

## GENDER DIFFERENCE AS RISK FACTOR FOR ADVERSE DRUG REACTIONS: DATA ANALYSIS IN SALVINI HOSPITAL

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### Abstract

Gender medicine and pharmacology have an important role in the development of a personalized therapy on every single patient. In particular, gender medicine could predict the difference response to a pharmacologic therapy on the basis of patient's sex. Pharmacovigilance could help in this process through a continuous monitoring of adverse drug reactions (ADRs) ensuring a safer drug therapy. The aim of this study was to systematically evaluate ADRs in the general populations on the basis of gender during a 6-month period of observation in order to draw attention to eventual risk factors. During the observation period were collected 405 ADRs: women represented 54,57% overall and 56,23% considered only the ADRs in adult population (>17ys) excluding intentional overdoses. Antibiotics were the most reported class of drug for suspected ADRs without significant gender difference. On the other hand female patients resulted most involved in suspected contrast media adverse reactions (77,27%) and opioid analgesics adverse reactions (81,80%). Female gender has been identified as a general risk factor for ADRs, especially due to contrast media and opioid analgesics. These data underline the importance of gender medicine and gender pharmacology to minimize safety problems and, at the same time, optimize the therapy efficacy. Moreover an increased inclusion of women in clinical trials could help in the evaluation of drug safety for adverse events and drug toxicity.

Keywords: Adverse Drug Reactions, Pharmacovigilance, Gender medicine

## Introduction

In the last decade, biomedical research has turned increasing attention to gender differences between men and women in drug research: the aim now declared by the scientific community is in fact to go more and more toward personalized therapy for the patient (or group of patients), maximizing the effectiveness of a drug while minimizing the risks to safety and the associated costs of treatment borne by the national health system.

A first step towards the personalization of drug therapies is the medicine typically understood as the study of the differences related to gender, not only from the standpoint of anatomical / physiological, but also differences psychological, social and cultural rights, as well as response to treatment (1,2). In particular, the study of the pharmacokinetic and pharmacodynamic differences between the sexes allows a better evaluation of the different profiles of efficacy and safety of drugs in relation to sex with obvious advantages for the patient.

In the literature it is described as the frequency of occurrence of adverse drug reactions (ADR) is greater in women than in men, which makes the female one of the risk factors for ADR, along with age (over 65 years) and polytherapy (1, 3-7).

This difference is partly explained by the smaller number of female individuals enrolled in clinical trials for drug development (1,2), then the resulting therapies developed and studied in pre-marketing for the predominantly male.

Pharmacovigilance, from this point of view, can play a major role in defining the proper safety profile of a drug (including in relation to sex) after its marketing, as well as in raising awareness of the various health care workers in the correct use of drugs in the light of the risk factors highlighted.

The aim of this study was to evaluate possible gender differences in the reporting forms of suspected ADRs in the population of patients attending at the Hospital (AO) G. Salvini, with specific reference to all the different structures (emergency room, inpatient, outpatient access ) of the 4 hospitals Garbagnate Milanese, Rho, and Passirana Bollate, for a total of 493 920 hospital admissions in the first half of investigation, on a catchment area of 412913 inhabitants (8).

## Materials and methods

The study analyzes the ADRs collected as part of

two projects active pharmacovigilance at the AO Salvini in the six months from January to June 2013. Suspected ADRs were reported in accordance with European Directive 2010/84/EU considering what Adverse Reaction to Medication any harmful effect and unwanted resulting from the use of a medicinal product, including medication errors, use off-label use or abuse of the drug. To ensure the consistency and completeness of reporting was used the special form AIFA reporting of suspected ADRs, pursuant to the recent legislation on pharmacovigilance, updated in July 2012.

All reports have been entered into the National Pharmacovigilance exploiting the coding MedDRA (Medical Dictionary for Regulatory Activities) 9 for the classification and diagnosis of clinical events.

For the definition of the criteria for severity of ADRs has been referred to the AIFA criteria derived from EU Directive 2010/84/EU, considering all serious ADRs that led to the patient hospitalization or prolongation of it, life threatening, disability serious or permanent, congenital abnormalities or deficiency in the newborn, death, or a condition clinically relevant.

