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Adverse drug reactions and gender differences: what changes in drug safety?

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Summary. Gender differences are influenced by cultural, social, psychological and biological factors. A specific area of medicine has been identified to understand the mechanisms underlying gender differences affecting health status, the course of a disease and pharmacological therapy outcomes. The main gender-related variables affecting drug response are weight, body surface area, height, fat mass, plasma volume and total body water. Gender differences can also influence the drug safety profile; indeed, real-world epidemiological data show a greater incidence and severity of adverse drug reactions in women than in men. Because of several biases in conducting pre-marketing gender-specific studies, post-marketing studies are needed in order to evaluate gender differences in terms of drug efficacy and safety. Therefore, the aim of this review is to provide further evidence in order to show the incidence of specific gender-related adverse drug reactions (ADRs). In this context, we analyzed ADRs reported across the 2001-2018 period in the spontaneous reporting system in the Campania Region (Italy), in terms of number and severity. In line with literature data, our results showed a higher number of reports involving women than men, especially in those aged 18-64 years. Similarly, severe ADRs were more frequently reported in women. Therefore, an implementation of gender-specific pharmacovigilance activities would allow a further better characterization of the safety profile of drugs used in clinical practice.

Key words. Gender differences, adverse drug reaction, pharmacovigilance, safety profile.

Differenze di genere e reazioni avverse a farmaco: cosa cambia rispetto al profilo di sicurezza dei farmaci?

Riassunto. Le differenze di genere risultano influenzate da molteplici fattori che possono essere di natura culturale, sociale, psicologica e biologica. Sulla base di questi ultimi, in ambito medico è stata identificata un'apposita branca di studio finalizzata a comprendere le modalità con cui le differenze legate al genere influenzano lo stato di salute, l'insorgenza e il decorso di numerose malattie, nonché gli outcome di molteplici terapie farmacologiche. Peso corporeo, altezza, superficie corporea, massa adiposa, volume plasmatico e quantità di acqua totale corporea sono alcune delle principali variabili legate al genere che influenzano le differenti risposte ai farmaci negli uomini e nelle donne. Differenze di genere emergono anche in ambito di reazioni avverse ai farmaci. Infatti, dati epidemiologici provenienti dalla pratica clinica evidenziano una maggiore incidenza e gravità delle reazioni avverse a farmaci nelle donne. La carenza di indagini pre-marketing specifiche rivolte alle donne rende difficile la valutazione di eventuali differenze di genere in termini di efficacia e sicurezza dei farmaci che, pertanto, possono emergere solo nella fase post-marketing in un contesto di *real life*. In tale contesto sono state analizzate le segnalazioni di sospetta reazione avversa a farmaco inserite in Regione Campania nella Rete nazionale di farmacovigilanza. Da tale indagine sono emerse differenze di genere in termini di numero di segnalazioni e gravità delle reazioni avverse, in particolare nella fascia di età compresa tra i 18 e i 64 anni. Pertanto, un'implementazione delle attività di farmacovigilanza genere-specifiche permetterebbe un'ulteriore migliore caratterizzazione del profilo di sicurezza dei farmaci utilizzati nella pratica clinica.

Parole chiave. Differenze di genere, reazione avversa a farmaco, farmacovigilanza, profilo di sicurezza.

Introduction to gender-specific pharmacology

When we talk about 'gender differences', we refer to a time-variable that depends on the cultural, social and psychological factors of each individual[1]. This concept is particularly important in a specific branch of medicine known as 'gender-specific medicine' that aims to investigate and understand the mechanisms by which gender-related differences affect health, the onset and evolution of various medical conditions and the outcomes of a number of pharmacological therapies. Considering gender in the medical field makes it possible to develop personalized patient-oriented therapies; this approach constitutes one of the innovative horizons towards which current biomedical research is directed. Due to the pathophysiological differences between the genders, men and women with the same medical condition have very different symptoms, disease progression and responses to treatment. With this perspective, 'gender-specific pharmacology' studies the differences in pharmacological treatments in terms of efficacy and safety, by carefully considering all the physiological variables that could affect response to a medicinal prod-

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uct, in order to promote treatment equality and appropriateness.

