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Female Hypoactive Sexual Desire Disorder: A Practical Guide to Causes, Clinical Diagnosis, and Treatment

Sheryl A. Kingsberg, PhD,[1,2] and James A. Simon, MD[3]

Abstract

Hypoactive sexual desire disorder (HSDD) in women is defined as the persistent or recurrent absence of sexual thoughts or fantasies and/or lack of desire for sexual activity that is associated with marked personal distress and/or interpersonal difficulties, and cannot be better attributed to another primary disorder, medication, or general medical condition. Notably, HSDD shares some similarity with depression, as its etiology can be explained using a biopsychosocial model that includes biological, psychological, and sociocultural factors, as well as interpersonal influences. Due to its high prevalence and negative impact on the overall health and well-being of women, primary care health professionals and women's health practitioners need to be actively aware of HSDD, particularly because patients may be reluctant or unwilling to initiate a discussion about their sexual concerns during routine visits. HSDD is well established as a valid and treatable clinical entity. Even for those inexperienced in treating sexual problems, there are simple and validated screening tools such as the Decreased Sexual Desire Screener that can help identify HSDD and a need for further evaluation and treatment. There have been few established pharmacologic treatments for HSDD. Flibanserin was the first drug approved for the treatment of HSDD by the U.S. Food and Drug Administration (FDA). Bremelanotide, a novel melanocortin receptor agonist, was recently approved by the FDA for the treatment of acquired, generalized HSDD in premenopausal women. Increased awareness and recognition of HSDD as a medical condition should provide an incentive for further clinical development of effective treatments for HSDD.

Keywords: bremelanotide, female sexual dysfunction, flibanserin, hypoactive sexual desire disorder, testosterone

Introduction

Female sexual dysfunctions (FSDs) refer to problems of low sexual desire, diminished arousal, orgasmic difficulties, and pain with sexual activity. There is evidence that sexual concerns among women in the United States are highly prevalent. One study showed that over 40% of U.S. women reported some type of sexual problem, and 11.5% of these women considered these problems distressing.[1] Similar incidences of sexual problems and associated distress have also been reported in European populations.[2–5]

Hypoactive sexual desire disorder, or HSDD, is one of the most prevalent FSDs, and has been estimated to occur in ~7 million women in the United States.[2,6] HSDD has been defined by the International Society for the Study of Women's Sexual Health (ISSWSH) as a medical condition characterized by decreased or absent spontaneous or responsive sexual desire (*i.e.*, sexual thoughts or fantasies) associated with negative emotional states and personal distress.[7] FSDs, including HSDD, can have a profound effect on women's quality of life, overall health, and well-being.[8–10]

With almost 50% of women reporting some type of sexual concern, it is important that health care professionals (HCPs) most likely to encounter women with FSDs, namely, family practitioners, obstetricians/gynecologists, primary care physicians, physician assistants, and nurse practitioners, understand FSDs, including HSDD. FSDs may be infrequently addressed due to poor mastery of discussions involving

[1]Division of Behavioral Medicine, University Hospitals Cleveland Medical Center, MacDonald Women's Hospital, Cleveland, Ohio, USA.
[2]Departments of Reproductive Biology and Psychiatry, Case Western Reserve University School of Medicine, MacDonald Women's Hospital, Cleveland, Ohio, USA.
[3]*Intim*Medicine™ Specialists, George Washington University School of Medicine, Washington, District of Columbia, USA.

sexual health, inadequate medical training/education, evolving definitions of FSD, and limited knowledge of available diagnostic tools.[2,11] With ongoing research, expanded educational efforts, and public advocacy and awareness, there is increasing recognition that female (and male) sexual dysfunctions are best understood from a biopsychosocial perspective. Despite the biological component of HSDD, there have been few effective pharmacologic treatment options for this condition, although some are currently under development.

In this article, we focus specifically on HSDD, as low desire with associated distress is the most widely reported sexual complaint among women.[1,12] Until as recently as 2015, treatment for HSDD was limited to psychotherapy, homeopathic remedies, over-the-counter therapies, and off-label prescription medications; even now, there remains a significant unmet need for safe and effective pharmacologic treatments. There has, however, been some recent progress in the diagnosis and the treatment of this condition.[9,12] This review will highlight the causes, diagnosis, and treatment of HSDD.

Characterization of HSDD

HSDD is characterized by a lack or loss of motivation to participate in sexual activity and decreased spontaneous desire or responsiveness to erotic cues/stimulation that is accompanied by personal distress, and is not due to another medical condition or medication side effect.[13,14] The classification of HSDD can also be primary or secondary, acquired or lifelong, generalized or situational.[7] In 2000, the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV), revised the definition of HSDD to include a requirement for the condition to cause marked distress.[15–17] In view of the importance of distress as a component of HSDD, clinicians should also be cognizant of hearing words like ''bother'' or ''bothersome'' when taking a history or evaluating sexual issues in patients, as this may be an indicator of underlying distress that includes frustration, grief, guilt, incompetence, loss, sadness, sorrow, or worry.[14]

In 2013, controversy around FSD nomenclature was introduced with DSM-5, as HSDD and female sexual arousal disorder were absorbed into a single condition termed female sexual interest and arousal disorder (FSIAD). While there is overlap between the diagnostic criteria for HSDD and FSIAD, the reclassification has been the subject of considerable debate.[18–20] We strongly favor the clear and efficient classification of HSDD as a distinct diagnostic category. Notwithstanding any lingering debate over nomenclature and definitions, simple tools are available to HCPs that can facilitate the recognition, diagnosis, and subsequent treatment of HSDD in everyday practice.[7]