To shed light on gender differences in relation to the onset of ADRs was carried out a descriptive analysis stratified by gender and age groups; the investigation has focused population of patients aged greater than or equal to 18 years (thus excluding patients of relevance pediatric), omitting any analysis ADRs due to possible attempted suicide or intentionally self-inflicted overdose of the drug by the patient.

The suspected drugs reported were analyzed for active ingredient (PA) and pharmaceutical grade, omitting the trade name of medicinal products in data processing. The clinical events and diagnoses were instead analyzed by System Organ Class (SOC) and Preferred Term (PT), exploiting coding using MedDRA. It shows how each ADR can be traced to more PA suspects.

All phases of the study were carried out in accordance with the Legislative Decree No.196/2003 (Code relating to the protection of personal data) currently in force in Italy.

## Results

In the first half analyzed were recorded a total of 405 ADRs of which 221 (54.57%) against female individuals and 184 (45.43%) occurred in patients male.

Excluding the signs for the pediatric wing 0-17,

reports for patients aged 18 years and above, of which 155 278 are to be borne by females (55.76%) and 123 against males (44.24 %).

Further narrowing the selection criteria, excluding all reports due to overdose of the drug voluntarily self-inflicted and suicide attempts (TS) only in the over-17 patients, the percentage of ADRs for females rises to 56.23% (149 ADRs ) against 43.77% of the males (116 ADRs). (Table 1)

Considering only serious ADRs, the difference between males and females is reduced: analyzing all serious reports collected in the first half only 52.43% related to the female sex, while the percentage drops further to 50.72% considering only the patient population over-17 excluding TS / overdoses. (Table 1)

It was therefore decided to analyze in greater depth the over-17 population of patients from which they were excluded any and all overages voluntarily self-inflicted or TS: an analysis stratified by age has been observed that women are generally more vulnerable the occurrence of ADRs than men except for the age group 20-29 where the reports are highly unbalanced load of the male. (FIGURE 1)

The analysis for SOC shows that, for absolute numbers, ADRs affecting the skin and the subcutaneous tissue occur more in women (87 messages) than men (60 reports, of which 20% concentrated in only one age group 20 -29 years).

In particular, skin disorders account for 58.39% of the adverse reactions reported for women and 51.72% of those reported in men, making it the most common type of ADR recorded.

To the ADRs in the nervous system is a superposition in terms of numbers of males and females (11 M vs. 13 F), while women appear to have reported more gastrointestinal adverse reactions (5 M versus 13 F) .

The analysis by PT reflects the general trend of the analyzes conducted for SOC: for both males and females erythema (26F versus 24M), urticaria (24F versus 13M) and rash (16F against 11M ) represent the first three types of ADRs reported.

The ADRs based haemorrhagic turn out to be superimposable, in terms of absolute numbers, with 12 cases found in women and 11 in males.

There seems to be sex-specific ADRs related to SOC "disorders of the reproductive system and breast disorders" or deficiency in the newborn.

There have been reports an average of 1.17 active ingredients suspected ADR: in the female share of

PA for suspected ADR is equal to 1.2, while in males is reported to be 1.13. The class of drugs most reported of all is that of antibiotics with 45 PA reported in males (34.35% of total drugs reported for men) and 46 women (25.84% of total drugs reported for women) while NSAIDs are the second category of drugs reported to number with 22 reports in males and 29 in females. (Table2)

The ADRs from iodinated contrast agents in women turn out to be the third highest frequency with 17 reports (9.55% of total drugs reported for women), while in males occupy a marginal place with only 5 ADRs (3.82% the total number of drugs reported for males). Of these 22 ADRs from MDC recorded, as many as 77.27% is therefore to be borne by female patients. (Table 2)

Likewise also the opioid ADRs appear to be greater in absolute values in females: in fact, while for women it is observed 9 ADRs from this class of drugs (for a total of 10 PA reported as suspected), for males have been reported only 2 ADRs. (Table2)

The antibiotic most noted for both sexes appears to be the amoxicillin with or without combination with clavulanic acid (ADR 28 F and 25 M), followed by clarithromycin and levofloxacin. The ADRs from MDC are, on the whole, be due to iopromide in 59.9% (13 F and 3 M) and the remaining 40.91% of the time in iomeprol (9 F and 2 M). (Table 2)

In particular, 19 ADRs from MDC iodinated to 22 (83.36%) are affecting the skin and subcutaneous tissue, proving to be mostly on the basis of allergic or idiosyncratic.

