Pharmaceutical and Energy-Based Management of Sexual Problems in Women

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KEYWORDS

• Female sexual dysfunction • Medicalization • Hypoactive sexual desire • Cognitive sexual arousal • Genital sexual arousal • Laser therapy • Radiofrequency therapy • Electric stimulation therapy

KEY POINTS

- Female sexual dysfunction (FSD) has been inconsistently defined and characterized, so that changes in nomenclature complicate its diagnosis and treatment.
- Whether and how FSD ought to be medicalized is controversial, with associated problems of biomedical nihilism and unregulated proliferation of quack remedies under the aegis of "wellness."
- Because of frequent discordance of cognitive and genital sexuality in females, therapeutic interventions that benefit genital tissue are not necessarily helpful for overall sexual function.
- Medications and energy-based interventions available for FSD provide small, statistically significant improvements in sexual function, as measured by the Female Sexual Function Index; whether these improvements are clinically significant is a question that is most reliably answered by each individual patient.

BACKGROUND TO A NEW ERA

To discuss "a new era" in the management of sexual dysfunction implies progress from a previous norm, so that discussion must begin with an understanding of the historical foundations and associated assumptions undergirding that progress. This is particularly true of the diagnosis of female sexual dysfunction (FSD), which is a prerequisite to application of the novel and experimental therapeutic interventions that are the focus of this article. FSD is a category of diagnoses infamous for its changeability and its constancy over time: in the past three decades, its nomenclature and classification have gone through multiple iterations by various national and international organizations[1]; at the same time, historical and now medically anachronistic terms, such as "frigidity," continue to be used in the context of doctor-patient encounters and popular discourse about female sexuality.

Despite incontrovertible progress in medical science and an evolution of social norms since the early modern period, medical historians describe remarkable continuity in the terms of debate about FSD. These have included argument over whether sexual problems in women deserve significant medical attention (given that they do not necessarily preclude successful reproduction, in contrast with male erectile dysfunction [ED]) and the extent to which they signify a moral or psychological disorder versus a problem of anatomy or physiology.[2] The residue of these debates persists today, in the inequitable distribution of research funding and clinical attention to male sexual dysfunction and FSD, and in the tension between

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different classification systems used to define and diagnose these diseases.

NAVIGATING NOMENCLATURE

The various classification systems currently in use to describe sexual problems have changed over time (Table 1) and will likely continue to evolve in response to biomedical research and the bureaucratic structure of medical practice. Practitioners of different medical disciplines preferentially use the nomenclatures with which they are most familiar: psychologists and psychiatrists generally privilege the Diagnostic and Statistical Manual of Mental Disorders terminology[3]; urologists and gynecologists typically use that of the International Classification of Diseases and Statistics (ICD)[4] and/or the International Consultation in Sexual Medicine (ICSM)[5] and International Society for the Study of Women's Sexual Health (ISSWSH) diagnostic systems.[6] The ICSM and ISSWSH nomenclatures are the most recently coined, and are thus based on the most up-to-date understanding of sexual pathophysiology.[1]

This pathophysiology is interdisciplinary, relying not on traditional Cartesian mind-body dualism, but on biopsychosocial modeling and an integrated view of neuropsychiatry and genital physiology as mutually influential. It is anticipated that the upcoming ICD-11 will base its terminology primarily on the ICSM/ISSWSH classification system, eliminating the ICD's previous distinction between physical and psychological sexual disorders by combining the two groups into a single section titled "Sexual Dysfunctions" within a chapter called "Conditions Related to Sexual Health."[7] It will acknowledge the multifarious and overlapping potential causes of sexual dysfunction, including social and cultural factors, and reinforce the inherent subjectivity of sexuality, proscribing against any normative functional standard.

