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Counseling Your Patients About Hypoactive Sexual Desire Disorder and Advances in its Diagnosis and Treatment

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Counseling Your Patients About Hypoactive Sexual Desire Disorder and Advances in its Diagnosis and Treatment

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Kahlil Demonbreun, DNP, RNC-OB, WHNP-BC, ANP-BC, FAANP receives consulting fees from Hologic and Symbiomix Therapeutics.
Carole Drexel, PhD, CHCP has nothing to disclose.
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Ashley Rosenthal has nothing to disclose.
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LEARNING OBJECTIVES

After participating in this educational activity, participants should be better able to:

- Identify the symptoms of hypoactive sexual desire disorder (HSDD)
- Cite barriers in their clinical practice that inhibit the appropriate diagnosis and management of HSDD
- Identify the screening tools that allow for accurate diagnosis of HSDD
- Explain causal factors for HSDD and common comorbid conditions
- Identify the therapeutic modalities available to manage HSDD including their benefits and potential side effects

TARGET AUDIENCE:

This activity is designed to meet the educational needs of the obstetrician and gynecologist, family physician, internal medicine physician, physician assistant, nurse practitioner, and certified nurse midwife.

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Introduction

For women, sexual health involves both body and mind. Conditions that compromise a woman's sexual health interfere with intimacy and ultimately impact all areas of her well-being. Female sexual dysfunction (FSD) is defined as disorders of sexual desire, arousal, orgasm, and sexual pain. Symptoms can have a physical, psychological, relational, or sociocultural basis, but there is no doubt that such symptoms contribute to personal distress. Increased awareness and training of women's health care professionals will improve identification of FSD and facilitate multidisciplinary care to improve the patient's quality-of-life.

Hypoactive sexual desire disorder (HSDD) is the most common of the female sexual dysfunctions. HSDD occurs in women of all ages but is continuously underdiagnosed and undermanaged. The major factor for this is a lack of physician-patient communications regarding female sexual health and functioning. This communications dysfunction is equally shared by these two groups – patients are reluctant to discuss sexual difficulties with their health providers, and clinicians are reluctant to inquire about sexual health. Clinicians are reluctant to raise issues of sexual behavior in their female patients owing to concerns of it being too time-consuming, and that they do not have the necessary knowledge and ability to diagnose and treat HSDD.

The articles in this CME journal supplement comprehensively address the areas of concern that inhibit women's healthcare clinicians in effectively addressing HSDD—namely patient communications, diagnostic strategies, and therapeutic modalities for treating HSDD. The information presented will allow these healthcare providers to implement strategies that will improve the sexual health of their patients presenting with HSDD, with the intent of improving these patients' overall sense of well-being.

Hypoactive Sexual Desire Disorder (HSDD): Communication and Counseling

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Introduction

Specialists in obstetrics and gynecology are ideally situated to raise, discuss, and manage sexuality problem reports with their patients. Yet, there is consistent evidence demonstrating an absence of (effective) communication between patients and their providers regarding sexuality issues. In addition to structural barriers of limited time or needing to prioritize illness over "quality of life"' issues, providers often cite lack of comfort, lack of knowledge or training, and/or lack of available treatments as the predominant barriers to raising sexuality discussions. Providers also assume patients will raise concerns that are particularly bothersome to them. At the same time, patients hope their providers will inquire about their sexuality and sexual functioning (or lack thereof) and fear they might embarrass their providers with their questions or symptom reports. Patients might not be aware that what they are experiencing is problematic and not part of normal/healthy sexual functioning, or they may lack knowledge that there are treatments for their sexual symptoms. Female sexual dysfunctions (FSDs) encompass problems related to sexual arousal, desire, orgasm, and sexual pain.[1] Taken all together, FSDs are not routinely being addressed, not adequately getting diagnosed, and therefore not appropriately being managed.

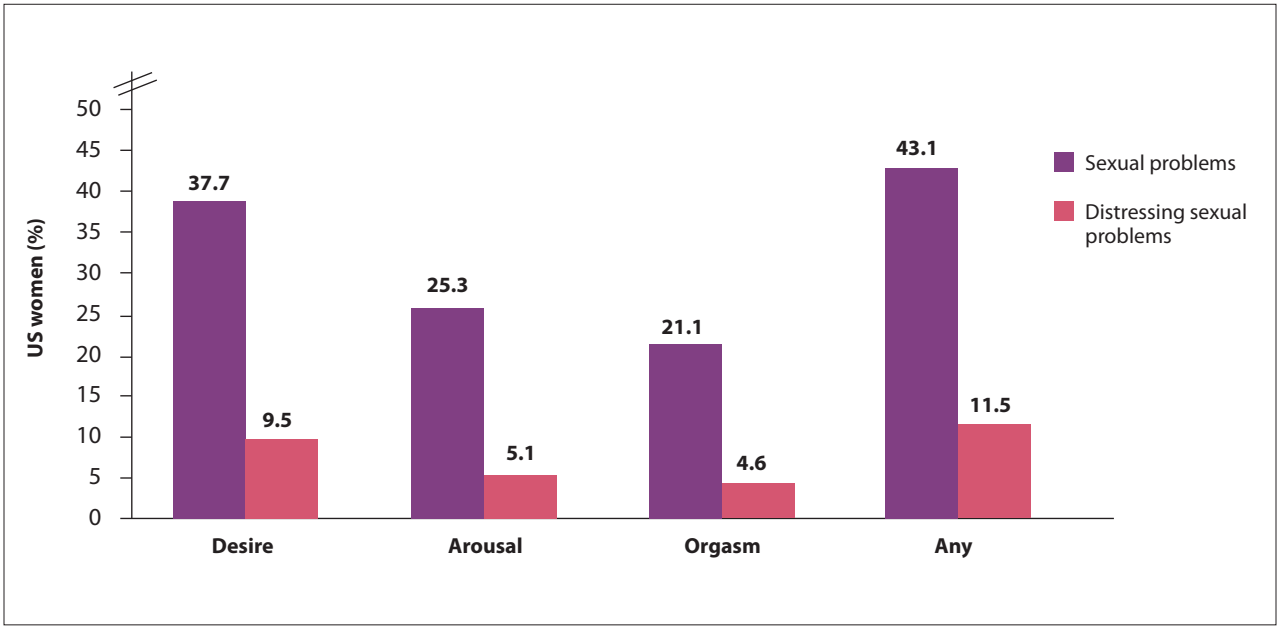
Prevalence of Female Sexual Dysfunctions

Hypoactive sexual desire disorder (HSDD) is believed to be the most common of the various FSDs.[2,3] Accurate estimates are difficult to determine, owing to disparities in how HSDD is defined or diagnosed and differences in the populations studied. Nevertheless, epidemiologic studies estimate that approximately 24% to 43% of women report low sexual desire in the previous year.[4] By contrast, prevalence estimates of women reporting frequent problems with low libido range between 5.4% and 13.6%.[4]

There are few studies on premenopausal female sexuality, and particularly on HSDD in women. Currently, the cross-sectional, population-based Prevalence of Female Sexual Problems Associated with Distress and Determinants of Treatment Seeking (PRESIDE) study, is the largest, involving 31,581 women aged 18 years or older (**FIGURE 1**).[3] PRESIDE reported on both prevalence of various sexual complaints as well as bother associated with these complaints. Nearly 38% of women self-reported low or hypoactive sexual desire, and 9.5% of women self-reported low sexual desire with distress/bother, which are the conditions necessary for a diagnosis of HSDD.[3] The study authors noted that, although more older women reported low sexual desire than younger women, the older women didn't appear to be as bothered/distressed by this. Nevertheless, the study highlighted the importance of assessing older women for the presence of distressing sexual problems, as they too may require clinical interventions.[3]

