Gender Differences in Clinical Psychopharmacology

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Biological differences between men and women appear, at least in part, to be related to variation in levels and changes in sex steroids that subsequently interact with neurotransmitters. Reproductive-aged women have repetitive variations in sex hormones with each monthly cycle that influence the onset, chronicity, and outcome of a variety of psychiatric illnesses. Variations in brain structure and function and in pharmacokinetics may also contribute to psychiatric outcomes. The term *gender differences* includes these biological variables plus psychosocial, cultural, and behavioral factors that may magnify the physiologic differences between men and women. These interactions are complex and, as yet, poorly understood.

Physiologic Differences

Sex hormones have direct effects on reproductive and sexual functioning and regulatory effects on psychiatric conditions. The hypothalamic-pituitary-adrenal (HPA) axis modulates the cyclic release of estrogen, progesterone, and probably testosterone in women via gonadotropin-releasing hormone. While each of these hormones has direct effects on reproductive organs, they also have effects on brain and mediate neurotransmitters. Estrogen increases synaptic connections in the hippocampus (neuronal growth and verbal memory) and modulates serotonin function. A progesterone metabolite acts as an agonist of the inhibitory neurotransmitter γ-aminobutyric acid (GABA). Both estrogen and progesterone stimulate the release of dopamine while increasing the metabolic enzyme monoamine oxidase.[1] In addition, testosterone influences vitality and energy as well as sex drive, with low levels being associated with depression in men. Endogenous sex steroids such as hormonal contraceptives and hormone replacement therapy (HRT) may lead to a relative reduction/deficiency in vitamin B6, a necessary coenzyme in the production of serotonin. For women who have been particularly sensitive to the changing milieu of sex hormones during their reproductive years, some relief may be found with the stable, albeit low, levels of the postmenopausal years.

Differential and redundant systems also impact physiologic effects of steroid hormones. Gonadal steroids affect gene transmission through classic intracellular mechanisms, and directly at neuronal membranes. Each sex steroid may affect others, as testosterone can be aromatized to estrogen, and progesterone may antagonize the effects of estrogen. Production of other hormones may also be affected, as estrogen may also alter the activity of transcription factors for glucocorticoids and thyroid hormone. In response to stress, sensitivity to glucocorticoid-related negative feedback through the HPA axis may be affected by gonadal steroids, which can lead to an excessive and/or prolonged stress response, thereby decreasing serotonin receptor–mediated effects. This may, in part, explain the increased frequency in women of stress-related conditions such as anxiety and depressive disorders. Pharmacokinetic differences between the sexes may also be associated with hormonal fluctuations, particularly seen premenstrually, during pregnancy, and during the menopausal transition. In addition, a bidirectional relationship exists in the mediation of effects between the neurotransmitters and sex steroid function.

Psychiatric Conditions

Clear differences exist between men and women in the epidemiology, risk factors, presenting symptoms, course of illness, treatment response, and prognosis of psychiatric conditions. While most anxiety and depressive disorders are more common in women, bipolar disorder and schizophrenia occur with equal prevalence in men and women. These differences may represent stimulatory effects on onset of anxiety and depressive disorders and inhibitory or delaying effects on bipolar and psychotic spectrum disorders, with women often presenting later in life and manifesting a more benign course of these latter illnesses than men. Not all differences can be explained by physiologic variation, however. The greater frequency of eating disorders in women may represent a sociocultural effect, with body weight affecting a woman's self image to a far greater degree than a man's. Men may abuse substances to manage emotional responses that are discouraged or viewed as unacceptable in men. Aggressive suicidal behavior in men may be related to levels of 5-HIAA in cerebrospinal fluid, to a greater propensity than women to take action, or perhaps to both.

Comorbid medical conditions are more likely in women, including thyroid disease, migraine, fibromyalgia, irritable bowel syndrome, sexual disorders, and obesity. Onset appears to be somehow related to changes in estrogen (HPA hyperactivity) and serotonin hypofunction, perhaps contributing to more frequent presentation in women. Comorbid conditions not associated with estrogen or serotonin dysfunction, such as obstructive sleep apnea, either occur with equal frequency in men and women or may be more prevalent in men. Comorbid medical conditions may also complicate treatment by decreasing tolerability to medications and through potential drug interactions.

These biological differences may suggest a basis for differential response to medication treatment by gender. Men appear to respond equally well to selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants, whereas women preferentially respond to SSRIs.[2] Addition of HRT to antidepressant therapy in women during the perimenopause may improve/stabilize mood and climacteric symptoms that negatively impact mood.[3] Women may require lower doses of medications than men, even when adjusted for body weight, due to hormonal influences on blood drug levels.[1] Finally, women may be more likely to demonstrate a chronic course of illnesses with female predominance, so long-term tolerability of treatment is essential.

State of our Knowledge

The relatively recent requirement to include women with reproductive potential in National Institutes of Health–funded studies and pharmaceutical industry clinical trials has enhanced the focus on gender differences in psychiatric illness. Increasing numbers of journals focus on gender and medicine, and at least one comprehensive review of women's mental health has been published.[4] However, funding of studies to specifically investigate gender differences remains low.[5] Much still needs to be done.

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