This subjectivity is a crucial problem in any assessment of female sexual health. It creates space for the use of diagnostic and therapeutic

Table 1
Evolution in female sexual diagnostic nomenclature over the past 25 years

DSM-IV (1994)	ICD-10 (1999)	DSM-5 (2013)	ICSM-5/ISSWSH (2015/2016)
Female hypoactive desire disorder Female arousal disorder	Lack or loss of sexual desire Female sexual arousal disorder	Female sexual interest/arousal disorder	Hypoactive sexual desire disorder Female genital arousal disorder
Female orgasmic disorder	Female orgasmic dysfunction: failure to reach orgasm	Female orgasmic disorder	Female orgasm disorders Anorgasmia Decreased frequency Muted intensity Premature or delayed Anhedonic
Dyspareunia Vaginismus	Nonorganic dyspareunia Nonorganic vaginismus	Genitopelvic pain/penetration disorder	Female genital-pelvic pain dysfunction
Sexual aversion disorder Sexual dysfunction caused by a general medical condition	Sexual aversion		
Substance/medication-induced sexual dysfunction		Substance/medication-induced sexual dysfunction	
Sexual dysfunction NOS		Other specified sexual dysfunctions Unspecified sexual dysfunction	Female orgasmic illness syndrome Persistent genital arousal disorder

Abbreviations: DSM, Diagnostic and Statistical Manual of Mental Disorders; ICD, International Classification of Diseases and Statistics; ICSM, International Consultation in Sexual Medicine; ISSWSH, International Society for the Study of Women's Sexual Health; NOS, not otherwise specified.

terminologies that are rich with personal, social, and cultural meaning but lacking in certain scientific or clinical significance. An example of this is the diagnosis of "vaginal laxity" (a term with scant biomedical basis but cultural salience), which may be treated with "vaginal rejuvenation" (again, a term with unclear meaning but strongly positive connotations). This subjectivity complicates the determination of treatment success or failure, because studies of female sexual arousal have shown that vaginal lubrication, tissue engorgement, and other genital changes consistent with arousal are not necessarily associated with subjective arousal by research subjects.[8,9] The epistemology of science is reliant on outcomes that are objectively measured and repeated in diverse individuals; the subjectivity and idiosyncrasy of sexuality is in tension with the premise of evidence-based medicine.

CRITIQUING FEMALE SEXUAL DYSFUNCTION

Some practitioners have responded to this tension with opportunistic quackery, promoting and selling dubious and expensive treatments for FSD under the auspices of promoting "wellness."[10] Others have embraced nihilism: faced with the impossibility of separating sexual science from its biased social, political, and economic contexts, they argue against any medicalization for management of sexual concerns.[11] Feminist scholarship reveals how medicine has historically pathologized the female body[12] and idealized heteronormative, penovaginal intercourse,[13] arguing that FSD diagnosis and treatment is a patriarchal tool of the medical-industrial complex.[14] However, feminism is also vulnerable to commodification: "Even the Score," a seemingly grassroots campaign that agitated for the first Food and Drug Administration (FDA) approval of medication for FSD as an antidote to systemic sex-gender inequity in health care, was ultimately revealed as the creation of the drug manufacturer and owner.[15]

These biases, gendered and financial, explicit and implicit, represent violations of bioethics that merit serious consideration and rectification. Although science may be flawed by bias, it remains an important and helpful source of knowledge. Medical studies, diagnoses, and therapies offer a potentially meaningful and effective structure in which to operationalize that knowledge toward patients' goals of care. Sexual dysfunction, regardless of how and by whom it is defined, has long been and continues to be a source of real suffering for women of all ages worldwide: the rest of this article is devoted to the description and analysis of the currently available treatment options.

PHARMACEUTICAL MANAGEMENT

The ahistorical and biomedically nihilistic narratives about FSD as a disease invented by medical industry to sell its products all begin in 1998, with sildenafil.[16] The commercial success of Viagra for treatment of ED increased enthusiasm for research into female sexual medicine, in hope of identifying a similarly lucrative "female Viagra"; it was this promise and the industry funding that followed from it that enabled the research and medical conferences that were immediate past precursors to ISSWSH.[17] Ultimately, the clinical trials of Viagra in female subjects failed to show clear benefit and in 2004 Pfizer chose not to apply to the FDA for the drug's approval in women. But the "Viagra effect" remains strong, with subsequent medications for FSD consistently compared with it, and the particular way it failed to benefit women provides an important insight into FSD.