Prevalence and Impact of HSDD

In 2006, the Women's International Study of Health and Sexuality (WISHeS) reported a prevalence of low sexual desire in 24%–36% of U.S. women in a cross-sectional study that included premenopausal women, surgically postmenopausal women, and naturally postmenopausal women.[21] The prevalence of HSDD ranged from 9% to 26%, with a higher incidence of HSDD in surgically postmenopausal women in the 20- to 49-year-old age group (Table 1).[21–23] Notably, difficulties with arousal and orgasm, infrequent initiation of sexual activity, and lower relationship satisfaction accompanied by low sexual desire were observed in women with HSDD.[21] When compared with women with normal desire, women with HSDD scored significantly lower on seven of eight domains of the Short Form-36 health assessment, a measure of functional health and well-being from the patient's perspective.[21]

In 2008, the Prevalence of Female Sexual Problems Associated with Distress and Determinants of Treatment Seeking (PRESIDE) survey evaluated the prevalence of self-reported sexual problems among three key areas of sexual function (desire, arousal, and orgasm) in 31,581 U.S. adult women.[1] The age-adjusted prevalence estimates of any sexual problems and sexually related distress were 43.1% and 22.2%, respectively.[1] The corresponding incidence for any desire, arousal, or orgasm problem was 37.7%, 25.3%, and 21.1%, respectively, and these problems caused distress in 9.5%, 5.1%, and 4.6%, respectively.[1] Age-stratified prevalence of sexual problems that were associated with distress is shown in Table 2.[1] The highest prevalence of desire problems, 38.1%, was found in the 45- to 64-year-old age group.

A limitation of this study was that it did not determine whether low desire with personal distress was primary or secondary to other illnesses or pain; for example, ~27% of respondents reported current depression in PRESIDE, and depression was associated with distressing problems with desire (odds ratio = 2.34).[1] Distress is a crucial component of HSDD, and factors associated with sexual distress in women with low sexual desire were also investigated using a subset of women from the PRESIDE study.[24] Among women in PRESIDE who self-reported low desire ($n = 10,429$), approximately one-third (27.5%) has sexual distress; these

Table 1. Proportion of Women with Low Sexual Desire and Hypoactive Sexual Desire Disorder by Age and Menopausal Status (Women's International Study of Health and Sexuality)[21]

	Age 20–49 years			*Age 50–70 years*		
	Premenopausal (n = 414)	*Surgically postmenopausal (n = 89)*	p[a]	*Naturally postmenopausal (n = 252)*	*Surgically postmenopausal (n = 197)*	p[a]
Low sexual desire[b]	24%	36%	0.028	29%	33%	0.351
HSDD[c]	14%	26%	0.002	9%	14%	0.067

[a]Based on logistic regression model, adjusting for age (years).
[b]Defined as Profile of Female Sexual Function Index–desire domain score <40.
[c]Defined as Profile of Female Sexual Function Index–desire domain score <40 and Personal Distress Scale score <60.
HSDD, hypoactive sexual desire disorder.

Table 2. Prevalence of Sexual Problems Associated With Distress (PRESIDE)

Age-stratified prevalence (years)	*Desire 2,868/28,447*	*Arousal 1,556/28,461*	*Orgasm 1,315/27,854*	*Any 3,456/28,403*
18–44	8.9	3.3	3.4	10.8
45–64	12.3	7.5	5.7	14.8
65 or older	7.4	6.0	5.8	8.9

PRESIDE, Prevalence of Female Sexual Problems Associated with Distress and Determinants of Treatment Seeking.

patients had a mean age of 48.6 years, were more frequently postmenopausal (64%), and the presence of a current partner was most strongly associated with distress (80.7% vs. 44.4% without distress).[24] Collectively, these findings suggest that women's sexual problems, including HSDD, are common in both premenopausal and postmenopausal populations, and these problems are distressing in a sizable proportion of women, particularly those with a partner.

In addition to demonstrating the considerable population of patients with HSDD and low sexual desire, results from WISHeS and PRESIDE show this condition has consequences beyond the bedroom. Indeed, poorer health status and health-related quality of life (HRQoL) were reported for women with HSDD compared with those without HSDD in a nationally representative sample of naturally or surgically postmenopausal women in the United States ($n = 1,189$).[10] Women with HSDD reported a greater overall health burden and were nearly twice as likely to report comorbidities such as depression, fatigue, back pain, and memory problems, and decrements in HRQoL in women with HSDD were comparable to national norms of adults with other chronic conditions such as diabetes and osteoarthritis.[10]

While the results from these studies show an association between HSDD and poorer HRQoL, whether HSDD itself is causative of the decrement in HRQoL is uncertain. Regardless, the association between HSDD and poorer HRQoL indicates that FSDs such as HSDD should no longer be viewed as inconsequential to women, and a failure to recognize and treat HSDD should not be considered benign. Our recent findings regarding the burden of illness for HSDD among both pre-and postmenopausal women include a more profound effect of HSDD on mental health and psychosocial parameters in premenopausal versus postmenopausal women, and that the burden of HSDD was driven largely by interference with the relationship/partner and an adverse effect of HSDD on mental/emotional well-being.[25]

Etiology of HSDD

Although women's sexual problems, including issues with low desire, had been viewed dismissively as solely psychological, we now know that sexual function in women (and men) encompasses not only psychological and behavioral factors (*e.g.*, relationship quality, life stressors, and cultural beliefs), but is also dependent on a range of hormones and neurotransmitters that underlie the biology of sexual response.[26–28] The neurobiology of HSDD and the key signaling molecules involved in the sexual response have been previously reviewed; these are summarized in Figure 1.[2,29–32]

