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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.

DA and DA Agonists

DA transmutes desire into action, making it a classic excitatory target for pro-sexual drugs. Decades of rodent studies have shown that DA orients attention to salient, novel, and unexpected cues in the environment and assigns value to these cues to motivate approach (reward) or avoidance (aversion) behavior.[48–50] The initial encoding of an incentive stimulus into memory relies on experience-dependent cortical potentiation of emotional learning in the nucleus accumbens-ventral tegmental area, which receives glutamatergic projections from the hippocampus, amygdala, and medial prefrontal cortex.[49,51] Essential to DA-mediated "wanting" is the mesocorticolimbic and nigrostriatal circuitry that facilitates associative learning of incentive salience.[52] Within this framework, associative learning reflects the iterative cycling of incentive-related information throughout these massive brain circuits, and DA receptors mediate the strength, or "gain," of these cycles.[51] Animal research has shown that plasticity of these circuits is regulated by two mutually antagonistic "flavors" of striatal DA receptors, classified by their functional properties: (i) DA receptor D1 (DRD1)-like receptors (including DRD1 and DRD5) located along the "direct" striatonigral pathway mediate the acquisition of reward learning by promoting approach behavior; and (ii) DRD2-like receptors (including DRD2, DRD3, and DRD4) located on the "indirect" striatopallidal pathway mediate the inhibition of cognition and approach behavior and the adaptation of reward learning to new incentive stimuli.[53–55] Current development of selective DA agonists aims to refine pharmacodynamics based on these parameters. However, it can be argued that all pro-sexual drugs that influence motivation and motivated behavior must directly or indirectly act through dopaminergic mechanisms.

Clinical data on non-selective DA agonists have reinforced their limited use in enhancing sexual desire, arousal, and orgasm. The pro-sexual effect of DA was first recognized in patients with Parkinson disease, and these effects have only recently been systematically quantified. Well-designed prevalence studies in patients with Parkinson disease showed clear evidence of the pro-sexual effects of the DRD2-DRD3 agonist pramipexole, but to a pathologic degree—the drug appeared to disinhibit the regulation of impulsive behavior and promote risky "hypersexual" behavior and pathologic gambling.[56,57] A selective DRD3 agonist for FSD is currently under development by Pfizer (New York, NY, USA; PF-219,061).[58]

Apomorphine (LOE = 1b)

Strong preclinical and clinical data in men prompted the use of apomorphine (APO) in women with FSD. APO increases DA binding to DRD1-like and DRD2-like receptors (with no relation to morphine). In women, experimental studies have indicated that the timing and frequency of APO administration and potentially its administration before planned sexual behavior are critical parameters in determining its effectiveness.[59,60] In parallel with preclinical findings in the rabbit,[61] a prospective double-blinded crossover randomized controlled trial (RCT) conducted in premenopausal women with anorgasmia showed that APO priming (3 mg sublingual administration) 40 minutes before genital vibratory self-stimulation increased peak clitoral blood flow velocity (139%), self-reported lubrication, and subjective arousal compared with placebo vibratory stimulation.[59] A second double-blinded crossover trial of daily APO (2 or 3 mg or placebo, sublingual administration) in premenopausal women with desire and arousal disorders showed that daily (but not biweekly) APO improved orgasm, sexual enjoyment, and satisfaction with frequency of sexual activity, yet these gains did not result in more frequent sexual behavior. Therefore, women were more satisfied with the same frequency of sexual behavior. Moreover, dose-dependent side effects (nausea, vomiting, and headaches) motivated 16% of the sample to withdraw from the study, which could limit the therapeutic potential of APO.[60] A direct comparison between the two trials is difficult, because the study by Bechara et al[59] only examined acute effects of APO and used sexual behavior to elicit APO-mediated increases in subjective and genital arousal. Initially promising preclinical data that reported increased brain distribution and accumulation of an intranasal formulation of APO have been tempered by high clinical trial dropout rates.[62]

Bupropion (LOE = 2b)

The atypical antidepressant bupropion is a DA-norepinephrine reuptake inhibitor and nicotinic acetylcholine receptor antagonist with potential anti-inflammatory properties. Standalone or adjunct use of bupropion can partly reverse selective serotonin reuptake inhibitor (SSRI)-induced FSD in depressed women, regardless of ethnic background.[63–66] Across studies, the strongest clinical effect was partial restoration of sexual desire at 150 mg as needed or twice daily. Early observations that bupropion also might benefit non-depressed women with anorgasmia or female sexual arousal disorder (FSAD) must be confirmed with RCTs.[67,68] Notably, none of these studies demonstrated full restoration of normal sexual function.

Pharmacokinetic data from preclinical studies have shown that sildenafil increases serum levels of bupropion and venlafaxine without affecting their concentrations in the brain.[69] Therefore, sildenafil might be a promising adjuvant treatment for enhancing desire and arousal in women with HSDD.[69,70] Animal work determined that vardenafil or testosterone alone had no impact on female sexual behavior of HSDD model rats, but their combination restored proceptive, receptive, and paced mating behaviors.[71] Similarly, combined tadalafil and bupropion treatment improved sexual behavior in rats with HSDD.[72] Human studies have yet to examine the potential synergistic effects of phosphodiesterase type 5 (PDE5) inhibitors and bupropion, and investigational use of this drug combination could meaningfully expand FSD treatment options in the near future.

