Pharmacogenetics and personalized medicine: Does gender have a role?

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Educational aims
- To increase awareness of the contribution of gender to therapeutic outcomes
- To discuss the interaction of gender with drug pharmacogenetics
- To gain an appreciation of the genetic contribution to personalized medicine

Key words
Pharmacogenetics, gender, polymorphisms, drug response

Abstract
The study of the role of genetic polymorphisms in drug responses, is now a firmly established field of pharmacology research. It has robust applications in predicting drug effect, and therefore contributes to the process of optimum selection of drug and dose for specific patients. Since the last 10 years, the FDA as well as the EMA have set up their own pharmacogenomics advisory groups, and have flagged an increasing number of medicinal products with specific genotyping recommendations in order to reap their greatest benefit. The contribution of gender to therapeutic outcomes has long been recognised, but recent research suggests that gender influence may not only occur via well recognised hormonal pathways, but also via direct non-hormone-mediated mechanisms. This influence may confound pharmacogenetic predictors, and gender stratification may therefore be an important consideration in pharmacogenetic-based drug trials.

Introduction
As early as 1993, in the “Guideline for the Study and Evaluation of Gender Differences in the Clinical Evaluation of Drugs” the FDA encouraged the participation of women in clinical trials and recommended that “sponsors should collect gender-related data during research and development and should analyze the data for gender effects.” However a scan of the literature indicates that clinical trials carried out during drug development phases have rarely considered gender as a stratification parameter in therapeutic outcome investigations. Evidence supporting gender-specific therapeutic outcomes, mainly stems from Phase IV post-marketing studies. The gradual but expanding trend towards rationalized medicine, is however set to change the “one size fits all” paradigm to a scenario where specific patient parameters, including genetic factors and gender, form part of a treatment algorithm which is optimized on a patient-per-patient platform. This is the basis of personalized medicine.

Gender and drug response
Gender may modify therapeutic drug outcomes through pharmacokinetic, pharmacodynamic as well as pharmacogenetic mechanisms. From a pharmacokinetic aspect, gender differences in metabolic enzyme activities is a well-known phenomenon. For example, the anti-anxiety and sedative drug midazolam, as well as verapamil (a calcium channel blocker) both show higher bioavailability in females than males due to gender specific variations in several CYP450 enzyme expression levels; while the selective α2-adrenergic agonist azepexole shows a higher degree of vеноconstriction in men than in women, despite various non-gender-specific single nucleotide polymorphisms (SNPs) in the ADRA2B gene which codes for its target, the α2-adrenergic receptor.
Pharmacogenetics and gender

Polygenic variation in the human genome is recognised to contribute to a profound effect on the therapeutic and adverse effects of several drugs. Drug outcomes may be influenced by variation in genes which code for drug receptors, metabolic enzymes, membrane transporters, signalling molecules or any other proteins which influence any aspect of drug mechanisms and actions. For example, polygenic variability in the CYP2D6 gene, may influence the outcomes of more than 70 drugs by modifying their rate of metabolism. Fast CYP2D6 metabolisers may not respond adequately to CYP2D6 substrates such as desipramine and nortriptyline (tricyclic antidepressants), carvedilol and metoprolol (β-blockers), clozapine (an antipsychotic), flecainide (an anti-arrhythmic), tramadol (an opioid analgesic) and others, while slow metabolizers may develop toxic effects at conventional therapeutic doses. Codeine, is a rather special case, since CYP2D6 contributes to its metabolism to morphine, and therefore fast CYP2D6 metabolisers may show opioid toxicity with conventional doses of codeine.5

The influence of gender on pharmacogenetics has just started to be debated in the scientific literature. Its contribution as well as the mechanisms through which it exerts it, are complex and still not well understood. Firstly, gender may exert effects on therapeutic outcome, in a manner which is independent of pharmacogenetic contributions. For example, multiple regression analysis of variability in S-oxazepam (an anti-anxiety benzodiazepine drug) glucuronidation, attributes about 35% of variability to presence of the D85Y [PvuII- / XbaI+] haplotype.7 Torasemide, a drug used for the management of heart failure, is a substrate for CYP2C9 metabolism and the SLCO1B1 membrane transporter and plasma concentrations of the drug depend on the genotypic contributions of these genes. In addition, female gender has also been determined to be a predictor of higher plasma torasemide concentrations. Factorial ANOVA analysis has however indicated that the contributions these genes and gender, occur independently of each other,6 therefore indicating that a separate mechanism must be in operation for the gender influence.

