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Review

Gender differences in drug responses

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Abstract

This review summarizes gender differences (GDs) in drug response. Although GDs have been described both in pharmacodynamics and pharmacokinetics, their role in clinical practice is not yet completely elucidated. The evidence that women have been less enrolled in clinical trials and that a gender-specific analysis usually is not included in the evaluation of results, contributes largely to this uncertainty. Consequently, adverse drug reactions (ADRs) are still higher in females than in males. Since sex is a fundamental biological variable that cannot be discounted, GDs in pharmacology have to be considered in order to improve drug safety efficacy and to optimize medical therapy both in men and women.

Keywords: Gender differences (GDs); Drug response; Pharmacodynamics; Pharmacokinetics

Contents

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1. Introduction

Although numerous gender differences (GDs) have been described in humans, so far most clinical research has been carried out considering the male can fulfil the function of the true representative of the human species. This in spite of the increasing evidence pointing out physiological and pathological differences between the sexes, beyond those related to the reproduction [1]. As women differ from men in gene expression and regulation, in the susceptibility to, and risk for many medical conditions and in the response to numerous drugs [1–8], GDs in drug response may explain, at least in part, the inter-individual variations occurring in therapeutic response and toxicity, especially considering that female sex has been shown to be a risk factor for the development of adverse drug reactions (ADRs) [2].

Given the complexity of gender pharmacology, the scant availability of adequate animal models and human studies, specific GDs are quite difficult to be evidenced [3]. Nonetheless, current results indicate that GDs in pharmacological response are more widespread than believed before and involve pharmacodynamics and pharmacokinetics, being the pharmacokinetic one of the most investigated [2–4,6–8].

The role of pharmacokinetics versus pharmacodynamics is not completely appreciated yet and only a few contributions have evaluated the impact of genetics, hormonal variations and their relative interactions. Indeed, GDs in drug response are not only a matter of differences between genders, but also they necessarily involve critical periods of both sexes. Only a few studies have been dedicated to evaluate how the biological rhythms influence drug responses [9] and even more limited researches have investigated whether and how they influence drug-to-drug, drug-to-herb and drug-to-food interactions and whether this occurs in a gender-dependent manner. Additionally, fertile female population has to be divided in two subpopulations depending on the use of oestrogen–progestin association, because of the huge hormonal influence on endocrine and metabolic pathways [10]. Oral contraception can modify the metabolism and the concentrations of co-administered medications, which, in turn, can affect the hormone activity [11].

The purpose of the present manuscript is to highlight a few specific examples in some areas, in which GDs may be important, considering beyond its aim to provide an extensive and detailed overview of GDs in pharmacokinetics, pharmacodynamics and pharmacogenetics. Moreover, this article gives a quick snapshot view of GDs in drug response as a basis for considering when GDs start, how they influence placebo response and therapy appropriateness.

2. Have gender pharmacological differences an early onset?

Although GDs in growth and susceptibility to diseases are generally believed to start at puberty, they have been evidenced since foetal and neonatal life [1]. Actually, GDs seem to initiate in uterus. Indeed, Y chromosome is known to accelerate the growth and increase glucose metabolism [12]. At birth, growth curve and heart rate are different in males and females [13], while sexual dimorphism in fat patterning starts at 5–7 years of age [14] and a difference in body composition could influence pharmacokinetics (see below). After 2 years of age, creatinine clearance is higher in male than in female [15] and it is possible to assume that renal drug excretion may diverge after this age. Activity of cytochrome P450 (CYP), a major family of enzymes involved in the metabolism of xenobiotics (see below), may be sex-dependent even before puberty, at least in rats [16].

This is not surprising considering that the genetic sex controls the development of gonadal sex. The question is whether sex chromosome genes, which are present in different quantities in the genome of the two sexes, might be expressed differently, inducing sex-specific patterns of development and/or functioning. Male mammals possess genes on the non-recombining region of the Y chromosome (NRY), absent in females and encoding for 27 different proteins, that might cause masculine patterns [17]. Alternatively, genes on the non-pseudoautosomal portion of the X chromosome (NPX), which are present in two doses in females but only in a single dose in males, could cause sex-specific development because of such different dosage. These differences are balanced by X silencing. Nevertheless, a significant percentage of NPX genes escapes inactivation, at least in humans [18]. Therefore, cells containing genes, which escape to silencing, could express higher gene products and this could have important implications. For instance, the gastrin-releasing peptide is expressed both in active and inactive X chromosomes. More elevated levels of this peptide have been detected in smoking females and have been related to the increased risk of lung cancer observed in smoking women [1]. The angiotensin II type 2 receptor (AT2R) gene, which is located on X chromosome, is involved in left ventricular hypertrophy in women, but not in men [19]. In an animal model of vascular damage, the protective effect of valsartan has been related to the upregulation of AT2R occurring in female mice [19].

Answering the question on sex chromosome genes may have multiple implications. It involves the importance of non-hormonal events on gender pharmacology, the possible different responses of embryos, foetuses and infants to maternal pharmacological treatments and their relevant consequences, for example, in developmental toxicology [20]. GDs in pharmacological response in early life and throughout paediatric age remain to be examined, although no significant GDs have been found for anticancer agents [21]. However, recent observations have revealed that boys display a higher prevalence (55.8%) for non-steroidal anti-inflammatory drug (NSAID) hypersensitivity than girls [22].