Bupropion and Trazodone (LOE = 5)

Lorexys is a combination of bupropion (225 and 450 mg) and the anxiolytic drug trazodone, a serotonergic (5-HT) antagonist, reuptake inhibitor, and transporter inhibitor that acts primarily as a 5-HT_{2A} receptor antagonist and partial 5-HT_{1A} receptor agonist. Notably, 5-HT_{1A} agonism inhibits sexual behavior in female rodents.[73] Results from a recently completed phase Ib open-label trial of Lorexys were not available at time of publishing.[74]

Melanocortins (LOE = 2b)

MC agonists also are thought to mediate the positive appraisal of sexual stimuli through sexual attraction.[75] The pro-sexual effects of MCs were first realized during a University of Arizona dermatologic trial of an MC agonist cream, Melanotan, when study participants reported increased libido, weight loss, and enhanced tan-like pigmentation.[76] Melanotan-II is a synthetic analogue of the endogenous peptide α-MC stimulating hormone (α-MSH) but 1,000 times more potent.[77] The pharmacodynamics of Melanotan-II can be inferred from bioactivity of α-MSH. In the brain, α-MSH preferentially targets MC4 receptors in the paraventricular hypothalamic nucleus and MC3 receptors located on 30% of dopaminergic neurons in the ventral tegmental area, two regions that mediate sex and reward, respectively.[78] MC3 and MC4 binding increases DA and norepinephrine levels, and their inhibition of β-endorphin is thought to underlie increased attention and arousal.[75] In the periphery, α-MSH (1 μm) effectively relaxes rabbit vaginal wall and vaginal artery smooth muscle,[79] and parallel studies in humans are needed. The clinical utility of α-MSH is limited by poor bioavailability with oral consumption.

Bremelanotide (PT-141; Palatin Technologies, Cranbury, NJ, USA), the active metabolite of Melanotan-II, agonizes MC1 and MC4 receptors, with preference for MC4.[75] After 5 days of bremelanotide priming in female rodents, robust changes in sexual appetitive behaviors were observed, including heightened proceptive sexual behavior in rats and restoration of female-paced mating after inflammatory pain in mice.[38] Women with FSD exhibit enhanced sexual arousal and sexual interest after intranasal and subcutaneous administration of MC agonists.[44,45,80,81] Phase II and IIb trials of bremelanotide (1.25 and 1.75 mg) in healthy premenopausal women have reported increased frequency of satisfying sexual events, sexual desire, arousal, and satisfaction.[82–84] Phase III trial results are anticipated by 2016, yet consistent reports of increased blood pressure during bremelanotide treatment have raised concerns about the drug's side effect profile. Palatin Technologies also has a more selective MC4 receptor agonist peptide (PL-6983) in preclinical development that is associated with less pronounced increases in blood pressure compared with bremelanotide.[85]

NA and α_1-Adrenergic Agonists (LOE = 3b)

The central excitatory effect of NA is thought to underlie sympathetically mediated female sexual arousal,[86] which could enhance the salience (and potentially reward value) of emotional experiences.[87,88] For example, the central administration of α_1-adrenergic agonists in non-anxiolytic doses is associated with increased sexual behavior in male rodents, likely due to promotion of postsynaptic-mediated catecholamine release.[89–91] In contrast, peripheral α-adrenergic agonism inhibits NA release in a presynaptic manner to promote increased vaginal smooth muscle tone and decreased blood flow, thereby suppressing vasodilation associated with arousal. These divergent effects are attributed to the differential modulation of central and peripheral adrenoreceptor subtypes α and β; although these receptor subtypes exhibit some functional overlap, they might yield conflicting subjective and genital arousal responses. Therefore, it has been hypothesized that centrally mediated subjective and/or physiologic responses to sexual cues and/or stimulation might "override" these more subtle changes with vasodilation.[92]

The pharmacologic manipulation of adrenergic function is not straightforward, because adrenergic compounds often exhibit affinity for the two receptor subtypes, and α_2-receptor antagonists readily cross the blood-brain barrier in humans, thereby exerting peripheral and central nervous system effects that are difficult to disentangle. On the one hand, replicated rodent studies have demonstrated that α_2-blockade decreases non-paced sexual behaviors in female rodents[93]; on the other hand, α_2 antagonism with atipamezole has no effect on female-paced mating or receptivity.[94] In women, acute sympathetic activation with moderate exercise, experimental induction of mild anxiety, and NA agonism (with ephedrine) augments genital arousal in healthy women and HSDD.[95–98]

Equivocal evidence supports a pro-sexual impact of the α_2-adrenergic receptor antagonist yohimbine, a drug that readily penetrates the blood-brain barrier in humans and prevents presynaptic inhibitory feedback of endogenous NA to augment unbound NA in the synapse. However, its combination with L-arginine, an amino acid precursor for nitric oxide (NO), yielded significant increases in genital but not subjective arousal 1 hour after oral administration.[99] Recent in vitro and in vivo evidence of adrenergic β-receptor—mediated vaginal lubrication has linked adrenergic modulation to a specific feature of genital sexual arousal that could be correlated with self-reports of lubrication.[100]

The clinical utility of adrenergic drugs remains unclear, because the equivocal animal and human findings are biased by methodologic inconsistencies across studies. The timing of drug administration and its maximum physiologic effect might not correspond with study time points.[94] For instance, the adrenergic nerve fibers distributed throughout the female genital tract aid in the regulation of vaginal and clitoral smooth muscle tone; these changes are unlikely to covary with the ebb and flow of subjective arousal.[92,101]

Oxytocin (LOE = 1b)

OT is an endogenous nonapeptide hormone synthesized in the hypothalamus and released by the posterior pituitary gland into the bloodstream, yielding central and peripheral nervous

system effects. OT is thought to enhance sexual response by increasing a sexual partner's incentive value through bonding-mediated sexual attraction and mate guarding[102,103] and alleviating anxiety that could otherwise hamper courtship.[43] Similarly, maternal OT enhances positive mood, decreases anxiety in breastfeeding mothers, and promotes maternal aggression when offspring are threatened.[104] OT produced in the medial preoptic area and ventromedial hypothalamus exerts central effects through projections to brainstem, limbic, and olfactory targets and affects genetic and epigenetic modulation of estrogen, progesterone, and testosterone.[105,106] In female rodents, estrogen upregulates OT production and release, with a diminished pro-sexual impact after hysterectomy.[43] In contrast, testosterone-mediated upregulation of vasopressin in female rodents functionally opposes the biological effects of OT to suppress sexual behavior. More research is needed to determine OT-hormone interactions in women.