An analysis of the 11 ADRs from opiates has shown that 9 of them are borne by the females (81.8%) and in 5 of 11 cases (45.45%), have resulted in diseases of the nervous system which bradypsychia and confusion. The active ingredient was found to be the most reported with tramadol 5 reports (all dependents of female individuals) out of a total of 12 opioid drugs reported as suspected.

## Discussion

This study has shown that the female sex is generally a risk factor for the occurrence of ADR.

In particular, this higher propensity onset of ADRs by the female appears to be more pronounced in patients over-17 thus excluding the fascia of patients of the pediatric category.

Studies in the literature have shown the percentage of ADRs for the female (on the over-17 population excluding TS / overdoses) is equal to 56.23%.

Emergency departments in the U.S., the figure is 57.2% of ADRs at the expense of women (10), while, in a similar study in 2011 based on the active monitoring of ADRs in the emergency Lombard 4, the percentage of ADR for patients females appeared to be of 55.14% compared to 44.86% male with the differences between the sexes that were tapered to 51.54% for females and 48.46% for males considering only serious ADRs. Also in this case there is a match with the data resulting from this study which shows that the gap between men and women becomes thinner at 50.72% (F) versus 49.29% (M) (always in a population over-17) considering only serious ADRs.

The absence of sex-specific type of ADRs Reproductive or any deficit charged to the newborn or unborn child is the strong point of the investigation.

Stratified analysis of the distribution of ADRs by age has allowed us to evaluate the difference between the sexes in relation to the age of patients.

The aim was to evaluate another critical factor for the occurrence of ADRs as often related to polypharmacy and polyopathy (5,6,10,11).

This type of analysis has therefore allowed us to confirm that the study data are not only resulting from the difference in average life expectancy between men and women in Italy (76.8 years versus 82.9 for women in 2008) 12: in fact the female turns out to be more susceptible to the onset of ADRs for them all age groups, with the except for age 20-29.

One of the age groups with the greatest difference between the sexes is that between 40 and 59 years, a period in which the female menopause occurs on average (with an average western white women between 47.5 and 52 years ) (13). In post-menopausal women are actually more vulnerable than men to the onset of ADRs (with particular reference to adverse cardiovascular reactions) as well as to increase the number of drugs used in therapy incurring greater risk of drug interactions and the onset of reactions conditions (14).

The number of active reported as suspected ADRs for each individual is found to be slightly higher in females (1.2 F against 1.13 M), except that, although minimal, reflecting the increased use of medications by women also highlighted in the report OSMED edited by AIFA in 2011 15. Women, children and the elderly are in fact the most exposed to drugs in Italy.

The apparatus most frequently involved by ADRs appears to be the skin and the subcutaneous tissue. The female seems to be generally most affected by this type of adverse reactions which are mostly based on allergic or idiosyncratic: Part of this difference is explained by the higher incidence of allergic reactions to contrast media in women. The results obtained show that there are as many as 77.27% of ADRs by MDC are dependent on female patients, as compatible with the 63% obtained by an analysis of 507 adverse reactions to MDC over a range of ages of 18-96 16 years.

Similarly to what already described in letteratura16, 17, the female is therefore to be a strong risk factor for the onset of adverse reactions related to the use of contrast media, although it is not yet know the reasons and mechanisms that are at the base of this gender difference.

The female is also more susceptible to ADRs from opiates. The data obtained show it as 81, 8% of adverse reactions to this class of drugs is only to the detriment of women.

Information in the literature confirm that age and gender may in fact influence the response to opiates, as well as highlighting how the onset of toxicity in women there is a greater prevalence of ADR such as vomiting and nausea. The possible reason may be the mistaken management of patients during treatment of pain, in which no account is taken of the female lower pain threshold and physiological differences between men and women (18).

It also highlights that women older than 50 years are generally more susceptible than men, in conditions of chronic pain requiring opioid therapy lasting more than 1 year (19).

