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FEMALE SEXUAL FUNCTION

Understanding the Role of Serotonin in Female Hypoactive Sexual Desire Disorder and Treatment Options

Harry A. Croft, MD

ABSTRACT

Background: The neurobiology of sexual response is driven in part by dopamine and serotonin—the former modulating excitatory pathways and the latter regulating inhibitory pathways. Neurobiological underpinnings of hypoactive sexual desire disorder (HSDD) are seemingly related to overactive serotonin activity that results in underactive dopamine activity. As such, pharmacologic agents that decrease serotonin, increase dopamine, or some combination thereof, have therapeutic potential for HSDD.

Aim: To review the role of serotonin in female sexual function and the effects of pharmacologic interventions that target the serotonin system in the treatment of HSDD.

Methods: Searches of the Medline database for articles on serotonin and female sexual function.

Outcomes: Relevant articles from the peer-reviewed literature were included.

Results: Female sexual response is regulated not only by the sex hormones but also by several neurotransmitters. It is postulated that dopamine, norepinephrine, oxytocin, and melanocortins serve as key neuromodulators for the excitatory pathways, whereas serotonin, opioids, and endocannabinoids serve as key neuromodulators for the inhibitory pathways. Serotonin appears to be a key inhibitory modulator of sexual desire, because it decreases the ability of excitatory systems to be activated by sexual cues. Centrally acting drugs that modulate the excitatory and inhibitory pathways involved in sexual desire (eg, bremelanotide, bupropion, buspirone, flibanserin) have been investigated as treatment options for HSDD. However, only flibanserin, a multifunctional serotonin agonist and antagonist (5-hydroxytryptamine [5-HT]$_{1A}$ receptor agonist and 5-HT$_{2A}$ receptor antagonist), is currently approved for the treatment of HSDD.

Clinical Implications: The central serotonin system is 1 biochemical target for medications intended to treat HSDD.

Strengths and Limitations: This narrative review integrates findings from preclinical studies and clinical trials to elucidate neurobiological underpinnings of HSDD but is limited to 1 neurotransmitter system (serotonin).

Conclusion: Serotonin overactivity is a putative cause of sexual dysfunction in patients with HSDD. The unique pharmacologic profile of flibanserin tones down inhibitory serotonergic function and restores dopaminergic and noradrenergic function. **Croft HA. Understanding the Role of Serotonin in Female Hypoactive Sexual Desire Disorder and Treatment Options. J Sex Med 2017;14:1575−1584.**

Key Words: Serotonin; Hypoactive Sexual Desire Disorder; Female Sexual Dysfunction; Flibanserin

INTRODUCTION

During the past 50 years, our understanding of the female sexual response has evolved from a single linear model to several models that incorporate desire and acknowledge the interplay of many processes, including the influences of physiologic, psychological, interpersonal, and sociocultural factors,[1−5] which suggests that the female sexual response is heterogeneous. The diagnosis of female sexual dysfunction requires the presence of signs and symptoms of sexual dysfunction accompanied by clinically significant distress.[6] Female sexual dysfunction is reported by approximately 12% of women, with low or absent sexual desire cited as the most common problem.[7] Although psychological, interpersonal, and sociocultural factors play a significant role in sexual response and dysfunction, the importance of the physiologic aspects should not be overlooked.[6] Many neurotransmitters are required to sustain so-called normal sexual functioning, and sexual dysfunctions have been associated with specific neurotransmitter systems.[6,8]

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CNS Studies, Clinical Trials of Texas Research Center, San Antonio, TX, USA

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This article reviews the role of the neurotransmitter serotonin (5-hydroxytryptamine [5-HT]) in sexual functioning and the effects of pharmacologic interventions that target the serotonin system in the treatment of women with hypoactive sexual desire disorder (HSDD).

FEMALE SEXUAL DESIRE AND HSDD

Sexual desire is complex, with many etiologic components.[9–11] Using a biopsychosocial approach, sexual desire can be conceptualized as a composite of sexual drive (biological component), sexual beliefs (cognitive component), and sexual motivation (emotional or interpersonal component).[10,12] Sexual drive is understood to be modulated primarily by neurochemical mechanisms[10,12–15] whereas sexual beliefs are influenced by sociocultural and personal expectations. Sexual motivation, or the willingness to engage in sexual activity, is affected by psychological and relationship factors and is distinct from sexual desire.[10,12,13]

