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Sex Differences in Adverse Drug Reactions and Liver Disease

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ABSTRACT

Adverse drug reactions represent a significant public health problem. Quite a few episodes of particularly severe drug reactions can even lead to the death of a patient. Furthermore, hepatitis induced by severe drug reactions is a rare but potentially fatal event. Although gender medicine is a relatively recent concept, it is now emerging as an important field of research, supported by the discovery that many diseases manifest differently in men and women and, therefore, may require different treatments. Sex-related differences in the epidemiology, progression and treatment strategies of some liver diseases have been known for some time, but most epidemiological and clinical studies still report results only on one sex, resulting in rates of response and adverse reactions to treatment among different men and women in clinical practice. This review reports the data present in the literature on gender differences for the most representative liver diseases.

Keywords: Liver diseases, Adverse drug reactions, Sex/Gender differences

INTRODUCTION

Gender Differences in Pharmacological Response: Sex and Adverse Reactions

A drug-induced adverse reaction is a condition that appears in humans as a result of a significant association between some new onset symptoms and the intake or consumption for discretionary or therapeutic purposes of drugs, herbs, natural products, and minerals leading to liver dysfunction and even life-threatening clinical situations [1]. The diagnosis is made from abnormal results on clinical tests of hepatic, renal, pancreatic, haematological, and

cardiological function, excluding that such alterations are reasonably attributable to other reasons. The progression and therefore the natural history of an Adverse Drug Reaction (ADR) may follow a predictable dose-dependent course or an unpredictable and non-dose-dependent course [2]. Most cases of ADR have the appearance of an idiosyncratic reaction and studies have shown that this condition is the manifestation of the complex interaction between potentially immunogenic drugs or metabolites and the host's immune response [3,4]. Most cases of acute drug reaction resolve with withdrawal of the causative agent, but approximately one-fifth of patients continue to progress and develop into a chronic injury [5]. The global and specific incidence and prevalence of these conditions are still only partially known, making them one of the most difficult to manage from the clinical point of view globally [6]. Overall, 5%-10% of drug-treated patients experience an adverse reaction and about 5% of hospital admissions are due to Adverse Drug Reactions (ADR), while the incidence of ADRs among hospital patients is higher than 10% [7]. In the case of ADRs, it is preponderant and important to take into account the gender differences that exist in drug metabolism. Gender pharmacology is a nascent branch of pharmacology that defines differences in the efficacy and safety of drugs, differentiating effects by gender, to obtain a safe and efficient evaluation of treatment. The aim is to obtain a treatment that is as personalized as possible, and suitable for the type of patient and dosage. When it comes to reporting adverse drug reactions, women are more vulnerable than men. Female patients have a 1.5 to 1.7 time's greater risk of developing ADR, including adverse skin reactions than male patients. In Italy, data from the National Pharmacovigilance Network show a higher number (59% in 2011) of adverse drug reactions reported in female subjects than in men [8]. The tendency to a greater severity and frequency of ADRs in women is due to the combination of some factors that often coexist with each other: i) a particular female susceptibility to side effects and adverse reactions; ii) the presence of polytherapy, especially the association between drugs and substances for luxury use, which is more common in women; iii) some reactions to drugs are also a function of advanced age and we must consider that there are many more elderly women than elderly men; iv) possibility of overdose due to issues related to the pharmacokinetics and pharmacodynamics of some drugs that often do not take into account the differences between genders; v) presence of a higher rate of depression more than commonly translates in women to a daily consumption of more drugs than the male counterpart; there the preliminary studies of some drugs especially those in use for a longer time have not been tested in pre-clinical studies in women, as previously only men were enrolled in studies to test new drugs with the consequence that often these substances were used in women without a clear knowledge of the physiological basis of drug metabolism in this category of people [9-11].