3. Is the placebo effect a gender-related phenomenon?

Since the pioneer work of Beecher [23], it has become evident that whenever a supposedly inert treatment or inert preparation is used, a certain number of patients exhibit some benefit from such “placebo” (from Latin “I shall please”) treatment. Placebo-controlled trials show that the supposedly inert treatment can even produce harmful side effects or frankly toxic effects, the so-called “nocebo” (from Latin “I shall harm”) effect [24].

The question of whether women and men respond differently to placebo administration has hardly received any attention. According to Rickels [25], women report side effects from both active drug and placebo, whereas men have side effects mainly on active drug. Some years later, it was shown that women seem to be overall less responsive to placebo than men [26]. Similarly, Compton et al. [27] found a greater placebo effect in men, whereas other authors described a more important effect in women [28,29]. However, other studies failed to observe any GD in placebo response [30–33]. At the moment, the issue is still controversial and largely understudied. Therefore, further investigations are needed, as gender-specific placebo effects would have many relevant implications for pharmacological research. This is true especially for clinical trials performed in the absence of golden standards, and in those clinical situations (e.g., pain and cough) in which the placebo effect is commonly considered relevant [23,34].

4. Gender-related pharmacokinetic and pharmacodynamic differences

4.1. Pharmacokinetics

Gender-related variations in pharmacokinetics have been frequently considered as potential relevant determinant for the clinical effectiveness of therapeutic agents.

Differences in the four major determinants of pharmacokinetic variability – bioavailability, distribution, metabolism and elimination – are theorized to stem from variations between the sexes in factors such as body weight, plasma volume, gastric emptying time, plasma protein levels, CYP activity, drug transporter function and clearance activity. Sex-related discrepancies in the pharmacokinetic of drugs have been extensively reviewed by numerous authors [6–8,35,36], so that the present paper reports just a few examples derived from seminal studies and considered explicatory.

4.1.1. Bioavailability

Changes in bioavailability will depend on the route of drug administration and differences in organs of absorption. Regarding pharmacokinetic parameters of drugs assumed by the oral route, gastrointestinal motility has been shown to be affected by sex hormones [37,38], with the transit time reported slower in females than in males [39,40]. Gastrointestinal enzymes responsible for drug metabolism also differ by sex. For example, GDs in gastric alcohol dehydrogenase activity have been described with higher levels occurring in males compared to females, so that more elevated alcohol concentrations may be found in women than in men, also following an equivalent drink [41].

Enterocytes express high levels of isoenzymes of CYP, which contribute significantly to the first-pass metabolism of a number of orally administered drugs. Investigations using midazolam have demonstrated higher bioavailability in women [42]; the bioavailability of oral verapamil resulted also greater in women [43]. Potential gender variability in intestinal-specific expression of enzymes that modulate gut transport of drugs such as P-glycoprotein (or multidrug resistance transporter-1, MDR-1) has been postulated, mainly based on reports of differences in the hepatic content [44]. Recent studies, using oral fexofenadine as a probe of P-glycoprotein in humans, failed to find any GDs in the profile of plasma concentration time of this compound [45], thus weakening the hypothesis that significant GDs occur in the expression of intestinal P-glycoprotein.

4.1.2. Distribution

The distribution of a drug is influenced by numerous factors including body mass index, composition, plasma volume and the extent of plasma protein binding of the drug. Body composition differs with the sex.

The disparity in body fat may explain the current greater volumes of distribution for lipophilic agents, even though such differences commonly exert only scant influences on the pharmacokinetic profile of drugs. Clinical exceptions include the reduced distribution volume of alcohol in women, responsible for the increased initial levels and stronger effects for an equivalent ingestion [46], and the major volume of distribution for diazepam in women, responsible for the longer duration of effects induced by the prolonged elimination time [47,48]. Enhanced fat stores have been also regarded as motive for the faster onset and increased duration of neuromuscular blockade occurring in women with vecuronium and rocuronium [49,50].

Since protein binding affects drug distribution volume, GDs in the binding might theorically lead to different pharmacokinetics for some compounds. Concentrations of albumin, the major plasma protein involved in reversible drug binding, do not consistently vary with the gender, whereas α-1 acid glycoprotein and α-globulins have been reported to change with both endogenous and exogenous oestrogens [51–53]. The clinical relevance of these observations has not been fully defined in humans yet, even if their practical impact has been questioned by investigations that failed to observe GDs in free fractions of highly bound drugs [54].

It is commonly believed that the most prominent factor in adapting medication dosages between the sexes is to tailor for body size. Therefore, at steady state some of the pharmacokinetic sex differences, due to different body weight and composition, can be corrected by normalizing the dose for body weight or surface [55], and such corrections are particularly proper when drugs with a narrow therapeutic index are administered. However, it is not obvious that adjustments for body size automatically optimize the therapy, since there are differences in drug metabolism that remain also after these corrections have been performed. Table 1 summarizes gender-related differences identified for the pharmacokinetic parameters, such as bioavailability and distribution.

4.1.3. Metabolism

Discrepancies in drug metabolism between sexes are currently thought to play a leading role in determining GDs in pharmacokinetic parameters. The CYP450 superfamily is one of the major drug metabolizing systems in humans and significant GDs in some key CYP450 enzymes have been demonstrated. Genes encoding for CYP isoenzymes are prevalently located on

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

Bioavailability by oral route	Gastrointestinal emptying time	↑ in women
	Drug transporter such as P-gp	No sex differences
Distribution volume	Gut enzymes	
	AD	↑ in women
	CYP3A4	No sex differences
	Water soluble drugs	↑ in men
	Lipophilic drugs	↑ in women
Protein binding	Albumin	No sex differences
	α_1 acid glycoprotein	↑ in men

AD: alcohol dehydrogenase; P-gp: P-glycoprotein.

autosomal chromosomes, so that gender-associated dissimilarities based on allele variations are not expected [56]. Therefore, the reported sex discrepancies can be ascribed to changes in the regulation of their expression and activity, most probably through environmental factors (inducers and inhibitors) and endogenous hormones influences [55]. In the following examples, individual CYP isoenzymes are discussed in the attempt to demonstrate sex-based variance in drug metabolism.