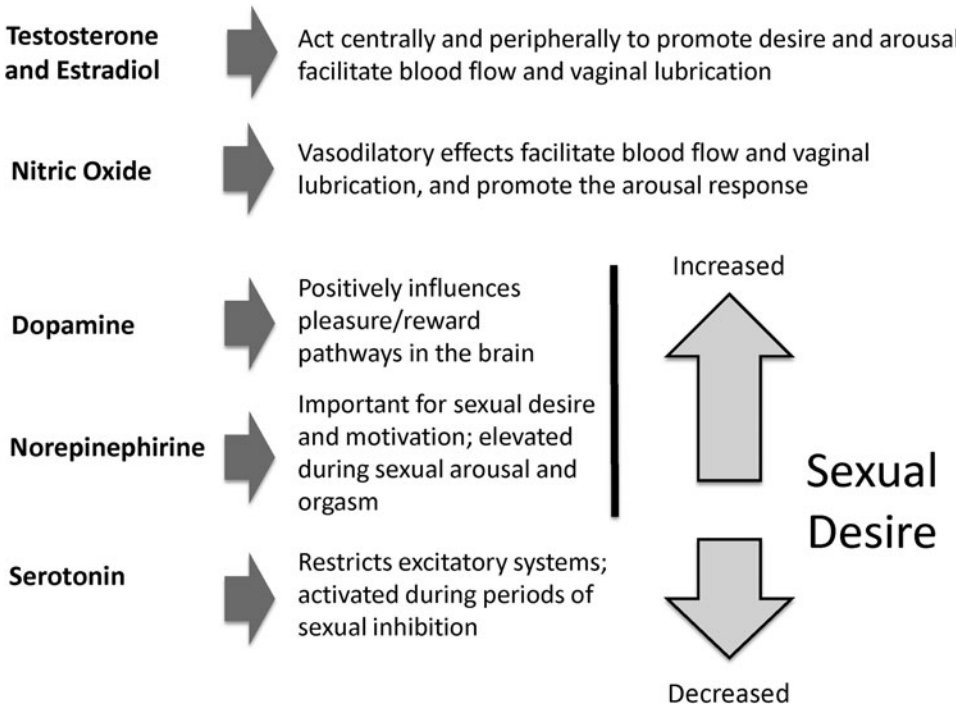

FIG. 1. Hormones, neurotransmitters, and HSDD: what you need to know. HSDD, hypoactive sexual desire disorder.[2,12,27]

Normal sexual response is believed to be dependent upon a balance of excitatory and inhibitory signals in the brain.[2] Excitatory neurotransmitters include dopamine, which is vital to central behavioral reward signaling, and norepinephrine, which acts centrally to promote sexual arousal and peripherally to regulate autonomic components of sexual function and excitement. Also important in the excitatory response are the melanocortin receptors, MC3R and MC4R, as agonists of these receptors appear to stimulate sexual desire and arousal. Neurotransmitters such as serotonin (5-hydroxytryptamine, or 5-HT), on the other hand, as well as molecules stimulating the endocannabinoid and opioid systems, have an inhibitory effect on sexual behavior.[2] Sex hormones, including testosterone and estradiol, are also essential proexcitatory components of sexual response, as are mediators of vasodilation, such as nitric oxide. Although the exact role of each of these neurobiological components in the context of HSDD is not fully understood, the etiology of HSDD is thought to involve an imbalance between the excitatory and inhibitory aspects of the sexual response, whereby a hypoactive excitatory response, a hyperactive inhibitory response, or a combination of the two, gives rise to the symptoms of HSDD.[2,29,30,32–34] Accordingly, hormones (*e.g.*, exogenous testosterone) and a range of pharmacologic agents that can modulate the neurotransmitters involved in the sexual response have been investigated as treatments for HSDD in women.

Although much of the early work determining the physiology of female sexual response has been demonstrated in rodent models, evidence for the neurobiological component of HSDD also comes from positron emission tomography imaging studies in women viewing an erotic video, which have suggested changes in neural activity when women with or without HSDD were compared: those with HSDD appeared to have weaker activation in the right hemisphere of the cerebral cortex, possibly resulting in muted responses to sexual cues, versus those without HSDD.[35] Women with HSDD also had less deactivation in the left hemisphere, that is, an apparent inability to deactivate higher-order processing, suggesting a perpetuation of sexual inhibitory pathways. Similarly, differences in brain activation, including cognitive arousal to erotic stimuli were found in women with HSDD versus those with no history of sexual dysfunction, using functional magnetic resonance imaging. These differences suggested that women with HSDD may pay greater attention to assessing and/or monitoring their responses to erotic cues, which could be disruptive to the normal sexual response.[36]

Screening for HSDD

Despite the impact of HSDD, it remains underreported and undertreated. Patients with sexual problems are often reluctant to seek help from or initiate discussions with HCPs on sexual issues; reasons include a fear of embarrassing their HCPs and the belief that their HCPs should initiate discussions on the topic.[13] Many women also believe symptoms of HSDD are simply a part of aging; over one-third of participants in a recent study cited this as a primary reason for not seeking treatment.[25] Thus, screening for HSDD can be challenging for some primary care HCPs.

Annual physical exams represent a good opportunity to explore possible sexual issues with the patient.[13] It is important to recognize that barriers to communication exist for both HCPs and patients (Table 3)[13]; for example, the patient may be inherently modest or reluctant to discuss sexual issues due to cultural beliefs and norms.[37] Parish and Hahn have suggested that HCPs use a ''ubiquity statement'' followed by an open-ended question to draw further discussion from the patient, and to show that they are not embarrassed, are open to discussing sexual issues, and recognize their importance (Table 3).[13] As noted earlier, HCPs should be mindful of patients using words like ''bother'' with a specific issue, as this is often the language used to indicate concomitant distress.

The Decreased Sexual Desire Screener (DSDS), a five-item self-reported questionnaire for detecting and diagnosing generalized, acquired HSDD, is validated for use in general practice, and is specifically designed for HCPs who do not specialize in FSD (Fig. 2).[7,13,38] Through a series of short questions, the DSDS may be useful as an initial screener for HSDD and is helpful for a quick assessment relative to taking a personal medical history. Questions 1 through 4 (Q1–Q4) detect the presence of HSDD, whereas Q5 is used to evaluate the self-assessed associated factors to determine their relative contribution.