A meta-analysis of observational studies noted substantial variations of prevalence estimates of FSD.[5] Overall, the meta-analysis estimated that about 41% of premenopausal women worldwide have any FSD, and approximately 28% of premenopausal women have low sexual desire.[5] Prevalence of low sexual desire was shown to be higher in menopausal women compared with premenopausal women in a survey of more than 2200 US women aged 30 to 70 years.[6] This cross-sectional study estimated the prevalence of low sexual desire (as defined using the Profile of Female Sexual Function desire domain) at nearly 27% in premenopausal and 52% among naturally (versus surgically) menopausal women.[6] Data from the Women's International Study of Health and Sexuality (WISHeS) reported that the prevalence of HSDD ranged from 9% in naturally postmenopausal women to 26% in younger, surgically menopausal women.[7] Further, the

FIGURE 1 Prevalence of female sexual problems associated with distress[3]



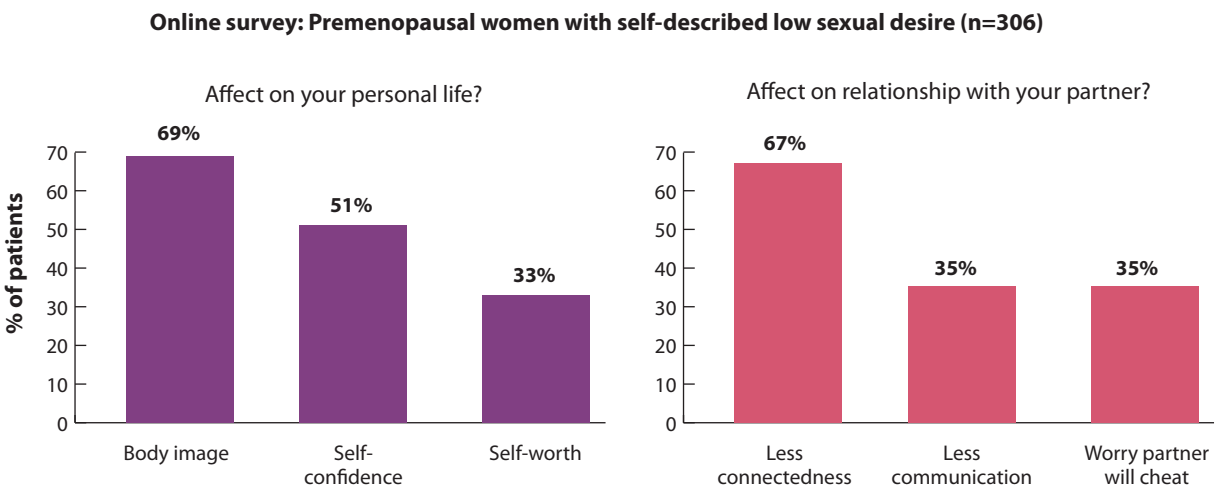
study found that low sexual desire, as determined by the Profile of Female Sexual Function, the Personal Distress Scale, and the Short Form-36, was associated with psychological and emotional distress, and lower sexual and relationship satisfaction.[7] More than 80% of women with HSDD expressed concern about letting their partner down, and women with HSDD were 11 times more likely to be dissatisfied with their sex lives and 2.5 times more likely to be dissatisfied with their relationship than women without HSDD.[7]

Although HSDD occurs in women of all ages, with potentially substantial consequences, it remains under-diagnosed and undermanaged.[2,8] HSDD is associated with lower health-related quality of life, lower general happiness, lower satisfaction with partner, and more frequent negative affective states.[9] Notably, a recent online survey was conducted that included 450 premenopausal and postmenopausal women aged 20 to 60 years who had self-reported low sexual desire and related distress.[10] Data pertinent to the 306 premenopausal women noted that 69% of these participants indicated their low sexual desire influenced their body image, 51% noted it impacted their self-confidence; 35% acknowledged it impaired their communication, and 35% admitted being worried their partner would cheat on them (**FIGURE 2**).[10]

Although physicians (and other health care providers [HCPs]) acknowledge that FSD is common and distressing, clinicians rarely address it, often owing to low confidence, time constraints, and/or lack of treatment.[9,11,12] Historically, very few patients would spontaneously raise a sexual issue to discuss with their provider. In one study involving nearly 890 gynecologic outpatients, only 3% of patients spontaneously raised sexual issues, although 19% of them reported a problem upon direct inquiry.[13] Data from 2 decades later demonstrated little improvement. A study of nearly 3250 women aged 18 years or older investigated help-seeking behaviors of women with self-reported distressing sexual problems and found that only slightly more than 1 in 3 women had sought formal care for their distressing sexual problem.[14] About 80% of the time, the woman, and not her clinician, initiated a conversation about sexuality. Only 6% of women specifically scheduled an office visit to discuss a sexual problem.[14] A unique study which used an in-person diagnostic interview along with questionnaires assigned a diagnosis of generalized acquired HSDD to 7.4% of the more than 700 participating women.[15] Of note, only 53% of the women diagnosed with HSDD had sought care from a healthcare professional for this issue.

Evidence suggests clinicians are not confident in their ability to diagnose FSD or comfortable discussing all female sexual dysfunctions. In 1 study, 155 residents and faculty in an academic primary care clinic

FIGURE 2 Low sexual desire negatively affects self-image and partner relationships



were invited to participate in a web-based questionnaire regarding HSDD. Data from the 53 physicians who responded highlight the need to improve patient care regarding sexuality: only 10% of the respondents reported confidence in making a diagnosis of HSDD; 90% of them had not screened a patient for HSDD, and only 1 respondent had prescribed medication for a patient with HSDD.[16]

More recently, a survey of 1154 US obstetrician/gynecologists suggested some improvements in communication regarding sexuality. Nearly two-thirds of the respondents self-reported routinely asking about sexual activities, and 40% routinely asked about sexual problems (**FIGURE 3**). However, fewer than 15% asked women if they have pleasure during sexual activity.[17] Further, additional data suggest that clinicians are selective in who they ask—primarily focusing on otherwise healthy, heterosexual, married women.[11]

