A POOR EVIDENCE-BASED PSYCHIATRY FOR EVE

Emilio Sacchetti, Claudio Mencacci

Editors-in-Chief,
Evidence-Based Psychiatric Care;
Past President and President of the Italian Society of Psychiatry

The existence of an association between gender and mental illnesses is clearly reported in the writings of Moudsley, Grisienger, Kraepelin, and Bleuler at the beginning of the era of scientific psychiatry.

Since that time, a large body of research in psychiatry and neurosciences has challenged this issue and many facts have been learned, in addition to the incontrovertible evidence of clear-cut male/female differences in the prevalence of numerous psychiatric disorders.

First of all, it has been clearly learned that sex hormones affect thoughts, emotions, behaviour and cognition.

It has also been learned that genes located in the sex chromosomes plausibly participate in vulnerabilities to specific mental disorders and iatrogenic health effects.

At the same time, it is known that many stressors and trauma are at least partially gender-specific, and that sometimes the expression of epigenetic processes varies according to the sex of the subject.

Furthermore, the brain is charged by multiple sexual dimorphisms relative to cytoarchitecture, grey- and white-matter morphometry, hemispheric asymmetries, gyrification, growth trajectories, biochemistry, metabolism, functional circuits and distribution, structure and modulation of a number of receptor families. Within the same research line, in addiction, mental disorders may play moderating effects on some “physiological” sexual dimorphisms.

In turn, with different degrees of validity and reliability, the gender of the patients with severe mental illness exerts differential effects on numerous clinical variables such as age at disease onset, symptom profile and severity, placebo response, efficacy and safety of psychopharmacological therapies, adherence to prescribed medications, posology, early discontinuations, pharmacokinetics and pharmacodynamics. Last but not least, the influence of gender on effectiveness of medications may be drug-specific to some degree.

Despite these relevant progresses, current knowledge about the impact of gender on psychiatric disorders and their treatment remains strongly subject to two main interdependent criticisms.

The first is that studies focusing on the role of gender in psychiatry continue to be substantially relegated in a niche for experts. Consequently, possibilities of a translational application of information to the daily clinical routine appear hampered.

The second is that a great deal of research in both animals and humans

Correspondence

Emilio Sacchetti
emilio.sacchetti@unibs.it

FIGURE 1.
Ludolphus de Saxonia (supposed author). From Le Miroir de Humaine Salvation (The Mirror of Human Salvation), about 1455.

continues to be highly subject to the risk of sex biases. On the one hand, it is for example common to encounter animal studies that involve only males, do not specify the sex of the participants, or exclude the sex variable even from post-hoc sub-analyses [1]. On the other hand, studies centred on psychiatric patients generally include both males and females, but the former are frequently overrepresented. A disproportionate representation of the two sexes is especially maximised in clinical trials where lactating women or those with childbearing potential in absence of adequate contraceptive measures are generally excluded a priori. Furthermore, most of the research in humans has not been powered for independent analyses by gender, and are placated with rough demonstrations of sex-matching between different experimental groups, and do not subdivide women according to pre-, peri- or post-menopausal status.

Taken together, these relevant weaknesses duly explain not only why the product labels of the preponderant majority of psychotropic medications do not mention gender differences of efficacy and tolerability, but also why the most influential health agencies have explicitly recommended a larger enrollment of females in animal and human studies and (have) invited a systematic search for sex-specific differences. Despite the wide number of evidence to the contrary and the influential advice, psychiatric and allied disciplines continue, however, to adopt a largely unisex experimental approach. This favours unjustified generalisations of findings emerging from samples characterised by an unbalanced male/female ratio, and thus denies in daily practice sexual parity at the main expense of women. Furthermore, poor attention to gender-selective effects may preclude or delay the development of new therapies and the recognition of otherwise hidden adverse events.

Without appreciable changes, the label “evidence-based” appears therefore only partially applicable to psychiatry, and women remain at increased risk to pay the highest consequences. Alike almost all other branches of medicine, psychiatry too seems to have forgotten that Eve originates from Adam’s rib (Fig. 1), but it is far from being Adam.

Reference

[1] Beerya KA, Zuckerb I. *Sex bias in neuroscience and biomedical research*. Neurosci Biobehav Rev 2011;35:565-72.