OT decreases sympathetic arousal, anxiety, cortisol levels, and skin conductance and promotes greater heart rate variability and pupil dilation.[107] Moderate levels of sympathetic activation (by exercise) transiently enhance female physiologic arousal,[96] and OT might inhibit the deleterious effects of high anxiety, a notorious inhibitor of female sexual response.[43,108] Because OT release can be cognitively regulated and conditioned in women,[109] its therapeutic potential to enhance central processing of desire and arousal is immense.

OT facilitation of approach behavior is of great clinical significance for blunted sexual desire. OT differentially modulates appetitive approach behavior in unattached vs pair-bonded couples.[110] Intranasal OT delivered to pair-bonded couples before sexual activity enhanced the quality of sexual encounters.[111] However, these findings were contradicted by an 8-week prospective, double-blinded, placebo-controlled RCT found that intranasal OT (32 IU) administered 50 minutes before sexual activity in pre- and postmenopausal women did not outperform placebo in enhancing sexual function.[112] In behavioral studies, a double-blinded RCT showed that intranasal OT facilitated women's social approach behavior toward male confederates.[113] Conversely, monogamous (but not single) men maintained greater physical distance from an attractive female confederate after intranasal OT.[114] A similar phenomenon was observed in male rodents after OT-conditioned pair bonding that appeared to override the incentive value of female mice.[115] These nuanced social effects might require the physical presence of a potential mate rather than visual representations of "him" or "her"[116] and could shift after pair bonding has occurred. OT also might participate in the peripheral modulation of sensation and pain, because a recent study supported the use of topical OT to reverse vaginal atrophy in postmenopausal women, which could have important implications for sexual dysfunctions characterized by genito-pelvic pain.[117]

Despite these promising findings, the current repertoire of OT agents cannot predictably cross the blood-brain barrier. However, two OT compounds are under development—a non-peptidergic OT receptor agonist (WAY-277,464) and an enzyme inhibitor (placental leucine aminopeptidase)—that modulate OT degradation. These compounds have performed well in preclinical trials unrelated to FSD, with measurable increases in OT correlating with behavioral indices.[118] At least for WAY-277,464, vasopressin receptor binding remains an issue, because vasopressin functionally opposes OT activity.[119]

Sex Steroid Hormones (LOE = 1a)

Sex steroid hormones provide the biochemical machinery to facilitate a state in which sexual stimulation is likely to result in sexual desire, arousal, and orgasm.[120] A thorough review of sex steroid hormone physiology is beyond the scope of this review. Receptors for estrogen, progesterone, and androgens are distributed throughout the brain, spinal cord, and periphery. Testosterone,[121–124] 17β-estradiol,[125,126] and progesterone[127] bind to their respective androgen, estrogen, and progestin receptor complexes. The 17β-estradiol and progesterone receptor location can permit rapid non-genomic effects within seconds and slower genomic signaling over minutes to hours (or longer) that requires protein synthesis.

In the brain, they promote neurotransmission and the restructuring of synaptic pathways (eg, dendritic branching and spine volume, myelination) required for neuroplasticity.[128] Receptors vary in their sensitivities to sex steroid hormones and this affects the global effects of these hormones. Receptor polymorphisms alter the ultimate activity of sex hormones, yet genetic anomalies also could play a role. The length of DNA segments containing repeated CAG nucleotide sequences (CAG triplet repeats) is a heritable trait linked to Huntington disease and fragile X syndrome, yet CAG repeat length in hormone receptors also correlates with variation in sexual motivation.[129]

More CAG repeats are associated with weaker testosterone receptor activity and higher testosterone levels in men, although this has not been confirmed in women. Fewer CAG repeats are associated with higher levels of androgens in women, suggesting a stimulatory effect (ie, more CAG repeats leading to stronger receptor activity).[129] Similarly, androgen receptor CAG repeat length (ie, long and short CAG repeat lengths) has been related to greater female sexual desire in a small study of oral contraceptive users.[130] In other hands, short CAG repeat of the estrogen receptor β-gene suppresses estrogen receptor function.[129] Future research focused on modifying effects genetic polymorphisms underlying sex steroid receptor sensitivity and activity undoubtedly will introduce promising options for individualized treatment of FSD.

Various forms of testosterone replacement therapy have been tried for HSDD treatment, including a transdermal patch (300 μg/d; Intrinsa; Warner Chilcott, Rockaway, NJ, USA) and topical gel (Tostrelle; Cellegy Pharmaceuticals, Boyertown, PA, USA; ProStrakan Group, Galashiels, UK; Futura Medical, Guildford, UK) that restored testosterone levels in menopausal

women in recent phase I and II trials.[131] The European Medicines Agency approved Intrinsa for treatment of hypoactive sexual desire in surgically menopausal women in 2006, but its marketing authorization was pulled in 2012.[132] There is no evidence of Tostrelle development (renamed FSD500) after 2008. The testosterone cream Androsorb (Novavax, Gaithersburg, MD, USA) is in early-stage clinical trials and preliminarily results show heightened libido in postmenopausal women.[131] In an RCT of testosterone intranasal gel Tefina (Acerus Pharmaceuticals, Mississauga, ON, Canada) for orgasmic disorder, women treated with Tefina reported more intense feelings of sexual arousal after stimulation and exhibited statistically significant increases in vaginal plethysmographic genital response compared with placebo. Although studies have shown some benefits in testosterone supplemental therapy, conflicts regarding clinical efficacy and adverse effects remain.[125]