The choice of the 'ideal' pharmacological treatment depends on a number of factors. More specifically, a number of biological factors affect the way in which medicinal products are absorbed, distributed, metabolized and excreted; other factors to be considered derive directly from environmental and cultural settings[2]. Men and women differ in their response to medicinal products due to the main gender-related variables, such as weight, height, body surface area, fat mass, plasma volume and total amount of body water. Men and women have also been seen to have different attitudes towards health and therapy. The most recent OsMed report on medicine consumption data showed that 70.2% of medicinal products are used by women, with the greatest gender gap in the 15-64 years age range, where women have an average prevalence of use that is 10% higher than that of men[3]. Some authors believe that this difference can be attributed to the higher percentage of women in the general population and their different lifestyle to men, as well as the higher prevalence of disease associated with hormonal differences. Indeed, one Italian study that analyzed gender differences in terms of medicinal product consumption showed that women consume more medicines for the treatment of osteoporosis, depression and thyroid conditions, as well as preparations containing iron, folic acid and vitamin B12, than men. Conversely, men consume more medicinal products used to treat hypertension (ACE-inhibitors) and benign prostatic hyperplasia[4]. Clinical practice, epidemiological data and the suspected adverse events reported through the Italian National Pharmacovigilance Network (RNF), show a higher incidence and greater severity of adverse drug reactions (ADR) amongst women, who appear to be more prone to possible pharmacological interactions. Gender also influences the type of ADR; for example, diuretics tend to cause hyponatremia in women, whereas they tend to reduce plasma volume in men[5]. The higher ADR rate observed amongst women could be a result of fewer women being included in clinical trials. Indeed, women are still 'underrepresented' both qualitatively and quantitatively in clinical trials. This phenomenon could have a number of explanations. In clinical trials on medicinal products, women are considered 'weak subjects' for social, environmental, economic and, above all, biological reasons. The biological reasons, due to variations induced by hormonal mechanisms, and the economic reasons are particularly important and pharmaceutical companies are less likely to invest in trials on women, as they are expensive. For example, women of childbearing potential enrolled in clinical trials must be guaranteed estrogen-progesterone therapy in order to prevent pregnancy, which has an impact not only from an economic standpoint, but also on drug-drug interactions. These are caused by concomitant therapy with estrogen-progesterone agents and involve both pharmacokinetics and pharmacodynamics. More specifically, estrogens contained in oral contraceptives can interfere with the metabolism of other medicinal products, by inhibiting the specific cytochromes involved in the process. For instance, some anxiolytics belonging to the benzodiazepine class, such as alprazolam, diazepam and triazolam, are metabolized mainly by hepatic microsomal enzymes belonging to the cytochrome P450 (CYP) family (CYP2C19 and CYP3A4); therefore, concomitant use of these medicinal products and oral contraceptives causes a slight increase in the plasma concentration of benzodiazepines, with a consequent increase in their sedative effect[6]. Conversely, certain antibiotics[7] (rifampicin, macrolides) and anti-epilepsy drugs[8] (phenytoin, carbamazepine, etosuccimide and topiramate) interfere, through enzymatic induction mechanisms, with oral contraceptives, reducing their plasma concentration and potentially exposing the patient to unwanted pregnancies. Oral contraceptives can also interfere with preparations containing medicinal plants such as hypericum, which is used by women for its antidepressive and sedative properties, and can reduce the efficacy of the oral contraceptive by approximately 13-15% through the induction of certain cytochrome P450 isoenzymes (in particular CYP3A4)[9]. However, the lack of epidemiology studies makes it impossible to establish the true entity of these interactions, as the data currently available are primarily based on observational studies, spontaneous reports or case reports.

The problem associated with the limited involvement of women in clinical trials is also reflected in the choice of the most appropriate pharmacological treatment in the event of pregnancy; indeed, 80% of pregnant women are still prescribed pharmacological treatments that have not been adequately tested in this population[10].

In order to improve the quality of clinical trials, the European Medicines Agency (EMA) introduced into its guidelines for the enrollment of patients in clinical studies the need to take gender into consideration, so that the samples used are representative of the whole population[11]. Similarly, in Italy, the Italian Medicines Agency (AIFA) has set up a 'Medicines and gender' working group in order to raise pharmaceutical company awareness on the need to process clinical trial data according to gender, in order to bring to light any differences.

The shortage of trials conducted specifically on women does not make it possible to establish the true efficacy and safety of the medicinal products, which can therefore only be evaluated in the post-marketing phase with the real-life use of the product. Pharmacovigilance

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therefore constitutes a valid tool for reducing the risks associated with the use of medicinal products in populations not adequately assessed in clinical trials.