Gender Pharmacology

Speaking of drug metabolism, gender differences begin as early as gestation and can change throughout life. Gender differences in pharmacology include both differences in Pharmacokinetics, i.e. the temporal evolution of drug concentration in the body which involves four phases: absorption, distribution, metabolism, excretion, and in the pharmacodynamics to which biological, biochemical, and biophysical effects are linked [12]. Different sizes, body composition, drug assimilation administration procedures (Steps 1 and 2), and different elimination provide the basis for the Pharmacokinetics of sex differences. Renal clearance is generally higher in men than in women, providing

the basis for the Pharmacodynamics of sex differences. Despite this, reviewing treatment with respect to renal function and body weight has not been a common activity in the past decades. The recommended dose for most drugs on the market is calculated for a 70 kg man [12]. Some variables, important for oral drugs such as gastric emptying time are influenced by hormonal changes and increase during pregnancy and pathological conditions. Another important parameter is the body composition of women who have more adipose tissue than men and therefore a reduced volume of distribution for hydrophilic drugs. In addition, the pharmacokinetic standards of drugs depend on the effect of hormonal changes in women which include the use of Estrogen and Progesterone for therapeutic and contraceptive purposes [13]. Knowledge of the dynamic differences between drugs is poor, but it is well known that women and men can have different drug targets. Even compared to organ systemic classes, except renal and urinary adverse reactions, which are more common in men, a greater number of reactions are reported in women. However, it has been recognized in recent years that clinical trials have not always adequately enrolled women or analyzed sex-specific differences between data. The enrollment of women in phase 1 and 2 clinical trials remains highly deficient. Only a few years after the introduction of heparin on the market has it been observed that women have a greater tendency to bleed with a greater frequency of thrombocytopenic purpura. It was also observed that more than 100 molecules of very heterogeneous molecules, within which there are antiarrhythmics, antipsychotics, antidepressants, and antibiotics such as macrolides (e.g., erythromycin), azole antifungals, can prolong the QT interval more in women, who therefore show a greater tendency to develop serious arrhythmias that can even be fatal, such as torsades de pointes [14]. The latter figure would seem to depend on the fact that, after puberty, cardiac repolarization in females is longer than in males [14]. It would also seem that the cardiovascular side effects in women were greater than in their male counterparts. Data updated to December 2015 show that most of the ADRs collected for Bevacizumab are common in women. Gender would also seem to influence the therapeutic effect of some drugs and therefore, in theory, also the reaction adverse; for example, some diuretics at high doses can cause hyponatremia in women while a marked decrease in plasma volume in men [15]. Some non-steroidal anti-inflammatory drugs such as ibuprofen, at the same plasma concentration, appear to be more effective in men than in women [16]. Finally, an increase in the number of bone fractures in females has been reported for current oral anticoagulants. In conclusion, although the literature and reporting data suggest a higher frequency of adverse reactions in females, most of the available information is derived from post-doc analyzes, meta-analyses of clinical trials, and reports. However, it is a bit late in considering gender as a determining factor in the complexity, of pharmacodynamic and hormonal changes, in the various periods of life and depending on the lifestyle, certainly different in the two sexes.

LITERATURE REVIEW

Sex Differences in Drug-Induced Liver Injury

Drug-Induced Liver Injury (DILI) is a highly variable condition that causes poorly predictable clinical outcomes. Consequently, considerable efforts have been made to unravel the risk factors responsible for worsening DILI to Acute Liver Failure (ALF) to prevent mortality related to this situation. Hepatitis induced by serious drug reactions