HSDD was defined by the American Psychiatric Association (APA) in its *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision* as a persistent or recurrent deficiency (or absence) of sexual fantasies and desire for sexual activity that causes marked distress or interpersonal difficulty.[16] When the disorder is generalized (ie, not limited to certain types of stimulation, situations, or partners), it is often a persistent condition that can be driven more by neurobiological factors than by psychological issues or environmental influences.[17] HSDD is not uncommon; studies have shown that the prevalence is 8% to 12% of women in the United States.[7,18] Because it affects so many women, its impact on quality of life is not insignificant. In fact, many studies have shown that low sexual desire or HSDD affects overall quality of life, health-related quality of life, and emotional state.[19–22]

Diagnostically, some confusion exists because the 2013 update to the APA's diagnostic manual (*Diagnostic and Statistical Manual of Mental Disorders, 5th Edition* [DSM-5]) merged disorders of desire (HSDD) and arousal (female sexual arousal disorder [FSAD]) in women to create a new diagnostic category termed,[23,24] whereas the *International Classification of Disease, 10th Revision* still contains a diagnostic code for HSDD (F52.0). Critics of the DSM-5 diagnostic change note that HSDD and FSAD have distinctive presentations and symptom patterns.[24] In addition, analysis of studies of women with HSDD that used the more recent, more stringent criteria for diagnosis showed that many women did not reach the threshold for a diagnosis of female sexual interest/arousal disorder. Thus, these criteria could exclude from the diagnosis (and therefore treatment) women with moderate to marked, rather than only severe, HSDD.[24] The new criteria also could complicate matters, because our current knowledge of the etiology and management of low sexual desire in women is based on years of research on HSDD.

The etiology of HSDD is multifaceted, encompassing a wide range of biomedical (eg, physical health, endocrine function, medications), psychological (eg, performance anxiety, depression, past trauma), and social (eg, relationship quality, cultural norms) causes.[9,10,25] Given the large number of potential contributing factors, substantial interindividual variability in HSDD etiology would be expected, and a biopsychosocial approach has been recommended to individualize evaluation and treatment.[10] It has been proposed that the effects of these biopsychosocial influences on sexual desire are mediated by excitatory and inhibitory neural pathways.[9] Specifically, sexual excitation and inhibition exist in a dynamic interaction that is sensitive to psychological and social factors and to the physiology and biochemistry of the brain.[9,26] For other central nervous system disorders—namely depression and anxiety—there is confirmatory evidence that psychosocial influences can affect brain function.[27] Neuroimaging studies have demonstrated an effect of psychotherapy and pharmacotherapy on the neural activity associated with anxiety and depression.[28–30] However, similar research studies have not yet been reported in patients with HSDD.

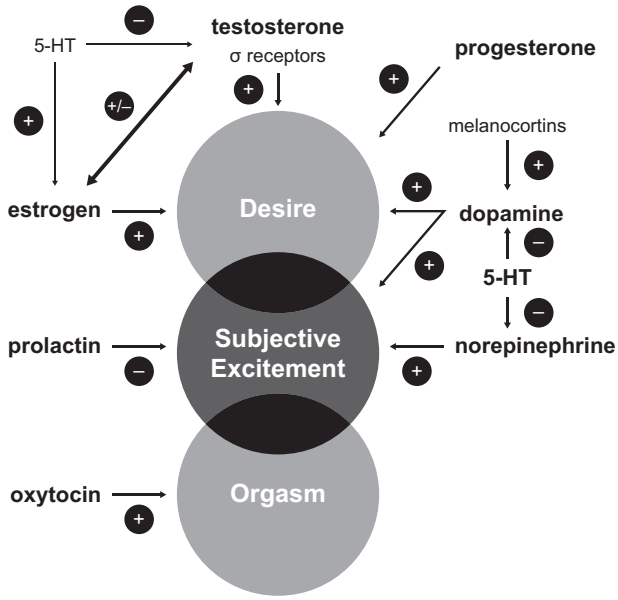

Figure 1. Central effects on sexual function. + = excitatory effect; − = inhibitory effect; 5-HT = serotonin. Adapted with permission from Clayton,[31] with additional data from Clayton and Hamilton[6] and Cohen.[32]

NEUROBIOLOGY OF FEMALE SEXUAL DESIRE

Sexual response is regulated by sex hormones, such as testosterone and estrogen, and by several neurotransmitter systems (Figure 1).[6,31,32] Different neurotransmitters work in separate but related neural systems for sexual excitation and sexual inhibition.[33] Dopamine, norepinephrine, oxytocin, and melanocortins are postulated to serve as key neuromodulators for the excitatory pathways,[15] whereas dopamine appears to facilitate sexual desire and the subjective sense of arousal[2,6] and is believed to be responsible for regulating the reward processing aspects of arousal and desire.[17] Norepinephrine apparently acts primarily to promote sexual arousal.[2,6,17] Conversely, serotonin, opioids, and endocannabinoids are postulated to serve as key