Gender differences in terms of pharmacokinetic and pharmacodynamic properties

The first scientific evidence on gender differences in the pharmacology field dates from 1932, when two researchers, Nicholas and Barron, observed that the sleep-inducing dose of barbiturates was 50% lower in female rats than in males[12]. Gender differences involve both pharmacokinetic and pharmacodynamic aspects, with a consequent variation in pharmacological response in men and women[13]. Pharmacokinetic parameters are affected by the hormonal changes that characterize the reproductive life of women, such as the menstrual cycle (follicular, ovulatory and luteal phases), pregnancy, breastfeeding and menopause[14].

For example, in women ormonal contraceptives can cause interactions with the protease inhibitors used to treat HIV; their efficacy can also be reduced by certain common antibiotics, such as rifampicin and rifabutin, or by certain anti-epilepsy drugs, such as lamotrigine. Women are also more likely to develop osteoporosis and fractures induced by medicinal products (corticosteroids, aromatase inhibitors, proton pump inhibitors and heparin), as well as long Q-T syndrome and iatrogenic *torsades de pointes,* as cardiac repolarization is longer after puberty[15]. In specific analysis, gender differences were identified for all four processes characterizing pharmacokinetics, namely, absorption, distribution, metabolism and excretion. Absorption, the phase in which the medicinal product passes from the point of administration into systemic circulation, is influenced by gender and is closely related to the route of administration used. When administered orally, the absorption of a medicinal product is affected by a number of factors, including intestinal transit time, gastric pH, the solubility of the drug, the degree of ionization and lipophilia and, lastly, intestinal motility. These parameters are usually lower in women than in men, because they are influenced by hormonal changes. More specifically, the gastric juices are more acidic in males than in females (pH = 1.92 vs pH = 2.59) and gastric secretion is lower in women (it decreases by a further 30% during pregnancy); consequently, due to the lower pH, in men the absorption of weak acids is lower and the absorption of weak alkalis is greater[14].

The bioavailability of medicinal products, i.e. the amount of product that reaches systemic circulation unmodified, is also influenced not only by the chemical and physical properties of the drug and its formulation, but also by individual differences such as age, phenotypical differences, enterohepatic circulation and gender.

Gender difference also induces variations in the mechanisms of intestinal metabolism by the CYP enzymes and P-glycoprotein (P-gp)[16]. Men appear to have greater activity than women for CYP enzymes; for example, the hepatic expression of CYP2D6, which is responsible for the metabolism of certain medicinal products such as anti-arrhythmics, beta-blockers and antidepressants, would appear to be greater in men. Consequently, the lower expression of CYP2D6 explains why women treated with beta-blockers are more prone to the onset of adverse events[17]. Conversely, the expression of CYP3A4, which is responsible for the metabolism of 50-60% of medicinal products, is higher in women, and it varies depending on estrogen and progesterone production and age. This difference implies that many CYP3A4 substrates have a 15-30% higher clearance in women, even when the dose is adjusted for weight and this could expose female subjects to a higher risk of gender-specific interactions[18]. Lastly, in women, CYP2C9 expression would appear to decrease with age, whereas the use of oral contraceptives may reduce the expression of CYP2C19[19]. As far as the hepatic activity of P-glycoprotein is concerned, certain studies have shown that it is 2.4 times lower in women than in men[20]. P-gp is a membrane glycoprotein belonging to the ATP-dependent transport protein superfamily, which is involved in regulating drug outflow from the cells. Consequently, its lower expression in women causes a greater build-up in the medicinal product in the liver and faster metabolization.

The second phase of pharmacokinetics is distribution, namely the passage of the medicinal product from the bloodstream into the peripheral tissues. This phase is influenced by body composition, the medicinal product's liposolubility, which, in turn, affects its distribution volume, capillary permeability, blood flow to the various organs and plasma protein binding. On average, females have a lower body weight than men, but a higher percentage of adipose tissue, which reaches 33% during the fertile age and 48% during the menopause[21]. These bodily differences lead to a greater Vd and faster total clearance in men than in women[22]. Women also have a lower plasma volume than men, reduced blood flow and lower concentrations of α-1-acid glycoprotein, whose expression is regulated and controlled by the sex hormones. For this reason, α-1-acid glycoprotein can be reduced by the activity of oral contraceptives and by pregnancy. As a consequence, the amount of free medicinal product not bound to this glycoprotein is higher amongst females, as described in literature for diazepam and imipramine[23].