4.1.4. Phase I metabolism

4.1.4.1. CYP1A2. CYP1A2 is involved in the clearance of several medications, including caffeine and theophylline. Evaluation of urinary concentrations of caffeine metabolites revealed a lower CYP1A2 activity in women, at least in some specific ethnic groups, such as the Chinese population [57], with no sex-related differences in poor metabolizers. Conversely, theophylline metabolism was found to be faster in women than in men [58]. The antipsychotic agents thiothixene, olanzapine and clozapine, all CYP1A2 substrates, also exhibit a significant higher clearance in men than in women [59]. Similarly, studies on riluzole pharmacokinetics showed lower clearance in women [60]. Interestingly, oestrogen replacement treatment or contraceptive pills have been demonstrated to remove the GDs in metabolism of CYP1A2 substrates such as caffeine [61], paracetamol [62] and ronipirole [63].

4.1.4.2. CYP3A4. CYP3A4 is the most abundantly expressed member of the CYP450 superfamily in human liver [64]. There is substantial evidence to support a role of sex in the control of these enzymes, since many drugs, substrates for CYP3A4, exhibit higher clearance in women, and this difference even persists after correcting for physiological factors such as body weight [65]. CYP3A4 drug substrates showing greater clearance in women include cyclosporine [66], erythromycin [67], tirilazad [68], verapamil [69], nifedipine [70], diazepam [48] and alfentanil [71].

The observation that the excretion of CYP3A4 substrates is frequently higher in females than males was initially assumed to be the consequence of enhanced CYP3A4 protein expression in women, although there is no firm evidence to substantiate such hypothesis. Conversely, higher CYP3A4 enzyme activity of human liver microsomes from women was repeatedly detected [72,73]. To clear up this in vivo/in vitro discordance, it has been suggested that changes in P-glycoprotein expression levels should impact on the intracellular drug concentrations and, in turn, the rate of metabolism [74]. The evidence that hepatic P-glycoproteins were lower in females suggested the hypothesis that gender-associated discrepancies were induced by dissimilar levels of P-glycoprotein rather than CYP3A4 [75]. According to the proposed hypothesis, higher P-glycoprotein in men would result in lower intracellular hepatocyte levels of drug compared to women, with subsequent reductions in CYP3A4 metabolism and clearance in this group. Many convincing observations seem to corroborate this assumption, even though some counterexamples are available, too. For instance, alfentanil and nifedipine that are substrates of P-glycoprotein have been demonstrated to be more metabolized by women [70,71], suggesting that, at least in some circumstances, the supposed contribution of P-glycoprotein to sex-related pharmacokinetic differences of CYP3A4 substrates has to be considered uncertain.

Substrate-dependent differences could also be caused by heterotrophic cooperativity, which seems to be common for CYP3A4 [64,76]. For instance, St. John's worth has been reported to be able to increase CYP3A4 activity more in women (90%) than in men (50%), also enhancing CYP1A2 (20%) in women but not in men [77]. In conclusion, gender represents a relevant factor for CYP3A4 expression in humans, thus accounting for many of the previous reported observations of sex-dependent discrepancies in drug clearance. Finally, the evidence that drugs metabolized by CYP3A4 could be eliminated faster by women should be carefully evaluated for the potential clinical consequences.

4.1.4.3. CYP2D6. Although most studies carried out to investigate potential sex differences in CYP activity have prominently focused on CYP3A4, other isoenzymes should be taken into account. CYP2D6 represents the second most frequent enzyme implicated in the biotransformation of therapeutic drugs.

Numerous medications are partially or exclusively processed by CYP2D6 including sparteine, codeine, dextrometorphan, amitriptilyne, clomipranine, imipranine and β-blockers such as propanolol and metoprolol [78]. Earlier studies failed to demonstrate any gender influences on the metabolism of sparteine [11] and debrisoquine [79]. Conversely, more recent studies with dextrometorphan and metoprolol in extensive metabolizers showed faster clearance in men compared to women [80]. Levels of sertraline, a CYP2D6 substrate, were reported to be higher in young men [81] as well as oral clearance of desipramine has been found greater in males compared to females [82]. Similarly, mirtazapine, an antidepressant metabolized mainly by CYP2D6 and CYP3A, has been reported to exhibit faster clearance in men [83]. One study showed that tardive dyskinesia, a side effect of some antipsychotics, occurred more frequently in female Chinese subjects than in males, probably due to enhanced frequency of a defective CYP2D6 allele [84]. Sex differences in propanolol metabolism have been also shown in Caucasians [85] and Chinese subjects, with propanolol clearance found decreased in women compared to men [86]. Considering the combined data,

it appears that CYP2D6 activity may be higher in men than in women.

4.1.4.4. CYP2C9. Several drugs including phenitoin, warfarin, naproxen, piroxicam, tolbutamide and irbesartan are predominantly substrates for CYP2C9 isoenzymes [78]. Although very limited information is available on any sex difference in the metabolism involving this CYP, its activity does not appear to be gender specific, at least not to a clinically significant extent [65].