It is imperative for the examining HCP to recognize underlying conditions that may contribute to the problem of reduced desire such as major relationship or physical issues. Therefore, obtaining as complete a gynecologic history as possible, including any sexually transmitted diseases, history of sexual abuse, urinary or bowel complaints, and/or prior

Table 3. Discussing Sexual Issues with Patients[13]

Potential HCP barriers	*Potential patient barriers*
Embarrassment	Embarrassment
Lack of confidence in treating HSDD	Social/cultural attitudes toward sex
Time constraints	Reluctance to discuss sexual issues with HCP
Beliefs that there are no effective treatments	Belief that HCP may be embarrassed or reluctant to discuss
Inadequate medical/residency training on obtaining a sexual history	Belief that HCP will not treat as a serious issue

Starting the HSDD discussion: ask the right question

Use a ''ubiquity statement,'' followed by an open-ended question, to show that you are not embarrassed and willing to talk about sexual issues, and recognize their importance for the patient:
''A lot of women with [characteristics of the patient] have concerns about sexual function…How about you?''

HCP, health care professional.

Table 4. Overview of Off-Label and Combination Hypoactive Sexual Desire Disorder Treatments[2,30]

Agent	*Mechanism(s)*	*Key findings*
Buspirone[45]	Partial agonism of the 5-HT1A autoreceptor; reduction of serotonergic tone	Study of 119 depressed patients; improvement in sexual function observed in 58% of patients on buspirone vs. 30% on placebo[46]
Bupropion[47]	Inhibition of dopamine and norepinephrine reuptake; antagonism at nicotinic acetylcholine receptors	In a study of nondepressed females with HSDD, 29% responded to treatment with bupropion SR; drug was well tolerated[48,49]
		Randomized, double-blind, placebo-controlled study; showed bupropion SR was effective and well tolerated in ovulating women with HSDD[50]
Testosterone	Topical exogenous systemic testosterone gel	For postmenopausal women with HSDD, off-label prescription of an approved male formulation of testosterone at ~1/10th the male dose may be done in the absence of an approved female formulation. Compounded products are not recommended as they lack evidence for efficacy and safety for the treatment of HSDD[51]
Testosterone combinations[52] Lybrido Lybridos	Testosterone+sildenafil (phosphodiesterase -5 inhibitor) Testosterone+buspirone	Study of premenopausal or postmenopausal women with HSDD or FSAD; significant increases in subjective indices of sexual function (sexual desire, arousal) for testosterone/sildenafil vs. placebo[53]
		Study of premenopausal or postmenopausal women with HSDD or FSAD; significant increases in subjective indices of sexual function (sexual desire, arousal) for testosterone+buspirone vs. placebo[54]
Bupropion/trazodone (Lorexys®)	Norepinephrine and dopamine reuptake inhibitor; blockade of serotonin 5-HT2A receptors and serotonin transporter	Phase 2a clinical study completed in premenopausal women with HSDD; significantly more treatment responders on with bupropion/trazodone vs. bupropion alone[55]

FSAD, female sexual arousal disorder; SSE, satisfying sexual event; SR, sustained release.

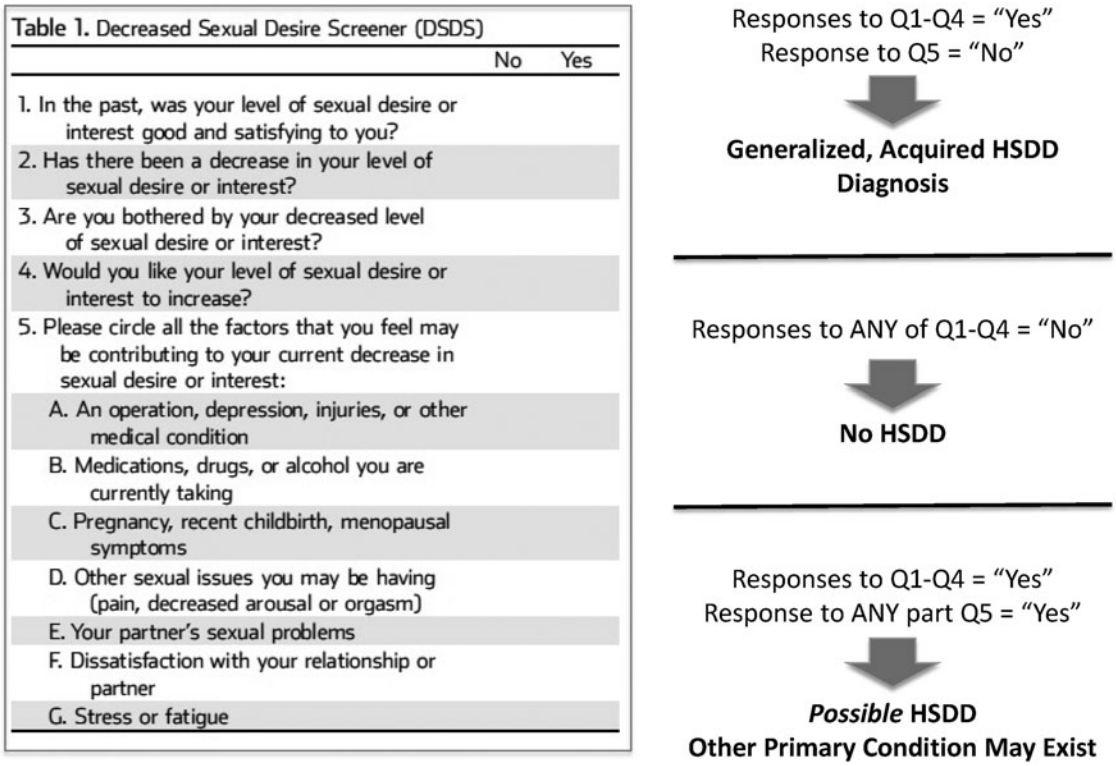

FIG. 2. The DSDS: a simple and effective tool to identify HSDD.[7,13,38] Table (on left) from Clayton et al.[38] © 2009 International Society for Sexual Medicine, with permission from Elsevier. DSDS, Decreased Sexual Desire Screener.