is a rare event but potentially fatal. The reported rate is between 1/10,000 and 1/100,000 patients. Approximately 20%-30% of cases of acute liver failure, associated with a high degree of mortality, seem to be related to the use of medications [17]. Drug-Induced Liver Injury (DILI) is the most frequent cause of acute liver failure and liver transplantation in Western countries. The events range from a mild and asymptomatic increase in transaminases, which occurs with a relatively high frequency and with a high number of drugs, up to fulminant liver failure [18]. DILIs are classified as intrinsic or idiosyncratic ADRs. Intrinsic hepatic ADRs occur with a short latency of time and have a high incidence in people taking high doses of the drug; these adverse reactions are not associated with hypersensitivity events. The idiosyncratic adverse reactions, on the other hand, occur only in a minority of susceptible subjects, have variable latency, and are not related to the mechanism of action of the drug [19]. The main mechanisms that can induce or favor the onset of DILI are i) the change in the irreversible chemical structure of a protein whose main effect is an alteration of its function; ii) the formation of antigens that are capable of causing an immune reaction against that substance; iii) irreversible chemical modification of DNA [19]. The factors that can most predict the risk for DILI are childhood or old age, female sex, concomitant drug therapy, concomitant illnesses, excessive alcohol consumption, malnutrition, underlying disease, and susceptibility. Genetics of the individual. Establishing a diagnosis of drug-induced liver injury is very difficult [20]. Therefore, after excluding other possible causes, it is important to identify a specific hepatic effect of one of the drugs the patient is taking. Some drugs that cause hepatic ADRs are Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), Troglitazone, Paracetamol, Fluvastatin, Isoniazid, Flucloxacillin, Ipilimumab, and Pazopanib. To accurately detect early signs of liver injury, we need clinical biomarkers that can distinguish drug-induced hepatotoxicity from other forms of liver injury and can differentiate mild from clinically important liver injury [20]. The liver is the organ most vulnerable to toxic damage from drugs because most of the metabolic transformations of drugs occur in the hepatocytes, through the enzymatic action of Cytochrome *P-450*. These enzyme systems are not always the same from a structural and functional point of view but are subject to genetic polymorphism, making some patients particularly susceptible to drug interactions of Cytochrome s with certain substances [21]. Many drugs are lipophilic substances that transform into hydrophilic in passing through Cytochrome *P-450* with the frequent formation of intermediate metabolites which are highly polar compounds with high reactivity. Advanced age, pre-existence of liver disease, enzyme induction/inhibition, and genetic variants, but above all the intrinsic characteristics of the molecule itself, affect the harmful event [22,23]. The diagnosis of liver damage caused by drugs is still today often a diagnosis of exclusion. The chronological order that correlates the intake of a drug with the onset of symptoms, or signs rather than changes in laboratory values, is very important. In addition, other clinical criteria are also useful (exclusion of all other causes of liver damage, knowledge of the recent and remote pharmacological history of the various therapies, especially of drugs known for hepatotoxicity). Some scores and tables on adverse reactions can help you decipher the suspicion of a DILI [24,25]. The World Health Organization-Uppsala Monitoring Center (WHO-UMC), Naranjo, Roussel Uclaf Causality Assessment Method (RUCAM), Maria and Victorino (M and V), and Digestive Disease Week-Japan (DDW-J) assessment scales were used to compare the causalities in all the reported cases of DILI in our Adverse Drug Reaction (ADR) [26]. In particular, the Naranjo algorithm is a questionnaire designed by Naranjo et al. to determine the likelihood that an ADR is due to the drug or is the result of other factors. Probability is assigned by a

definite score (≥ 9), probable (5-8), possible (1-4), or doubtful (0) [26]. Although there are significant discrepancies between the different causality scales in the DILI assessment, they are still used today as a screening for suspected acute drug injury. Surely. A personalized assessment that incorporates the latest information on specific risk factors and evidence-based criteria for diagnosing DILI would be more helpful. Like other adverse reactions including hepatic ones, the likelihood that that event is related to the toxic effect of a drug or substance can be divided into a predictable, dose-dependent, high-incidence (type A), or unpredictable reaction. Dose-independent, low incidence (type B). Type A liver injury should be suspected if liver function test abnormalities, often without symptoms or with specific symptoms (nausea, dyspepsia, malaise) are found in a person who has started new drug treatment in the last few weeks or months. Type B is associated with the onset of jaundice or an increase in total *Bilirubin*> 3 mg/dL, with more than 50% direct bilirubin. Jaundice can be isolated or associated with other symptoms (nausea, dyspepsia) and in some cases with extrahepatic manifestations (rash, Lymphadenopathy, Eosinophilia, Thrombocytopenia, Neutropenia, renal failure with serum creatinine). Budd-Chiari syndrome is a rare presentation and is often related to the use of progesterone, usually in women with a thrombophilic predisposition to hereditary (the most frequent is the factor V Leiden mutation) or acquired (most frequently myeloproliferative syndromes) causes [27-30]. Therefore, type B reactions are the most dangerous and can be at high developmental risk with a fatal prognosis in some cases and can present with different clinical conditions: acute hepatocellular necrosis, acute hepatitis, steatosis, cholestasis with or without hepatitis, hepatitis chronic active, fibrosis and cirrhosis, chronic cholestasis, granulomatous hepatitis, Budd-Chiari syndrome, liver tumors [31,32].

