Eur Arch Psychiatry Clin Neurosci (2017) 267:283–284
DOI 10.1007/s00406-017-0797-7

EDITORIAL

Gender does matter in clinical research

Florence Thibaut[1]

Received: 30 March 2017 / Accepted: 31 March 2017 / Published online: 7 April 2017

In 2013, the leading cause of Disability-Adjusted Life Years (DALYs) for ages 10–24 in both sexes was mental health disorders and substance misuse. However, during adolescence, depressive disorders were the leading cause for females (15–24 years), whereas road injuries were the leading cause for males of the same age. Sexual abuse was also a higher cause of DALYs for women than for men [5]. Additionally, prevalence, age of onset, clinical symptoms or outcome of many neuropsychiatric diseases substantially differs according to gender. Sexual chromosomes and sexual hormones may play an important role long before the age of puberty and especially during brain development. The organization of sexually differentiated brain circuits is based on many factors including sexual hormones, locally synthetized estradiol, androgens, genes located in the sex chromosomes including Sry and many others, as well as epigenetic mechanisms occurring at the DNA level. Neurosteroids may also influence DNA methylation and epigenetics. Examples of male-biased conditions mainly include early onset neurodevelopmental disorders such as autistic spectrum disorders, attention deficit hyperactivity disorders, language impairments or even schizophrenia; whereas examples of female-biased conditions rather include emotional disorders such as anxiety, depressive or stress and trauma-related disorders or even anorexia nervosa, which usually starts during puberty or later in life. In addition to sex differences in brain neuroanatomy and circuits, sex-specific variance was identified in various biological functions which may also result in sex differences in neuropsychiatric disorders [4, 7]. Finally, men and women are not equally exposed to psychosocial stressors, such as violence among many others during lifetime [2]. How much of the differences are due to biology and how much are the consequence of behavioral and sociological factors remains to be sorted out.

Traditionally, based on the false hypothesis that men and women are identical, medications have been studied in men and the data obtained about the clinical efficacy and the potential side effects have been extrapolated to women. Yet, pharmacokinetic and pharmacodynamic properties of many compounds may differ according to sex and consequently may be associated with different adverse effects. In fact, as a result of severe teratogenic effects observed with certain compounds, the Food and Drug Administration (FDA) published in 1977 “General Considerations for Clinical Evaluation of Drugs” (Washington D.C., FDA) which recommended that women of childbearing age should not be included in early phases of clinical trials. Since then, this decision resulted in the almost complete exclusion of women from clinical trials. In 1993, the FDA changed its perspective and published “Guidelines for the study and evaluation of gender differences in the clinical evaluation of drugs” (Department of Health and Human Services, FDA ed. Rockville, USA; Federal Register. pp. 39409–11) which recommended the stratification of the results of the research studies by sex. Interestingly, in the USA, of the 300 new drug applications received by the FDA between 1995 and 2000, only 163 included sex-based pharmacodynamic analysis. Of those, 11 drugs showed a 40% or greater difference in pharmacokinetics between males and females. This information was listed on the drug label; however, no differences in dosing between males and females were

✉ Florence Thibaut
florence.thibaut@aphp.fr

[1] Department of Psychiatry and Addictive Disorders, University Hospital Cochin (Site Tarnier), INSERM U 894, Centre Psychiatry and Neurosciences, University Sorbonne-Paris Cité (Faculty of Medicine Paris Descartes), Paris, France

recommended [1]. In the same way, in the vast majority of clinical studies, pregnant or breastfeeding women are excluded, resulting in limited evidence in these fields, even though a significant percentage of women receive psychotropic drug treatment during pregnancy or breastfeeding.

Later on, in 2005, the European Medicines Agency published "Gender considerations in the conduct of clinical trials" (International Conference on Harmonisation (ICH). http://www.ich.org/products/consideration-documents.html) (EMEA/CHMP/3916/2005-ICH.). Most recently, the Canadian Institute of Health Research, the European Commission, the Sex and Gender Equity in Research (SAGER) and the American National Institute of Health have called for sex and gender analyses in clinical research. In 2016, the Cochrane Sex-Gender Methods Group wrote a paper entitled "Why sex and gender matter in health research synthesis" (http://methods.cochrane.org/equity/sex-and-gender-analysis). The International Committee of Medical Journal Editors recommended the inclusion of representative populations in all studies and the inclusion of sex as a variable. The European Association of Science Editors has recently proposed guidelines on reporting sex and gender in medical journals [6]. They wrote that sex was not reported for 22–60% of animals used in biology and immunology. In a study based on 768 trials (http://www.ClinicalTrials.gov), 89% reported recruitment of males and females but <1% reported that they will analyze gender effects. Howard et al. [3] recently analyzed 728 papers published in JAMA psychiatry and the British Journal of Psychiatry between 2012 and 2015. Among them, 16% stratified analyses by sex but no studies reported a calculation powered for the analysis of its primary outcome by sex.

Finally, one month ago, during an interview with the European Parliament magazine, Beatriz Becerra Basterrechea said "Gender differences are not taken into account in clinical and preclinical research. However, perhaps where this inequality is most evident is in mental health. Women are dramatically underrepresented in biomedical research, despite making up over half of the EU population." She is Parliament's rapporteur on promoting gender equality in mental health and clinical research and has coordinated a report on this topic (Draft report on promoting gender equality in mental health and clinical research; Committee on Women's Rights and gender Equality; 2016/2096 (INI)). A recent motion of support of this report was adopted by the European Parliament in February 2017.

In conclusion, biomedical research reflects predominantly a male perspective, assimilating women to men. The integration of a gender-sensitive perspective in all aspects of research is urgently needed. Participation of women of reproductive age in clinical trials is also necessary, providing there is adequate risk protection in case of pregnancy. Every pharmaceutical compound should clearly mention whether trials were conducted on women or not, and whether different side effects might be expected in women. Recently and interestingly, the European Parliament urged the European Medicines Agency (EMEA) to draw up separate guidelines for women as a specific population in clinical trials.

References

1. Anderson GD (2005) Sex and racial differences in pharmacological response: where is the evidence? Pharmacogenetics, pharmacokinetics, and pharmacodynamics. J Women's Health (Larchmt) 14(1):19–29
2. Garcia-Moreno C, Rössler A (2013) Violence against women and mental health. Karger, Basel
3. Howard LM, Ehrlich AM, Garnlen F, Oram S (2016) Gender-neutral mental health research is sex and gender biased. Lancet Psychiatry 4(1):9–11
4. Mc Carthy MM (2016) Sex differences in the developing brain as a source of inherent risk. Dialogues Clin Neurosci 18(4):361–372
5. Mokdad AH, Forouzanfar MH, Daoud F et al (2016) Global burden of diseases, injuries, and risk factors for young people's health during 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet 387:2383–2401
6. Schiebinger L, Leopold SE, Miller VM (2016) Editorial policies for sex and gender analysis. Lancet 388(10062):2841–2842
7. Valentino RJ, Bangasser DA (2016) Sex-biased cellular signaling: molecular basis for sex differences in neuropsychiatric diseases. Dialogues Clin Neurosci 18(4):385–393