Communicating About Sexuality: Provider and Patient Barriers

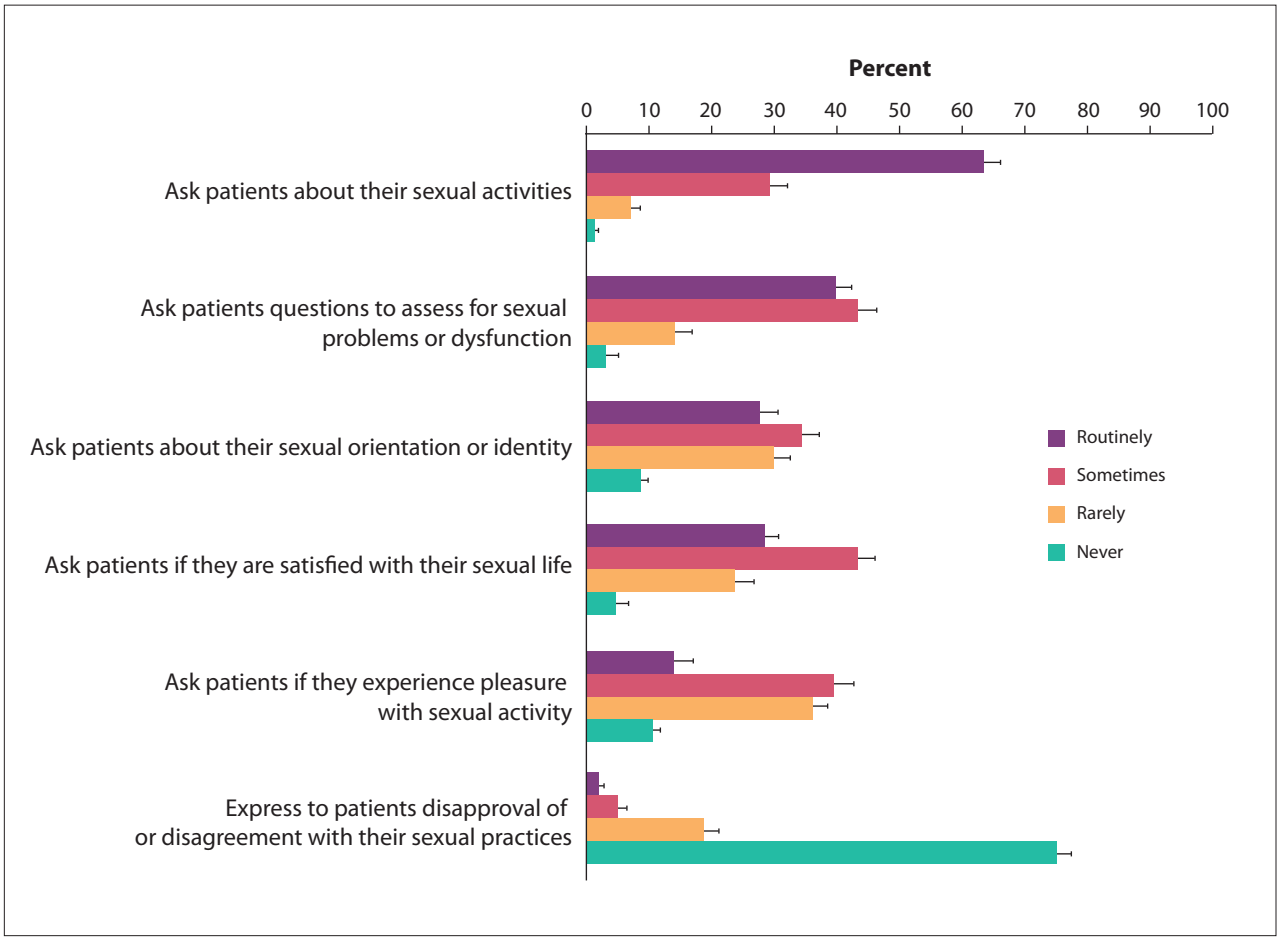
Both patients and providers contribute to the lack of communication regarding female sexual health/functioning, creating a conspiracy of silence. Women want to talk with their HCPs about sexual issues but cite numerous real or perceived barriers, including personal embarrassment, fear of embarrassing the provider, having the problem 'minimized,' having no treatment for their problem, or being told the problem was "all in their head." Nevertheless, women would like for their HCPs to be proactive in raising sexuality-related issues.

Patients are reluctant to raise sexual issues owing to their own embarrassment or fear of embarrassing their providers; clinicians report lack of time, lack of knowledge, and lack of comfort as primary barriers to raising the topic themselves.[18] HCPs admit embarrassment in discussing patients' sexuality-related concerns, and many perceive their sexuality knowledge and comfort levels as "fair" or "poor."[11] The amount of time historically devoted to sexual health education in medical schools or in physician assistant training programs was minimal and continues to decrease. In addition, the focus has been on prevention of unintended pregnancy and sexually transmitted infections, not on sexual function and dysfunction.[19-21] A survey of members of the American Urogynecologic Society reported that about one-third of their member physicians lacked familiarity with questionnaires to assess female sexual dysfunction (FSD), and only 13% of those who were aware of available tools used them for screening purposes.[22] This survey also found that 69% of the physicians underestimate rates of FSD, and 50% of those who had received postresidency training in urogynecology reported their FSD-related training was unsatisfactory.[22]

Integrating Sexual Health Communications into Routine Care

Since 2000, the World Health Organization has determined that maintaining sexual health is under the

FIGURE 3 Are ObGyns asking?[a]



[a]1154 practicing US ObGyns (53% male; mean age, 48 years) were surveyed regarding their practices of communication with patients about sex.

purview of physicians.[23] However, studies indicate that teaching about sexual health is not a high priority in most medical school curricula.[24,25] Consequently, many clinicians lack the training to facilitate competence and confidence in addressing sexual health concerns. Nevertheless, studies indicate that training in communication skills is the strongest predictor that a physician will take a sexual history.[26]

A sexual history or assessment should be included during the initial patient evaluation, during the annual visit and/or during routine visits (especially among patients with chronic illnesses), prior to and after surgery or other medical procedures, and around all major life events (pregnancy, postpartum, menopause).[27,28] A thorough sexual history, covering the patient's medical, surgical, reproductive, psychiatric, and social history, is time consuming and often untenable in the context of a routine office visit. However, routinely asking even a few general questions to screen for possible issues is manageable and can then be followed by asking more targeted questions if problems are disclosed.[29]

Clinicians can integrate simple counseling strategies into routine discussions to initiate talks about sexuality. One means is to normalize sexual concerns, such as by noting that "many women have questions or concerns about their sexual functioning, including their lack of desire or response."[30] Clinicians need to use straightforward, simple language that is appropriate to the age, ethnicity, and culture of the patient, minimizing the use of medical terminology. Clinicians should encourage women to ask questions, whether aloud or written on paper. Discussions should be nonjudgmental, using open ended questions.

One longstanding simple approach for raising discussions about sexuality is the PLISSIT model.[31] The PLISSIT model involves 4 levels of increasing interaction and information: Permission, Limited Information, Specific Suggestions, and Intensive Therapy. Each level requires a little more knowledge and comfort, and clinicians can refer the patient to an expert at any point. At the most basic level, the clinician gives the woman permission to discuss her sexuality, to raise concerns or complaints, to talk about lack of desire and how it is affecting her. It is incumbent upon the clinician to listen to the concerns, to normalize them, to demonstrate understanding and empathy from a nonjudgmental stance. The clinician can then provide limited information about female sexual anatomy, female sexual response, and sexual desire, as well as educational resources regarding lack of desire. As one would expect, specific suggestions is an opportunity for the clinician to provide recommendations to address the sexual complaint. For women who report hypoactive sexual desire, these might include recommendations about improving communication with one's partner, the use of sensate focus techniques, or consideration of available medications. For women who continue to report this complaint, a referral to a specialist, such as a sex therapist or a specialist in mindfulness-based cognitive therapy, for intensive therapy may be indicated.

Conclusions

HSDD is considered the most prevalent FSD and is associated with substantial personal and interpersonal consequences that extend well past the bedroom. Despite this, clinicians and patients alike are reluctant to initiate dialogue about this complaint, leading many women (and their partners) to continue to suffer in silence. However, clinicians easily can raise and integrate discussions regarding sexual health into routine office visits to optimize their patients' sexual health and improve their overall quality of life.

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Diagnosing Hypoactive Sexual Desire Disorder

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Overview

ObGyn practitioners, including physicians, nurses, and physician assistants, are particularly well positioned to screen women for female sexual dysfunctions (FSDs) and to diagnose sexual dysfunctions such as hypoactive sexual desire disorder (HSDD). As HSDD is the most prevalent female sexual health problem affecting about 10% of women, it is likely that clinicians see numerous patients with this disorder.[1,2] However, in general ObGyn settings, detection rates are low; it likely that many women remain undiagnosed and thus untreated.[3]

Defining Hypoactive Sexual Desire Disorder

HSDD is defined by the International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10) nomenclature system as a distinct diagnostic entity characterized by "a recurrent or persistent lack of desire for sexual activity" that is "not attributable to another psychiatric disorder or to the physiological effects of substance use or a general medical condition".[4] The Diagnostic and Statistical Manual of Mental Disorders, 4th edition, Text Revision (DSM-IV-TR) of the American Psychiatric Association (APA) similarly defined HSDD as "a deficiency or absence of sexual fantasies and desire for sexual activity, which causes marked distress or interpersonal difficulty, and which is not better accounted for by a medical, substance-related, psychiatric, or other sexual condition. HSDD can be either generalized (not limited to certain stimulation, situations, or partners) or situational, and can be either acquired (develops only after a period of normal functioning) or lifelong."[5] However, in the most recent DSM-5 iteration, published in 2013, HSDD was merged with female sexual arousal disorder (FSAD) to form a new diagnostic category of female sexual interest/arousal disorder (FSI/AD), in light of a perceived significant overlap between sexual arousal and desire.