Types of Acute Liver Injury

Paracetamol is the most common cause of ADR, followed by antibiotics, NSAIDs, and anti-tuberculosis drugs. There are three types of acute liver injury

- **Hepatic:** prevailing increase in transaminases Aspartate Transaminase (AST) and/or Alanine Transaminase (ALT), with or without jaundice. The increase in transaminases AST and/or ALT can be moderate (3.5 × N or at least >2 × N) or significant (50-100 × N). It can coexist with a modest increase in alkaline phosphatase. Acute liver injury is typically associated with isoniazid (which can also give chronic hepatitis), Pyrazinamide, Halothane, and Troglitazone.
- **Cholestatic:** increased alkaline phosphatase >2 × N with no increase or moderate increase of transaminases AST and/or ALT, and often increased *Gamma-Glutamyl Transferase* and *Bilirubin*. The Cholestatic disease acute injury is typically associated with Estrogen, Tamoxifen, Anabolic Steroids, *Cyclosporine*, and *Azathioprine*.
- **Mixed:** *Associated Increase in Transaminases* AST and/or ALT and *Alkaline Phosphatase*, with or without jaundice. Joint acute liver injury is typically associated with Amoxicillin-Clavulanic Acid, Tricyclic Antidepressants, Phenothiazines, and NSAIDs.

Acute or mixed-type liver failure can be severe in features and lead to acute liver failure. The first severity criteria are the presence and intensity of jaundice, the association of extrahepatic manifestations, the increase in serum *Creatinine*, and finally the rapid decrease in prothrombin. Thrombosis of the hepatic veins (Budd-Chiari syndrome)

is the most severe form of acute liver injury. This clinical presentation mode requires immediate admission to a well-equipped hospital where a transjugular portocaval shunt is placed. After discontinuation of the drug, this clinical picture cannot regress and may evolve into a chronic portal hypertension syndrome [33-38].

The Influence of Gender on Drugs Metabolism

The pathogenesis of acute life-threatening drug injury involves the exhaustion of drug metabolism pathways, the activation of cell death mechanisms, the activation of local immune cells, such as Kupffer cells, and the recruitment of Inflammatory Leukocytes, including Monocytes and Lymphocytes [39]. All of these are key factors in the progression of DILI. Taking into account that the liver is a sexually dimorphic organ, more evidence has recently emerged that recognizes gender differences as a factor that implies the onset of DILI [39]. The predominant factors that determine the differences in liver damage between males and females are various. The slower metabolizing capacity is linked to hormonal interference for which women are more often exposed to drug interference events. Women are also exposed to gender-specific elective treatments (progesterone-based contraceptives, hormone replacement therapy) which can cause alterations in the pharmacokinetics of other drugs taken at the same time, or in turn, be altered in their activity by other drugs (e.g. increase the likelihood of unwanted pregnancies due to the interaction between *Progesterone* and *Carbamazepine*). Furthermore, in recent years alcohol abuse has become much more widespread among women, especially among Western women and, in parallel, there has been an increase in alcohol-related problems, including drug metabolism. It has been shown that, due to the greater consumption of alcohol and due to the reduced tolerance to it, women develop more serious diseases in a shorter time than their male counterparts. This phenomenon of the female gender is described as a "telescopic effect" [40-42]. The protective/ aggravating effect of sex hormones on the hepatic metabolism of drugs has already been mentioned. Gonadal hormones have been observed to exert their effects on drug metabolism by acting directly on the liver [43-44]. It is known that drug metabolism in the liver is regulated by the expression of the so-called major drug metabolizing enzymes including Cytochrome *P-450*, *Sulfotransferase, Glutathione Transferase, and Uridyldiphosphate Glucuronyl Transferase* [45-49]. Sex hormones influence the bioavailability of drugs taken orally by having modulatory effects on motility and thus on gastrointestinal transit. Estrogen, for example, inhibits gastric emptying. Hormonal fluctuations also affect the bioavailability of drugs. Body weight (usually lower in women), body fat (usually higher in women), plasma volume (lower in women but with large variations in menstruation and pregnancy), and blood flow of major organs (higher in women) may determine the efficacy or different risk of side effects compared to the female counterpart. In women with a history of alcohol abuse or consumption, Estrogen, and progesterone can affect the gastric and hepatic activities of alcohol dehydrogenase, making women most susceptible to drug harm [46-50]. Some hormones and in particular Growth Hormone (GH) can modulate the transduction and gene transcription of some of the main human liver enzymes involved in drug metabolism [51,52]. *CYP3A4,* the most important of the Cytochrome *P450* catalyst molecules, is more expressed in women, and this expression is closely related to the high expression of the mRNA encoding [53]. High *CYP2B6* activity has also been found in women and these parallels increased the expression of its gene [54]. Also, in the human *CYP3A4* gene, many gene sequences are sensitive to the endogenous hormonal environment such as values.