Phosphodiesterase-5 Inhibitors

The mechanism through which sildenafil and other phosphodiesterase-5 inhibitors (PDE5i) affect sexual function is by promoting vasodilation within the genital tissues: by preventing degradation of cGMP, the vasodilatory effects of nitric oxide on the genitalia are potentiated.[18] Although this mechanism has been most extensively studied within the male corpora cavernosa and in the context of male erection, it is equally relevant to female sexual function.[19,20] The physiology of female genital arousal also features smooth muscle relaxation and vasocongestion of the cavernous tissues (clitoral and bulbovestibular), which is mediated by nitric oxide. Vasoactive intestinal polypeptide is another vasodilatory neurotransmitter that is also involved in relaying the proarousal signal from the sacral parasympathetic nerves to the genital tissue in both sexes, but its relative significance remains unclear and it has not been instrumentalized for therapeutic purpose.[12] Whereas in men increased genital blood flow manifests with penile erection, in women its most obvious manifestation is swelling and increased lubrication of the vulvovaginal tissues.

Studies of sildenafil in female subjects with various sexual dysfunctions and comorbidities consistently demonstrated physiologic changes of increased genital arousal in response to the medication when compared with placebo. These include increased vaginal lubrication, increased blood flow on Doppler ultrasound, increased fullness on vaginal plethysmography, and decreased genital vibratory perception thresholds.[21–23] However, just as consistent was a disconnect between these objective physical changes and their

subjective interpretation by the women who experienced them: whether assessed by simple self-report or validated questionnaire, subjects who were given sildenafil often failed to report improvements in sexual arousal or other aspects of their sexual experience.[24]

This inconsistent relationship of physiologic and psychological response is characteristic of female sexuality, reaffirmed by scientific studies of responsiveness to various interventions and appealing and aversive stimuli. In response to this discordance, the most recent diagnostic nomenclature not only distinguishes between sexual desire and arousal, but also parses female sexual arousal disorder into two distinct problems: female genital arousal disorder, which is a problem of genital physiology; and female cognitive arousal disorder, a problem of mental state, in which genitally erogenous cues are not experienced as being sexually arousing.[6] That a diagnostic classification system purposefully designed to integrate the physical and psychological aspects of sexual problems so readily falls back on Cartesian dualism is ironic evidence of the strength and rhetorical utility of this model. Patients with female genital arousal disorder, especially those with comorbid diabetes,[25,26] may benefit from treatment with a PDE5i, and it is for this reason that research studies of these medications in women continue to be published more than a decade after Pfizer gave up on sildenafil for women.

Psychoactive Medications

Modulation of genital response has not reliably led to improvement in women's sexual experience. A biomedical approach has, however, had some utility in addressing subjective arousal/libido. The two medications that are FDA-approved for treatment of an FSD, specifically, hypoactive sexual desire disorder (HSDD), act within the brain, according to the logic that where thought and emotion lead, the body and behavior will follow. It is important to keep in mind that just as affective disorders are most effectively treated by a combination of medication and psychotherapy,[27] medications to address sexual dysfunction may work best when used in conjunction with psychotherapeutic sex therapy.[28]

Flibanserin

Flibanserin was discovered serendipitously; initially investigated as an antidepressant, it was ineffective at managing depression but trial participants were incidentally noted to be more sexually active than their placebo-group peers. In this fashion, flibanserin is similar to sildenafil for ED, which was also a serendipitous discovery. This oral medication is commonly known as "the female Viagra" or "the pink pill," in contrast with sildenafil's (Viagra) blue. These superficialities are where the similarity ends: unlike sildenafil, flibanserin is a psychoactive medication that is intended for chronic use to counter patients' generalized, acquired HSDD by increasing their interest in and receptivity to sexual cues. This standardized 100-mg daily dosing appeals to patients for whom sexual spontaneity is important, because it ensures that the medication will be available to support their libido at all times. As of 2015, flibanserin is only FDA-approved for premenopausal women, but clinical research suggests equivalent efficacy postmenopause.[29]

The mechanism by which flibanserin alters sexual function is incompletely understood; it is a multifunctional serotonin receptor agonist/antagonist, whose complex action has a net result of decreasing serotonin activity within the brain while increasing noradrenergic and dopaminergic activity.[30] All of these neurotransmitters have been implicated in the maintenance of sexual interest within the central nervous system (CNS). Norepinephrine and dopamine stimulate attention, appetite, and reward in response to erotic cues, whereas serotonin (mostly) inhibits sexual interest and responsiveness.[31] The net result of flibanserin's biologic actions is to tilt CNS neurochemistry in a prosexual direction, as one of the many biopsychosocial influences that provide motivation for or against sexual activity according to the Sexual Tipping Point Model.[32]