According to the DSM-5, a diagnosis of FSI/AD requires a complete lack of or significant reduction in sexual interest or arousal for at least 6 months duration that causes clinically significant distress.[6] Women must present with at least 3 of 6 criteria regarding their lack (absent or reduced) of interest in sexual activity, including sexual/erotic thoughts or fantasies, lack of initiation of sexual activity or lack of receptiveness to the partner's sexual advances, lack of sexual excitement or pleasure during at least 75% of sexual encounters, lack of interest or arousal to internal or external sexual or erotic cues, and lack of genital/nongenital response during sexual activity at least 75% of the time.[6]

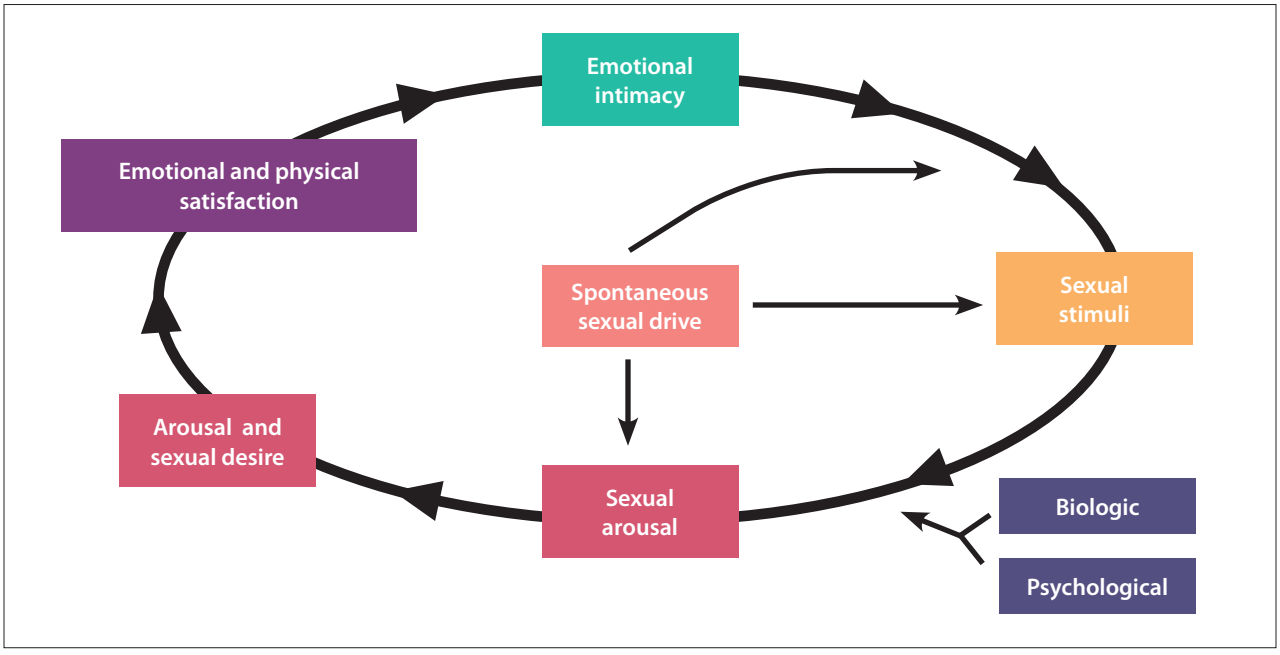
However, the International Society for the Study of Women's Sexual Health (ISSWSH) Expert Consensus Panel Review asserts that the revised DSM-5 diagnostic classification is controversial in light of the lack of empirical support or validation for the combined category.[1,7] Consequently, the ISSWSH defines HSDD as the manifestation of any of the following for a minimum of 6 months:

- Lack of motivation for sexual activity as manifested by:
  - Decreased or absent spontaneous desire (sexual thoughts or fantasies); or
  - Decreased or absent responsive desire to erotic cues and stimulation or inability to maintain desire or interest through sexual activity;
- Loss of desire to initiate or participate in sexual activity, including behavioral responses such as avoidance of situations that could lead to sexual activity, that is not secondary to sexual pain disorders;
- And is combined with clinically significant personal distress that includes frustration, grief, guilt, incompetence, loss, sadness, sorrow, or worry.[1,7,8]

As with the DSM IV-TR definition, according to the ISSWSH nomenclature HSDD, may be lifelong or acquired and either generalized or situational.[3,7]

In concert with ICD-10 and ISSWSH, the International Consultation on Sexual Medicine (ICSM) defines hypoactive sexual desire dysfunction as a "persistent or recurrent deficiency or absence of sexual thoughts, fantasies, and/or desire for sexual activity that causes marked personal

FIGURE 1 Circular model of female sexual response



distress".[9] As with the DSM IV-TR definition, according to the ISSWSH nomenclature, HSDD may be lifelong or acquired and either generalized or situational.[3,7] As part of a new chapter on 'Conditions Related to Sexual Health,' ICD-11 intends to use the diagnostic category "Hypoactive Sexual Desire Dysfunction," which will encompass hypoactive desire in both females and males; separate categories will be used where sex differences are related to distinct clinical presentation of sexual dysfunctions, such as with female sexual arousal dysfunction.[10]

Models of Female Sexual Response and Desire

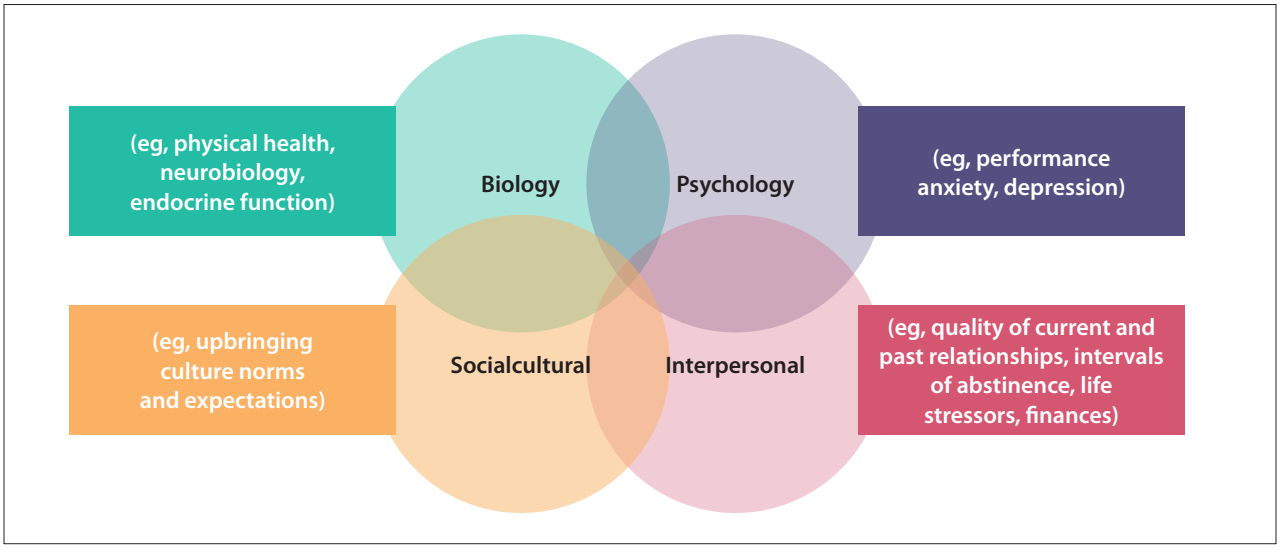
To be able to diagnose (and ultimately treat) HSDD, it is important to first understand female sexual response and the psychosocial mechanisms and biology and physiology underlying female sexual desire. Numerous models of female sexual response have been proposed over the years. Despite their differences, what is clear is that in females, sexual health and response involves both body and mind.