4.1.4.5. CYP2C19 and CYP2E1. CYP2C19 represents the major catabolic pathway for therapeutic agents such as (*S*)-mephenytoine, omeprazole, pantoprazole, citalopram [87]. The existence of a gender effect in the activity of this isoenzyme remains still controversial.

Although a few studies suggested that CYP2C19 activity might be higher in men than in women [78], the bulk of data supports no significant GDs in the clearance of CYP2C19 substrates.

On the contrary, GDs have been reported for CYP2E1 activity in healthy subjects, with higher metabolism occurring in men compared to women [88,89].

Finally, in addition to CYP isoenzymes, sex-related variations have been reported for other enzyme systems implicated in phase I metabolic reactions. For instance, xantine oxidase, which mediates the clearance of caffeine and theophylline, exhibits a greater activity in women than in men [90].

Table 2 reports sex-based differences in metabolic factors, phase I.

4.1.5. Phase II metabolism

Phase II reactions involve glucuronidation, sulfation, acetylation or methylation of the parent drug or its phase I metabolite to generate polar conjugates for renal excretion. Although most evidence indicates the existence of substantial racial variations in prevalence of specific genotypes, some findings support the occurrence of GDs in reactions involved in phase II metabolism (Table 3).

In fact, convincing data suggest GDs in the glucuronidation of some therapeutic compounds, but not others [35,91]. For example, a gender effect has been demonstrated for both paracetamol and diflunisal glucuronidation, being higher in men than in women [90,92], whereas glucuronidation of zidovudine was found as not gender-dependent [93].

GDs have also been reported for some sulfotransferase isoenzymes [94], as well as sex-specific disparities have been documented in thiopurine methyltransferase activity with more elevated levels detected in male liver biopsies [95]. A number of clinical investigations have also found that both fluorouracil and doxorubicin show a lower clearance in women than in men [96–98].

Similarly, when human liver samples have been analyzed for catechol-O-methyltransferase (COMT), which metabolizes the neurotransmitters norepinephrine, epinephrine and dopamine as well as catechol drugs (such as L-dopa), it has been demonstrated that women have shown about 25% lower levels of enzyme activity than men [99]. Such variations might be of significant importance for drugs with a narrow therapeutic index and also in neurotransmitter metabolism that, in turn, influences the effect of psychopharmacological agents.

Table 2
Gender differences in pharmacokinetic parameters: phase I metabolism

Hepatic	Model substrate	Clearance
CYP1A2	Caffeine, paracetamol	?↑ in men
CYP3A4	Midazolam, nifedipine, erythromycin	↑ in women
CYP2D6	Dextrometorphan, debrisoquine, sparteine	↑ in men
CYP2C9 CYP2C19	(*S*)-Mephenitoine	No sex differences
CYP2E1 Transporter hepatic P-gp	Chlorzoxazone	↑ in men ↑ in women

P-gp: P-glycoprotein.

Table 3
Gender differences in pharmacokinetic parameters: phase II metabolism

Conjugative	Model substrate	Clearance
Thiopurine methyl transferase	6-Mercaptopurine	↑ in men
Glucuronidation	Paracetamol	↑ in men
Dihydropyrimidine dehydrogenase	6-Mercaptopurine	↑ in men
UDP-gluronosyl transferase	Caffeine	↑ in men
N-Acetyltransferase	Caffeine, dapsone	No sex differences
Catechol-O-methyl transferase	Norepinephrine, epinephrine	↑ in men

4.1.6. Excretion

Renal excretion of compounds that are non-actively released or reabsorbed is determined by the Glomerular Filtration Rate (GRF) that is known to be proportional to body weight. Since on average GRF is higher in men than women, some apparent sex differences might merely be body weight effects that usually disappear after adjustment for weight.

However, it is noteworthy that population kinetic analysis of methotrexate reported a gender effect on kidney excretion even after normalization for body weight [100], suggesting that, in some circumstances, sex-adjusted dosages are required, mainly for renally eliminated compounds with narrow therapeutic index.

Actually, medications actively secreted by the kidney have been found to display more pronounced GDs. For amantadine, an organic cation with renal clearance, a significantly higher excretion has been observed in men [101]. These findings agree with studies carried out in rats, showing that sex hormone differences are responsible for gender disparities in kidney clearance for organic ions [102,103]. However, additional investigations on sex differences in renal excretion are needed to better understand the real contribution of this factor in humans.

The above reported examples demonstrate a sex dimorphism in drug pharmacokinetics, since several mechanisms relevant to absorption, disposition and metabolism have been shown to exert gender-specific activity differences. GDs in pharmacokinetics

are often only subtle and clinical relevance is probably achieved only by medications with narrow therapeutic index. Therefore, in light of all these considerations, the evaluation of GDs in pharmacokinetics, especially during drug development, appears mandatory and the potential impact of GDs on clinical practice deserves a more adequate attention, even if their importance should not be overemphasized in any case.