Placebo (LOE = 1b)

The placebo effect—an improvement in symptoms with a sham treatment that is disguised to be indistinguishable from an active medical treatment—is a psychobiological phenomenon observed across diseases and biological systems.[133–135] The mechanisms of placebo are controversial and fall into two camps: (i) biological predispositions to placebo and (ii) expectancy-based conditioned learning mechanisms that reflect the reinforcing value of verbal cues, medication-related behavior, social support through participation, and patient-researcher interactions.[133] Although many placebo studies are fraught with potential confounds, the placebo response remains the most robust treatment phenomenon in the biomedical literature and, for some disease states, appears to be increasing in strength.[136]

The most successful treatment for FSD is placebo, which consistently yields up to 40% treatment success in RCTs.[137,138] The pro-sexual impact of placebo has yet to be systematically studied in women with and without FSD, and it is unclear whether placebo produces sustained, replicable clinical improvement. Neuroimaging research indicates that the neural mechanisms for placebo analgesia propensity are mediated by prefrontal cortical function.[139] The detection of placebo responders before randomization into treatment arms can allow investigators to evaluate drug efficacy in placebo responders and non-responders to enhance the statistical power needed to detect significant treatment effects.

Sexual Inhibition

Inhibitory neurochemicals such as serotonin, endocannabinoids, and opiates suppress the physiologic mechanisms underlying sexual motivation and behavior because their release signals that pleasure has already been obtained.[140] This satiety signal is indicative of hedonic "liking," which is mediated by DA-mediated learning that a cue, behavior, or mate is associated with sexual pleasure (as opposed to DA-mediated salience, or "wanting," of a potential sexual reward).

Endocannabinoids (LOE = 5)

The endocannabinoid system is broadly implicated in the inhibition of female sexual function, yet little human data are available to confirm or deny this assumption. The term *cannabinoid* (CB), which refers to C_{21} terpenophenolic metabolites of the *Cannabis sativa* plant, was used for 30 years before the CB receptor subtypes CB1 and CB2 were identified in the early 1990s.[141] CB1 and CB2 are distributed throughout the central and peripheral nervous systems, respectively, and are bound by (at least) two primary endogenous ligands, anandamide (AMA) and 2-arachidonoylglycerol (2-AG). CB1 receptors are localized in brain regions that mediate movement, emotion, and the release of neurochemicals and peptides that mediate sexual function.[142] Therefore, the sexual impact of CBs could reflect the participation of multiple interacting cortical systems.

Classic comparative studies have shown that Δ^9-tetrahydrocannabinol, the psychoactive component of cannabis, alters estrus cycle length and suppresses ovulation[143,144]; however, these findings have not been replicated in women. Rodent studies using the CB1 receptor antagonist AM251 and agonists HU-210 and CP55,940 demonstrated a negative effect of CBs on female sexual behavior.[145–147] However, Δ^9-tetrahydrocannabinol—mediated increases in female sexual behavior also have been described and are dependent on hypothalamic progesterone and DA function.[148]

In women, a single non-replicated sexual psychophysiology study of high quality demonstrated that decreased serum AMA correlated with greater subjective and physiologic arousal, whereas decreased serum 2-AG uniquely correlated with greater subjective arousal.[149] Given that activity-dependent neuronal signaling triggers the production of AMA and 2-AG, this study design capitalized on the biologic significance of state-dependent dynamic changes in endocannabinoids (vs basal levels, which are minimally informative of their actual physiologic impact). The correlations with different aspects of sexual arousal are intriguing because AMA and 2-AG have independent synthesis and degradation pathways that might capture distinct physiologic cascades mediating unique aspects of sexual arousal.[150] When considered with the extant literature on female sexuality and cannabis use—which primarily consists of self-report studies from the 1970s supporting its facilitation of desire and arousal[151]—it becomes clear that future work must carefully differentiate the impact of dynamic endogenous from exogenous CB activity on sexual function.

Endogenous Opioids (LOE = 1b)

Minimal human research has been conducted to explore the impact of opioids on sexual function. Evidence suggests that OT, prolactin secretion, and the analgesic effect of vaginal-cervical stimulation—a phenomenon demonstrated in rodents and women—is mediated by opioids,[152,153] yet this analgesia can occur independent of sexual arousal. In addition to their impact on genital sensation, endogenous opioids can mediate hedonic

learning. Endogenous opioids mediate sexual reward for female rodents, because their blockade with the μ-opioid receptor antagonist naloxone prevents the development of a behavioral preference for a normally rewarding behavior: female-controlled, or "paced," mating.[154] These sparse data reinforce the need for basic science and clinical research that acknowledges the profound sex differences in endogenous opioid signaling.

A single phase IIa multicenter, double-blinded, placebo-controlled crossover trial evaluated the safety profile of a selective μ-opioid antagonist (CP-866,087) in 51 premenopausal women presenting with FSAD.[155] The side effect profile was acceptable; however, positive gains observed with treatment did not outperform placebo.

Serotonin (LOE = 5)

Serotonin is the most prominent and well-studied neurochemical linked to sexual inhibition. Much of this work is based on pharmacologic treatments that stimulate serotoninergic activity, particularly SSRIs, and their capacity to decrease sexual desire and promote arousal and orgasmic dysfunction. Negative sexual side effects have been attributed in part to the 5-HT_{2A} receptor, because antidepressants with 5-HT_{2A} antagonism (eg, flibanserin, nefazodone) do not provoke these symptoms.[156] A second hypothesis is that central and peripheral serotonergic mechanisms affect sexual response by altering genital sensation, thereby disrupting a woman's ability to accurately perceive sexual stimulation.[157] For example, SSRI-associated decreases in tactile sensitivity likely will affect unmyelinated primary afferent nerves that mediate pleasant touch[158] and necessitate greater mechanical pressure to be subjectively perceived as "arousing."