More than 40 years ago, Masters and Johnson developed the first model of human sexual response, a 4-phase linear explanation of the human sexual response cycle after they directly observed the anatomic and physiological changes women (and men) experience during sexual activity.[11] Their model proposed that women progress from excitement through plateau, achieving orgasm and then, during resolution, returning to the original non-aroused state. Each of the 4 phases were characterized by specific physiologic and anatomic changes. This linear model was amended more than 10 years later when Kaplan added "desire" as the initial stage.[12]

In recognition of the multifactorial etiology of female sexual response, Basson introduced her intimacy-based circular model, which recognizes that sexual arousal may precede desire (**FIGURE 1**).[13] This model proposes that women may enter a sexual encounter from a place of sexual neutrality and in the presence of sexual stimuli may experience "responsive desire." Basson asserted that arousal from sexual stimulation may trigger the desire to continue and lead to sustained desire through a sexual experience. Further, the learning from the pleasure of that experience may lead to her agreeing to engage in sexual activity in the future, even if she is starting in a sexual "neutral" state. Notably, Basson asserted that women may engage in sex for many reasons, including the recollection of pleasure, a desire for intimacy, and/or wanting to satisfy her partner.[13]

As discussed above, more than a decade later, the APA Diagnostic and Statistical Manual of Mental Health Disorders (DSM-5) merged the prior distinct diagnoses of HSDD and FSAD from the DSM-IV-TR into the current female sexual interest/arousal disorder (FSI/AD).[5,6] The basis of this modification was the observation that many women have difficulty differentiating between desire and arousal and that difficulties with mental arousal

FIGURE 2 Biopsychosocial model of female sexual response



rarely occur in the absence of sexual desire problems.[14] Two international panels of experts in sexual medicine (the ISSWSH Nomenclature Committee and the ICSM) retain hypoactive sexual desire disorder/dysfunction as its own distinct entity and diagnosis.[1,8]

The biopsychosocial model of female sexual response recognizes the influence of, and interplay between, biologic, psychological, sociocultural, and interpersonal factors (**FIGURE 2**).[15,16] The biologic "drive" encompasses the spontaneous craving for sexual activity, sexual dreams or unprompted thoughts, and genital sensations. It is driven by neuroendocrine mechanisms and can be influenced by physical health, endocrine function, and hormonal levels. Data from the PRESIDE study highlighted that aging can cause secondary loss of desire such as in women with pain stemming from vulvovaginal atrophy.[2] A woman's psychological health, including the presence or absence of depression, anxiety, other psychologic/psychiatric parameters, and sociocultural values, based on her ethnic and religious background/beliefs regarding sex, can support or ameliorate the drive. Studies suggest women choose to engage in sexual activity for a variety of reasons, including a desire to be close to their partner or to feel wanted[13]; personality disorders, body image concerns, stress/distraction, or a history of sexual trauma can all be barriers to sexual desire. Similarly, sexual desire is influenced by interpersonal factors, such as her relationship with her current partner(s) or her willingness to engage in sexual activity (either alone or with a partner).

The most recent additions to theories regarding female sexual desire are the dual control biopsychosocial models, including Bancroft's dual control and Perelman's sexual tipping point (STP) models, each of which describes the balance between sexual excitatory versus inhibitory psychological and biological processes.[17,18] The STP model emphasizes that sex is always both mental and physical.[19,20] Further understanding of the human sexual response suggests that "on/off" switches may be continuous and not discrete categories; individuals slide back and forth along a continuum rather than "tipping" one way or the other (on vs off).[21] In addition, it is also understood that responsiveness and sexual interest may vary over time in an individual.[21] Regardless of the theoretical perspective, it is clear that female sexual desire is a complex, multifaceted construct, underscoring why there is no universally accepted definition or description.[22]

Physiology of Female Sexual Desire

Female sexual desire is influenced by both neuroendocrine and hormonal mechanisms. However, much of our understanding of the physiology of female sexual desire is based on the understanding of male sexual functioning and/or animal sexual biology. It is believed that central mechanisms involve the brainstem, hypothalamus, and forebrain (including the amygdala).[23] In addition to estrogen, testosterone, and melanocortin, other excitatory factors for female sexual desire include oxytocin and the neurotransmitters dopamine and norepinephrine.[18] By contrast, serotonin, prolactin, and endogenous opioids are inhibitory factors. It is believed that the biological drive of desire is triggered in the hypothalamus, activated by the dopamine system (along with norepi-

nephrine); the physiologic responses of excitement also indicate noradrenergic involvement.[18]

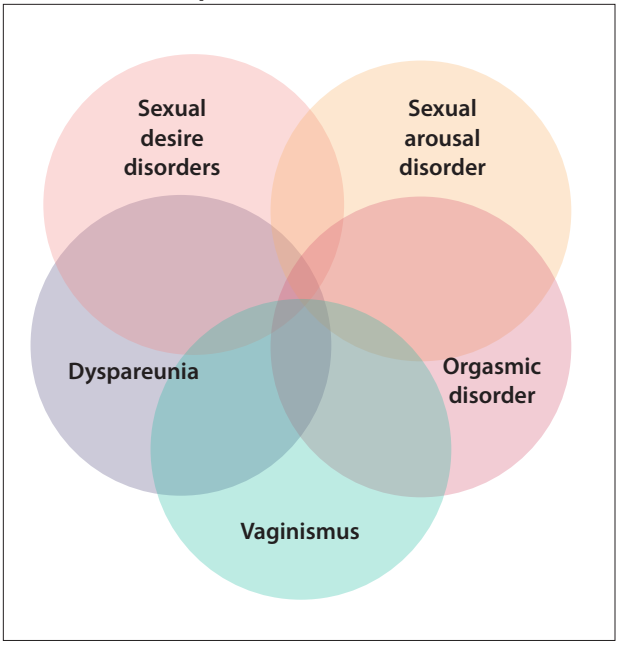
Hormones also influence female sexual desire, although it is not clear exactly what role(s) they play. While estradiol is the only hormone critical for sexual desire/behaviors in nonhuman mammals, both estrogen (particularly estradiol) and androgen (testosterone) have been implicated in humans.[24] Estradiol levels substantially decrease with age and menopause; however, while low sexual desire increases with age, distress about it decreases, keeping the prevalence somewhat constant.[25] As will be discussed in Portman's article later in this supplement, evidence has shown that estrogen-only therapies can increase women's sexual desire postmenopause, and adding testosterone enhances the benefit.[24] Recent research found that estrogen and testosterone changes throughout the menstrual cycle, and particularly during the follicular phase, appear to influence women's response to sexual stimuli.[26] A large cross-sectional study reported that low sexual desire was associated with significantly lower mean levels of free testosterone and androstenedione compared with levels in women without low sexual desire; however, there was no direct association with FSD in general or HSDD in specific.[27]

Diagnostic Assessment

There does not appear to be one universal explanation of sexual desire, making it particularly difficult at times to diagnose HSDD. HSDD can occur without obvious contributing factors or it may be associated with etiological risk factors that may be amenable to intervention (such as medical or psychiatric conditions); it can occur alone or in combination with other sexual disorders (**FIGURE 3**).[7] Nevertheless, clinicians can often screen for and diagnose HSDD in routine office visits without the need for additional laboratory testing or imaging studies, unless there is a need to rule out infection or other medical concerns.