4.2. Pharmacodynamic

4.2.1. Drugs acting in the central nervous system

GDs have been repetitively described for a number of drugs acting in central nervous system. Women have been reported to exhibit significantly higher dopamine D2-like receptor binding than men in the frontal cortex. This may contribute to GDs in the incidence, clinical course, or treatment response of neuropsychiatric diseases associated with changes in cortical dopaminergic neurotransmission [104]. Although the literature is still not completely concordant, it seems that antipsychotics induce a greater improvement and more severe ADRs in women [35,105–107]. In a study comparing conventional and unconventional antipsychotic agents, clozapine and fluphenazine resulted equally effective in increasing basal ganglia and decreasing cingulate metabolism in women but not in men [108]. Women displayed higher [^{18}F]-fluorodopa uptake than men into striatum [109], thus suggesting that female sex hormones enhance presynaptic dopamine turnover. A large body of results from preclinical studies supports this claim [110–112]. Indeed, the effects of gonadal hormones have been postulated to have important implications for GDs in the acute and chronic responses to psychostimulants. In general, females are more sensitive to cocaine and methylphenidate [113] as well as to other psychostimulant drugs [114]. However, in humans a marked sex difference in striatal dopamine response to amphetamine has been reported with women exhibiting lower neurotransmitter release [115]. Differently from preclinical investigations, human studies have shown that women in the luteal phase of menstrual cycle display reduced subjective responses to amphetamine and cocaine compared to men [116,117]. Women are also less vulnerable to methamphetamine toxicity [118], and female stimulant abusers show decreased electroencephalogram (EEG) abnormalities than male stimulant users [119]. At moment, it is possible to assume that differences between women and men in striatal dopamine release may serve as possible mechanism underlying the observed GDs in consequences of stimulant use.

Depression is twice as common in women as in men, although it seems that there are no differences between genders in the severity and symptomatology of the depressive pathology [120]. In women, the incidence of depression peaks during childbearing years seems to be associated with cyclic hormonal changes [121]. Oestrogens and progesterone are, indeed, regarded as responsible for the lower serotonin reserve and activity reported in female brain [122]. This suggests that women could have a more susceptible serotonergic system compared with men, and therefore could respond disproportionately to extraneous factors, including medications. It this regard, PET and MRI scans provided evidence that young depressed women have a higher impairment of serotonin synthesis than men [123], and acute tryptophan depletion produces more profound depressive symptoms and signs in women than in men [122,124]. Tryptophan pyrrolase, which reduces blood tryptophan levels, is relatively overactive in women, especially during childbearing years [125]. Fluoxetine treatment raises serum tryptophan about 83% and 32% in women and in men, respectively [125], and L-triiodothyronine augmentation hastens the onset of tricyclic antidepressant (TCA) response to a greater extent in women than in men [126].

Some studies reported that women seem to respond better to selective serotonin uptake inhibitors (SSRI) than TCA, whereas men tend to respond better to TCA than SSRI [127,128]. A recent investigation, including SSRI and selective noradrenaline reuptake inhibitors (SNRI), showed that premenopausal women respond better to SNRI than men, even if not to the same extent as that found with SSRI medications [129,130]. Finally, some authors described a gender-dependent pharmacokinetic profile [131,132]; nevertheless, it has been assumed that the pattern of antidepressant response in men and women is similar [132–136]. The previous findings could suggest the need for clinical studies conducted with a gender-specific approach, since GDs might have implications for the design and interpretation of antidepressant clinical trials and raise the possibility that antidepressants may work somewhat differently in men and women.

Conversely, only minor differences in clinical responses to mood stabilizing agents have been demonstrated between genders [137].

Anxiety disorders are the most common psychiatric diseases and women are two-fold more likely than men to develop them during lifetime [138]. Anxiolytics are largely prescribed medications, which, beyond pharmacokinetic GD [139], may display some gender-related effects, such as the benzodiazepine-induced sexual dimorphism on EEG [140]. Benzodiazepines have dependency-producing properties, and the majority of patients who are prescribed benzodiazepines and are treated for benzodiazepine dependency are women. These differences might be ascribed to different brain levels of neuroactive steroids, which have been reported to affect $GABA_A$ receptors in a sex-specific manner [140–142]. However, differently from preclinical studies, which demonstrate sex discrepancies in the activity of anxiolytics, clinical data, at present, indicate no relevant GDs in pharmacodynamics, although the existence of subtle GDs, which require larger and specifically designed studies to be recognized, can not be ruled out.

GDs in pharmacodynamics have been also observed in drug-induced analgesia and anaesthesia, showing that females are less sensitive (30–40%) than males to propofol [143] and that they display a greater sensitivity to morphine. It is, indeed, calculated that males need morphine doses 60% higher than females to achieve equivalent pain relief [139]. On the other hand, females experience respiratory depression more frequently than males [139]. Furthermore, females are also more sensitive than males to the analgesic effect of κ (OP2) receptor agonists pentazocine, nalbuphine and butorphanol [30,144]. Gender-specific analgesic responses to NSAIDs have been less explored. Walker and Carmody [145] indicated ibuprofen as a compound more active in

men than in women, although this does not represent a general finding for the majority of NSAIDs [27].

Sex hormones control excitability of cortex and may alter seizure threshold [1]. Therefore, for many women the seizure control is more difficult to reach in puberty, in certain period of cycle (e.g. catamenial epilepsy) and during perimenopause [1]. Oestrogens administered in menopausal period may exacerbate seizures. In addition some antiepileptic drugs may decrease sex hormones, leading to sexual dysfunction [1]. Optimal management of epileptic women incorporates the understanding of the role of hormones, both endogenous and exogenous.

Aetiology, epidemiology, consequences and mechanisms of drug abuse seem to be different in male and females [146]. Most reported findings are based on laboratory research in animals, but there are corroborating reports from human clinical and epidemiological studies [147]. GDs occur in all phases of drug abuse, from the initial acquisition of drug self-administration in drug-naive animals, to maintenance, escalation and relapse [147]. Female animals appear to be more sensitive to the rewarding effects than males throughout these phases, and oestrogens seem to be a determining factor. In addition, females are more affected by behaviours related to drug abuse, such as conditioned place preference, intracranial self-stimulation, and intake of preferred dietary substances [147]. Generally, prospective animal studies agree with initial epidemiological reports in humans, which show that females progress from drug-use to abuse faster than males, even if they respond to treatment as well as males, or even better [147,148].