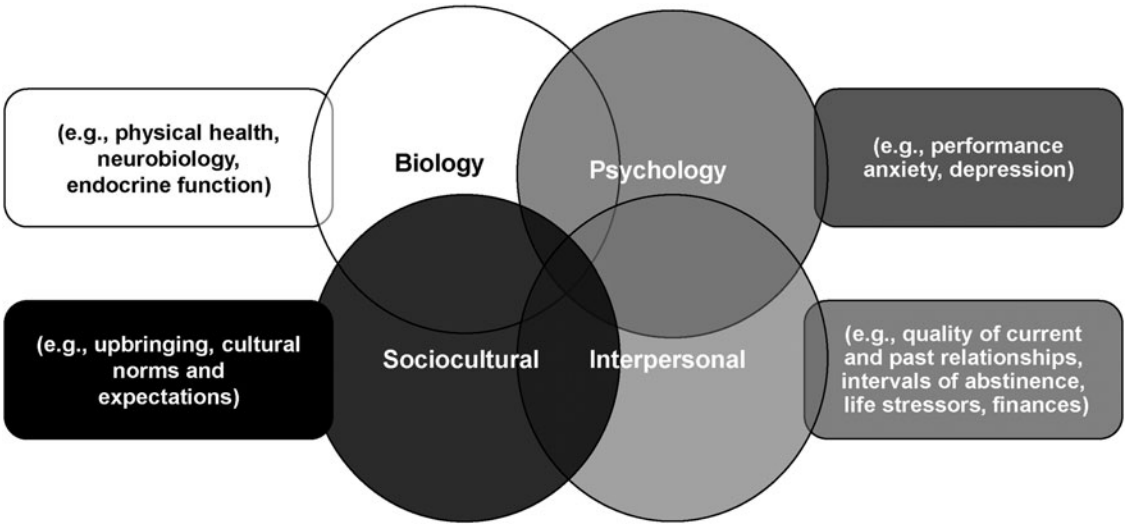

FIG. 3. The biopsychosocial model for female sexual response.[40,41]

surgery, is essential when assessing a patient for HSDD, and concomitant psychological conditions. For example, depression may contribute to sexual issues and should be noted.[8] For HCPs who typically conduct physical exams, a pelvic exam is highly recommended for HSDD evaluation as occult organic or physical factors or unknown comorbidities may be revealed.[13,39] Laboratory testing may also help to determine potential modifiable factors and include measurements of testosterone, estradiol, progesterone, luteinizing hormone, follicle-stimulating hormone, prolactin, and thyroid-stimulating hormone to evaluate potential comorbid conditions. Referral to a specialist for further testing and treatment should be considered if contributing comorbid disorders are complex, or if lifelong sexual disorders, anatomical deformity, physical or psychological trauma, or treatment failure are present or have occurred.[39]

Treating HSDD

As mentioned, an imbalance between excitatory and inhibitory neurotransmitter pathways is thought to play a significant role in HSDD etiology. A woman's desire for sex, however, may also be influenced by other factors such as sexual intimacy, past sexual experiences, quality of the relationship, and degree of personal satisfaction.[2] As such, the female sexual response has been described using a biopsychosocial model that integrates all of these components (Fig. 3), which can serve as a basis for understanding HSDD and its treatment.[28,40,41] In the context of this model, some of the key contributing parameters that the practicing HCP might consider when evaluating HSDD include issues such as performance anxiety and depression, poor mental or physical health, quality of the overall relationship, and life stressors such as financial problems or children, all of which can feed into the sexual response. Focusing on medical interventions alone for a specific sexual dysfunction, including HSDD, may fail to adequately address these underlying issues.[41] Instead, we suggest that HCPs integrate psychological and interpersonal approaches as well as pharmacologic therapy to optimally treat their patients with HSDD.

Therapeutic approaches for HSDD may thus include a multimodal approach, such as office-based counseling, individual and/or couple's psychotherapy, and hormonal and psychopharmacological treatments.[9,37,42] Some of the nonpharmacological options for HSDD include traditional sex therapy and cognitive behavioral therapy (CBT).[8,9] In traditional sex therapy, problems with desire, arousal, orgasm, and pain are addressed using specific techniques. In general, sex therapy is a short-term treatment lasting $\sim$3 months and conducted in individual, couple, or group settings. It usually comprises psychoeducation, couples' exercises, including sensate focus, and counseling. A classic example of sex therapy, sensate focus therapy (nongenital touching followed eventually by genital touching and stimulation), is integrated into this approach. Sensate focus exercises and counseling are often moderately effective at improving sexual desire, especially when patients perform the recommended exercises.[9,43] This therapeutic program can help to increase intimacy and communication between partners and reduce sexual anxiety.[8,9]

Other potential therapies include mindfulness-based cognitive behavioral sex therapy, which includes psychoeducation about sexual response and cognitive therapy combined with mindfulness training in a group format.[9] Another technique to consider is self-help education; potential advantages include its wide availability, low cost, and absence of side effects. Materials related to self-help education would be of particular use for patients lacking resources for therapy or medications, including those without insurance, or whose insurance does not cover low sexual desire treatment.[9]