Plasma GH. The GH secretion continues and participates in the activation of specific female genes of the *CYP3A* family by converting at the level of nuclear heterochromatin (a non-coding portion of DNA) into *Euchromatin* (encoding the portion of DNA) which in the case of some transcription factors activate liver cells for *P450* gene expression [55,56]. The difference in body structure mainly modifies the bioavailability of the drug in women compared to their male counterparts, as it largely depends on the distribution of body fat and lean body mass, the distribution of fluids between the circulating volume, and the third organ space [57]. This may in turn affect the bioavailability of drugs and lead to delays in both the Pharmacokinetic and Pharmacodynamic activity of drug metabolism which is distinctly lipophilic for women who are hydrophilic compared to their male counterparts [58].

Liver Disease in Women: The Influence of Gender

The pathophysiology of liver disease is different in the two genera, but although this difference has been ascertained, the different potential mechanisms underlying this phenomenon are not yet fully identified. Among the hypothesized mechanisms we must certainly mention:

- The effects of sex hormones on the metabolism of the liver and the determinism of oxidative stress induced by the metabolic activity of drugs and substances [59,60].
- The structural differences of Cytochrome *P450*, *Glucose 6-Phosphatase*, and *Glutamine Synthetase* are genetically determined [61,62].
- The role of Estrogens not only on oxidative stress but also as an element influencing the levels of steroid-binding *Globulin*, *Angiotensinogen*, *Ceruloplasmin*, and transport proteins that are involved in the transfer of metabolites of various drugs and substances [63].
- A different response between the two genders, in gene transcription after pathological stress, is observed in an ischemic/reperfusion injury in the liver, especially after acute drug injury [64].
- Different responses of the immune system in women compared to men in response to acute drug injury. Except for autoimmune diseases, liver Fibrosis is predominantly male [65]. Epidemiological studies have shown that the male sex is an independent predictor of the progression of fibrosis, in cases of hepatitis B, and C in steatohepatitis [65,66].

This data, even if not confirmed by experimental studies, could also be applied to cases of severe hepatic fibrosis after ADR. It has long been known that the proliferation of Kupffer (KC) cells, as well as peaks in their phagocytic activity, are correlated with increased Estrogen levels [67,68]. In addition to numerical differences, hormones are also relevant: Estrogens, for example, exert anti-inflammatory and antioxidant actions, inhibiting the production of pro-inflammatory *Tumor Necrosis Factor-A* (*TNF-α*), *Interleukin-1b*, and -6 [69,70]. Consequently, menopause is associated with spontaneous increases in the aforementioned *Cytokines* in women. Another functional consequence of KC dimorphism lies in the susceptibility to alcohol, which is greater in females and this could be decisive in the pathogenesis of an ADR [71]. We hypothesize that thanks to Estrogen, in women, there is a greater regenerative potential as demonstrated by some studies on rats [72,73], and on humans [74,75], even if the data are very few. Bizzaro et al analyzed sex-dependent differences in experimental acute liver injury and regeneration in mice,

observing a delay in the recovery process in male animals associated with higher recruitment of Monocytes expressing the Androgen Receptor (AR) than in females [76]. Treatment of male mice with *Flutamide*, a drug antagonist of RA, reduced the recruitment of monocytes in mice. Similarly, male patients with DILI showed higher and potentially more inflammatory circulating immature Monocytes. Collectively, these observations provide new insights into sex-dependent immune mechanisms in the context of acute liver injury, suggesting gender-disparate inflammatory and regenerative responses after DILI, which are more beneficial for the female sex than their male counterpart. This could be based on gender differences in the ability to respond to any ADR. In conclusion, gender dimorphism, as regards the hepatic parenchyma, extends from genes to enzymatic activities up to the morphological determinism of the various cellular elements, but they are important elements that reinforce the concept of gender-specific hepatology.

