular disease, they were poorly represented in drug studies looking specifically at that endpoint [14].

In 1993, the FDA revised the 1977 guidelines and suggested that drugs be studied in a full range of patients likely to receive the drug [15]. It also provided that pharmacokinetics ought to be evaluated and described by sex. The Clinical Hold Rule was introduced in the 1993 guidelines, allowing the FDA to put a hold on enrollment or stop clinical trials in cases of excess adverse risk to either males or females or in trials where males or females were specifically excluded because of presumed risk to reproductive potential.

In 2001, the GAO (now called the Government Accountability Office) evaluated 10 drugs removed from the US market beginning in January 1997 through December 2000. They found that females experienced more adverse reactions to these drugs than did males. Eight of the drugs evaluated had evidence of greater health risks in females; the risks were identified from post-marketing data. Of these, three were introduced before 1993 and five after 1993, when the revised guidelines encouraging the inclusion of women in clinical studies were released. Two of the remaining drugs had no evidence of greater health risks in females using the post-marketing data. These two drugs were both introduced after 1993 [16].

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■ Drug Development

The process of drug development is both lengthy and costly (Fig. 1). According to a study published in 2006 the cost to bring a new drug, one with a new chemical entity (NCE), to the market ranged from 500 million to 2 billion US dollars [17]. Consequently, much of the focus of new drug development is on chronic or serious diseases with large populations of potential users (e. g. coronary artery disease, hypertension, diabetes or hyperlipidemias). Many companies feel government-required tests (e. g. including women in clinical studies) are barriers to expanded research and development. Although the revised FDA guidelines have provided for the inclusion of women in clinical trials there is still often little review of the data for potential sex differences in dosing, efficacy or adverse drug risks [1, 18–21].

In 2000, a review of data on acute coronary disease found that the number of women included in clinical trials only increased from 20 % to 25 % [19, 22]. Unfortunately, this problem is also compounded by the fact that the participants are often not an accurate representation of the intended population [23]. Additionally, in these studies the drug is also administered for a shorter period of time than its projected use. In an analysis of data submitted to the Center for Drug Evaluation and Research (CDER), the FDA found that 28 % of data sets documented a significant difference between the sexes and that the potential for the disparity in drug exposure could be greater than 50 % [24]. In a response by the FDA to the GAO on review of the draft “Drug Safety: Most Drugs Withdrawn in Recent Years Had Greater Health Risks for Women”, the agency did however agree that it was crucial that drugs with an increased risk in women be identified as early as possible in the process of drug development [16].

In Figure 1, timelines and estimated costs (direct and opportunity costs) on the part of pharmaceutical companies across the course of drug development are illustrated [17]. Note in phase one of a clinical trial the toxicity and dosing (pharmacokinetics) are evaluated in a small number of individuals (typically less than 100). Phase two tests the efficacy and safety of the drug in small trials of individuals with the disease of concern (typically several hundred individuals). Phase three evaluates in substantially greater detail the efficacy and adverse effects in a much larger population, often 1000s of individuals [14]. The consideration of sex differences in pk and pd must begin at the earliest stage of this process and be continued throughout all of the subsequent preclinical and clinical studies.

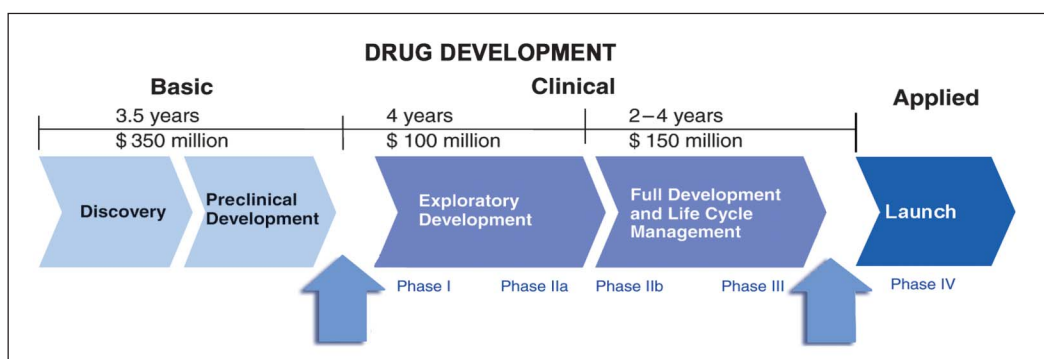


Figure 1. Steps in drug development. The processes, costs, and time needed for drug development is long and costly. Early steps involve identification of a molecule which may be used for the disease of interest and evaluation of that molecule in animal studies or in vitro. Following these preclinical evaluations, if the data continue to support the potential for the molecule in treating human diseases studies will begin in humans.