The pharmacokinetic differences also concern the excretion of the medicinal product (or its metabolite),

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which is characterized by renal glomerular filtration processes, tubular secretion and tubular reabsorption. More specifically, glomerular filtration processes are influenced by body weight, and are consequently 10% lower in females than in males[24]. Similarly, as glomerular filtration is directly proportionate to body weight, renal clearance is generally higher in men than in women[25].

Oral contraceptives may increase or decrease the clearance of the medicinal product due to the induction or inhibition of CYP isoforms in the liver and intestine. The activity of hepatic enzymes can also be influenced by the increase in estrogen and progesterone levels with a consequent increase or decrease in the excretion of certain medicinal products.

Compared to the studies that analyzed the impact of gender on pharmacokinetics, knowledge regarding gender differences in pharmacodynamics is far more limited. The analysis of pharmacodynamic parameters is more complex, in that it should be based on the demonstration that a medicinal product produces different pharmacological effects in the two sexes[16]. However, some of the scientific evidence available in the literature has shown that these parameters could be influenced by sex hormones, genes and the environment. Sex hormones act as chemical messengers that respond to the various needs of the body by regulating gene expression, and they determine true gender-specific pharmacodynamic differences.

The need to define 'gender-specific' pharmacological posologies, in order to reduce the risk of adverse events in women, was stressed in a position paper published by the European Society of Cardiology (ESC) with regard to cardiovascular therapies. It came to light that acetylsalicylic acid has a greater anti-platelet effect in women than in men, whereas acetylsalicylic acid resistance is more common in women, who are therefore exposed to a depleted protective effect with regard to myocardial infarction[26]. As regards treatment with direct oral anti-coagulants, one recent meta-analysis evaluating gender differences in terms of the efficacy and safety of treatment with these medicinal products in patients with atrial fibrillation, showed that women are exposed to a lower risk of bleeding but a higher risk of stroke and embolisms, most likely due to the lower dose used on account of their lower body weight. More specifically, in females, apixaban and edoxaban are associated with a significantly lower risk of bleeding than other direct oral anticoagulants[27]. Similarly, the use in women of beta-blockers, in particular metoprolol and propranolol, causes a greater decrease in blood pressure and heart rate than in men[26]. Lastly, some antidepressants, such as amitriptyline and sertraline, reach higher blood concentrations in females than in males[28], and diazepam has a longer half-life of diazepam in females than in males[29]. Further gender-related pharmacodynamic differences are discussed in Table 1.

Adverse drug reactions and gender differences: pharmacovigilance

According to the definition provided by the World Health Organization (WHO), pharmacovigilance is the set of activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem[36]. Monitoring the safety of a medicinal product also means promoting its rational

Table 1. Pharmacodynamic differences for various active substances according to gender.

Drug class	Active substance	Gender differences
Anesthetics	Propofol	Propofol is metabolized more quickly in women and therefore they need higher doses than men to achieve the same pharmacological effect[30]
Antidepressants	Sertraline Fluoxetine Paroxetine	A number of studies have shown that women have a better response to selective serotonin reuptake inhibitors (SSRI) than men[31]
Antipsychotics	Aripiprazole Quetiapine Aloperidol	Some studies suggest that female patients respond to lower doses of antipsychotics than male patients[32]
Benzodiazepines	Diazepam	Diazepam impairs psychomotor abilities to a greater extent in women than in men. It is therefore recommended to start treatment at a lower dose[33]
Neuromuscular blocking agents	Rocuronium Vecuronium	Women are more prone (20-30%) to the effects of neuromuscular blocking agents than men. The dose should therefore be adjusted according to gender, using lower doses in women[34]
Oral anti-platelet drugs	Warfarin	Women require lower maintenance doses of warfarin than men[35]

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use and guaranteeing the appropriateness of prescriptions. To achieve these aims, pharmacovigilance uses a number of different tools, including spontaneous reporting, epidemiological studies and clinical studies. The most common form of adverse event reporting is spontaneous reporting, defined as an unsolicited communication by a healthcare professional or consumer to a regulatory authority that describes one or more ADRs in a patient who was given one or more medicinal products. Once it has been filled out, the report must be sent to the pharmacovigilance manager of the facility involved, who will enter it in the RNF.