Dangerous Adverse Drug Reactions and gender

Therapy is considered effective if its use contributes to the improvement or decompensation of symptoms or improves a certain function of our organism. An ideal drug would be a substance that is highly healing but free from negative side effects. Side effects often cause treatment failures, prevent patients from regularly taking the doses they need, and often cause severe health damage, sometimes contributing to mortality in cases of hyperacute damage. In preventing unwanted and harmful, in addition to the type, the dose, and the hourly intervals of a drug, it would be useful to ask us about the interactions between different drugs and also the inter variability between the two sexes. There are many categories of drugs that show differences in pharmacokinetics and pharmacodynamics between the two sexes. Of these categories, the most important and most used ones will be the subject of this review.

Antipsychotics

The category of antipsychotic drugs is widely used and their consumption increases especially in the older population groups, linked to the increase in the incidence of behavioural disorders related to dementia. About these drugs, women generally achieve optimal therapeutic outcomes and usually require a lower dosage to achieve control of their symptoms than men [77]. Although schizophrenia affects men and women equally often, the disease expresses itself differently between the sexes. Women in general tend to have a shorter duration of the disease because usually, the symptoms of this disorder arise late, in subjects who already have a shorter life expectancy and are characterized by a better course and a smaller number of cognitive deficits. Pre-menopausal women appear to have a higher response to common antipsychotics used than men and postmenopausal women [77]. It has been hypothesized that the cause of this is due to the role of Estrogens which would end up enhancing the effect of drugs according to various modes of action, that is, by increasing the absorption and metabolism of these drugs [77]. The higher ability of women to respond with symptomatic improvement even at low doses of the drug has been attributed to a greater capillarity of the cerebral blood flow compared to men, and the greater presence of cellular receptors more sensitive to antipsychotic drugs [77]. To these phenomena must be added the fact that the presence of Estrogen would slow down dopaminergic transmission which, if excessive, as often happens in these disorders, is responsible for an aggravation of psychotic symptoms. Recently, a meta-analysis demonstrates how the reduction of

the dosage of antipsychotic drugs below the therapeutic doses is associated with an increased risk of relapse of schizophrenia, not finding any gender difference in this phenomenon [78]. In a recent study, more women than men described serious side effects related to antipsychotics, including difficulty concentrating, excessive sedation, blurred vision, nausea and vomiting, constipation, positional dizziness, cardiac arrhythmias, itching, skin photosensitivity, skin hyperpigmentation, weight gain, Galactorrhea, and headache [79]. In addition to these side effects, which are more negligible and resolvable with the interruption of treatment, it is necessary to take into account that these drugs can represent cofactors capable of interacting with more serious risk factors. These drugs are associated with an increase in the state of hypercoagulability which increases the intrinsic risk of systemic or localized thromboembolic manifestations in the limbs, lungs, or cerebral circulation. In women on antipsychotic therapy, concomitant use of oral contraceptives, as well as hormone replacement therapy, pregnancy, postpartum status, and obstetric complications is an aggravating factor for the emergence of acute cardiovascular events. Female sex is a distinctive element for some risk factors such as Torsades de Pointes, which are potentially malignant forms of tachycardia frequent in patients who show a prolonged QT interval as an ECG abnormality [80,81]. This anomaly is much more common in women than in men and therefore two-thirds of these malignant Tachyarrhythmias affect women [80,81]. Regarding the potential of antipsychotics to increase breast cancer risk through weight gain and prolactinoma, there is no concrete evidence yet, although the cancer death rate of women with schizophrenia has been observed to be higher compared to women in the general population [82,83]. The phenomenon currently cannot be attributed to the use of various antipsychotic drugs [84].