■ Sex Differences

Genetic and physiological differences between men and women can influence how the body handles the drug as well as the drug response by the body – both pk and pd [2, 3, 5, 20]. For example, many genes on the Y chromosome, which are expressed only in males, have no counterpart on the X chromosome. The Y chromosome has genes involved in basic cellular function and some genes on the X chromosome are expressed at higher levels in females. Gene expression and regulation are likely to be influenced by hormonal differences between males and females. Genomic imprinting, body size, organ size, body fat, absorption, distribution, metabolism, and elimination can also affect pharmacological outcome. Other factors such as gastrointestinal transit time, liver enzyme function and urinary creatinine clearance are influenced by both age and sex [9, 25–27].

Clinical factors to consider that of sex differences include the observation that in many developed countries women take more medications, creating the potential for adverse effects based on drug interactions, they appear more sensitive to adverse events [21, 28, 29], and may be overdosed more frequently [21, 30].

Across the trajectory of a woman’s life it is necessary to consider the stages of ovarian function to appreciate the potential for drug, sex, and age interactions as they influence our thinking about rational drug development. Use of oral contraceptives and hormonal changes which occur throughout the menstrual cycle influence pharmacological results. Necessary considerations during pregnancy are alterations in body composition, cardiac output, pulmonary and renal function as well as changes in immune and gastrointestinal systems. In menopause, the ovaries, uterus, urinary tract, hypothalamus, cardiovascular systems, and liver are some of the tissues, organs or systems which are altered by the loss of estrogens, androgens, and progestagens. These hormonal changes are also associated with the expression of different diseases after menopause [5].

■ Pharmacokinetics

Pharmacokinetics (what the drug does to the body) encompasses absorption, distribution, metabolism, and the elimination of drugs and their metabolites from the body (Tab. 1), each of these are influenced by sex [30]. Another way to con-

sider sex differences in pharmacokinetics is to characterize sex differences in the volume of distribution, clearance, and half-life of a drug [26]. Absorption is the process a drug takes to reach the blood from the route of administration (e. g. gut, skin, intramuscular injection). The gastrointestinal tract has many sites at which absorption occurs. Factors that affect absorption include pH along the GI system, gut transit times, ionization, molecular weight, and lipid solubility of the drug. Distribution is how the drug is dispersed from the absorption sites throughout the body. This process of distribution can have varying response due to sex differences such as body composition, body mass, blood volume, and protein binding. Metabolism and elimination are the two processes that eventually stop the action of the drug in the body. Metabolic processes are divided into phase-I and phase-II reactions. Phase-I enzymes involve oxidation and phase-II enzymes conjugation. Although a drug can be metabolized in most organs and tissues, it is primarily done in the liver.

Table 1. Sex differences in pharmacokinetic parameters: bioavailability, distribution volume, protein binding.

Pharmacokinetic Parameter	Physiological Parameter	Sex Difference
Bioavailability by oral route	Gastrointestinal emptying time	Increased in women, even more prolonged during pregnancy
	Drug transporters such as P-glycoprotein (P-gp)	Sex differences are substrate-(drug-) specific
	FDA bioequivalence studies	In 39 % of the data evaluated, there was more than 20 % difference in either area under the concentration-time curve or maximum concentration
Body weight	Male body weight greater than female, FDA bioequivalence studies	Drug dosing without consideration of body weight produces 20–88 % higher area under the concentration time curve in women
Gut enzymes	Alcohol dehydrogenase activity lower in females	Increased alcohol bioavailability in women
Hepatic enzymes	CYP3A4 and CYP3A5	Sex differences are substrate- and ethnicity-specific but generally F > M
	CYP1A2	M > F
	CYP2B6	F > M
	CYP2C9 and 2C19	2C9 M = F, 2C19 M = F
	CYP2D6	M = F
Distribution volume	Water-soluble drugs	Volume of distribution is larger in men
	Lipophilic drugs	Volume of distribution is larger in women
Protein binding	Albumen	No sex differences
	Alpha 1 acid glycoprotein	Increased in men
Renal clearance	Glomerular filtration is lower in women than men	Renal clearance is lower in women than men

Modified from [18, 25, 30]

■ Pharmacodynamics

Pharmacodynamics is how and in what form a drug impacts the biological processes within the body. How the body responds can be described in one of two categories; graded or continuous and quantal or dichotomous. Examples of a graded response include blood pressure or heart rate; quantal responses include death or cancer. Targets for drugs and metabolites within the body include enzymes, receptors, ion channels, and transporters [18, 31].

Given the pharmacokinetic and pharmacodynamic differences between men and women, and the fact that essentially all drugs were developed in men, gaps in knowledge about dosing, safety, and efficacy leave clinicians estimating the appropriate use of a drug in women. This also leads to a higher possibility of an adverse drug reaction in women (Tab. 2). Several studies have shown that women are at risk for adverse events and have as high as a 1.5–1.7fold greater risk for having a reaction [25, 32]. A few of the adverse events noted with women are rashes, hepatitis, liver failure, QT prolongation, and torsade de pointes.