In addition psychoactive effects of 3,4-methylenedioxymethamphetamine (MDMA) have been reported to be more intense in women than in men [149]. Women especially exhibited higher scores for MDMA-induced perceptual changes, thought disturbances, and fear of loss of body control. The evidence that equal doses of MDMA produce stronger responses in women compared to men is consistent with an enhanced susceptibility of women to the 5HT-releasing effect of MDMA.

4.2.2. *Drugs acting on the cardiovascular system*

Men and women differ in some aspects of cardiovascular system in terms of anatomy, physiology and ageing [1]. For example, women have a smaller heart, higher resting heart rate (three to five beats higher than in men) and the cardiac cycle length is prolonged during menstruation [150]. GDs have been demonstrated for the coronary left main and left anterior descending arteries that are smaller in women, independent of their body size [151]. Simply by virtue of their smaller diameter vessels, women may be more prone to coronary occlusion than men. Moreover, there is initial intriguing epidemiological evidence that the inflammatory process associated with plaque development may differ in women and men. Interestingly, C reactive protein (CRP) appears to be enhanced in the presence of increased oestrogen levels, as evidenced by recent clinical trials of hormone replacement therapy (HRT) [152,153]. Together, these findings suggest that oestrogens may be involved in altering plaque stability, via inflammatory mechanisms. Recent data show that a greater incidence of plaque erosion rather than plaque rupture occurs in women compared to men [154].

Traditional risk factors differ between men and women. Although in the past the difference was attributed to the presence of oestrogens in the premenopausal period, one of the most significant differences to be considered is diabetes mellitus, which is associated with a three- to seven-fold increased coronary artery disease (CAD) risk in women, compared to a two- to three-fold elevation in CAD risk in men. The reason for this gender difference is not known [155]. In women older than 65 years, dyslipidemia may also put women at a greater risk than men. High levels of triglycerides and low levels of high-density lipoproteins (HDLs) are strongly correlated with CAD in women [156]. In addition to these data, further sexual dimorphic targets have been identified (e.g. Akt, α_{1a} and α_{1b} receptors, β2 receptors, endothelin and ryanodine receptors, K^+ channels) [157–160]. Some of them (but not all) have been demonstrated to be hormone-dependent [19,159–161].

Despite the first GD in clinical setting (hypertension) was described in 1913 [162], more than one-third of the drugs approved by FDA between 1998 and 2000 lack information on sex-related responses; in particular 22% of reports fail to provide separate efficacy data for women and men, and 17% omit sex-based safety data in their New Drug Applications [163]. The numerous GDs in sympathetic, pararasympatethic and rennin–angiotensin systems [1,19,164] could explain GDs in cardiovascular drug responses. Sexual dimorphism has been documented with angiotensin converting enzyme (ACE) inhibitors [165], which seem to produce less benefits in old women, than in men or younger females [166]. Subgroup analysis of the CONSENSUS study demonstrated a statistically significant reduction in mortality with enalapril (after 6 months of treatment) in men but not in women [167]. CONSESUS II study evidenced that 13.5% of women treated with enalapril died compared with 11.2% of women treated with placebo [168]. Furthermore, the SOLVD study confirmed again a wider reduction in mortality and in the rate of first heart failure hospitalization in men than in women [169]. Captopril resulted associated with a 22% decrease in the risk of death in men, but only with a 2% decrease in women [170]. However, an overview of 30 randomized controlled trials with ACE-inhibitors in heart failure identified a total of 5399 men and 1991 women, revealing that the previous results can reflect, once again, the relatively exiguous number of women enrolled in each single study [171]. Moreover, a recent meta-analysis has evidenced that women with asymptomatic left ventricular systolic dysfunction may not achieve a mortality benefit when treated with ACE-inhibitors [172]. Finally, the frequency of cough, the major concern for therapy discontinuation, has been reported to be higher in women than in men [173].

The classical β-blockers propranolol and metoprolol reach higher plasma concentrations in women than in men [174,175] and a gender stereoselective metabolism has been also described for these drugs [175]. The same dose of these β-blockers in women is able to induce a larger decrease in heart rate and systolic blood pressure than in men. However, no gender-related differences were measured in either heart rate or blood pressure when concentration–response curves were performed. This suggests that the greater pharmacodynamic effect measured in

women is the result of the higher plasma concentrations and greater drug exposure, secondary to pharmacokinetic differences [175].

Regarding heart failure, the under-representation of women (<21%) is maintained also in clinical trials with β-blockers, this small number being, at least in part, responsible for the uncertainty of results. The "Metoprolol for the Treatment of Congestive Heart Failure" (MERIT-HF) and "The Carvedilol Prospective Randomized Cumulative Survival" trials failed to find any mortality benefit for women enrolled [176,177]. However, a successive evaluation of the Packer's study reported an equal morbidity benefit over 65 years of age [178]. On the other hand, the post hoc analysis of the "Cardiac Insufficiency Bisoprolol Study", adjusted for older age, found a major benefit in women [179]. Finally, a meta-analysis of β-blocker trials, enrolling women with class III and IV congestive heart failure, demonstrated a beneficial effect of drug treatment in women, after adjustment for age and risk factors between men and women [180]. These findings have been also confirmed later [172]. It is still a matter of discussion whether the response to an old drug such as digoxin is gender related. Women usually present, indeed, higher digoxin serum levels and have higher mortality [181,182]. Actually the question of gender-specific risk with digoxin might not be properly answered in the absence of appropriate gender-specific randomized clinical studies [183], although it has been evidenced that prudentially the dose of digoxin, in women, should be selected in order to maintain plasma levels below 0.8 ng/ml [19].