Antibiotics

Inappropriate use of antibiotics through self-medication can cause significant adverse effects, such as antibiotic resistance, treatment failure, and drug toxicity. Antibiotic resistance is considered to be one of the most pressing public health problems in the world [85]. The emergence of multidrug-resistant bacterial strains. A recent meta-analysis has evoked that socio-cultural, economic, and regulatory factors were the most commonly cited reasons for self-medication with antibiotics, but failed to assess a possible gender difference [86]. *B-lactam* antibiotics (*Penicillins, Cephalosporins, Monobactams*, and *Carbapenems*) are among the most commonly used antibiotics for the treatment of severe infections, especially in intensive care units due to their broad spectrum, low probability of drug interactions, in waiting to obtain clues for an even more specific and targeted antimicrobial therapy [87]. Although *β-Lactam* antibiotics have a relatively large therapeutic window, sometimes even an increase in the standard dosage is not recommended and is not considered an optimal strategy, as high dosage regimens may have a high risk of toxicity [88]. The increase in *β-Lactam* side effects is very common in the male gender, as this category of individuals is usually associated with a poorer achievement of the therapeutic target [89-91]. This is because on average, men have a greater volume of distribution, a greater plasma volume, and a greater amount of intra/ extracellular water which results in a greater dispersion of the drug on the body surface and also in the more accelerated clearance of the drug [92].

Among the antibiotics that are most important for the incidence of serious side effects are anti-tuberculosis drugs. In addition to having a high toxicity profile, these drugs must be unlike other antibiotics, which are also used for much

longer with further time-dependent toxicity [93]. The most frequent adverse effects of anti-tuberculosis treatment are hepatotoxicity, severe skin reactions, and an increased possibility of gastrointestinal and neurological disturbances. Hepatotoxicity is securely the most serious as it is associated with morbidity and mortality and involves a high rate of failure and abandonment of treatment. The hepatotoxicity from antituberculous drugs varies from asymptomatic elevations of transaminases up to cases of severe hepatic insufficiency which can be fatal if not recognized early as the interruption of treatment could block the adverse manifestation. *Isoniazid*, *Rifampicin*, and *Pyrazinamide* are potentially hepatotoxic drugs, as they are largely metabolized by the liver. In contrast to the above drugs, hepatotoxicity for ethambutol or streptomycin is not described. From the point of view of gender medicine, it would seem that the female sex may be more exposed to the side effects of antituberculous drugs, due to the low body mass index or in the case of calorie-protein malnutrition. In particular, women are also associated with older age, which leads to greater vulnerability to hepatotoxic reactions due to the reduced clearance of drugs metabolized predominantly by enzymes belonging to the Cytochrome *CYP450* class. A possible explanation for the increased sensitivity of women to these drugs is related to the greater activity of Cytochrome *CYP3* is greater in females than in males [93]. *CYP3A4* is the most common enzyme involved in most drug interactions. Almost 50% of all clinically relevant drugs are metabolized by *CYP3A.* Anti-tuberculosis drugs are one of the pharmaceutical classes most inducers of CYP3A and when used in combination with glucocorticoids, carbamazepine, phenobarbital, and phenytoin they worsen the general toxicity of the organism. As *CYP3A* is involved in the metabolism of many drugs, this has clinical implications for drug dosages during pregnancy. In particular, *CYP3A* substrates may fall below effective concentrations during gestation and therefore some drugs should not be used unless dosage adjustments are made [94].

Antidepressants

Regarding antidepressants, studies suggest that males might respond better to tricyclic antidepressants, while females would have greater therapeutic results from Selective Serotonin Reuptake Inhibitors (SSRIs), possibly due to their improved tolerability [95,96]. In general, the studies did not identify significant sex-related differences in the therapeutic effect of antiepileptic drugs but as regards the adverse reactions to these drugs, it was found that they are related to the concentrations of sex hormones. The use of antidepressants means that women are more at risk of developing various side effects, such as metabolic dysfunctions, cardiovascular disorders, and hyperprolactinemia. These side effects seem to depend on the pharmacokinetic characteristics of women and are influenced by various factors, such as a reduced body mass, especially linked to a reduction in lean mass, a higher percentage of body fat, and slower gastrointestinal motility. Female sex hormones alter the activity of liver enzymes, which can lead to decreased elimination and accumulation of some drugs. Furthermore, greater side effects related to the use of antidepressants, occur in the case of concomitant use of proton pump inhibitors or the case of atrophic gastritis (higher gastric pH), or the case of a reduced intestinal enzymatic activity and a filtration rate glomerular slower. Among the more serious adverse reactions, it would appear that women are more likely to experience QT interval

