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Gender bias in therapeutic effort: from research to health care

Sesgos de género en el esfuerzo terapéutico: de la investigación a la atención sanitaria

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Abstract

There are relevant dimensions from a gender perspective related to therapeutic effort. To illustrate and discuss possible gender bias related to medicines, through the consumption analysis in women, the prescription of biological drugs according to sex, the potential gender inequality in adverse drug reactions, and research with clinical trials, as well as the decisions of international institutions in the marketing of medicinal products.

There is greater tendency to prescribe pain relievers, regardless of pain, and drugs for low intensity depressive symptoms in women than in men. The opposite occurs in the prescription of statins and adequate doses, and with the greater probability of prescribing anti-tumor necrosis factor in men than in women with ankylosing spondylitis, despite a similar disease burden. Adverse drug reactions are observed more frequently in women than in men, where determinants such as body weight are having little influence on the dosage. It is currently scarcely considered in the prescription that women have differences in the activity of cytochrome CYPP450 enzymes, which can affect the liver's metabolism rate. There are even immunological, genetic and epigenetic effects (due to heredity and uneven gene dosing located in the X and Y chromosomes) that can influence

KEYWORDS
Gender; Gender bias; Clinical trial; Adverse effects; Statins; Infliximab; Hormonal therapy; Oral hormonal contraceptives; Sexual dysfunction.

Resumen

Existen dimensiones relevantes desde una perspectiva de género relacionadas con el esfuerzo terapéutico. Se pretende ilustrar y traer a debate posibles sesgos de género relacionados con los medicamentos, mediante el análisis del consumo en las mujeres, la prescripción de fármacos biológicos según sexo, la potencial desigualdad de género en las reacciones adversas a los medicamentos y la investigación con ensayos clínicos, así como las decisiones de las instituciones internacionales en la comercialización de medicamentos.

Se observa una mayor tendencia a prescribir analgésicos, con independencia del dolor, y fármacos para síntomas depresivos de baja intensidad en mujeres que en hombres. Lo contrario sucede en la prescripción de estatinas y dosis adecuadas, y con la mayor probabilidad de prescripción de antifactor de necrosis tumoral en hombres que en mujeres con espondilitis anquilosante, pese a la similar carga de la enfermedad. Las reacciones adversas a los medicamentos se observan con más frecuencia en mujeres que en hombres, donde determinantes como el peso corporal están influyendo poco en la dosificación. En la actualidad se considera escasamente en la prescripción que las mujeres presentan diferencias en la actividad de las enzimas del citocromo CYPP450, que puede afectar a la velocidad del metabolismo hepático. Incluso hay efectos inmunológicos, genéticos y epi-

PALABRAS CLAVE
Género; Sesgos de género; Ensayo clínico; Efectos adversos; Estatinas; Infliximab; Terapia hormonal; Anticonceptivos hormonales orales; Disfunción sexual.

these differences by sex. Finally, through cases of hormonal therapy clinical trials, a drug for women's inhibited sexual desire and a contraceptive for men, gender bias and stereotypes are shown to influence a potential generation of inequalities, especially in adverse drug reactions to the detriment of women.
In conclusion, health professionals frequently attribute physical symptoms to women's emotionality, influencing their greater prescription of symptomatic drugs. Whether the same reason influences the lower prescription of therapeutic drugs in women than in men should be analyzed. There are biological determinants to consider due to their influence on a greater pharmacological toxicity in women. Clinical trials should improve according to the gender recommendations by the Food and Drugs Administration.

genéticos (por la herencia y la dosificación desigual de los genes ubicados en los cromosomas X e Y) que pueden influir en estas diferencias por sexo. Por último, mediante los casos de ensayos clínicos de la terapia hormonal, un fármaco para el deseo sexual inhibido de las mujeres y un anticonceptivo para hombres, se muestran sesgos y estereotipos de género que influyen en una potencial generación de desigualdades, especialmente en las reacciones adversas a los medicamentos en perjuicio de las mujeres.
Concluyendo, los profesionales sanitarios atribuyen con frecuencia a la emocionalidad de las mujeres lo que son síntomas físicos, influyendo en la mayor prescripción de fármacos sintomáticos en ellas. Debe analizarse si la misma razón influye en la menor prescripción de fármacos terapéuticos en mujeres que en hombres. Existen determinantes biológicos a considerar por su influencia en una mayor toxicidad farmacológica en las mujeres. Los ensayos clínicos deben mejorar atendiendo a las recomendaciones de género de la Food and Drug Administration.