Secondly, gender may exert effects which operate within a pharmacogenetic framework. Since very few known pharmacogenetically-relevant gene variants are located on any of the sex chromosomes, gender-dependent pharmacogenetic differences are therefore likely to be due to male/female differences in the autosome, in transcriptional regulation or in post-transcriptional changes. More specifically, this may relate to (a) hormonal-dependent gene expression alterations, (b) gender-dependent differences in allelic frequencies of specific polymorphisms; sexually dimorphic pharmacogenetic allelic frequencies manifest as a gender-dependent skewness in the distribution of these polymorphisms within a population, and therefore may contribute to gender-biased therapy outcomes, and (c) physiological and/or psychological male/female differences which contribute to particular behavioural phenotypes, especially in the case of drugs which act on the central nervous system. Such differences may cause the same pharmacogenetic genotype to generate what may appear to be a different phenotype in males and females, but what in reality may be the result of an independent separate male/female characteristic which modifies the phenotype expression of the pharmacogene. For example, males and females may perceive pain differently, and therefore a single genotype which influences analgesic efficacy may have different influences in males and females carrying the same allele due to this psychological effect. Nortriptyline pharmacokinetics are known to be strongly influenced by the metabolic enzyme CYP2D6, and genotyping of the CYP2D6 gene can be used to help provide clinical dose optimization.8 However female patients carrying the same CYP2D6 genotype as their male counterparts, may require lower doses in order to attain the same clinical effect, and this is thought to be due to physiological effects of oestrogen on the brain.9 The cyclic variations in oestrogen secretion may further compound these issues. Dorado et al., (2012)10 later reported gender-dependent differences in CYP2C9-dependent hydroxylation of the angiotensin II receptor antagonist losartan (an antihypertensive), to its more active metabolite E3174, with females expressing a higher losartan:E3174 ratio than males, post administration of a single 25mg losartan dose. However it is not clear whether this observation could be attributed to differences in male/female frequencies of specific CYP2C9 genotypes, and whether other confounding factors such as bodyweight, were taken into consideration in this study.

Emerging data suggests that several classically recognised pharmacogenetic genotype/phenotype associations may need to be reanalysed in a gender-stratified manner, in order to understand the gender contribution, and better qualify the applicability of such associations to the field of personalized medicine.

Gender-dependent gene expression

Evidence for significant gender-dependent influences on gene expression is accumulating. Microarray-based work on murine RNA expression levels in several somatic tissues, revealed several thousand genes to exhibit sexually dimorphic expression in liver, fat and muscle, while several hundred exhibited sexually dimorphic expression in brain tissue.12,13 Such dimorphic expression has also been shown using in vitro generated bovine blastocystes, where one third of RNA transcripts have been shown to be expressed at different levels in males and females.14,15 This provides evidence to indicate that significant male/female differences in gene expression, may occur at a very early stage in development, and in the absence of hormonal influences. Such events also occur in humans.16 The mechanisms by which the sex chromosomes impose this extensive transcriptional regulation upon
autosomal genes are yet unclear. In adult humans, gender-dependent gene expression has been detected in various tissues, such as the brain, salivary glands, heart, and liver [24].

The cytochrome P450 enzyme CYP1B1 is expressed at higher transcript levels in Caucasian females than males, and this effect is not due to CYP1B1 genotype. Therefore CYP1B1 substrates, such as the chemotherapeutic agents docetaxel, epirubicin, capcitabine, paclitaxel, gemcitabine and cisplatin may have higher rates of metabolism in females. Moreover, this gender-dependent gene expression effect, may co-exist with other CYP1B1 polymorphisms, creating a phenotype for which the genetic contributions are difficult to dissect.