■ Research Needed to Improve Drug Development for Women

The under-representation of women in all phases of clinical trials has been noted with concern as early as 1981 [19]. A review of inclusion of women in clinical trials published in 2001 noted that the proportion of studies including both men and women had increased from 50 % (during the period 1969–1991) to 65 % in 2002, unfortunately it appears that the more recent literature is less likely to include a gender-specific analysis [19]. Our review of the literature available in PubMed, Scopus, and Medline demonstrates an increased awareness and a greater need to define how and why sex influences disease processes and appropriate therapeutic approaches, including pk and pd. Interestingly, it was often noted that the number of female participants included in these studies was not described, suggesting that personalized medicine, at least for women, remains an elusive goal [1, 19, 23, 33].

Table 2. Sex differences in adverse events

Possible Clinical Factors	Pharmacological Factors	Physiological and Molecular Factors
Women are overdosed	Pharmacokinetics	Volume of distribution smaller for water-soluble drugs
		Free fraction of drug larger
		Clearance slower
Women take more medications	Drug interactions	Alteration in pharmacokinetics
Women are more sensitive	Pharmacodynamics	Alteration in receptor number
		Alteration in receptor binding
		Alterations in signal transduction pathways following receptor binding

Modified from [30]

Table 3. Examples of sex differences in drug responses

Condition Being Treated: Drugs	How Women Differ From Men
HIV: NNRTI, PI, nRTIs	Greater risk of adverse events: rash, hepatitis, lactic acidosis
Anesthesia: • vecuronium, pancuronium • rocuronium • propofol • morphine	– Increased sensitivity – Decreased effect – More sensitive to both analgesic effect and respiratory suppression
Antiepileptic drugs	Twice as likely to develop rash
Antipsychotics: • olanzapine, clozapine • chlorpromazine, pimozide	– Increased plasma concentrations – Greater risk for QT prolongation or torsade de pointes
Aspirin	– Higher plasma concentrations and lower clearance than men
Cefotaxime	– Clearance is slower
Gemcitabine	– Clearance is slower
Heparin	– Clearance is slower
Methylprednisolone	– Higher clearance and shorter half-life

An analysis of coronary heart disease research during the period 1985–2001 by the Agency for Healthcare Research and Quality noted that most studies excluded women [1]. Similarly, a recent Cochrane analysis found that of the 117 articles on HIV only 8 touched upon sex of the participant in the analysis [1]. As the number of women with AIDS and HIV continues to grow and surpass that of males in some countries, it is especially important to increase research and awareness of sex-associated drug response. In HIV treatments, sex differences have been noted (Tab. 3) with nevirapine (NNRTI), protease inhibitors (PI), and antiretroviral nucleoside reverse transcriptase inhibitors (nRTIs). Among women, nevirapine has an increased risk of cutaneous adverse reaction and hepatitis. The use of PIs in women has found a greater risk of gastrointestinal upset and an increase in metabolic disorders. The use of nRTIs is known to have an adverse reaction of lactic acidosis in women [34].

Anesthetic drug research has found that volume of distribution, clearance, receptor sensitivity, and elimination of half-life vary among men and women especially in the use of propofol, opioids, and muscle relaxants [33]. Pleym et al [33] found that women are 20–30% more sensitive to vecuronium, pancuronium, and rocuronium.

Table 3 summarizes some of the known sex differences in drug response. Even if a drug has no overt causative reaction such as QT prolongation or rash it is imperative to understand how the body, male or female, processes and responds to a drug.

■ Conclusions

In recognizing how crucially sex-specific analysis of drugs can assist in therapeutic treatments, it is essential that potential sex differences be included in the drug development process from the very beginning. Preclinical studies should consider sex differences in expression and function of target receptors, both for efficacy and safety. Studies conducted in animals to understand disposition and response should always

include animals of both sexes. First, human studies also should include both males and females in sufficient numbers to be able to define human disposition and response. Only when sex is considered from the initiation of the drug development process, the goal of the practitioner of providing individualized therapy is approachable. *“The big picture is that we believe that there’s a major benefit to medicine and society by understanding the natural differences between men and women, it’s not just being politically correct; it’s good business, good health, and good science [11].”¹*

■ Practical Relevance

- Determining sex differences in dosing, efficacy, and safety is an essential first step in personalizing treatment.
- Sex differences are biologically based, arising from genetic, physiologic, and metabolic differences between men and women.
- Drug development, a long and costly process, must evaluate the potential for sex differences in every step.
- While not all drugs exhibit sex differences in pharmacokinetics or pharmacodynamics, examples of significant differences between men and women suggest that clinicians must always consider that possibility.

¹ Raymond Woosley, vice president of the Arizona Health Sciences Center in Tucson as quoted in [35].

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Dr Mattison earned a BA (Chemistry and Mathematics) from Augsburg College, Minneapolis, MN, an MS (Chemistry) from the Massachusetts Institute of Technology, Cambridge, MA, and an MD from the College of Physicians and Surgeons, Columbia University, New York, NY. His clinical training in Obstetrics and Gynecology was at the Sloane Hospital for Women, Columbia Presbyterian Medical Center, New York. His training in Pharmacology and Toxicology was at the National Institutes of Health, Bethesda, MD, and the National Center for Toxicological Research, FDA, Jefferson, AR.



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