The prosexual push that flibanserin provides is subtle: in the randomized controlled trials pursuant to its FDA approval,[33–35] the coprimary end points of numerical improvement in numbers of satisfying sexual events per month and in the desire domain for the Female Sexual Function Index (FSFI) measured only a fraction above the placebo response. Trial participants who received flibanserin reported only 0.5 to 1.0 more satisfying sexual events per month and 0.3 to 0.4 additional points in desire domain for the FSFI (on a 1.2- to 6-point scale) compared with placebo group participants.[36,37] Measurements of distress related to low sexual desire, a secondary study end point, were similarly slight, with distress decreased by 0.3 to 0.4 points (on the Revised Female Sexual Distress Scale, a 0- to 4-point scale) with flibanserin compared with placebo.[38] The relevance of these various end points is debatable: increased sexual interest does not necessarily correlate with a rise in sexual activity, and the FSFI, which is a 4-week retrospective inquiry into sexual symptoms, has inherent limitations and biases.[37,39]

Although the improvements in sexual desire and satisfaction, and decreases in distress associated with low sexual desire, associated with flibanserin were statistically significant and are clinically significant for some patients, the question of whether flibanserin's benefits outweigh its risks is controversial. Like many serotonergic medications, it can be sedating, and induce dizziness, hypotension, or syncope; bother from these adverse effects (AEs) is decreased by dosing at bedtime and avoiding combination with other CNS depressants, such as alcohol.[40] It is also important to avoid combination with medications that inhibit CYP3A4, because these interfere with metabolism of flibanserin to increase the risk of AEs. Hepatic disease is a similar contraindication to its use. Various placebo-controlled studies have been done to characterize the degree of AE risk, including assessments of next-day driving performance[41] and of orthostatic hypotension and syncope when flibanserin is combined with alcohol.[42] These risks are confirmed to be low. Nevertheless, these low risks must be weighed against the medication's potential benefit for each individual patient. A robust process of informed shared decision making regarding flibanserin treatment is essential and reinforced by the FDA's risk evaluation and mitigation strategy.[43]

Bremelanotide

The second medication to be FDA-approved for the treatment of HSDD is bremelanotide (Vyleesi), a melanocortin receptor agonist. This agent was incidentally found to increase sexual interest and arousal response in studies intended to determine its dermatologic utility as a sunless tanning agent.[44] Like flibanserin, it is only FDA-approved for the treatment of generalized, acquired HSDD in premenopausal women, but studies of its intranasal spray formulation (also called PT-141) also demonstrated erectogenic properties in male subjects, suggesting its potential utility for treatment of sexual problems in both sexes.[45] Ultimately, the bioavailability of intranasal bremelanotide, and consequent lability in blood pressure, were deemed too variable. The drug was FDA-approved in 2019 in the alternative form of a subcutaneous injection pen, for administration of a standard 1.75-mg dose as needed approximately 45 minutes before sexual activity. Taken this way, randomized controlled trial participants experienced small, statistically significant increases in sexual desire as measured by the FSFI, and decreased distress related to low sexual interest.[46]

Similar to flibanserin, whether the marginal improvement in sexual symptoms with bremelanotide is worth the risk of AEs from taking the medication is an open question that can ultimately only be answered by the patient herself. Some AEs are mitigated by thoughtful dosing: the risk of permanent hyperpigmentation of the skin and gums is substantially reduced by injecting no more than once daily and no more than eight times monthly. Injection is characteristically followed by a transient increase in blood pressure; bremelanotide is therefore contraindicated in patients with uncontrolled hypertension. High rates (up to 40%) of trial participants reported nausea; interestingly, only 8.1% of study participants chose to discontinue use because of nausea.[46] This is an important caution against making assumptions about what ratio of risk-benefit patients with sexual problems will find favorable based on grouped biostatistics, and reinforces the need for individualized and informed choice. The current status of bremelanotide in the form of intranasal PT-141 is a further caution: in the absence of FDA approval, it remains available for online purchase without a doctor's prescription, putting ill-advised customers at substantial risk of harm.

