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Commentary

Considering sex-specific adverse drug reactions should be a priority in pharmacovigilance and pharmacoepidemiological studies

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In the context of drug safety, being a woman is often assumed as a risk factor for developing adverse drug reactions (ADR) [1–3]. Confusion between terms "sex" and "gender" still appears common in the scientific community. The World Health Organization (WHO) defines sex as "the different biological and physiological characteristics of males and females", and gender as "the socially constructed characteristics of women and men". Sex differences result from chromosomal, genetic differences as well as hormonal difference conducting in biological, reproductive function and physical differences Gender differences result from social roles, norms, education, behavior, lifestyle, environmental exposure, nutrition, etc. over the time. It is important to note that sex effect is reproducible through cultures, ethnic groups, countries, socioeconomically conditions, whereas gender is dynamic and modifiable process in permanent interaction with other characteristics.

In medicine, influences between sex and gender could be difficult to distinguish as well as sex- and/or gender-related specific differences. A recent review investigating sex-specific ADR data related to recommended medications in the context of heart failure [4] reported a general lack of information about sex-specific ADRs in this context. It is suggested that women may have more ADRs related to ACE inhibitors and digoxin, whereas men may experience more ADRs related to mineralocorticoid receptor antagonists, but the currently available evidence remains inconclusive given the scarcity of data. The authors pointed out that sex-specific ADR reporting in articles has not increased over the past 3 decades, despite it is well recognized, and known since some time now that women remain underrepresented in clinical trials and only observational studies may compensate for this lack of evidence. The authors also plaid to incorporate sex-specific reporting into scientific practice. In this article of *EClinicalMedicine*, Watson et al. add a piece by presenting an analysis of the WHO pharmacovigilance database focusing on sex differences in ADR reporting worldwide [5]. This objective and integrative overview of ADR reporting in men and women clearly exhibits differences potentially related to sex and to gender dimensions. Several overrepresentations of women in ADR are potentially related to the level of exposure in the population (sex hormones and modulators of the genital system, thyroid therapy, drugs for bone diseases) and represent a marker of diseases more frequently managed in women for medical and sociological reasons (gynecological troubles, obesity, calcium homeostasis). On the opposite (level of exposure potentially higher in men), this is probably similar in men for antigout or urological drugs, but a male sex sensitivity may be responsible for the higher ADR reporting with radiopharmaceuticals for example. Finally, as reported in some national studies, men seem to be more frequently concerned by the more serious ADR, including those leading to death. Adjusting on sex in safety studies is not enough to investigate sex and gender differences in drug safety.

It is generally admitted that substance use disorders are more frequent in men, and consequently men predominate in most of studies investigating analgesic use disorders in patients managed in addiction specialized care centers. In that studies, sex is most often considered as a confounding factor (women representing 25–40% of patients). However, recent pharmacoepidemiological studies found that women are more frequently exposed to opioid analgesics [6,7]. When investigating specifically factors associated with opioid overdose deaths, female gender, having ever been married, and presence of benzodiazepines as a contributing cause for death were associated with increased odds of opioid overdoses in the Tennessee population [8]. This specific risk might not have been identified if we had only considered the population as a whole, with women representing in all categories (prescription opioid overdoses or heroin overdoses) less than 40% of cases. However, because of gender differences (women can be considered as less at risk of misuse and diverted use than young men [9]) and sex differences (increased susceptibility of female rats in an experimental conditioned preference place procedure with oxycodone [10]), the potential different impact of female sex/gender in the risk related to opioid analgesics is under-investigated. Consequently, clinicians are not aware about these differences when prescribing.

In summary, the recent literature confirms that women may experience different ADRs compared to men when treated with the same drugs, and that the differences of ADR reporting between men and women are probably heightened because prescribing and management

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practices are often related to the patient's gender. However, in most circumstances, the sex-specific data remain scarce. Pharmacovigilance and pharmaco-epidemiological studies can play a role in improving knowledge, by considering sex stratified reporting or when designing new studies. This will aid a better understanding of 'sex-related' ADR and will aid the discovery of sex-specific ADRs in many fields.

Declaration of Competing Interest

None.

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