prolongation with an increased risk of torsades de pointes as also observed for antipsychotics. It also appears that men and women have different reactions to the adverse reactions of all those drugs that show anticholinergic activity. The main side effects of tricyclic antidepressants such as dry mouth, constipation, sedation, sweating, and tremor appear to be milder and better tolerated in men than the adverse drug reactions induced by serotonin reuptake inhibitors. Furthermore, activation of *5-Hydroxytryptamine* receptors alters all stages of the sexual response, and therefore, serotonin reuptake inhibitors cause impaired desire and arousal, inhibition of orgasm, delayed ejaculation, and male impotence [95,96].

Antineoplastic Agents

Sex differences in pharmacokinetics have also been found in antineoplastic agents. It is known that women have a greater blood passage effect and therefore longer drug elimination times than men, at the same dose administered. This correlates with higher plasma volume, organ perfusion, and higher fat percentage in women [97,98]. Furthermore, this all-female phenomenon is also linked to the fact that some of these drugs, by binding to erythrocytes, can dare even with low hematocrit values [99]. Gender expression differences in the pharmacodynamics of these drugs are also related to the levels of drug-metabolizing enzymes resulting from genetic polymorphisms. Considering the data on the differential expression of the various *CYP450* isoforms, it was observed that the *CYP3A* isoform has greater activity in women than in men. In contrast, the expression levels of the drug efflux pump *P-GP* encoded by the MDR1 gene are higher in men and may partly explain the lower toxicity rate observed in men. Male sex steroids negatively regulate *P-GP* expression by implementing drug absorption through the small intestine of rats [100,101]. Due to this pharmacokinetic diversity, women have a lower elimination capacity of several of the most used anticancer drugs, such as *Paclitaxel, 5-Fluorouracil, Doxorubicin, Tyrosine Kinase* inhibitors such as Imatinib, Sunitinib, and Monoclonals, Such as the vascular endothelial growth factor blocker (bevacizumab), and antagonists against the *CD-20 protein* (*Rituximab*) [102]. Men, therefore, have a greater renal elimination of these drugs than women. Despite these well-documented sex differences, most analyzes of the elimination and distribution of anticancer drugs does not include gender as an associable pathway. According to recent evidence, it would seem that the body surface is an element that prevents personalized anticancer treatment and this translates into the fact that the female sex was associated with a greater risk of toxicity from anticancer therapies [102]. Although these adverse events in the female gender may recognize various causes including social and cultural differences in the reporting of adverse events, the higher probability of toxicity is certainly linked to the presence of biological differences in the Pharmacokinetics and/or Pharmacodynamics of these subjects. The increase in drug exposure time is dependent on the hormonal regulation of proteins involved in drug metabolism and the direct effect of sex hormones on the drug target. It has been shown that for an anticancer drug the dose is directly correlated with the number of adverse events. This is because the recommended drug doses are often obtained from clinical data from generally male populations. Therefore, the administration of standard doses in women may result in an increased incidence of side effects. The role of computed tomography measurement of metabolically active lean body mass as an important factor in calculating the personalized dose of antineoplastic drugs has recently been evoked. This measure is significantly higher in men than in women, decreases with increasing age, and therefore

represents a more sensitive parameter in choosing the right dose. In a retrospective analysis, higher muscle and skeletal density at diagnosis were associated with a lower likelihood of severe hematological toxicity of chemotherapies. In addition, a prospective study conducted on colon cancer patients receiving adjuvant treatment with *5-FU* showed fewer collateral effects when calculating the amount of the drug dose in consideration of lean body mass. Given this evidence, the dosage of chemotherapies and targeted therapies based on metabolically active muscle mass would be more accurate, especially in respect of differences in gender, age, and body composition.

CONCLUSION

The Sex-related differences in the epidemiology, progression and treatment strategies of some liver diseases have been known for some time, but most epidemiological and clinical studies still report results only on one sex, resulting in rates of response and adverse reactions to treatment among different men and women in clinical practice. This review reports the data present in the literature on gender differences for the most representative liver diseases.

DECLARATIONS

Conflict of Interest

The author's declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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