From a regulatory standpoint, in Italy in 2012, the Ministerial Decree of 30 April 2015 (Official Gazette n. 143 of 23 June 2015) transposed two new European provisions on medicinal product safety, Directive no. 2010/84 and Regulation no. 1235/2010. The new pharmacovigilance decree introduced a number of rules intended to improve the likelihood of the signal being detected and expedited the European procedures in place to deal with medicinal product safety issues. More specifically, with the new Risk Management Plan (RMP) it is now possible to optimize the management of drug safety issues in the phase immediately after marketing authorization (MA), in addition to the data collected through spontaneous reports for signal detection[37]. The new regulation also defines the post-authorization safety studies (PASS) and post-authorization efficacy studies (PAES) that are conducted immediately after the medicinal product has been granted MA. Lastly, with the introduction of the new definition of ADR, which is now considered a "harmful and undesired effect deriving from the use of a medicinal product", reporting now includes ADRs caused by therapeutic errors, abuse, misuse, off-label use, overdose and occupational exposure.

As previously mentioned, scientific evidence has highlighted the possibility that women are more exposed to the risk of ADRs than men. Studies have been conducted on certain classes of medicinal products to identify the gender differences associated with the risk of ADRs. One Italian pharmacovigilance study evaluating 301,233 ADRs entered in the RNF between 2001 and 2016, showed that females are more likely to develop ADRs during a pharmacological treatment, especially with drugs belonging to the classes: thyroid hormones (levothyroxine), antimalarials (hydroxychloroquine), COX-inhibitors and antirheumatics (celecoxib and etoricoxib), selective serotonin reuptake inhibitors (citalopram, paroxetine and escitalopram) and benzodiazepines (lorazepam and alprazolam). The same study showed that, although severe ADRs are more common in women than in men, the latter have a higher mortality risk[38].

Similarly, a Bayesian statistical analysis showed that, with an equal number of adverse events in men and women, there is a prevalence of ADRs classified as serious amongst females, most likely due to pharmacokinetic and pharmacodynamic differences[39]. Considering that ADRs account for 5-10% of all hospital admissions[40], a study evaluated gender differences for hospital admissions due to ADRs to cardiovascular medicines. More specifically, 54% of hospital admissions involved female patients, predominantly due to treatment with loop diuretics, thiazide diuretics and cardiac glycosides[41].

Several studies suggest that ADRs most commonly associated with the female gender are the development of long QT syndrome, limb fractures following treatment with thiazolidinediones[42], fractures during treatment with high-dose corticosteroids in liver transplant patients[43] and metabolic alterations with consequent weight gain[44].

However, it is important to point out that other studies suggest that there may be no correlation between gender and the onset of adverse events. For instance, an Italian study conducted in the Campania Region to assess ACE inhibitor tolerance in both genders did not find any significant difference in terms of the onset of ADRs. The study analyzed the reports entered in the RNF in the Campania Region between 2001 and 2015 reporting at least one ACE-inhibitor as a suspect drug[45]. Moreover, an international study collecting data on spontaneous ADR reports associated with psychotropic drugs from pharmacovigilance centers in Veneto (Italy), Midi-Pyrénées (France) and Castilla y Leòn (Spain) between 1 January 2007 and 31 December 2009, did not show any significant gender differences in the number of reports[46].

In the light of this, the data currently available on the impact of gender differences on the safety profile of medicinal products are still contradictory. It is therefore necessary to encourage further studies in order to promote treatment appropriateness in both genders.

ADR in the Campania Region: data from the Italian National Pharmacovigilance Network

Between 2001 and 2018, a total of 36,659 ADRs entered in the RNF in the Campania Region. Of these, 16,508 report sheets regarded male patients and 19,747 female patients (45% vs 54%, respectively). The remaining 404 reports (1.1%) did not specify the gender of the patient. During this period, an overall increase was observed in the number of reports, from 69 reports entered in 2001, to 5430 in 2018. This increase was particularly significant after 2012, the year in which the new pharmacovigilance provisions (Directive no. 2010/84 and Regulation no. 1235/2010) came into force.

