GUEST EDITORIAL

Female Sexual Dysfunction and the Central Nervous System

This supplement will review new developments in understanding the etiology and diagnosis of female sexual dysfunction (FSD) and the potential role of centrally acting agents in the treatment of FSD. The central nervous system (CNS) represents an important unexplored potential pathway toward both a monotherapy and perhaps more importantly, a potential key modality in an integrated therapeutic approach to treating FSD.

At present, few treatment options specifically and simultaneously address most components of the sexual response cycle for women [1]. In part, this represents a lack of understanding of the multifactorial etiology of FSD. Earlier single-aspect treatment alternatives resulted in ongoing disagreement over issues such as clinical trial design, appropriate clinical trial outcomes, and reproducibility and reliability of treatment results across patient populations [2].

This reality remains the case despite many calls for a more integrated approach to the understanding and treatment of FSD [3–6]. There also is a need for improving our basic understanding of the physiologic and psychological pathologies behind FSD [7–9]. In this supplement, Dr. Clayton explores some of the neurobiological aspects of the female sexual response, as well as provides epidemiologic background.

Historically, the treatment of sexual dysfunction emphasized psychosocial and cultural dimensions, beginning with the work of Masters and Johnson and continuing through the 1980s with various attempts at refining their labor-intensive approach of daily counseling sessions conducted by mixed-gender therapy teams [10,11]. Commonly used therapeutic approaches for the late 20th century included psychodynamic counseling, behavioral therapy, sex therapy, and interpersonal therapy, either in individual or group settings [12].

In recent years, the study of female sexual response physiology has also resulted in enhanced understanding of FSD's etiology. Clinical trials have indirectly demonstrated the difficulty and complexity involved in FSD diagnosis. These trials primarily researched therapeutic options typically targeting only a single aspect of human sexual response [13]. Clinical research emphasized the vascular and hormonal aspects of the female sexual response and that knowledge was utilized in developing potential new treatments.

The advent of oral erectogenic agents revolutionized the field of sexual medicine for men. Simultaneously, the important role of vasocongestion in female sexual arousal had become better understood. It became clear through laboratory research that phosphodiesterase type 5 inhibitors (PDE5) could impact clitoral tissue [14]. This led to a number of clinical trials that attempted to mimic in females the success of PDE5 in males. Unfortunately, these trials also made it quite apparent that an increase in vasocongestion would provide only modest assistance to some women with a female sexual arousal disorder, let alone those suffering other sexual dysfunctions. Clearly the multidimensional etiology and contextual complexity of FSD was not to be meaningfully improved with a PDE5 monotherapy alone [15,16]. These results demonstrated the necessity of discerning whether or not an intervention positively impacted desire, arousal, and enjoyment of sex within a personal, interpersonal, and cultural framework.

Hormonal aspects of female sexual response have been under investigation for decades [17–19]. The potential for hormonal interventions in FSD has recently been a subject of keen interest, recently culminating in the European Union's approval of a testosterone patch for women [20]. However, this work remains controversial, and a 2006 consensus statement by The Endocrine Society made it clear that hormonal supplementation for the purposes of increasing sexual responsiveness and/or receptivity was questionable [21]. This society's statement was immediately challenged by a group of sexual medicine specialists led by Andre Guay, which further highlighted the controversy surrounding this issue [22].

The role of the CNS in human sexual response is now opening to exploration. Functional magnetic resonance imaging has been used to locate

the neurobiological processes associated with exposure to erotic stimuli [23–25]. The role of various neurotransmitters in signaling the human sexual response is beginning to yield to both basic and clinical research. Dopamine (DA) and serotonin (5-HT) are the neurotransmitters most directly involved in sexual activity [26]. Generally speaking, DA plays a stimulatory role while typically 5-HT has an inhibitory effect on sexual processes. These two neurotransmitters interact with hormones involved in sexual functional capacity; and hormones likewise interact with these and other neurotransmitters in the CNS. Clayton reviews aspects of these systems in this issue. Preclinical models have significantly helped advance the understanding of the role of the CNS in sexual response in humans and important aspects of that work are highlighted and described in this supplement by Pfaus et al.

CNS-acting agents may have a role in the treatment of FSD. Most recently, melanocortins have been identified as small-molecule peptides with both central and peripheral effects [27]. Melanocortins have been proposed as potential therapeutics for a variety of wide-ranging conditions from obesity to sexual behavior. The available clinical evidence for the treatment of FSD by one of those agents—bremelanotide—is reviewed later in this issue [28].

FSD treatment research has followed a continuum examining psychosocial-cultural, hormonal, vasculogenic, and neurobiological factors, in hope of developing effective interventions that addressed one or more of these components (Figure 1). However, our greatest need is to develop a comprehensive model that provides sufficient theoretical rationale and clinical research support for a multidimensional integrated approach to the treatment of sexual dysfunctions.

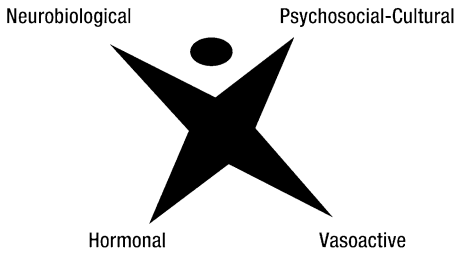

Figure 1 Historically, the management, clinical research, and treatment protocols for female sexual dysfunction have focused primarily on single-pathway methodologies. Psychosocial/cultural approaches such, as sex counseling and psychotherapy were the first to be initiated. Hormonal pathways to treat sexual dysfunction were investigated for decades, but only recently did a hormonal therapy obtain regulatory approval, and only in Europe. Interest in vasoactive therapies was engendered because of the efficacy of the phosphodiesterase type 5 inhibitors in male sexual dysfunction. The neurobiological role of central nervous system-acting agents has been explored, and recently there are signs of progress. However, combinations of approaches individualized to a patient's needs will likely prove to be the standard of care.

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