A key requirement for effectively identifying and managing sexual problems including HSDD is that the clinician is comfortable discussing sexual function, asks open-ended questions, normalizes discussions regarding sexual health or concerns, and legitimizes the importance of integrating questions regarding sexual function into the health assessment. Ideally, the clinician and not the patient raises these issues. Finally, the clinician should not make assumptions or judgments regarding the patient's sexual activity, her partner's gender(s), the number of partners she has, or that she is monogamous because she is married.

FIGURE 3 Overlap of female sexual disorders



Diagnostic assessment begins with a thorough medical history to assess for underlying medical or psychiatric condition that could be causing or contributing to the loss or decline of desire. Cardiovascular diseases, neurological disorders, cancer, depression, and a range of endocrinologic disorders, including thyroid disorders, diabetes, metabolic syndrome, and obesity, have all been associated with low sexual desire.[3] In addition, conditions that cause painful sexual activity, such as vulvovaginal atrophy, should be considered and investigated. Numerous medications can interfere with optimal sexual desire and response, including antidepressants, antipsychotics, barbiturates, benzodiazepines, anticonvulsants (eg phenytoin [Dilantin]), aromatase inhibitors, and other chemotherapeutics, prescription and illegal substances of abuse.[3,7] Estrogen deficiency and testosterone decline with age and can also contribute to HSDD.[28,29]

Screening Tools

There are a number of (validated) screeners to aid clinicians in the initial assessment for HSDD (**TABLE 1**). While some of the screeners are more appropriate for a research versus a clinical setting, many of the validated tools can be self-administered, are simple to understand, and require only about 10 to 15 minutes or less to complete. These tools can provide an initial qualitative and quantitative assessment of the patient's current and prior levels of sexual functioning and desire; they may also identify additional sexual concerns that may affect the lack of sex-

TABLE 1 Validated tools to assess female sexual distress

Validated tool	Assessment area
Decreased Sexual Desire Screener (DSDS)[1]	Brief diagnostic tool for Hypoactive Sexual Desire Disorder (HSDD)
Female Sexual Function Index (FSFI)[2,3,a]	Desire, arousal, orgasm, and pain
Female Sexual Distress Scale-Revised (FSDS-R)[4]	Distress

[a]FSFI questionnaire and scoring key vailable at: www.fsfi-questionnaire.com

ual desire, such as problems with lubrication, decreased genital sensation, or difficulties achieving orgasm.

The most widely used questionnaire to assess sexual function in women is the Female Sexual Function Index (FSFI).[30] The FSFI is a validated, 19-question self-assessment of female sexual function that contains questions divided into 6 different domains: desire, arousal, lubrication, orgasm, satisfaction, and pain.[30–32] The FSFI includes 2 questions that specifically address desire (**TABLE 2**).

The Decreased Sexual Desire Screener (DSDS) is a validated scale that was specifically developed for use by clinicians who are not experts in sexual medicine (**TABLE 3**).[33] This 5-question self-administered survey can help clinicians identify generalized acquired HSDD in pre-, peri-, and postmenopausal women.[33] The 7-question Brief Profile of Female Sexual Function assesses loss of sexual desire and function in postmenopausal women with HSDD.[34]

The Female Sexual Distress Scale (FSDS)/Female Sexual Distress Scale-Revised (FSDS-R) are validated self-assessment tools.[35,36] The FSDS is a 12-item scale, and the FSDS-R includes a 13th question that specifically measures sex-related distress.[37]

Additional office-based tools for premenopausal women include the Brief Index of Sexual Functioning for Women[38]; the Brief HSDD Screener[39]; and the 11-item Sexual Event Diary (SED), which assesses sexual function during a discrete sexual event as well as over longer periods.[40]

Diagnosing HSDD

Once a diagnosis of HSDD has been conferred, it must then be determined if the disorder has associated etiological factors, is lifelong or acquired, and is generalized or situational. The clinician needs to appraise whether the HSDD has developed as a consequence of (or secondary to) another disorder, such as dyspareunia. Women who have never espoused sexual desire, have never had sexual thoughts and fantasies or interest in engaging in sexual activity (alone or with others), and who are distressed about their lack of sexual desire, would be diagnosed with lifelong HSDD; those who can identify a prior time during which they experienced sexual desire would be classified with acquired HSDD. For some women HSDD is generalized to all encounters, whereas for other women, it may be specific to sexual activity with a particular person.

Conclusion

Screening for and diagnosing HSDD can easily be performed by ObGyn providers in an office setting. Establishing an open dialogue with the patient and routinely

TABLE 2 FSFI Desire Domain

1. Over the past 4 weeks, how often did you feel sexual desire or interest?

Almost never or never	A few times (less than half the time)	Sometimes (about half the time	Most times (more than half the time)	Almost always or always
1	2	3	4	5

2. Over the past 4 weeks, how would you rate your level (degree) of sexual desire or interest?

Very low or none at all	Low	Moderate	High	Very high
1	2	3	4	5

FSFI-D ≤3 may indicate the presence of HSDD
Abbreviations: FSFI-D, Female Sexual Function Index: Desire Domain; HSDD, hypoactive sexual desire disorder.

TABLE 3 Decreased sexual desire screener

1. In the past, was your level of sexual desire/interest good and satisfying to you?	○ No	○ Yes	If "No" to Q 1,2,3, or 4 = Not generalized acquired HSDD
2. Has there been a decrease in your level of sexual desire/interest?	○ No	○ Yes	
3. Are you bothered by your decreased level of sexual desire/interest?	○ No	○ Yes	
4. Would you like your level of sexual desire/interest to increase?	○ No	○ Yes	If "Yes" to all Q 1–4 and "No" to all Q 5 factors = clinician to use best judgement to confirm a diagnosis of generalized acquired HSDD
5. Please check all the factors that you feel may be contributing to your current decrease in sexual desire/interest:			
A. An operation, depression, injuries, or other medical condition	○ No	○ Yes	
B. Medications, drugs or alcohol you are currently taking	○ No	○ Yes	
C. Pregnancy, recent childbirth, menopausal symptoms	○ No	○ Yes	If "Yes" to all 1–4 and "Yes" to any Q 5 factor = clinician to use best judgement to determine diagnosis
D. Other sexual issues you may have (pain, decreased arousal, orgasm)	○ No	○ Yes	
F. Dissatisfaction with your relationship or partner	○ No	○ Yes	
G. Stress or fatigue	○ No	○ Yes	

[a]Co-morbid conditions such as arousal orgasmic disorder do not rule out a concurrent diagnosis of hypoactive sexual desire disorder.

inquiring about sexual health concerns can quickly identify the need for additional inquiry into possible female sexual dysfunctions. Integrating simple validated screening tools can also facilitate discussion about possible sexual problem reports during an office visit. For most patients, additional evaluation or testing is not required to make a diagnosis of HSDD, although it may be needed to rule out other possible factors contributing to the complaint.

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HSDD Pharmacotherapy: Current and Off-Label Treatments

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Introduction

In the absence of a clear understanding of the underlying pathophysiology of sexual desire, it has been challenging to develop treatments to improve low or hypoactive sexual desire. It is believed that sexual desire is governed by multiple areas of the brain leading to increases in dopamine and norepinephrine and decreases in serotonin. Consequently, pharmacologic treatments for hypoactive sexual desire disorder (HSDD) have focused on addressing imbalances in these key neuromodulators.