As regards the suspected ADR report trend, in all years a higher percentage of ADRs was reported amongst females, with the exception of 2009, when a slightly high-

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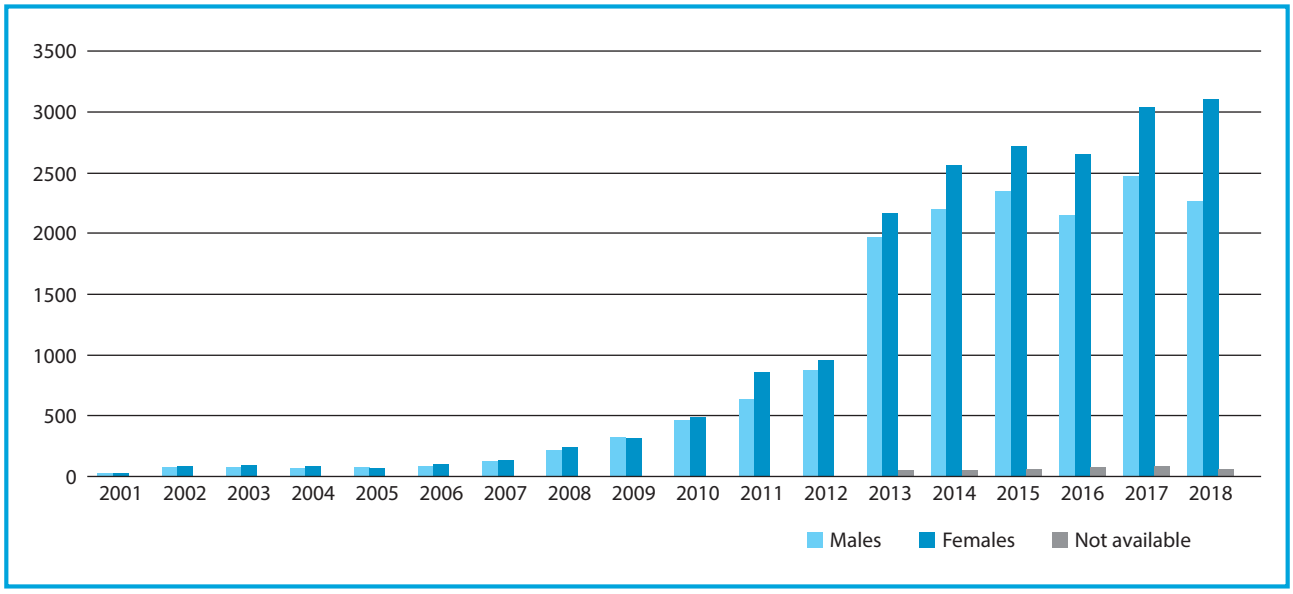

Figure 1. Adverse drug reactions report trend broken down by gender in the Campania Region between 2001-2018.