The range of therapies for HSDD has improved in recent years; we may now consider pharmacologic treatment options for HSDD patients in addition to CBT. Off-label use of agents approved for use in other conditions, such as depression and anxiety, have the potential for use in the treatment of HSDD, as they may favorably impact neurotransmitters involved in the sexual response (Fig. 1).[2,12,29] These agents include bupropion, a norepinephrine and dopamine reuptake inhibitor, and buspirone, which binds serotonin and dopamine receptors, as well as combination therapies with these agents (Table 4).[2,32,44–55] As some of these treatments have shown efficacy in clinical studies, which have included women with HSDD, the International Consultation on Sexual Medicine (ICSM) has assigned a level of evidence of 2 to

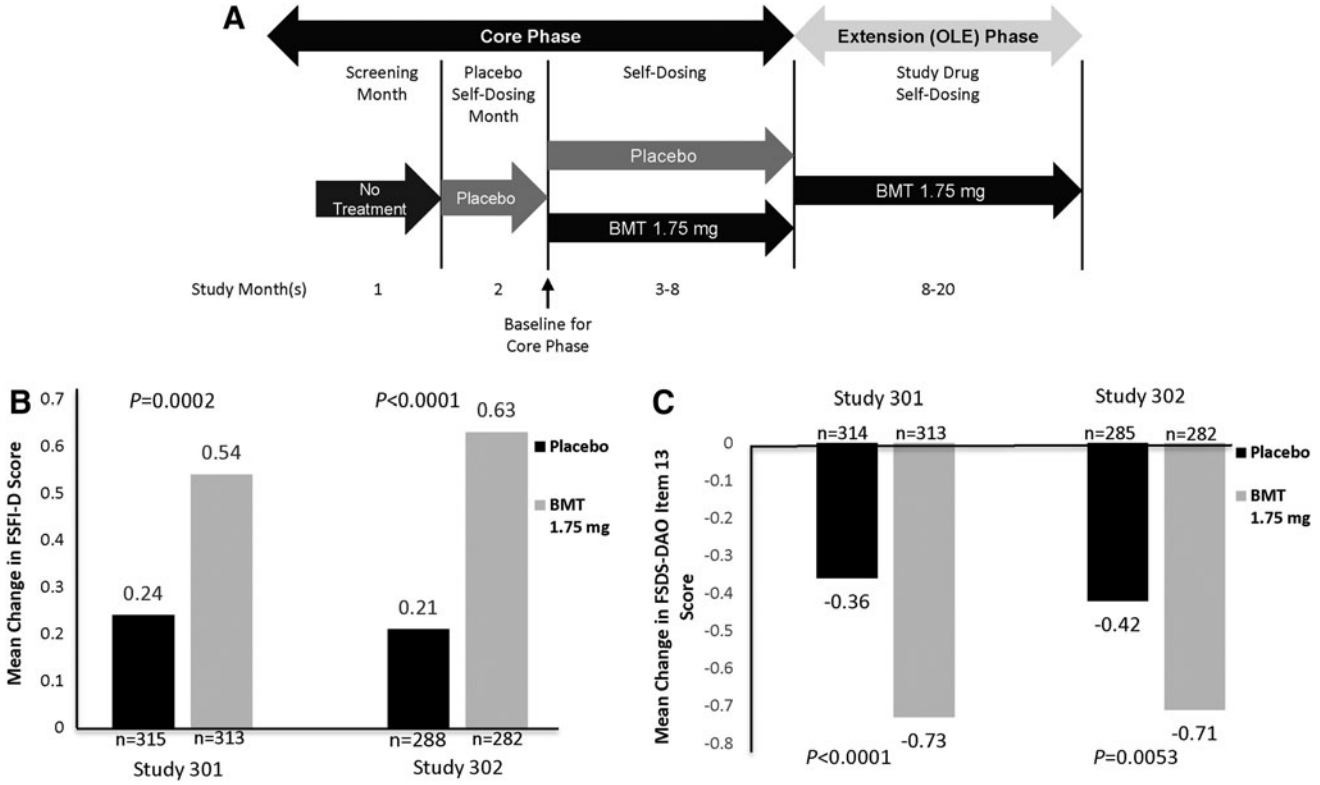

FIG. 4. RECONNECT trials: study design and results for coprimary endpoints: **(A)** study design.[76–78] **(B)** Change from baseline to EOS in the Female Sexual Function Index–desire domain score.[77] **(C)** Change from baseline to EOS in the score for feeling bothered by low sexual desire.[77] BMT, bremelanotide; EOS, end-of-study.

these interventions.[9] In the remaining sections we detail treatments for HSDD that have been ascribed a level of evidence of 1 by the ICSM.

Testosterone

Testosterone is known to positively impact sexual desire and has been prescribed as an off-label treatment primarily in postmenopausal women with low sexual desire.[56] Efficacy and safety of transdermal testosterone at a dose of 300 μg/day has been studied in surgically postmenopausal women.[57,58] Generally, testosterone therapy significantly improved sexual activity and desire, while decreasing personal distress although with mostly mild androgenic adverse events (AEs).[57,58] A 2015 report based on eight studies ($n = 2{,}820$) indicated that there was moderate evidence for testosterone improving satisfying sexual activity over 4 weeks relative to placebo.[59] Long-term AEs occurring across the INTIMATE SM1 and SM2 trials, which evaluated the efficacy and safety of the transdermal testosterone patch (TTP) for up to 6 months in surgically postmenopausal women with HSDD on estrogen therapy, have been previously reviewed. Overall, there were no long-term significant safety signals with TTP use over 4 years of treatment; application site reactions and androgenic effects such as acne, alopecia, and unwanted hair growth were the most prevalent AEs.[57,58,60,61]