Even after adjustment for baseline blood pressure, age, weight and dose for body weight, women had a higher response rate and a major decrease in blood pressure with amlodipine, compared with men [184]. Compliance did not account for the difference in drug response observed, being similar between the sexes. Also the hormonal replacement therapy did not help to explain the significant differences reported in women [184].

Slight GDs have been reported for diuretics, the hypokalemic and hyponatremic effects being more pronounced and occurring more frequently in women [185]. This might account for the greater vulnerability to arrhythmia that women exhibit, also in consideration of their QT length. A gender response to clonidine has been also observed; α_2 adrenoceptors display a dimorphic expression and density in kidney [186,187] and cutaneous vessels [188]. Significant GDs have been demonstrated in the local vascular response to azepexole. Men exhibit less venodilation than women at low dose of azepexole, but manifest more venoconstriction at higher dosage. This effect appears to be also age-dependent [189]. Furthermore, platelet α_2 receptors are influenced by menstrual cycle, being higher at the onset of menses [190].

GDs have been observed in haemostasis and platelet aggregation [191], since platelets were found less responsive to physiological ADP-induced aggregation in males [192]. Women have been reported to display a major risk of intracranial haemorrhage with fibrinolytic therapy [193]. Such risk could be reduced adjusting the dosage for body size, although the correction for body weight and renal functionality may be not sufficient to abolish the increased bleeding, thus suggesting an involvement of pharmacodynamic mechanisms [194,195]. Conversely, no significant GDs have been described with the glycoprotein IIb/IIIa inhibitors [196], even if women with acute ischemic stroke seem to get more benefits from recombinant tissue plasminogen activator than men [197]. In this contest, it is important to remind that women have poorer stroke outcomes than men, even after adjustment for age [198–200].

One of the main corner stone of antiaggregating therapy is aspirin. It has a higher bioavailability in women than in men, probably because men conjugate more aspirin with glycine and glucuronic acid [201]. As oral contraceptives can stimulate these metabolic processes, the difference in aspirin bioavailability disappears in women under hormonal contraception [201]. Additionally, aspirin has been reported to be more active in vitro in male than in female platelets [201], although this issue remains still controversial, since a recent study has shown that women experience the same or greater decrease in platelet reactivity after low dose aspirin therapy compared with men [201]. Aspirin therapy reduces the risk of cardiovascular disease in adults who are at increased risk. However, it is unclear whether women derive the same benefit as men.

In actuality, because of the paucity of data, the effect of aspirin in the primary prevention of cardiovascular disease in women remains uncertain. The recent Women's Health Study, the first primary prevention trial of aspirin therapy specific to women [202], has demonstrated that aspirin decreased the risk of stroke without affecting the risk of myocardial infarction (MI) or vascular death, an effect different from that found in studies that enrolled exclusively or predominantly men. Thus, a differential beneficial effect of aspirin therapy may exist between men and women.

Event rates of stroke and MI differ. Women have a greater proportion of strokes compared with MI, whereas men have a greater proportion of MI compared with strokes. In addition, aspirin resistance tends to be more common among women than men [203].

Clinical trials have demonstrated that lowering cholesterol decreases CAD morbidity and mortality and slows lesion progression in men, but most studies have included few women [204]. In general, both diet and pharmacological lipid lowering decreases first and subsequent cardiac events in women. The effect of lovastatin treatment on the reduction of first events has been reported to be greater in women than in men [205]. For recurrent cardiac events, women display twice the rate of risk reduction as men when given equivalent doses of pravastatin [206]. Diet and lifestyle changes can have a profound effect on morbidity and mortality from CAD in women. Therefore, there is strong evidence that CAD in women is largely preventable through diet and lifestyle modifications.

4.2.3. Energy metabolism

Many GDs are present in the control of energy homeostasis [207]. Interestingly, male rat brains are more sensitive to low doses of insulin, whereas female brains are more sensitive to leptin [207]. These observations, beyond their importance for energy balance control, imply that strategy for reducing body weight might be different in male and female. Insulin sensitivity,

insulin–receptor binding and tissue glucose utilization are not influenced by menstrual cycle [208]. However, peripheral insulin sensitivity is significantly higher in females as compared to men [209]; even if, age-induced increase in insulin resistance is more pronounced in females [208].

Sex hormones have a crucial role in the metabolism of lipids, such as high-density lipoprotein and triglycerides (TG). A meta-analysis has demonstrated that an 80-mg/dl increase in TG elevates cardiovascular risk by 75% in women [210]. Unfortunately, most of the existing guidelines on risk assessment are heavily based on low-density lipoprotein (LDL), the lipid abnormality so prevalent in males. A sexual dimorphism has been experimentally documented for fibrates, which activate the peroxisome proliferator-activated receptor (PPAR)-α [211–213]. In addition, GDs in the pharmacokinetics of pioglitazone, a PPAR-γ activator, have been described in rats and some authors suggest that this could help to explain, at least in part, why women have a higher response to this insulin sensitizer [19].

Despite some pharmacokinetic GDs, statins seem to have comparable effects in lowering cholesterol both in men and women [204], although, one paper evidenced a greater reduction of first events in women treated with lovastatin, as compared to men [205]. Recently, it has been experimentally reported that the polymorphism in oestrogen receptor α can be associated, in a gender-specific manner, with a greater HDL increase with atorvastatin [214]. However, women experience more myopathy and rhabdomyolysis, at least with cerivastatin, an agent recently withdrawn from the market [150].