Introduction

In the early 1990s, interest in research applied to health from a gender perspective arises based on powerful studies published in journals of high impact factor[1]. Medicine from a gender perspective, along with evidence-based medicine, demonstrates the existence of empirical inaccuracies in health care. Decades later and after an abundant body of scientific knowledge about gender bias in health care, the Gendered Innovations project is created, from Stanford University, to show through case studies how gender innovations contribute to improving professional practices, their efficiency and equity (https://genderedinnovations.stanford.edu/). Gender challenges, methodologies, guides, checklists, recommendations, and ultimately, gender innovations, have been occurring during this period. Therefore, it seems that the lack of knowledge about inequality in health care is not at the root of gender bias. This year, The Lancet dedicates a full issue to this topic with the title "Advancing women in science, medicine and global health" (https://www.thelancet.com/journals/lancet/issue/vol393no10171/PIIS0140-6736(19)X0006-9).

Gender bias is defined as "the difference in the manage of men and women with the same clinical diagnosis, which may have positive, negative or neutral health consequences"[2]. Evidence shows gender bias in diagnostic effort, such as diagnostic delay[3], and diagnostic errors[4]. There is also gender bias in the therapeutic effort, although the latter there provides less information, to the extent that they depend on the former.

Some gender bias in the therapeutic effort detected at the same health need occur in hospital use and readmission and in the application of therapeutic procedures, which is higher in men than in women regarding the delay and wait –less in men–, and in the prescription of major psychotropic drugs –higher in women–[5]. But there are multiple relevant dimensions from a gender perspective related to therapeutic effort, including that of drug therapy, the subject of this article.

More specifically, the aim of this article is to discuss potential gender bias related to medicines, through the consumption analysis in women, the prescription of biological drugs according to sex, the potential gender inequality in adverse drug reactions (ADRs), and research with clinical trials, as well as the decisions of international institutions in the marketing of medicinal products.

Increased consumption or greater prescription of drugs in women?

The scientific literature shows that gender stereotypes can guide interactions between professionals and patients. Professional perceptions, sometimes stereotyped, influence the needs of patients, especially in the manner in which treatment patterns are established and explained[6]. As Malterud stated, professionals interpret symptoms differently as presented by a man or a woman[7]. Accordingly, health professionals attribute psychological factors, such as physical symptoms, more easily to women than to men, or either show a greater tendency to prescribe drugs for low intensity depressive symptoms to women than to men[8], or prescribe anxiolytic drugs and sleeping pills more frequently to women than to men[9]. According to Spain's National Health Survey (ENS by it Spanish acronym) in 2017, out of all respondents, 7.4% of the surveyed men and 13.9% of the women reported the use of tranquilizing, relaxing drugs and/or prescribed sleeping pills.

In cardiovascular health, the ENS of 2017 collects information on the prescription of "heart medicines" (5.6% in men and 4.1% in women) and "medicines for blood pressure" (16.7% in men and 16.9% in women). The grouping of different drugs into these large categories does not allow us, in some cases, get into deeper analyses, but there is evidence of different therapeutic strategies. For instance, women are treated more frequently with diuretics and less frequently with angiotensin-converting enzyme inhibitors and angiotensin receptor blockers[10]. A recent meta-analysis, which analyzed the statins prescription, described that not only women were prescribed less statins than men (25.7% vs. 35.3%, $P < 0.0001$), but also that the prescription rate of adequate dose was lower in women (32.6% vs. 42.3%, $P < 0.0001$) than in men. The adjusted analysis for confounding variables showed that women were 24% less likely to be prescribed statins and 48% more likely to be prescribed with an inadequate dose[11].

It is important to draw attention to the fact that these results are kept adjusting for different confounding variables, which indicates that the prescription does not depend exclusively on the health problem presented by the female or male patient, but it is conditioned by gender bias.