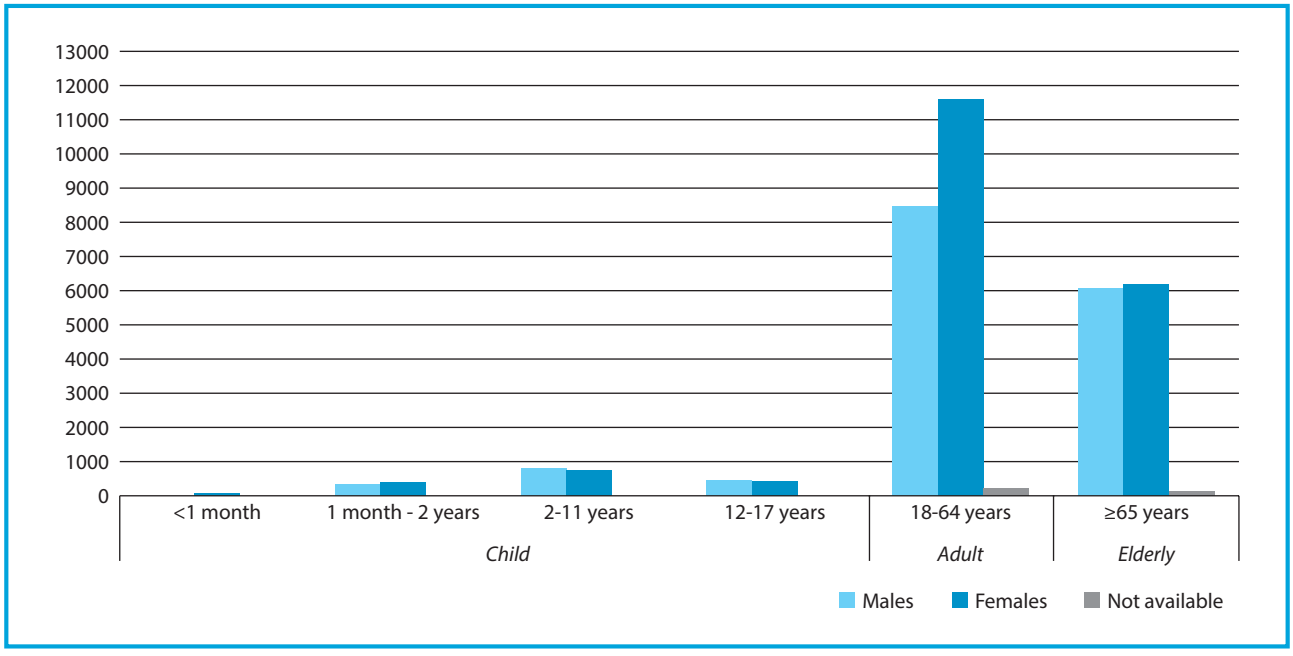

Figure 2. Adverse drug reactions report trend broken down by age range in the Campania Region for the period 2001-2018.

er number of reports involved male subjects (Figure 1). The exception was the pediatric age range, in which the male population would appear to be more affected. However, this difference is not significant (51% vs 48.3%).

As in the study conducted by Castellana et al.[38], the highest number of reports concerned the 18-64 years range: indeed, patients belonging to this age range are the main users of medicinal products, and in many cases they are patients on polytherapy and therefore more prone to the risk of an ADR (Figure 2). Once again in this case, the greatest number of suspect ADRs regarded the female population (57.2% vs 41.8%).

As regards the ADR distribution according to MedDRA System Organ Class (SOC), the analysis of reports showed that the most common ADRs, in both genders, where related to the SOC 'Gastrointestinal disorders' (9% of reports concerning female patients vs 7% in males), followed by SOCs 'Skin and subcutaneous tissue disorders' and 'General disorders and administration site conditions' (Figure 3).

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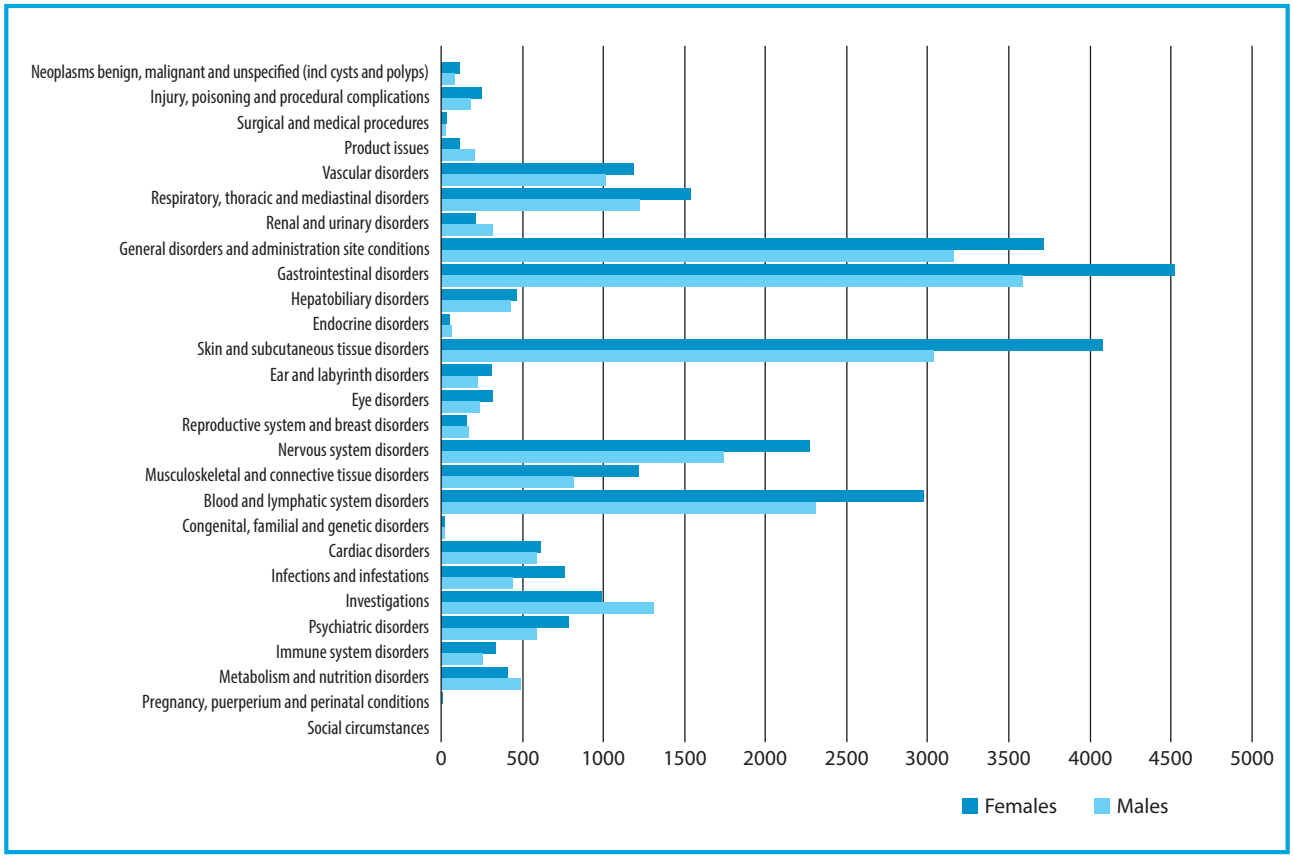