Sexually dimorphic allelic distribution
Alcohol provides an excellent example of a drug which has a gender-dependent pharmacogenetic profile. A study carried out in Korean alcoholic patients, found alcohol dependence in men to be associated with a significantly higher frequency of alleles *1/*1 of the aldehyde dehydrogenase 2 gene (ALDH2) and *1/*1 of the alcohol dehydrogenase gene (ADH2). However, in women, alcohol dependence was associated with a significantly higher frequency of a different allelic subset, namely ADH2*1/*1, ALDH2*1/*2 and ADLH2*2/*2. Moreover, the same study found the µ-opioid receptor gene (OPRM1) A118G allele, which is also recognised to contribute to a tendency towards alcohol dependence, to be present at a significantly higher frequency in alcohol-dependent females, than alcohol-dependent males. The same research group had earlier found naltrexone, a µ-opioid receptor antagonist, to be more effective against alcohol dependence in patients who were genotyped A/G or G/G at the OPRM1 118 locus, than those whose genotype was A/A. This data suggests that naltrexone may be more effective in females with alcohol dependence, than males.

The existence of gender-specific allelic frequencies, however, cannot always be considered to be independent of other variables. In some genes, sexual dimorphic distribution has been shown to be dependent on factors such as ethnicity. For example, the genes encoding 5,10-methylenetetrahydrofolate reductase (MTHFR) and thymidylate synthase (TYMS) are recognised methotrexate (a drug used in the treatment of cancer and autoimmune diseases) pharmacogenes. Specifically, the MTHFR C677T and A1298C SNPs, and the TYMS 5’UTR [28bp tandem repeat], and 3’UTR [6bp del/ins] polymorphisms are known to be important in methotrexate outcomes. Inoue et al., (2007) identified a statistically significant male/female difference between the allelic frequency of the TYMS 3’-UTR in a Japanese population (p=0.015), but the other 3 variants did not appear to exhibit any sexual dimorphic distribution. Moreover none of the variants demonstrated sexual dimorphism in Caucasians.

Conclusion
Pre-clinical and clinical trial design may often mask the effects of gender on drug response. The gender distribution of animals and human volunteers used is often not amenable to study such effects, and in vitro cell-based models are usually considered to be sex-less. The relevance of this variable is however now coming to light. Clinical studies need to be carried out in a way that makes them sensitive to detect gender-specific variations. Several commonly used drugs have been denied this opportunity. Adrenergic β2 receptors, the product of the ADRB2 gene, demonstrate a higher ligand sensitivity in women, compared to men, and this effect may compound known functional ADRB2 gene polymorphisms. Adrenergic β blockers such as metoprolol and propranolol, are sensitive to gender-dependent CYP2D6 metabolic activity. Statins also exert different therapeutic outcomes in males and females, but there is disagreement on the precise underlying mechanisms. Common drug adverse effects, such as hypokalaemia, hyponatraemia, nausea, vomiting, anti-coagulant induced bleeding and antipsychotic drug-induced weight gain are also more common in women than in men. Pharmacogenetics contributes to several adverse effects but is often unable to explain the unequal gender-distribution of these reactions. Clinical studies having a gender-sensitive design are required. Personalized medicine is a challenging target. A pre-requisite to its application is the unravelling and understanding of variables that contribute to inter-patient differences. Pharmacogenetics and gender are undoubtedly two major candidates.

Key points
- The understanding of genetically-influenced therapeutic outcomes is a critical component towards the development and application of personalized medicine.
- Gender may influence drug response, not simply through DNA sequences located on the sex chromosomes, but more commonly through gender-dependent variability present throughout the rest of the genome.
- The influence of gender on drug response, may act in isolation of other response-determining factors, but more commonly acts within a framework of pharmacogenetic determinants.
- During both preclinical and clinical drug development phases, there is an increased need to address gender as a potential variable in the assessment of therapeutic outcomes and adverse reactions.
- Prescribers should be aware of drugs which are reported to exhibit a degree of gender-dependent outcomes.

References