In Spain, the project "Inequalities in gender development and its effect on health inequalities: Construction of composite social indicators and their application to the contribution of information on over-prescription and consumption of medicines in Spain, INDIGENES" was carried out. Funded by the Women's Institute, this project analyzed the prescription and consumption of drugs in the Autonomous Communities according to gender equality indicators using the data from the ENS of the years 2006 and 2011. This study showed that women were prescribed more pain relievers than men. There is scientific literature that relates the greater prescription of analgesia in women with greater sensitivity and lower tolerance to pain and a greater need to report it. However, there is evidence that relates the prescription to a greater tendency of professionals to offer more prescriptions to women than to men with the same symptoms. In the INDIGENES study, even adjusting for the variable pain (which includes questions about chronic pain in the back, neck and head, but not joint pain), the probability of prescribing analgesia was higher in women. This would indicate that said higher prescription is not merely the result of a higher prevalence of pain among women. Being a woman and living in areas with lower gender development (of greater inequality between men and women), represents two conditions that increase the likelihood of analgesia prescription, the latter also affecting men. Additionally, women who live in a context of lower gender development are less often referred to specialized consultations, and receive symptomatic pain treatment more frequently than men. This fact could indicate a vicious cycle of visits at the same level of care, as well as a lack of access to specialized services, resulting in a non-specific, symptomatic treatment, blind to the causes, such as analgesia. The consequence is that the potential conditions that cause pain are dismissed, and therefore, the chances of benefiting from the prescription of correct treatments are reduced. This study contributed to the scientific evidence that indicates that disease patterns, but also therapy, are the reflection of social inequalities[12].

Spondyloarthritis, are women being treated the same as men?

Spondyloarthritis is a heterogeneous group of inflammatory rheumatic diseases that include ankylosing spondylitis –as a disease prototype–, undifferentiated spondyloarthritis, psoriatic arthritis, inflammatory bowel disease associated with arthritis and reactive arthritis[13]. In response to the occurrence of its symptoms or signs, spondyloarthritis is classified as predominantly axial, when it affects the spine –such as ankylosing spondylitis–, or predominantly peripheral when the main symptoms or signs are enthesitis, dactylitis or arthritis. The aforementioned ankylosing spondylitis, which is predominantly axial, has been considered for decades as a prototype of spondyloarthritis. In addition, it was considered a disease affecting only men[14], although it is now recognized that both men and women suffer from it[15]. On the contrary, it is considered that peripheral and extra-articular manifestations are most frequently suffered by women[16]. The fact that the prototype of spondyloarthritis is ankylosing spondylitis, an axial and male pattern, has resulted in a biased investigation towards a model with these characteristics, especially when women have been underrepresented in research. Research findings in axial manifestations have been extrapolated to people with peripheral and extra-articular manifestations, that is, mainly women.

The first TNFα (anti-TNF) inhibitor, infliximab, in Europe was approved 20 years ago[17]. Since then, new anti-TNF, biosimilars, and more recently, IL-17A[18] inhibitor drugs have appeared in clinical practice. Biological therapy is changing the natural history of spondyloarthritis by slowing the structural damage it causes[19], and that of people who suffer from it by reducing the impact that the disease has on their lives[20].

Knowledge about sex differences in the spondyloarthritis treatment is limited to cohorts of patients receiving biological therapy who generally have axial manifestations and whose studies from this type of patients with ankylosing spondylitis or axial spondyloarthritis rarely consider sex as the main variable. These studies have shown more women stopping or replacing biological therapy than men, which may be due to lower treatment efficacy or to a greater frequency of adverse effects in women[21,22]. It seems that obesity and overweight correlate with a lower response to infliximab[23]. This would justify that women having more fatty tissue than men have a worse response to this anti-TNF. Consistent with this view, also related to lifestyles, the lower efficacy of anti-TNF has also been correlated with tobacco[24], so it could be assumed that this would affect the response in men rather than in women, since smoking habit is nowadays still greater among men, however this gender relationship has not been found in the studies. On the other hand, the absence of enthesitis and the short duration of the disease are good predictors of anti-TNF. Thus, the worst response in women could be related to the greater presence of enthesis[4] and the greater diagnostic delay in women and, consequently, late access to biological therapy[16,25].