Serotonin stimulates the hypothalamic-pituitary-adrenal axis through the 5-HT_{2C} receptor, inducing acute peaks in sympathetic arousal that transiently suppress reproductive function. Estrogenic regulation of 5-HT_{1A} receptor activity and expression modulates this stress response, and the tightly coupled anatomical and functional relations between 5-HT and estrogen could underlie higher cortisol levels and greater sensitivity of women to stress.[159] Some have hypothesized that SSRI-mediated FSD might be mitigated with coadministration of estrogenic compounds to dampen hypothalamic-pituitary-adrenal reactivity and enhance 5-HT modulation.[160] Clinical trials of the combined testosterone and 5-HT receptor agonist have shown promising results in women with increased sexual inhibition.[161] Phase I and II trials have confirmed the safety and anxiolytic properties of a 5-HT_{1A} agonist and 5-HT_2 antagonist (TGWOOAA HCI, Fabre Kramer Pharmaceuticals, Houston, TX, USA) for generalized anxiety disorder, which developers plan to extend to FSD in future phase IV trials.

Peripheral Sexual Neurophysiology and Pharmacology

Sexual pleasure is mediated by the perception and positive appraisal of pleasant genital and non-genital sensations that are associated with sexual arousal and orgasm. Therefore, peripheral treatments for FSD aim to directly and/or indirectly support the integrity of genital tissue and its neurovascularization, facilitate normal function of primary afferent nerves, promote pelvic floor muscle tone and strength, and maintain the local hormonal milieu that sustains the physical and functional integrity of the reproductive tract.[162,163]

Topical Alprostadil (LOE = 1b)

Alprostadil ([13E]-[11R,15S]-11,15-dihydroxy-9-oxoprost-13-enoic acid) is a potent prostaglandin vasodilator involved in regulating blood flow to the female reproductive tract and potentiating sensory afferent nerve function. The clinical efficacy of topical alprostadil has been established for male erectile dysfunction, and current development for women with FSD is underway. A multicenter phase II clinical trial has found that alprostadil produces genital vasocongestion and enhances arousal to visual stimuli.[164]

Nine clinical studies of Femprox (Apricus Biosciences, San Diego, CA, USA) have been completed to date, including a 98-patient phase II U.S. study and a 400-patient phase III study in China. In a randomized clinical phase III trial of topical alprostadil 0.4% cream with a skin penetration enhancer, an ester of N,N-dimethylalanine and dodecanol (DDAIP), a 900-μg dose showed significant and clinically relevant improvements in primary arousal success and secondary efficacy outcomes (Female Sexual Function Index, Global Assessment Questionnaire, and Female Sexual Distress Scale).[165]

Intravaginal Dehydroepiandrosterone and Testosterone (LOE = 2b)

As a major precursor of endogenous estrogens and androgens, dehydroepiandrosterone (DHEA) has been evaluated for FSD. Although systemic DHEA has not consistently benefitted postmenopausal women with FSD, 2 weeks of daily administration of intravaginal DHEA (Prasterone) significantly improved self-reports of desire and sexual function, decreased vaginal atrophy, decreased the percentage of parabasal cells, increased superficial cells, and decreased vaginal pH in all treatment groups compared with no changes in the placebo group.[166,167] Serum levels of DHEA and measured metabolites remained in the normal postmenopausal range, with minimal or no changes detected during the 12-week observation period. A DHEA topical trial in vulvovaginal atrophy and dyspareunia showed significant improvement of pain intensity ratings compared with placebo. More recently, a low-dose (300 μg) gel formulation of topical testosterone (LibiGel; BioSante, Baudette, MN, USA) has undergone phase III clinical trials for the treatment of HSDD in postmenopausal women. The gel did not demonstrate efficacy in primary end points, and additional phase II trials are planned to evaluate its therapeutic potential further.[168]

PDE inhibitors (LOE = 2b)

Several PDE5 inhibitors have been evaluated as treatment for FSD. In contrast to the overwhelming success of PDE5 inhibitors in alleviating male erectile dysfunction, current evidence does not support their use to restore female sexual function. The use of PDE5 inhibitors to enhance genital arousal is theoretically supported by the presence of PDE isoforms in the human clitoris, vagina, and labia minora.[169,170] The nuances of female sexual arousal could provide insight into the limitations and potential opportunities in pursuing PDE5 inhibitors. For example, women with impaired subjective and genital arousal might not accurately perceive increases in genital arousal associated with successful PDE5 inhibitor use.[29] Therefore, discordance between subjective and genital arousal in women could account in part for the limited success of PDE5 inhibitors for FSD.

Early clinical trials in women with HSDD and FSAD described self-reported improvements in orgasmic capacity and arousal with sildenafil.[171–173] Two studies reported increased genital engorgement and blood flow with sildenafil, with no concurrent change in subjective sexual arousal[172,173]; these findings were not replicated thereafter.[174,175] Reports that sildenafil could reverse SSRI-induced FSD were premature, because they relied on a clinician's assessment of patient function (rather than a patient-reported outcome), and treatment effects were no longer statistically significant with correction for multiple comparisons.

These failed trials have not deterred PDE5 inhibitor development for FSD. A recently completed single-center, open-label, placebo-controlled phase I trial of dose-escalated topical sildenafil 5% cream (SST-6007) in postmenopausal women found few side effects and confirmed comparable bioavailability with oral consumption.[176] However, the efficacy of these compounds has yet to be demonstrated in FSD populations.

