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Future Targets for Female Sexual Dysfunction

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ABSTRACT

Introduction: Female sexual function reflects a dynamic interplay of central and peripheral nervous, vascular, and endocrine systems. The primary challenge in the development of novel treatments for female sexual dysfunction is the identification and targeted modulation of excitatory sexual circuits using pharmacologic treatments that facilitate the synthesis, release, and/or receptor binding of neurochemicals, peptides, and hormones that promote female sexual function.

Aim: To develop an evidence-based state-of-the-art consensus report that critically integrates current knowledge of the therapeutic potential for known molecular and cellular targets to facilitate the physiologic processes underlying female sexual function.

Methods: State-of-the-art review representing the opinions of international experts developed in a consensus process during a 1-year period.

Main Outcome Measures: Expert opinion was established by grading the evidence-based medical literature, intensive internal committee discussion, public presentation, and debate.

Results: Scientific investigation is urgently needed to expand knowledge and foster development of future treatments that maintain genital tissue integrity, enhance genital physiologic responsiveness, and optimize positive subjective appraisal of internal and external sexual cues. This article critically condenses the current knowledge of therapeutic manipulation of molecular and cellular targets within biological systems responsible for female sexual physiologic function.

Conclusion: Future treatment targets include pharmacologic modulation of emotional learning circuits, restoration of normal tactile sensation, growth factor therapy, gene therapy, stem cell—based therapies, and regenerative medicine. Concurrent use of centrally and peripherally acting therapies could optimize treatment response.

Key Words: Female Sexual Dysfunction; Pharmacotherapy; Treatment

INTRODUCTION

Contemporary examination of published clinical and experimental evidence has shown that female sexual function and dysfunction reflect a multidisciplinary, biopsychosocial cascade of behavioral, interpersonal, mood, and psychosocial events that are influenced by molecular, cellular, genetic, anatomic, endocrine, and hemodynamic systems, with strong peripheral, spinal, and cortical participation. However, government-approved pharmacologic agents aimed at treating variants of female sexual dysfunction (FSD), such as genital pain disorders (eg, ospemifene and conjugated equine estrogen vaginal cream) and hypoactive sexual desire disorder (HSDD; eg, flibanserin), have shown safety and efficacy in clinical trials.[1,2] The limited existing repertoire of pharmacologic therapies for FSD has faced several unique barriers. First and foremost, placebo responses are generally high in FSD clinical trials. Although this placebo phenomenon is replicated across many disciplines and diseases, there might be a more pervasive conflict in female sexual medicine that is ideological, rather than pharmacologic, in nature: how can we treat FSD as we still struggle to define it?

Unsuccessful clinical trials have adopted definitions of FSD that were, and continue to be, controversial, particularly the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* that created the

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chimera diagnoses of female sexual interest/arousal disorder and genito-pelvic pain/penetration disorder.[3] Similarly, the validity and clinical relevance of the patient-reported outcomes used to define treatment success in FSD trials have been sharply criticized by clinicians, researchers, and the Food and Drug Administration's advisory panels.[4,5] These historical trends reflect significant gaps in our knowledge regarding the biopsychosocial interactions that mediate and distinguish between desire, subjective and genital arousal, orgasmic capacity, and pain perception.

This article discusses future treatment options and regenerative therapies for women with sexual health conditions. Levels of evidence (LOEs) are indicated for each compound or intervention using the Oxford Center for Evidence-Based Medicine guidelines. Current evidence-based pharmacologic FSD treatment options and their putative mechanisms are integrated into a larger critical discussion of scientific and methodologic barriers that limit future drug development and offer hypotheses to stimulate future research.

UNIQUE CONCERNS FOR FSD

To date, the selection of therapeutic targets and the assessment of their clinical efficacy have been strongly influenced by two (often conflicting) assumptions. The first assumption, inherited from Masters and Johnson,[6] posits that (i) genital physiology is sufficient to define normal sexual function and dysfunction in men and women and (ii) the magnitude or frequency of genital response is proportional to the perceived intensity or quality of arousal and orgasm. The second assumption is that a woman's subjective experience of her sexual functioning and related distress is the gold standard for assessment and treatment.[4,7] Taken together, these assumptions imply that a woman's perception of her sexual problems will reflect her physiologic function, guide FSD diagnosis, and facilitate treatment success.

Unfortunately, this model of mind-body concordance is not consistent with clinical and experimental data.[8–12] Female sexual psychophysiology studies have repeatedly demonstrated inconsistent (or null) correlations between subjective and genital sexual arousal in healthy women, which has constrained the interpretation of similar findings in women with FSD.[13] This lack of concordance has been replicated across multiple international laboratories using several objective methodologies.[14–21] Even the excellent work proposing that rapid fluctuations in rectal pressure are objective biomarkers of orgasm was confirmed in only 29 of the 31 women tested,[22] and rectal contractions do not temporally correspond with orgasm onset and offset.[23] The strongest evidence for discordance was generated in a brain imaging study combining functional magnetic resonance imaging with vaginal plethysmography, wherein vaginal plethysmograph-derived vaginal blood flow and regional activity related to subjective sexual arousal were uncorrelated.[24–26] These data highlight the urgent need for a mechanistic understanding of subjective and genital arousal and their interaction to guide the development of novel therapeutic agents.

This controversial body of evidence has established that physiologic sexual arousal is necessary but not sufficient for subjective sexual arousal and desire in healthy women; in turn desire and subjective and genital arousal are necessary but not sufficient to achieve orgasm. The most parsimonious explanation is that female sexual response reflects independent physiologic processes with non-linear interactions, as suggested by circular or iterative models of sexual function.[27,28] It logically follows that treatments targeting one physiologic process might not influence other processes that also contribute to pathology.[29] If we continue to use the current framework to guide the selection of therapeutic targets, FSD diagnoses that rely on inconsistent and/or inaccurate estimations of subjective and genital sexual response will yield heterogeneous clinical populations with variable treatment response profiles, at best. At worst, women with impaired sexual function might fail to meet the expert-defined definitions of FSD.[12]

CENTRAL SEXUAL NEUROPHYSIOLOGY AND PHARMACOLOGY

The neural mechanisms that coordinate the sensory, cognitive-emotional, and behavioral aspects of the female sexual response are of keen interest to clinicians, researchers, and pharmaceutical companies. Given that the perceived quality and intensity of peripheral nervous system sensory input are dependent on cortical processing,[30–32] it is feasible that combined central and peripheral interventions could yield the greatest clinical gains.[29,33]

Sexual Excitation

It has been elegantly argued that sex is rewarding because it facilitates the rapid evolution needed to sustain genetic survival; therefore, a neural drive for sexual opportunity, as with food or water, is needed to generate the goal-directed behavior that defines reward.[34] This neural drive relies on excitatory neurochemicals to enhance appetitive "wanting" to gain access to a stimulus that predicts sexual reward, a process called *incentive salience*.[35,36] Sex steroid hormones mediate sexual excitation by optimizing the physiologic milieu in which excitatory neurotransmitters can facilitate responses to sexual incentive stimuli. Principal excitatory neurochemicals supported by female rodent research include dopamine (DA),[37–40] oxytocin (OT),[41–43] melanocortin (MC),[38,44,45] and noradrenaline (NA).[46,47] We briefly address how these neurochemicals act in parallel and synergistically to orient attention to salient sexual stimuli, enhance sympathetic arousal, facilitate interpersonal bonding, and trigger motivated approach behavior through motor activation. Conceptually, pharmacologic agents that activate the synthesis, release, and/or receptor binding of these excitatory neurochemicals should increase sexual excitation.