From a near future perspective, research on treatments based on the different clinical expressions of spondyloarthritis is recent, which could be an approximation to how the disease is expressed in women, although research would be more appropriate considering sex as a variable principal. New drugs are aimed at blocking specific immune mediators such as interleukins IL-6, IL-17A, IL-23, and Janus kinase (JAK) promise to be more effective in the most frequent peripheral or extra-articular manifestations in women[26,27]. Given the above, another line of research that has had limited follow-up until now[28] and that is relevant –taking into account that women are more prone to stopping or or changing anti-TNF drugs than men–, would be to explore whether women receive as often as men biological therapy when treated for spondyloarthritis.

Gender inequality in the side effects of drugs

The different responses to medications, according to the patient's sex, have been systematically ignored. Generally, men weigh more than women, which can affect the volume of distribution, clearance, and therefore, the plasma concentration of medicines. However, few drugs are dosed according to body weight[29]. In addition, women have differences in the activity of cytochrome CYPP450 enzymes that can affect the rate of liver metabolism. There are even immunological[30], genetic and epigenetic effects (caused by inheritance and uneven dosing of genes located on the X and Y chromosomes) that can influence these pharmacological differences between men and women[31]. As with the rest of the body, gonadal hormones would act to specify and regulate many of these differences. However, there are no conclusive studies and none of these aspects are currently taken into account in the prescription of medications[32]. This fact is especially striking in medications where women are the main consumers, such as analgesics and certain psychotropics (antidepressants, hypnotics, anxiolytics, antipsychotics and anticonvulsants)[33]. Even with these medications, the influence of female hormonal fluctuations –menstruation, pregnancy, puerperium, menopause– has not been analyzed where, apart from their influence on pharmacokinetic aspects, there may be changes in the central neurotransmitters, even in the number and sensitivity of the receptors[34]. A recent study conducted in Italy, France and Spain showed that there were more reports of suspected ADRs in women than in men. However, the reporting rates could be similar based on the higher prescription, e.g. of antidepressants in women[35]. This could also lead to bias, because in another study conducted in Sweden, suspected ADR was reported to be more frequently in older people and in women, the most serious being reported more frequently in men[36]. Consequently, there are still large gaps in our knowledge of sex differences in clinical pharmacology, and much more research is needed.

The term "scientific inequality" has recently been coined, referring to the fact that until the 1990s, women did not participate in the necessary clinical trials to authorize a new drug. In Spain, until the appearance of the Royal Decree 561/1993, women of childbearing age could not be included in clinical trials during the preliminary stages, where efficacy and safety were analyzed[37]. The same situation occurred in pre-clinical investigations, where the animals included were preferably male. Perhaps this is the cause of a greater and different adverse events patterns in women that in men. Women have a 1.5 to 1.7 times greater risk of developing a suspicion of ADR, including adverse skin reactions, compared to men[38]. Since biological sex is a fundamental variable, it should not be excluded from the analyses performed[39].

This situation is improving, and in the analysis of health problems, almost all include disintegration by sex. But the stratified gender analysis is not yet carried out, and therefore, neither does gender-based actions. In addition, most of the research does not address the impact of gender inequalities in the treatment of diseases. This fact is relevant, because in addition to hormonal, anatomical and metabolic peculiarities, gender assigns different roles and opportunities to women and men that can associate certain lifestyles. This can translate into differential health risks, varying degrees of health care, and it can also affect the pharmacological prescription, which includes the side effects of medications[40].

Biased research and gender paradoxes: clinical trials with medications

Although in 1994 the Food and Drug Administration (FDA) published recommendations for the inclusion of women in clinical trials and stratifying analyses by sex[41], 25 years later, these have not yet been fulfilled. As for the European Medicines Agency, the agency is not particularly sensitive to this perspective[42]. Experimental studies are the most accurate designs from the scientific empirical approach. However, the limited consideration of differences by sex in the aim of clinical trials influence the quality of their methodology, leading clinical trials to the category of bad science[43]. Thus, a selection bias is considered to be the failure to consider the prevalence of women (and men) who are drug users for the sample size calculation of the subjects that should be incorporated into the trial. The failure to consider women's hormonal variability in either their fertile stage, or the intake of contraceptive drugs, or for hormone replacement therapy in menopause, or cross-reactions with the tested drugs, is also erroneous methodology. This situation occurs in both symptomatic[44] and therapeutic drugs[45].