Figure 3. Adverse drug reactions distribution broken down by SOC and gender.

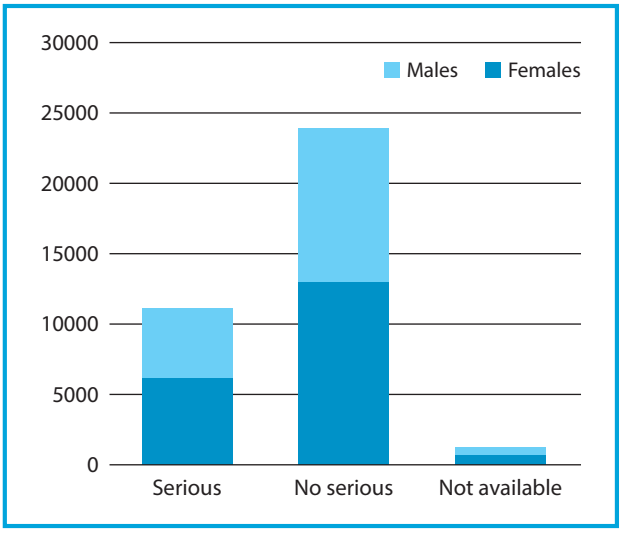

Figure 4. Adverse drug reactions severity according to gender.

Lastly, in both genders, again for the period 2001-2018, more 'no serious' ADRs were reported than 'serious' ADRs. More specifically, in women 66.6% of ADRs were reported as being 'no serious' vs 54.4% in men. Information on seriousness was not available for 3.3% reports for both genders (Figure 4).

Conclusions

Attention to gender in medicine rapresents an important strategy to be undertaken in order to develop personalized therapies that guarantee increasingly appropriate and efficacious treatments. In this context, pharmacology is essential to understanding the gender differences associated with pharmacological treatments, in order to identify the mechanisms underlying the differences in response to medicines that, in turn, influence their tolerability. Considering the persistent limitations regarding the inclusion of women in clinical trials, post-marketing studies, and therefore pharmacovigilance, represent an important tool for identifying the true safety profile of medicinal products in those populations that have not been adequately studied, in order to promote prescription appropriateness. Although the data available regarding the impact of gender on the safety profile of medicinal products shows a prevalence of ADRs amongst females over males, gender-specific pharmacovigilance activities must be undertaken in order to reduce the risks associated with the use of medicinal products and to analyze their risk/benefit assessment in greater detail, in the light of the differences between men and women in terms of pharmacokinetics and pharmacodynamics.

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Key messages

- Gender-specific pharmacology is the branch of medicine that studies gender differences in pharmacological treatments in terms of efficacy and safety, by carefully considering all the physiological variables that could affect response to a medicinal product.
- Men and women differ in their response to medicinal products due to the main gender-related variables, such as weight, height, body surface area, fat mass, plasma volume and total amount of body water.
- Women are still 'underrepresented' both qualitatively and quantitatively in clinical studies, as fewer females are enrolled than males.
- Clinical practice and epidemiological data show a higher incidence and a greater severity of adverse drug reactions for women, who are more prone to possible interactions or adverse reactions.
- Gender specific pharmacovigilance activities must be undertaken in order to reduce the risks associated with the use of medicinal products and analyze the relative risk-benefit assessment in detail.

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