Hormonal Medications: a Blast From the Past

The pharmaceutical industry's most recent forays into treatment of FSD have had somewhat ambiguous results. PDE5i medications target the genitalia to boost arousal response without adequately addressing the cognitive or emotional aspects of sexual function. Flibanserin and bremelanotide target the CNS, to produce only slight improvements in sexual interest and responsiveness when compared with placebo. An alternative to these is off-label use of older, hormonal medications, which act simultaneously on mind and body. It is not surprising that pioneering sexologist William Masters began his clinical research career in the 1940s with a focus on the positive effects of estrogen-replacement therapy on hypogonadal women.[47] At the same time, androgens were also studied and used in women for treatment of various medical problems, including sexual dysfunction.[48] Both sex steroids act within the CNS to stimulate sexual appetite[31] and within the genitalia to maintain vulvovaginal tissue integrity.[49]

Testosterone therapy, in isolation and in combination with estrogen (and sometimes progesterone), has been shown in many randomized controlled trials to increase sexual desire and satisfaction in postmenopausal women with HSDD.[50] Clinical application of these data remains a persistent challenge because it remains

uncertain: (1) to what degree testosterone, and not the estrogen into which it may be aromatized, is the relevant actor[51]; (2) whether testosterone supplementation might safely and effectively address sexual problems in premenopausal women[52]; and (3) how to most reliably dose this medication in a regulatory and financial environment that discourages development of testosterone products for women.[53] The risk of AEs, including hirsutism, acne, vocal changes, and clitoromegaly, is necessarily increased when products intended to produce adult male levels of testosterone are prescribed for women.[54] The probability of these AEs is reduced with careful monitoring and dose titration to maintain free testosterone within the normal female range,[55,56] but the optimal testosterone regimen for women has yet to be determined.

ENERGY-BASED MANAGEMENT

Given the concern for systemic AEs and associated uncertainty regarding risk/benefit ratio of the various pharmacotherapies that are used to treat FSD, it is tempting to use more localized treatments. These include various mechanical devices, which apply energy in various forms (eg, light, sound, shockwaves, or electricity) to different tissues (eg, vaginal epithelium, cavernous bodies, or nerves). Enthusiasm for the potential of these devices to improve genital health, including sexual function, is high, to a degree that is currently disproportionate to the quality of the evidence supporting their use for these purposes.

Vaginal Lasers

Various laser technologies are commercially available for vaginal application (**Table 2**).

The IntimaLase by Fotona (Dallas, TX) and Petit Lady by Lutronic, Inc (Fremont, CA) are nonablative erbium-doped yttrium-aluminum-garnet (Er:YAG) lasers[57,58] that heat the tissue to which they are applied, increasing heat shock proteins and collagen production without surface injury.[59] The most popular and aggressively advertised energy-based therapies are tissue ablative fractional CO_2 lasers, including the MonaLisa Touch, developed by DEKA (Calenzano, Italy) and distributed in the United States by Cynosure, Inc (Westford, MA)[60]; the FemiLift, by Alma Lasers (Buffalo Grove, IL)[61]; and the FemTouch, by Lumenis (San Jose, CA).[62] These fractional lasers disperse their energy into microscopic penetration points, such that only a fraction of the treated area is directly affected.[63] Focal injury and resulting areas of thermal necrosis within vaginal epithelial tissue from the laser activate heat shock proteins and growth factors, stimulating tissue remodeling with neoangiogenesis and deposition of collagen and elastin.[64–66]

Proponents of vaginal lasers claim that these tissue changes treat various female genital complaints that are relevant to sexual function, including atrophic vaginitis, vaginal laxity, urinary incontinence, and dyspareunia, in postpartum and postmenopausal contexts.[60–63] Small, single-arm studies of women with genitourinary syndrome of menopause demonstrate compelling improvements in tissue quality and sexual function.[64–68] Evidence from randomized controlled trials, in which laser is compared with sham treatment[69] or vaginal estrogen therapies,[70–72] is more ambiguous: although laser treatment did compare favorably with vaginal hormone therapies in its improving effects on various FSFI subdomains, these subdomain improvements were not consistent across studies, and in one study, patients in the CO_2 laser arm experienced increased vaginal pain.[71] Although CO_2 laser seems to rival vaginal estrogen for treatment of tissue changes related to genitourinary syndrome of menopause/vulvovaginal atrophy, patient expectations should