The case of hormone replacement therapy (HRT) and its effects is widely known[46]. Between 1939 and 1940, the first evidence about their relationship with breast cancer was provided. Despite doubts about its safety as a menopausal hormone therapy in the 50s, it had a great commercial success, announcing itself as "youth therapy". In 1975, the association between estrogen and endometrial cancer was evidenced. In the 80s, the combined estrogen-progesterone therapy was created as a lower risk formula. But in 2002, a discussion arose with the publication in *Journal of the American Medical Association* of new evidence by the "Women Health Initiative" on its association with breast cancer[47]. Despite evidence, there was a tendency

in Spain to maintain the indication in a large group of women, including those with early menopause; climacteric symptoms –neurovegetative syndrome, urogenital atrophy–; recent menopause with a high risk of osteoporosis, including women who, by their own choice, choose HRT as a therapeutic option –with the addition of having an adequate knowledge of the risks and benefits[48]–. Fortunately, the use of HRT has decreased in women over 40 years during the period 2001-2014, from 7.19% (95% confidence interval [CI] 6.97-7.40) in 2001 to 0.21% (95 CI % 0.20-0.22) in 2014, according to the Database for Pharmacoepidemiological Research in Primary Care, as has also happened internationally[49].

Regarding flibanserin, initially developed as an antidepressant, failed to show adequate efficacy. In phase II of the trials with this type of patients, when asked "How strong is your sexual desire?", this drug was shown to be more effective than placebo in terms of responses from the participants, so its possible usefulness as a potentiator of female sexual desire was contemplated.

During the review conducted in 2013 by the FDA, flibanserin posed a variety of safety problems including the risk of hypotension, syncope, and drowsiness, as well as adverse effects when taken with alcohol or CYP3A4 inhibitors –such as oral contraceptives or fluconazole–. Taking these concerns into account, as well as the general modest efficacy, the FDA rejected the application of the product and recommended additional safety studies.

In 2015, the FDA advisory committee, after reviewing the efficacy and safety of flibanserin, voted 18-6 in favor of approving, as long as risks were considered, a new molecular entity for the treatment of hypoactive sexual desire disorder in premenopausal women. It should be considered that this was the second meeting of the commission in relation to a product that had twice been rejected by the FDA due to an unfavorable risk-benefit profile. Also, the sponsoring industry did not provide new efficacy data, although on safety, including a study that suggests the absence of impaired driving, a comparison of the product's adverse effects profile with that of other marketed products, and an analysis of the potentiating effects of alcohol on adverse events. Surprisingly, the alcohol interaction study was carried out in a sample of 25 healthy volunteers, where only two of them were women[50], so as mentioned, it could be labeled as "bad science".

On the other hand, in 2016 a study of a highly effective contraceptive for men was suspended due to its side effects[51]. It is treated, therefore, with a different measuring standard with respect to previous cases. While with this drug depression and other mood disorders were detected in a small number of subjects, oral contraceptives in women cause depression in a large amount of females, and they still remain marketed.

Conclusions

Gender bias in health care undoubtedly relate to the teaching-learning process during university education, which in turn are derived from a biased generation of knowledge. However, it is difficult to accept that with all existing publications in this regard, gender biases continue to occur, for example, in the case of acute myocardial infarction. A potential booming explanation is that the existence of differences by sex in the way in which diseases appear –regardless of how women and men report their discomfort–, may be conditioning the delay and diagnostic errors, as has been argued lately for gender bias in the cases of heart attack[52] and spondyloarthritis[4]. Challenges linked to gender bias related to pharmaceutical therapy are multiple and have an origin. With the realization of clinical trials, the pharmaceutical industry undoubtedly contributes to the improvement of pathological processes. But in this generation of knowledge about new drugs, it is essential to carry out research, including an adequate sample of women as well as men, which should be representative of the potentially consuming population[53]. Beyond the consumption of drugs and the responsibility of those who consume them, one must think of those who prescribe them. Therefore, it is important to investigate the potential gender bias to the detriment of women in the treatment of health problems that can be suffered by both sexes.

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