In addition to psychological therapies (mindfulness), behavioral therapies (sensate focus), and cognitive-behavioral therapies (CBTs), a range of pharmacologic agents have been or are currently being used, often off-label, in the management of HSDD in women. Currently, the only agent approved by the US Food and Drug Administration (FDA) is flibanserin (in premenopausal women); testosterone, buspirone, and bupropion are all being used off-label.

Pathophysiology of Sexual Desire

It has been hypothesized that the neurobiological basis of sexual response, including HSDD, is an imbalance in the excitatory and inhibitory activity of the central nervous system that regulates sexual response (**FIGURE 1**).[1] Dopamine, norepinephrine, melanocortins, and oxytocin, along with estrogen, progesterone, and testosterone, are the key neuromodulators that regulate the excitatory pathways, and serotonin, endocannabinoids, prolactin (**FIGURE 1**),[2-4] and opioids regulate the inhibitory pathway, Dopamine has a positive effect on pleasure and reward pathways in the brain, and increased levels of dopamine may increase sexual desire.[5] Serotonin is activated during periods of sexual inhibition and decreases the ability of excitatory systems to be activated by sexual cues.[3,6,7] Norepinephrine has been linked with desire and motivation and has been shown to be elevated during sexual arousal and orgasm.[8] As such, HSDD is thought to result from an imbalance between the various neuromodulators leading to an overactive serotonergic system and an underactive dopaminergic system.[2] Consequently, centrally-acting agents that decrease serotonin or increase dopamine, or have some combination of these actions, such as bremelanotide, bupropion, buspirone, and flibanserin, have been and continue to be under investigation as potential therapies.[2]

Data also suggest that androgens are significant independent factors affecting sexual desire, sexual activity, and satisfaction, as well as other components of women's health (such as mood and energy). As early as the 1970s, testosterone was identified as a key component in sexual desire for both women and men.[9] Free testosterone affects both central and peripheral key receptors[10]; in women, testosterone is produced in ovaries, adrenal glands from precursor hormone undergoing final conversion in adrenal glands, and peripheral tissues.[11] Testosterone acts centrally to promote desire, and optimizes blood flow and facilitates lubrication by acting peripher-

FIGURE 1 Excitatory and inhibitory effects of neurotransmitters and hormones on sexual desire

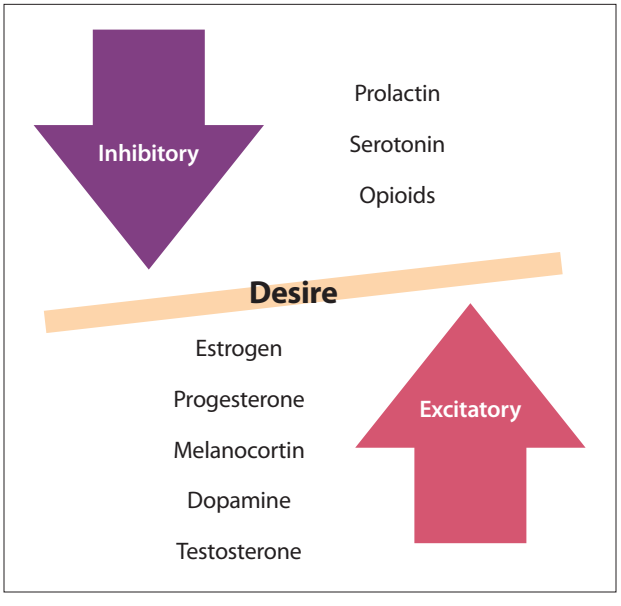
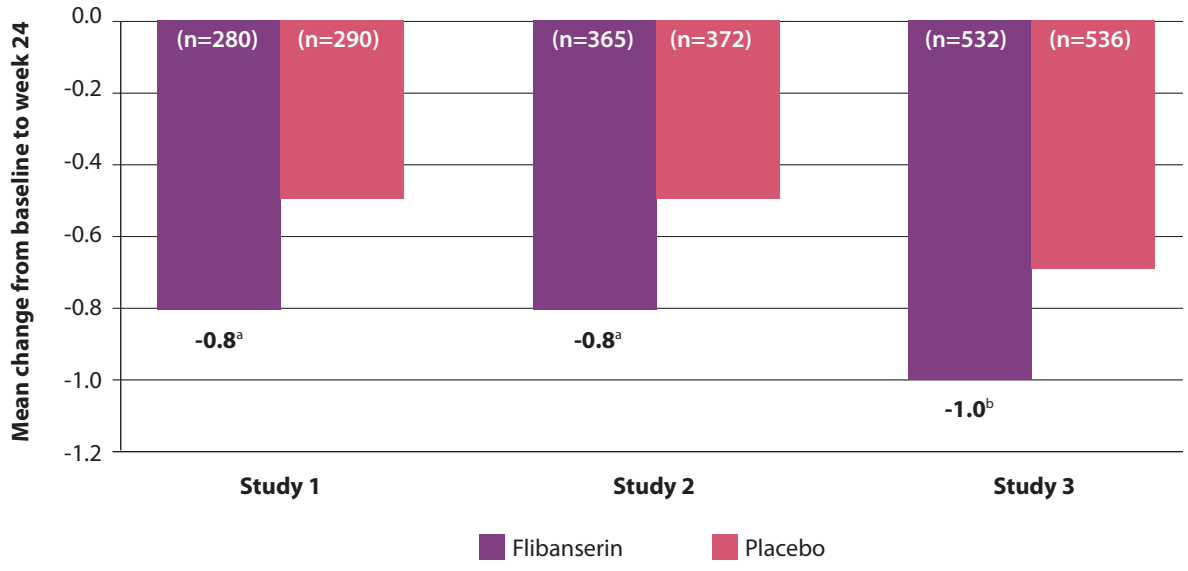


FIGURE 2 **Flibanserin showed a decrease in distress vs placebo across 3 randomized, placebo-controlled studies**[20–22]



[a]*P*-value not reported for secondary endpoints because the trials failed on the eDiary co-primary efficacy endpoint.
[b]*P*<0.001

ally in the vulva/vagina.[12] Centrally acting estrogen (and particularly estradiol) has also been associated with promoting desire, and, similar to testosterone, acts peripherally to promote blood flow, lubrication, and arousal.[10,13–17] Whether testosterone's actions are independent of its conversion to estradiol, or merely synergistic to them in both the central nervous system and the peripheral tissues, remains controversial.

Flibanserin

Flibanserin is both a serotonin (5-HT) receptor agonist and antagonist, and has been demonstrated to regulate levels of dopamine and norepinephrine and also transiently decrease serotonin.[18] Specifically, it is a serotonin (5-hydroxytryptamine [5-HT])1A receptor agonist and a 5-HT2A receptor antagonist.[2] This unique mechanism of action diminishes the inhibitory serotonergic actions and restores dopaminergic and noradrenergic function.[2] In August 2015 flibanserin became the first agent approved by the FDA for the treatment of acquired generalized HSDD in premenopaual women. It is not yet indicated for use in postmenopausal women, although it has been studied in this population with convincing benefits similar to those seen in premenopausal women.[19]

The efficacy of flibanserin 100 mg once daily at bedtime (qhs) as a treatment for HSDD is supported by results from 3 randomized placebo-controlled pivotal trials in North American premenopausal women with HSDD. The safety database for this compound is even larger—encompassing more than 11,000 women.[20–22] In these pivotal trials, flibanserin 100 mg qhs was associated with an increase in satisfying sexual events, an improvement in sexual desire (measured using the Female Sexual Function Index [FSFI]), and a decrease in sexually related distress. However, the co-primary endpoint of change in the desire score, measured using a daily electronic diary (eDiary), did not reach statistical significance in the 2 earlier trials. Given an increasing body of scientific data and expert opinion suggesting that the FSFI desire domain score is a more appropriate measure of sexual desire in women with HSDD than a daily eDiary measure, the electronic diary was abandoned in favor of the FSFI desire score in the third pivotal trial.[23]