4.2.4. Immune system and drugs

Laboratory and clinical studies have suggested that gender is a significant determinant of prognosis in patients after trauma and infection, with better outcomes generally reported for women [215–219]. The influence of sex hormones on the host immune response has been proposed as an explanation for this unequal gender distribution in sepsis [217,220]. Hormone factors regulate immunity and affect also susceptibility to autoimmune diseases. Indeed, many of gender biases in the susceptibility to autoimmune and allergic disorders become apparent after puberty, but there are obviously additional factors [221]. Asthma exemplifies the reciprocal effects of hormones and age: it is more common in boys than in girls until puberty, but, at that time, the ratio reverts [221]. In addition, asthma severity is affected by menses, pregnancy and menopause [221]. Moreover, a positive dose-relationship between oestrogen use and the risk of adult-onset asthma has been observed in postmenopausal women [222]. The previous findings emphasize the importance to develop a gender-related therapy in allergy. As already mentioned, male and female have different immune responses, women being privileged organ recipients [223]. No current suppressive therapy discriminates between genders [223] and only few studies have addressed this important clue. Indeed, a very small study evidenced a gender and ethnic effect with cyclosporin A, plasma levels being lower in African American men and higher in Caucasian women [224]. Interestingly, preclinical data show an oestrogen-independent gender dimorphic effect of cyclosporin A on bone [225]. Moreover, young male rats have lower cyclosporine plasma levels than young females, but they survive more after skin grafts [226].

A recent meta-analysis, which re-evaluated 49 randomized controlled trials, including only 12.25% women, evidenced that antiretroviral therapy seems to be more efficacious in women than in men [6]. Females have also more frequent and severe ADR with protease inhibitors and nucleoside reverse transcriptase inhibitors [6,227]. For instance, the protease inhibitor-associated lipodystrophy is more frequent in women [227]. Considering that females have lower expression of drug transporter P-glycoprotein and that antiretroviral agents are good substrates for this mechanism, it is conceivable that ritonavir and saquinavir achieve more elevated cellular concentrations in women [228,229].

5. Is gender difference a risk factor for ADR?

It has been estimated that ADRs occur approximately in 3–5% of subjects taking a drug [230] but the gender's importance as a risk factor remains a matter of debate. A recent study, which reviewed 10 years (1986–1996) of ADR in a Canadian institution, reported that more than 70% of the 2367 patients assessed were females [2]. Several reports have revealed that women are more exposed to ADRs than men [230–234] and this is in line with the evidence that 8 of 10 drugs, which have been dropped out from US market, were responsible for more ADR in women then in men. This was still true also when the analysis was performed in the absence of drugs that are more used by females [235].

Female sex is a risk factor to develop long QT syndrome [236,237], a ventricular arrhythmia induced by different classes of drugs, e.g., antipsychotic, antiarrhythmics, H_1 antagonists, antimicrobial and antimalarial agents [238], probably because women have a longer QT interval then men. Actually there are approximately 50 different drugs that can cause QT prolongation and torsades, most likely by blocking potassium ions currents of the heart. In single cell experiments, two repolarization currents, I_{Kr} (rapid delayed rectifier) and I_{K1} (inward rectifier), were measured and showed a lower outward current density in cells from female rabbit hearts, which may contribute to these sex-based differences [239]. In a small clinical trial the I_{Kr} blocking drug ibutilide was administered to normal human subjects and premenopausal women varied in response over their menstrual cycle, with greatest QT prolongation during the menses and ovulation phases. The change in QT length during the luteal phase was similar to the change in men [240]. Anorexigen drug-induced cardiac valvulopathy has been reported to be more frequent in women [241], whereas blood dyscrasias are more frequent in men [232,242]. Furthermore, women generally predominate among patients with drug-induced liver injury [243] and also they appear to be more susceptible to neuropsychiatric ADR, gastrointestinal (especially with NSAIDs) [231,244] and cutaneous allergic reactions [245]. Finally, genito-urinary, sex hormones, antineoplastic and respiratory agents give more ADRs in females than in men [242].

In conclusion, the majority of the studies indicate that females are more prone to ADR. This enhanced risk could be related to

the class of therapeutic agents, to the type of ADR, to the age and physiological status of female, but also to the fact that women are generally treated with doses that essentially reflect the results obtained by trials carried out mainly in men.

6. Conclusions

From the previous examples it is apparent that differences in the pharmacokinetics, pharmacodynamics and side effects of medications are gender-dependent and might correspond to different effect profiles of drugs. The effect of gender on drug response has begun to be investigated only recently for most drugs, and even more recently, the effect of specific dosages and routes of administration have begun to be explored. Despite the fact that, in the last years, more women have been enrolled in clinical trials, the frequency of ADRs in women has not significantly decreased [246]. This indicates the need for a specific gender analysis as the only suitable procedure to detect the differences. At moment the vast majority of product description does not include information about GDs. The paucity of data available both in scientific literature and from reference resources regarding such difference represents a clear demonstration that many issues remain to be addressed. There are more women than men in the population, more women with chronic diseases than men, and more women visiting physicians. It is, therefore, obvious that there is more interest in knowing how women react to drugs. Therefore, it is crucial to investigate the complexity of GDs, since a better knowledge on female biology at the end results in an ameliorated knowledge on male too. Ultimately, a better understanding of sex-related influences on drug responses will help to improve drug safety and efficacy and will also permit to "tailor" pharmacological treatments both in men and women.

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