A recent systematic review and meta-analysis of randomized controlled trial data on testosterone in women confirmed its efficacy in postmenopausal women with HSDD. Non-oral preparations (*e.g.*, transdermal) are preferred to reduce liver effects.[62] A recent consensus recommendation published by a multidisciplinary task force of clinicians from leading societies that reviewed the safety and efficacy of testosterone in women concluded that data support the use of physiologic testosterone for postmenopausal women with HSDD.[63] This group recommended only physiologic dosing, based on the efficacy and safety results of meta-analyses.[62–64] Owing to concerns over long-term safety, testosterone patch therapy currently lacks U.S. Food and Drug Administration (FDA) approval for HSDD. Although the treatment had been approved in Europe for postmenopausal women, it was withdrawn in 2012.[63,65]

FDA-Approved Therapies

Flibanserin

Flibanserin is a centrally acting, nonhormonal oral medication that affects levels of several key neurotransmitters involved in the biology of desire, including serotonin, dopamine, and norepinephrine.[12,66,67] The drug acts as a 5HT1A agonist and a 5HT2A antagonist, and may also increase levels of dopamine and norepinephrine; thus, it has been postulated that flibanserin serves to ''normalize'' neurotransmitters involved in sexual function resulting in enhanced sexual desire.[68]

In 2015, the FDA approved flibanserin for the treatment of HSDD in premenopausal women based on results from three clinical studies (VIOLET, DAISY, and BEGONIA) that evaluated its safety and efficacy in premenopausal women.[67,69,70] The three clinical trials demonstrated that treatment with flibanserin 100 mg once daily at bedtime (qhs) led to statistically significant improvements in satisfying sexual events (SSEs). Measures of sexual desire and overall sexual function (Female

Sexual Function Index–desire domain [FSFI-D]), and sexual distress (as measured by Female Sexual Distress Scale–Revised [FSDS-R] Item 13) also showed improvement in these studies, although coprimary endpoints were not met in two of the three trials. In the SNOWDROP trial, the efficacy and safety of flibanserin was evaluated in naturally postmenopausal women with HSDD. In this trial, flibanserin was associated with significant improvements in the number of SSEs and sexual desire, as well as reduced sexual distress, compared with placebo.[71] Dizziness, somnolence, nausea, and headache were the most commonly reported AEs.[71] Flibanserin 100 mg qhs was also associated with weight loss in both premenopausal and postmenopausal women with HSDD.[72]

The safety of flibanserin in premenopausal and postmenopausal women with HSDD was assessed in an open-label extension study that was discontinued early by the study sponsor.[73] Dizziness, somnolence, insomnia, and nausea were the most common AEs reported in at least 5% of patients; flibanserin-related serious AEs and suicidal ideation did not occur in the study.[73] Notably, approximately one-third of patients in this study reported alcohol use at baseline, which is contraindicated with flibanserin due to an increased risk for severe hypotension, syncope, sedation, and somnolence. During the study, AEs, including somnolence, moderate syncope, and sedation, were reported (8.6%, 0.2%, and 0.6%, respectively); in most cases, these events were associated with flibanserin.[73] Acute alcohol intoxication that resulted in death also occurred in one patient in the SNOWDROP trial.[72]

Currently, flibanserin is administered in the context of a Risk Evaluation and Mitigation Strategy program, and it has been recommended that flibanserin be administered at bedtime to limit the risk for hypotension/syncope, accidental injury, and central nervous system (CNS) depression.[66] In the original prescribing information, a boxed warning stated that concomitant alcohol use may contribute to significant CNS depression and hypotension/syncope, and should be avoided. However, postmarketing data indicate that risk of such events is low if at least 2 hours elapse between consumption of alcohol and taking flibanserin. Therefore, the prescribing information has been revised to state that patients should wait at least 2 hours after consuming one or two standard alcoholic drinks before taking flibanserin at bedtime, and to skip their dose if they have consumed three or more standard alcoholic drinks that evening. Additionally, women should not consume alcohol until the following day after taking flibanserin at bedtime.[74]

Bremelanotide

Bremelanotide, a melanocortin receptor agonist, was approved by the FDA in June 2019 for the treatment of acquired, generalized HSDD in premenopausal women.[75] The safety and efficacy of bremelanotide 1.75 mg administered through autoinjector as needed before sexual activity were evaluated in two identically designed, phase 3, multicenter, double-blind, placebo-controlled trials Fig. 4; ($n = 1{,}247$).[76] The two coprimary endpoints were change from baseline to end of study (EOS) in the FSFI-desire domain (Q1+Q2; range 1.2–6.0) and in distress related to low desire using Item 13 (Q13) of the FSDS-desire/arousal/orgasm (range 1.0–4.0). Both studies met the coprimary endpoints,[76] with bremelanotide treatment (vs. placebo) showing statistically significant improvements in desire (0.54 vs. 0.24; $p = 0.0002$ and 0.63 vs. 0.21; $p < 0.0001$) and distress (–0.7 vs. –0.4; $p < 0.0001$ and –0.7 vs. –0.4; $p = 0.0053$).