Table 2
Laser devices

Device		Number of Treatments
MonaLisa Touch, Cynosure	Fractional CO_2	3 treatments at 6-wk intervals
FemiLift, Alma Lasers	Fractional CO_2	3 treatments at 4-6-wk intervals
FemTouch, Lumenis	Fractional CO_2	2–4 treatments at 4-wk intervals
IntimaLase, Fotona	2940-nm nonablative Er:YAG	2 treatments at 8-wk intervals
Petit Lady, Lutronic	2940-nm Er:YAG	3 treatments at 2-wk intervals

Abbreviation: Er:YAG, erbium-doped yttrium-aluminum-garnet.

be set appropriately and potential users advised that these treatments may not fully restore "normal" sexual function.

One part of the appeal of laser treatment is its relative ease: monthly treatments typically last between 10 and 20 minutes, and various probe shapes and sizes are available to accommodate differences in patient anatomy. Most patients do not find the procedure uncomfortable, reporting only a sensation of heat during their treatments, and positive results of three to five monthly treatments are durable up to 12 months afterward.[73] Patients who do not wish to rely on chronic use of medication or are concerned about the potential risks of hormonal therapies might reasonably choose to pay out of pocket for vaginal laser treatments as an alternative. Unfortunately, the purported benefits of vaginal laser therapy claimed in many direct-to-consumer marketing campaigns have scant evidence base, leading the FDA to issue a safety communication in 2018, warning that "the safety and efficacy of energy-based devices to perform vaginal 'rejuvenation'…has not been established."[74]

Since publication of this FDA communication, analyses of the MAUDE (Manufacturer and User Facility Device Experience) and Bloomberg Law databases have discovered only 30 potential AE claims, suggesting that vaginal CO_2 laser procedures are low risk.[75] Er:YAG lasers seem to be similarly safe.[76] The financial considerations germane to this out-of-pocket therapy remain a source of concern. Furthermore, safety in the setting of various potential comorbid conditions and health states, including vulvovaginal infection, pregnancy, postpartum, previous pelvic radiation or surgery with mesh, conditions that impair healing, anticoagulant use, thromboembolic disease, keloid formation, preexisting vaginal or cervical lesions, or POP-Q stage 3 to 4 prolapse,[60] is as yet undefined. The efficacy of vaginal laser treatment of FSD remains an open question in need of further exploration.

Radiofrequency

Radiofrequency (RF) technology has been well-studied for treatment of dermatologic problems, such as cellulitis, laxity, and other age-related changes. RF has also been investigated as a noninvasive tissue-bulking treatment of stress urinary incontinence.[77–79] RF devices use an electromagnetic current, which is transformed into thermal energy as it contacts subcutical tissues. This transformation limits associated epidermal tissue injury and reduces energy loss to scatter, diffraction, or absorption by tissue outside the desired treatment area.[80] Thus, RF heats tissue in a controlled and focused fashion to prompt remodeling through collagen deposition and neoangiogenesis while avoiding surface tissue injury, in a manner comparable with nonablative laser treatment.[81] Commercially available vaginal RF devices include the Viveve System from Viveve Medical (Sunnyvale, CA) and ThermiVa from ThermiAesthetics (Southlake, TX).[82,83]

The scientific data regarding the effect of vaginal RF on female sexual problems is limited. Small, pilot, single-armed studies have been published, touting the beneficial effects of RF on vaginal laxity (as perceived by the patient); tissue quality (as perceived by the examining health care provider); and associated sexual satisfaction, including improvements of arousal, lubrication, and orgasm.[84–86] The two randomized sham-controlled trials that have been published focus on vulvar appearance (as perceived by the patient and health care provider) and vaginal laxity (as perceived by the patient) as their primary outcomes, with sexual function based on FSFI score a secondary consideration. Both studies describe improvement of genital appearance and self-image in the RF groups; FSFI scores did not substantively differ between the intervention and control groups, but the studies were not powered for robust evaluation of sexual function. Optimal dosing of RF intervention is uncertain: in the VIVEVE I trial, only one course of treatment was administered[87]; in contrast, eight weekly treatments were administered in the Brazilian study using a Tecatherap-VIP device (made by VIP-Eletromedicina, San Martín, Argentina).[88]