NO donor (LOE = 2b)

Pacher et al[177] demonstrated that topical application of the NO donor DS1, a linear polyethylenimine-NO-nucleophile adduct, increased vaginal blood flow in anesthetized rats. Combination therapy of L-arginine, the substrate in NO production, and yohimbine, a competitive α_2-adrenergic receptor antagonist (NMI-870; NitroMed, Charlotte, NC, USA), completed phase I and IIa clinical trials; however, trials were discontinued.[99] The non-selective α-adrenergic receptor antagonist phentolamine has shown promising results in estrogenized postmenopausal women, but no further report has been recognized.[178,179]

L-arginine products used as nutritional supplements have demonstrated positive results in the treatment of mild to moderate symptoms of FSD. In a 4-week placebo-controlled study, women (in the pre-, peri- or postmenopausal states) who reported low sexual desire exhibited statistically significant increases in clitoral sensitivity, sexual satisfaction, increased frequency of sexual intercourse, and decreased vaginal dryness compared with women in the control group.[180] Combined L-arginine with yohimbine outperformed placebo in increasing genital but not subjective arousal in postmenopausal women with FSD.[99] Recently, a dietary supplement containing pine bark extract, L-arginine, L-citrulline, and rose hip extract significantly improved sexual function across all Female Sexual Function Index domains in healthy women of late reproductive age.[181] Further scientific investigations regarding those sexual supplements are required.

COMBINED CENTRAL AND PERIPHERAL NEUROPHYSIOLOGY AND PHARMACOLOGY

Lybrido and Lybridos (LOE = 1b)

The clever strategy of combining peripherally and centrally acting agents has led to the development of a sublingual testosterone plus PDE5 inhibitor (Lybrido; Emotional Brain BV, Almere, The Netherlands) to improve the two processes concurrently. This hypothesis was confirmed in a subgroup of women with low sensitivity for sexual cues in laboratory and naturalistic sexual situations.[182,183] The same company is developing a drug combining testosterone with buspirone, the 5-HT_{1A} agonist (Lybridos; Emotional Brain). The advent of these combination treatments that combine PDE5 inhibitors with centrally mediated treatments is a promising avenue that warrants further investigation.

NOVEL FUTURE TREATMENTS FOR FSD

Repetitive Transcranial Magnetic Stimulation (LOE = 5)

Non-invasive brain stimulation with repetitive transcranial magnetic stimulation (rTMS) is a relatively new therapeutic technique for treating patients with neurologic and psychiatric conditions. Functional connectivity—guided rTMS derives patterns of region-to-region communication from an individual's resting-state functional magnetic resonance images. These paths of altered communication are used to generate a stereotaxic template of coordinates for targeted stimulation based on an individual's brain function and structure. Theoretically, this approach could normalize disturbed brain network dynamics in women with FSD; in turn this normalization has the potential to enhance efficacy of other treatments. For example, functionally guided rTMS stimulation of the dorsolateral prefrontal cortex led to significant treatment gains in depressed patients, making it the first rTMS treatment approved by the Food and Drug Administration for medication-resistant depression.[184] Future use of rTMS would require that a woman is assessed for her brain's unique communication pathways that correlate with her FSD severity and its sequelae. These brain regions would be used as stimulation targets to enhance central mediation of sexual desire and arousal.

Pharmacogenetics (LOE = 5)

The heritability of sexual response in non-human species strongly suggests that genetic variability also underlies the risk for sexual dysfunction. Theoretically, any genetic factor(s) that disrupt attention, motivation, somato-sensation, locomotion, and/or physiologic processes can adversely affect sexual response and facilitate sexual dysfunction. Clinical phenotypes reflect unique configurations of multiple gene interactions and their epigenetic modulation.[185] Pharmacogenetics were proposed within this framework to evaluate an individual's genetic background to guide the optimal selection of drugs.

The pharmacogenetic approach could involve analysis of single-nucleotide polymorphisms or use of genomewide association studies to evaluate a panel of common genetic variants. Genetic polymorphisms can provide information about individual differences in drug metabolism, side effects, abnormal signaling cascades, propensity to develop disease, and even resistance to disease. For instance, identification of cytochrome P450 polymorphisms can guide the selection and dosage of drugs that rely on this metabolic pathway, such as PDE5 inhibitors. Rapid cytochrome P450 metabolizers require higher doses of PDE5 inhibitors, whereas poor metabolizers are at greater risk for toxicity-related adverse events.[186] FSD treatment efficacy also could be modulated by allele variations in catechol-methyltransferase, a gene that participates in the metabolism of catechol drugs and endogenous catecholamines, including neurotransmission of DA (which mediates salience of sexual incentive stimuli), norepinephrine (which enhances encoding of fear memories in the basolateral amygdala), and endorphins (which affect pain susceptibility).[187]

Preliminary reports of genetic polymorphisms related to male sexual dysfunction and symptom severity[188] remain largely unexplored for FSD, with the exception of provoked vestibulodynia. Multiple studies (albeit with few replications) have suggested that women with provoked vestibulodynia are more likely to carry polymorphisms that affect pain sensitivity, host-pathogen interactions, and balance of pro- and anti-inflammatory responses. In such cases, genetic variation can provide information about disease mechanisms (eg, dysregulated inflammation) and optimal treatment (eg, drugs that counteract these mechanisms, their substrates, and/or their downstream physiologic consequences). Moreover, longer CAG repeats in the androgen receptor gene have been associated with the development of provoked vestibulodynia after oral hormonal contraceptive use and lower serum testosterone.[189]