The data obtained are therefore be in line with the data present in the literature; it is merely a descriptive analysis of 405 ADRs observed, one needs to put some caution in their interpretation. In particular cases the limited and the possible presence of BIAS not assessable through a simple descriptive analysis appear to be the main limitations of this study.

### Conclusion

The scientific community has recognized how gender differences affect both the different efficacy of some drugs as well as on the possible occurrence of any ADR 20.

It is therefore necessary to take account of these differences when setting up a drug therapy so as to

maximize its effectiveness and minimize the risk to the patient. The adverse drug reactions have indeed a strong negative impact on both the health of patients in health care costs.

Greater attention to gender differences thus represents a first step towards therapies focus more on the person in view of a "personalized medicine". To do this, however, should be studied in more detail the differences between the sexes in the pharmacological response up from patient recruitment in clinical trials pre-authorization of immisione in Commerce. As described in literature, the proportion of women represented in clinical trials is often still too low, and should reach around 50% as previously expected and required by regulatory authorities in the last decade.

This would get the marketing of the drug with the indicated use is not primarily focused on the male figure, but studied and optimized on both sexes.

The post-marketing surveillance is also an essential tool in the analysis of risks related to drug therapy in real populations also highlighting possible gender differences. Despite its limitations, this study provides, from this point of view, a first overview on the influence of gender differences in the onset of ADRs. In particular, it offers interesting insights for future studies of gender medicine applied to pharmacovigilance, outlining the populations most deserving of further study. Above all, in the light dell'importate lack of data and specific studies in the literature, there are the suspected ADRs to iodinated contrast agents in diagnostic radiology.

In this way, it would help to better delineate always different risk / benefit between men and women, always with a view to optimize the effectiveness of a drug while minimizing the security risks. In addition, the optimization of therapies and a greater focus on the patient, even on the basis of gender distinction, would result in a reduction of the national health expenditure, both in terms of direct and indirect costs.

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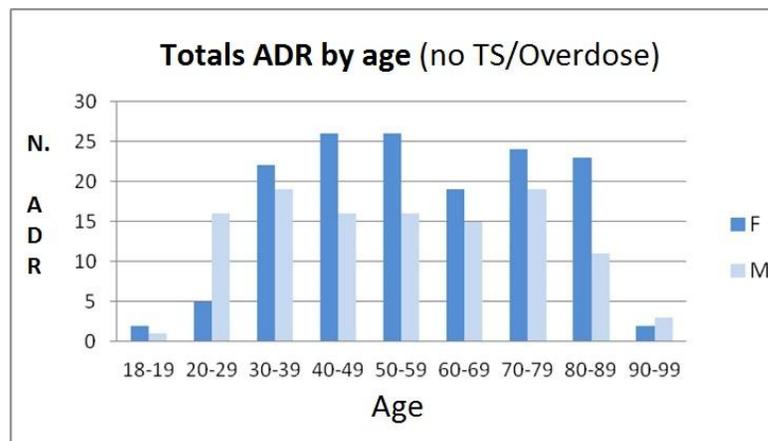
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Gender	ADR TOT IN OVER-17 (noTS)			
	Total ADR		Serious ADR	
	n°	%	n°	%
f	149	56,23	35	50,72
m	116	43,77	34	49,28
TOT	265	100%	69	100%

**Table 1:** Total ADR and serious ADR registered in the population of patients older than 17 years excluding attempted suicides. Figure 2 highlights the percentage of ADRs in patients over-17 differentiated by gender.



**Fig. 2:** graph of the age distribution of ADRs between males and females.

Class	Male >17AA (NO TS/Ov.dose)		Female >17AA (NO TS/Ov.dose)		Total	
	n°	%	n°	%	n°	%
Antibiotics	45	34,35	46	25,84	91	29,45
Fans	22	16,79	29	16,29	51	16,50
Iodinated Contrast Agents	5	3,82	17	9,55	22	7,12
Anticoagulants	8	6,11	11	6,18	19	6,15
Opiates	2	1,53	10	5,62	12	3,88
Antiplatelet	5	3,82	6	3,37	11	3,56
Other	44	33,59	59	33,15	103	33,33
TOT	131	100,00	178	100,00	309	100,00

**Table 2:** Analysis by class of pharmaceutical active ingredients reported as suspected