Low-Intensity Extracorporeal Shockwave Therapy

Shockwaves are sonic pulsations that can carry energy and propagate through a medium. Focused shockwaves are characterized by a sequential rapid rise in pressure (<10 nanoseconds), high-pressure peak (100 MPa), and short lifecycle (10 microseconds); when they are focused on a particular tissue, their energy creates a high-pressure load that causes mechanical shear stress.[89] This stress on the tissue provokes a healing response,[90–93] so that low-intensity extracorporeal shockwave therapy (LiSWT) holds promise for treatment of various medical problems, including chronic wounds and musculoskeletal disorders.[94,95] Since 2010, LiSWT has been investigated and used for the treatment of male sexual problems, including ED, Peyronie disease, and chronic prostatitis/chronic pelvic pain syndrome.[96] Recent policy statements from the

European Society of Sexual Medicine and Sexual Medicine Society of North America discourage the use of LiSWT for ED outside the context of clinical research, because "its efficacy for the treatment of ED is doubtful and deserves more investigation."[96] There is even less evidence for the benefits of LiSWT for treatment of FSD and no published studies on this subject.

Despite this paucity of evidence, the manufacturers of various sonic-wave generating devices nonetheless advertise themselves for this indication. For example, FemiWave claims to provide increased genital sensitivity, better lubrication with arousal, and orgasmic function, without any evidence to support these or any other claims.[97] Note that the FemiWave device applies radial acoustic waves to tissue, rather than the focused shockwaves used in most of the studies examining the helpfulness of LiSWT for male ED.[98] Thus, any extrapolation from research in men to application in women is doubly tenuous.

Neuromodulation: Sacral and Percutaneous Tibial Nerve Stimulation

Neuromodulatory devices traditionally used to treat voiding dysfunction include sacral neurostimulators (SNS) and percutaneous tibial nerve stimulators (PTNS). SNS stimulates the S3 nerve root via an electrode placed through the S3 foramen, to influence the afferent and efferent spinal nerves to the bladder and bowel.[99] These devices include Medtronic's InterStim (Minneapolis, MN) and the Axonics System (Irvine, CA). Percutaneous (also called posterior or peripheral) tibial nerve stimulation is a form of acupuncture in which electrical stimulation is applied to the posterior tibial nerve at the medial ankle. The posterior tibial nerve originates from the L4-S3 nerve root, so that stimulation of the distal nerve can modulate the afferent and efferent nerves of the sacral plexus (S2-4).[100] SNS devices provide more consistent and effective neuromodulation than 12 sessions of 30 minutes of weekly PTNS, but are more invasive, with a higher risk of bleeding, infection, and surgical complications.

SNS and PTNS devices are principally used to treat symptoms of overactive bladder (OAB), and is helpful for underactive bladder and bowel dysfunction. Epidemiologic data describe comorbidity of sexual and voiding dysfunction, but it is unknown whether their relationship is incidental, causative, or because of a common underlying pathology.[101] It has been hypothesized that fear of coital incontinence and low genital self-image secondary to incontinence motivates comorbid FSD in some women and that improved sexual function is expected after successful treatment of voiding symptoms. Studies comparing sexual function before and after SNS and PTNS demonstrate small, statistically significant improvements across various subdomains of the FSFI, but without consistent subdomain improvements or global improvement of sexual function between studies.[102–106]

The specific effects of neuromodulation on sexual function are uncertain, because all research to assess the influence of SNS or PTNS on sexuality has been conducted in populations that suffer from voiding dysfunction. A study of tibial nerve stimulation in a rat model demonstrated a 500% increase in vaginal blood flow on Doppler ultrasonography following treatment, suggesting that neuromodulation might improve genital arousal response independently of its effects on voiding function.[107] An observational study of women with dry-OAB demonstrated small, statistically significant increases in FSFI score after PTNS treatment, which were independent of lower urinary tract symptom improvement.[108] Research into the sexual benefits of neuromodulation compared with pharmacotherapy for OAB and the correlation of urinary and sexual symptom improvements is ongoing in the STOMP (Sexual function Trial of Overactive bladder Medication vs PTNS) study. At this time, there are no clinical data to support the use of SNS or PTNS to treat patients with isolated FSD.