Fine-Tuning the Tipping Point

Strategic pharmacologic management of FSD can create and sustain a physiologic milieu that is optimized for sexual expression, yet top-down cortical modulation of desire and subjective arousal will determine what a woman does with her milieu.[190,191] Therefore, the adjunct use of evidence-based psychological treatments, including cognitive-behavioral therapy or sex and couples' therapy, can maintain and further enhance treatment success of pro-sexual drugs. A recent meta-analysis determined that psychological interventions—regardless of theoretical orientation—can improve symptom severity in women with HSDD (Cohen d = 0.91, large effect) and modestly improve symptoms of FSAD, anorgasmia, and mixed FSD (Cohen d = 0.46−0.66, medium effects).[192] Cognitive-behavioral therapy with partner participation most effectively targets HSDD, whereas orgasm dysfunction requires more behaviorally oriented therapy (including sex therapy techniques introduced by Johnson and Masters[193]). Mixed FSD is optimally responsive to sex and couples' therapy, whereas women with sexual pain disorders might benefit from cognitive-behavioral therapy and pelvic floor muscle biofeedback.[194]

CHRONIC PELVIC AND GENITAL PAIN

Patients with chronic pelvic pain exhibit condition-specific alterations in brain function and structure that co-vary with pain intensity and duration. To a lesser degree, functional and structural abnormalities are described in women with low sexual desire.[195−197] The emotional learning that underlies these neuroplastic changes can be targeted with cognitive-behavioral and/or pharmacologic interventions, which are reviewed below.

d-Cycloserine (LOE = 5)

d-Cycloserine (DCS) is an antituberculosis drug approved by the Food and Drug Administration that exhibited antidepressant properties in patients with tuberculosis. DCS crosses the blood-brain barrier and selectively binds receptors in the basolateral amygdala, which is the primary brain region responsible for fear learning. Basolateral amygdala lesions prevent the induction of fear learning and its function impairment can downregulate negative emotion associated with aversive learning.[198] Given the emotional nature of chronic pain—which increasingly appears to reflect an "addiction" to an aversive state—DCS targets the neuroplasticity that develops from living with chronic pain. At low doses (<300 mg/d), DCS is a partial glycinergic N-methyl-D-aspartate agonist that could relieve anxiety.[199,200] At high doses (>500−600 mg/d), the function of DCS is reversed and it becomes a glycinergic N-methyl-D-aspartate antagonist that might be responsible for its anecdotal antidepressant effects. Low-dose DCS taken 1 hour before psychotherapy can enhance therapeutic effects of flooding-exposure therapy, likely by decreasing the negative emotional tone of the anxiety-related memory as it is reconsolidated. Daily low-dose DCS for several weeks can decrease pain intensity and unpleasantness in some individuals with chronic back pain (unpublished proof-of-concept clinical trial, manuscript in preparation). Similarly, long-term DCS administration has been found to alleviate chronic neuropathic pain in rodents.[201] Notably, there is no evidence that DCS must be taken indefinitely, unless new fear learning takes place.

Patients with vulvodynia might benefit from acute and long-term low-dose DCS. A phase IV clinical trial of DCS is currently underway in men with chronic pelvic pain (300 mg/d for 4 months, with placebo arm), with minimal side effects reported to date. Off-label use of DCS is permissible immediately, yet many physicians are hesitant to prescribe it owing to their limited experience with the drug.

P2X3 Antagonists (LOE = 5)

Properties of primary afferent nerve fibers, such as nerve diameter, presence of myelination, receptor expression, and density within a given area of skin, convey qualitative and intensity information about a stimulus.[202] Merkel cells mediate innocuous touch, whereas the P2X3 receptor encodes painful pressure—more specifically, the qualitative shift from innocuous to noxious pressure (ie, pain threshold). P2X3 receptors are located on transient receptor potential vanilloid-1—immunoreactive (TRPV1-IR) peptidergic and non-peptidergic nerve fibers, which strongly suggests they are located on nociceptors.[203] Therefore, this receptor is uniquely suited to mediate the central clinical feature of provoked vulvodynia in premenopausal and postmenopausal women, namely mechanical allodynia.

P2X3 expression is inhibited by estrogen binding to membrane estrogen receptor (ER)-α[204]; therefore, ample circulating levels of estrogen and adequate density of ER-α receptors would be required to maintain inhibition of P2X3-mediated nociceptive signaling.[205] Conversely, P2X3 could transmit nociceptive signaling with less mechanical force and at a greater magnitude when circulating estrogen and ER-α levels are low.[206,207] These alterations in nociceptive signaling are consistent with peripheral sensitization of primary afferents.[208] Evidence of abnormal ER-α expression in vulvar tissue[209,210] and beneficial effects of topically applied estrogen cream in suppressing vulvar mechanical allodynia provide indirect evidence that vulvar mechanical hypersensitivity could reflect abnormal P2X3 function that could be normalized with ER-α agonists. Moreover, evidence that estrogen deprivation promotes increased genital innervation in the female rat (reversible with 17β-estradiol) implies that the ratio of sensory nerve fibers to local estrogen could contribute to hypersensitivity in the postmenopausal state.[211] Importantly, altered P2X3 function reflects an abnormal functional response of otherwise normal nerve fibers rather than nerve injury.

Indirect support of this hypothesis is provided by reports of decreased vulvar pain with topical capsaicin (chemical TRPV1 agonist).[212,213] Capsaicin acutely enhances TRPV1-mediated signaling yet repeated application leads to the desensitization of nociceptor signaling that is thought to underlie its analgesic effects.[214] Critically, prolonged exposure to capsaicin also leads to the functional desensitization of the TRPV1-IR nociceptor, which renders it less responsive to other types of noxious stimulation.[215] Coexpression of P2X3 on TRPV1-IR nociceptors indicates that P2X3-mediated mechanical pain could be stabilized with prolonged capsaicin treatment; similarly, addition of capsaicin to the direct antagonism of P2X3 could amplify the net analgesic effect.[216] Moreover, removal of painful vulvar tissue that contains nerve endings with these dysfunctional receptor properties would remove the source of these aberrant pain signals. Collectively, these data provide strong theoretical support for the role of P2X3 receptor function in provoked vulvodynia.