While the change from baseline to EOS in the number of SSEs, a key secondary endpoint, was not significantly different between the treatment groups, in a *post hoc* analysis, the percentage of SSEs (*i.e.*, the number of SSEs per total number of sexual encounters) increased between two and threefold with bremelanotide relative to placebo (23.6% vs. 8.4%, $p < 0.0001$ and 26.6% vs. 11.3%; $p < 0.0001$ for Studies 301 and 302, respectively).[77]

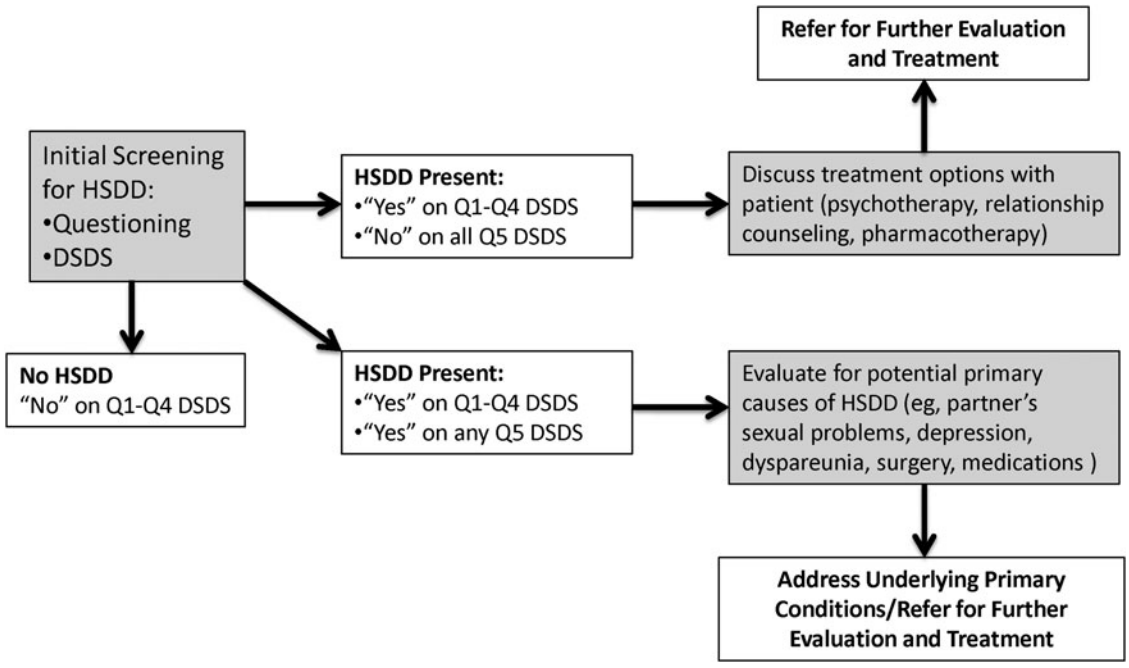

FIG. 5. What's next? Directing a patient toward HSDD treatments.

Importantly, the treatment benefits of bremelanotide (*i.e.*, improved desire and reductions in related distress) were observed early (1 month after the initiation of treatment), and were maintained throughout the 24-week double-blind treatment period. The primary results were also supported by an anchored responder analysis with prespecified definitions to support clinical meaningfulness, including the General Assessment Questionnaire question 3, which asked ''Compared with the start of the study (*i.e.*, prior to taking study drug), to what degree do you think you benefited from taking the study drug?'' This analysis for the coprimary endpoints showed clinically meaningful and statistically significant differences ($p < 0.0001$) between treatment groups (58.3% and 58.2% responder rates for the bremelanotide groups and 36.1% and 35.4% for the placebo treatment groups for Study 301 and Study 302, respectively).[76]

Among subjects who completed the 24-week double-blind study phase, ~80% continued in the 52-week open-label extension phase of RECONNECT and demonstrated sustained efficacy for up to 76 weeks.[76,78] In the double-blind portion of both trials, common AEs included nausea (40.0% vs. 1.3%), flushing (20.3% vs. 0.3%), injection site reactions (5.4% vs. 0.5%), and headache (11.3% vs. 1.9%) in patients who received bremelanotide versus placebo, respectively.[76] The majority of treatment-emergent AEs in both studies were transient and mild or moderate in severity.[76,78]

ISSWSH process of care

In 2018, ISSWSH published a Process of Care document for the management of HSDD, which included an algorithm developed to provide evidence-based guidelines for diagnosis and treatment of HSDD in women by HCPs. The algorithm details the physical, medical, and medication factors, patient relationships, and life situations, as well as sexual behaviors and history to be discussed with the patient. This will enable potential modification of existing factors and treatment. The latter should be based on decisions made between patients and their HCPs that are mutually acceptable. The ultimate goal of all treatment programs is improved function accomplished by means of a working partnership between patients and their HCPs.[7]

Treatment affordability

Despite the availability of treatments for HSDD, there are concerns regarding treatment affordability. Insurance companies may choose to not reimburse for treatment of HSDD, reasoning that sexual dysfunction treatment is a lifestyle issue and not medically necessary. As mentioned previously, self-help treatment may be of use at this juncture. However, as these treatments become more prevalent, like treatment for erectile dysfunction, some insurers may choose to reimburse for the treatment of HSDD.

Conclusions

HSDD continues to be an underrecognized and undertreated condition. However, the situation is improving with increased awareness of its impact on patients' health, well-being, and quality of life, as well as with the emergence of effective treatments. While its etiology is not entirely clear, we now have a fundamental understanding of the biological component of HSDD and the availability of effective pharmacologic treatments (*e.g.*, flibanserin and bremelanotide). In the past, HCPs and patients may have been reluctant to discuss sexual issues, but as HSDD has become established as a detectable, diagnosable, and treatable entity, this hesitancy should be overcome. HCPs should increase awareness of this condition and its impact, identify women who may be experiencing HSDD through simple tools, such as the DSDS, and move toward referrals or treatments that address the biological, psychological, and social aspects of the condition (Fig. 5). It is crucial to understand that the causes of HSDD are multifactorial; management should be viewed from an integrative perspective,[35] with an emphasis on issues that are most bothersome to the patient. It should be recognized that simple screening tools as well as effective treatments for HSDD are currently available, and there is no longer a reason for HSDD to be ignored.

Author Contributions

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Address correspondence to:
Sheryl A. Kingsberg, PhD
Division of Behavioral Medicine
University Hospitals Cleveland Medical Center
MacDonald Women's Hospital
Cleveland, OH 44106
USA

E-mail: sheryl.kingsberg@uhhospitals.org