Neuromodulation: Vagal Nerve Stimulation

The vagus nerve is the tenth cranial nerve and a major component of the parasympathetic nervous system. The vagus nerve mediates a wide variety of bodily functions, including heart rate, digestion, and mood. Surgically implanted vagus nerve stimulators are FDA-approved to apply an electrical stimulus to the vagus nerve at the neck for treatment of medication-refractory epilepsy and depression.[109] Vagal nerve stimulation (VNS) is currently being studied for many other indications, such as pain syndromes, neuropsychiatric disorders, bowel disease, and endometriosis.[110–114] Vagal innervation of the cervix is thought to contribute to female sexual sensation and response, enabling women with a history of spinal cord injury at or higher than the T10 level to have erotic awareness and orgasm with vaginal and/or cervical stimulation.[115] The existence of this proposed genital afferent pathway that bypasses the spine via the vagus nerve is supported by neuroimaging.[116]

Modulation of the vagus nerve is unique among the energy-based interventions discussed in this

Table 3
Clinical care points: medications for HSDD

Medication	Flibanserin	Bremelanotide	Testosterone (1%)
Timing	Routine	As needed	Routine
Route	Oral	Subcutaneous injection	Topical
Dose	100 mg (1 tablet) qHS	1.75 mg (single-dose autoinjector) At least 45 min before sexual activity No more than 1 time/d No more than 8 times/mo	5–10 mg/d Titrate dose to goal serum free T (0.6–0.8 ng/dL)[1]
Side effects	Sedation, hypotension, dizziness, syncope, insomnia	Nausea, flushing, headache, hypertension	Acne, alopecia, hirsutism, vocal change, clitoromegaly
Contraindications	CYP4A4 inhibitors, hepatic impairment	Poorly controlled hypertension, naltrexone	Preexisting symptoms of virilization

Data from[1] Guay A, Munarriz R, Jacobson J, et al. Serum androgen levels in healthy premenopausal women with and without sexual dysfunction: Part A. Serum androgen levels in women aged 20-49 years with no complaints of sexual dysfunction. Int J Imp Res 2004;16:112-20.

article for the scope of its impact: whereas other applications of energy act only on the tissues to which they are applied (vaginal laser, RF, LiSWT, and SNS) or their proximate branches (PTNS), alteration of vagal activity can affect multiple organ systems, and mood and emotional valence. VNS thus has the potential to address FSD in all its biopsychosocial complexity, as described by polyvagal theory.[117] Although this potential is exciting in its promise, there is a great need for caution. The surgically implanted VNS device was approved despite a deficit of research demonstrating its safety, and patients with the implant are at risk of lethal cardiac AEs.[118] Just as PTNS is a less invasive alternative to SNS, auricular acupuncture to stimulate the vagus nerve[113] or meditation to promote parasympathetic tone[119] are safer alternatives that also merit further consideration and evaluation.

SUMMARY

The enthusiasm with which energy-based treatments for sexual dysfunction have been adopted for sale in the medical marketplace is disproportionate to the amount of data that are currently available to support their clinical use. Neuromodulation and focal induction of a healing response hold promise for the improvement of tissue quality, genital arousal response, and related FSD symptoms. Caution and further study are required to determine whether this promise will be fulfilled, and if indeed fulfillment will lead to relief of sexual problems. Given the limited scope of action for most of these devices, the widely ranging biopsychosocial factors that are implicated in the manifestation of FSD, and the characteristic discordance of female arousal, it is likely that their helpfulness will be specific to defined FSD symptomatology and/or specific populations of women with relevant comorbidities.

Pharmacotherapy for FSD (**Table 3**) has considerably more research evidence to justify its use and the potential to promote sexual desire, cognitive and genital arousal, and orgasmic response. The functional improvements that are produced by these medications are generally small, and their benefits may not outweigh the bother of taking medications and hazarding their potential AEs. There is sufficient demand for medical treatment of sexual dysfunction that studies continue in an effort to expand the demographic for whom the drugs are FDA-approved to include older women and possibly men. It is essential that patients in all of these groups be empowered to make an informed, autonomous determination as to whether the ratio of risk to reward favors the use of pharmacotherapy, energy-based therapy, or some other treatment intervention.

DISCLOSURE

The authors have nothing to disclose.

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