Several P2X3 antagonists are in various stages of preclinical and clinical development.[217] AF-219 has advanced to phase II clinical trials for chronic cough,[218] yet a large portion of patients withdrew their participation owing to lingering "aversive taste" after drug ingestion. It is possible that a more aggressive effort to hyperpolarize the membrane potential of these nerves (using combined capsaicin and lidocaine to decrease discomfort) could incapacitate signaling of painful pressure without resorting to use of oral P2X3 antagonists.

Regenerative Medicine, Adipose-Derived Stem Cells, and Platelet-Rich Plasma Infusions (LOE = 4)

Stem cell—based therapy is a promising avenue for the recovery of female genital arousal function. Adipose-derived stem cells refer to a somatic stem cell population contained in fat tissue that possess the ability for self-renewal, differentiation into one or more phenotypes, and functional regeneration of damaged tissue.[219] There are several review articles that have assessed the available evidence in male animal models concerning adipose-derived stem cell availability, differentiation into functional cells, and the potential of these cells for the treatment of men with erectile dysfunction.[220—222] Data for female animal models with experimental female arousal disorders are limited concerning definition, characterization, differentiation, and application of adipose-derived stem cells for cell-based therapies.[223,224]

Adipose-derived stem cells have a paravascular location in the adipose tissue. Under specific induction medium conditions, these cells differentiate into neuron-like cells, smooth muscle cells, and endothelium in vitro. The insulin-like growth factor and insulin-like growth factor receptor pathway participates in neuronal differentiation, and the fibroblast growth factor-2 pathway is involved in endothelium differentiation.[225,226] In in vivo experiments, adipose-derived stem cells functionally recovered damaged genital arousal smooth muscle function. Although the underlying mechanism needs to be examined further, adipose-derived stem cells are a potential source for stem cell—based therapies, which imply the possibility of an effective clinical therapy for female genital arousal disorder in the near future.

A recent pilot study has pioneered the application of platelet-rich plasma (PRP), which includes platelets containing various growth factors such as platelet-derived growth factor, insulin-like growth factor-I, and vascular endothelial growth factor in the treatment of FSD. The basic idea behind PRP therapy is to deliver high concentrations of growth factors to an area that has pathology; in turn growth factors act locally to recruit undifferentiated cells to the site of injury, trigger mitosis in these cells,

and induce neoangiogenesis. PRP is an autologous product prepared from the patient's own blood through a 60-mL blood draw and centrifuged to separate its components, yielding red blood cells, PRP, and plasma. In 2014, the first study of its kind evaluated PRP injections in the Skene glands and clitoris in a small uncontrolled sample (N = 11) of women with mixed sexual dysfunction and yielded significant within-group decreases in sexual dysfunction and distress, although individual responses were highly variable.[227] Two patients reported side effects, including extreme genital arousal (including spontaneous orgasm), that completely resolved within 1 to 2 weeks. These promising findings have yet to be replicated in a standardized fashion, and it is anticipated that PRP benefits will be synergistic with stem cell infusion to increase and improve female genital tissue health, thereby enhancing sexual function.

Neuromodulation (LOE = 1b)

Pelvic neuromodulation is thought to modulate sympathetic outflow through the hypogastric nerves that supply genital sensory fibers, yet limited data exist regarding the use of neuromodulation for FSD. Some evidence suggests that sacral or pudendal neuromodulation could enhance primary afferent signaling during sexual stimulation, leading to improved sexual response and satisfaction. In women with voiding dysfunction, Yih et al[228] reported that sacral neuromodulation implants improved global sexual function at 12-month follow-up, whereas urinary and voiding dysfunction were unchanged. Although the handful of studies evaluating sexual function have reported some benefit of neuromodulation for treatment of lower urinary tract symptoms,[228–230] these findings remain controversial and could encourage neuromodulation to be restricted to select patients.[228,231]

Despite its frequent use in chronic pain management, limited evidence supports the effectiveness of transcutaneous electrical nerve stimulation (TENS) in alleviating clinical pain. Clinical literature reviews of the putative mechanisms of TENS efficacy—including the opioid-mediated induction of descending inhibitory pain modulation—are based primarily on rodent research with minimal relevance for the chronic pain state, which is characterized by spinal and brain functional and structural reorganization that is physiologically independent of new peripheral input.[232]

The only double-arm randomized placebo-controlled trial of 20 biweekly TENS treatments in 40 women with provoked vestibulodynia found significant improvement in pain intensity and sexual function, yet long-term follow-up data are lacking.[233] However, more recent data have linked vulvar pain relief with TENS to less need for vestibulectomy.[234]

FUTURE DIRECTIONS: A COMMENTARY

Moving forward, the most pragmatic strategy for the development and validation of new therapies is to identify and use patient-reported outcomes that best reflect a drug's mechanism(s).[191] As the field continues to rapidly evolve, we must sharply question the complacent assumption that existing "gold standard" technologies used to evaluate FSD treatments will meet these future scientific and clinical demands. One of the few points of consensus in the field pertains to the complexity of the female sexual response, and intricate theoretical models have identified cognitive, emotional, sensory, and behavioral targets for FSD treatment that have yet to be exploited. It is recommended that future assessments of FSD treatment efficacy incorporate these targets as secondary outcome measurements that might, eventually, outperform existing validated questionnaires, plethysmography, thermography, and Doppler ultrasound.

For instance, peripherally acting drugs that are assumed to modulate genital sensation should be evaluated with quantitative sensory testing, because the perception of cutaneous stimulation (with touch, heat, etc) corresponds closely with firing properties of nerve fibers.[235] Similarly, neuroimaging is ideally positioned to capture objective correlates of subjective sexual arousal using analysis techniques that dissociate central representation of stimulus encoding from its subjective appraisal,[236] including perceived controllability, predictability, anticipation, and other cognitive-emotional constructs implicated in contemporary models of female sexual response.

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