Thus, in the third randomized placebo-controlled pivotal trial the primary desire end point was changed to the FSFI desire domain score. This trial, known as BEGONIA, was a 24-week trial that enrolled more than 1000 patients—542 received flibanserin, 545 received

placebo.[21] Study results demonstrated that flibanserin 100 mg nightly at bedtime resulted in statistically significant increases (vs placebo) in satisfying sexual events ($P<.001$) and improvement in sexual desire ($P<.001$). Similar statistically significant results were shown for flibanserin in terms of improvements in sexual distress ($P<.001$) and distress associated with low sexual desire ($P<.001$) (**FIGURE 2**). Additionally, the increase in the FSFI total score was statistically significant ($P<.001$).[21]

Recent data suggest that use of flibanserin is associated with weight loss, with one publication noting an average statistically significant weight loss of 1.4 kg in a 24-week treatment course.[24] Across all of the studies, the most common adverse events associated with flibanserin use were somnolence, dizziness, and nausea.[25] In addition, women who drink alcohol while using flibanserin are at risk for severe hypotension and fainting,[26] and use of the drug is contraindicated in women who drink. However, recently performed trials demonstrate that the alcohol prohibition may not be necessary.[27,28] Flibanserin is also contraindicated in patients with liver impairment and those who concurrently use moderate or strong inhibitors of cytochrome P-450 isozyme 3A4, including some herbal supplements. Consequently, the FDA mandated the creation of a Risk Evaluation and Mitigation Strategy (REMS) to inform about the increased risk of hypotension and syncope due to an interaction with alcohol. Health care prescribers and pharmacists must complete training to become certified to prescribe or dispense the medication through the flibanserin REMS program. To become certified, prescribers and designated pharmacy representatives must review the flibanserin prescribing information and the prescriber and pharmacy training documentation, successfully complete a short knowledge assessment, and enroll in the flibanserin REMS program.

Testosterone

Over the years, physicians have used various androgen preparations to improve sexual function in postmenopausal women, based on the results of smaller clinical trials and personal clinical observations. Several randomized placebo-controlled trials demonstrate that low-dose testosterone treatment is efficacious in women with HSDD who have an established cause of androgen deficiency, such as natural or surgical menopause.[29-32] The most commonly reported side effects of testosterone treatment are mild hirsutism or acne, but long-term safety has not yet been established. As yet, the FDA has not approved a testosterone preparation for use in women with HSDD.

The fourth International Consortium of Sexual Medicine (ICSM) noted that the literature supports an important role for androgens in female sexual function.[33] An early study involving 10 premenopausal women with HSDD reported significant improvement with arousal after twice weekly application of transdermal testosterone gel prior to intercourse, as compared with placebo.[34] The ICSM reported that although trials consistently show improvements in sexual function and satisfaction with (off-label) use of transdermal testosterone therapy, its use is limited by the lack of any approved formulations, the absence of long-term safety data, and the absence of appropriate and accurate androgen assays for use in women.[33] Notably, measurements obtained by commercially available androgen assays are not informative for diagnosis, treatment, or prognosis in women, although they are often ordered by clinicians before prescribing testosterone.[35] New guidelines from both the International Society for the Study of Women's Sexual Health (ISSWSH)[36] and the International Menopause Society (IMS)[37] endorse the use of testosterone in postmenopausal women with HSDD.

Currently testosterone-based therapy is primarily being investigated in Europe. These approaches include a combination of testosterone with a phosophodiesterase-5 (PDE5) inhibitor, and testosterone with a 5HT receptor 1A agonist. It is hypothesized that polymorphisms in the androgen receptor gene, encoded by the nucleotides cysteine, adenine, and guanine (CAG), influence the effect of testosterone on sexual functioning. The results of a preliminary study demonstrated that women who use a low dose of selective serotonin reuptake inhibitor and have relatively long CAG repeats report a marked improvement in sexual function in response to both modalities compared with placebo.[32]

Other Off-Label Agents

Other agents have been explored or are being used, off-label, to increase desire in women with HSDD. Sildenafil is a PDE5-inhibitor that promotes vasodilation; although it is effective and FDA-indicated for the management of erectile dysfunction in men, it has only been shown to have minimal benefit in improving symptoms of HSDD in women, particularly when the HSDD is associated with antidepressants.[6,7,38]

Two other agents that have shown some promise for HSDD are bupropion and buspirone.[39] Bupropion is a norepinephrine-dopamine reuptake inhibitor currently

approved by the FDA for the treatment of depression (and smoking cessation). Studies have shown that bupropion improves sexual desire in patients with depression, as well as in patients with SSRI-induced HSDD,[5,40-42] leading to its off-label use. Studies have shown improvement in sexual function with sustained-release 150 to 400 mg daily dosing of bupropion.[5,42] Studies on bupropion for depression suggest that 10% of patients discontinue treatment owing to the adverse effect profile.[43]

Buspirone is an azapirone anxiolytic agent that binds to both the serotonin and dopamine receptors in the brain. A 5-HT1A partial agonist, it is approved for the management of generalized anxiety disorder or for short-term relief of anxiety-related symptoms. Studies suggest buspirone may hold promise for HSDD; currently, it is used off-label.[39,44-47] As with bupropion, about 10% of patients with anxiety disorders discontinue treatment with buspirone for adverse effects.[43]

Conclusion

Despite a wide variety of agents under investigation or being used off-label for HSDD, flibanserin is currently the only agent approved by the FDA. Its use is currently limited by the FDA warning, however, regarding its concomitant use with alcohol and the associated need for clinician REMS training. Similarly, studies demonstrate benefits of testosterone for HSDD in postmenopausal women, but there is, as yet, no approved formulation for women in the United States.

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New and Emerging Therapies

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Introduction

Although hypoactive sexual desire disorder (HSDD) is the most prevalent female sexual dysfunction, there is currently only 1 agent approved by the US Food and Drug Administration (FDA) to manage this disorder. Flibanserin, as discussed in Dr. Simon's article, has been shown to statistically significantly increase the number of sexually satisfying events and sexual desire compared with placebo; however, it remains underutilized owing to the warnings surrounding its use with alcohol ingestion. Among the numerous other agents being used, off-label, are testosterone, buspirone, and bupropion. The need for a safe and effective FDA approved agent is clear. Currently, 1 emerging melanocortin agonist has undergone phase 3 trials in the United States, and 2 testosterone-based oral agents are under investigation. In addition, an oral nonhormonal fixed-dose combination of 2 antidepressants, bupropion and trazodone, has completed a phase 2a clinical trial.

Bremelanotide (BMT)

A novel category of pharmacologic agents being investigated for use in HSDD involves melanocortin agonists. Melanocortins are peptide hormones produced in the pituitary; examples include adrenocorticotropic hormone and melanocyte stimulating hormone (MSH). Their novel mechanism of action involves activating endogenous melanocortin hormone pathways involved in sexual arousal and response. In addition to facilitating sexual desire, melanocortins also regulate food intake and body weight.[1] In preclinical studies involving rodents, MSH has been shown to facilitate lordosis—that is, body posture demonstrating sexual receptivity for copulation.[2]

Bremelanotide (BMT) is a novel cyclic 7-amino acid melanocortin receptor agonist that has high affinity for the type-4 melanocortin receptor, an analog of α-MSH. It is delivered via an auto-injector on an "as desired" basis and has demonstrated significant efficacy versus placebo in increasing sexual desire, while decreasing associated distress, in phase III investigations.

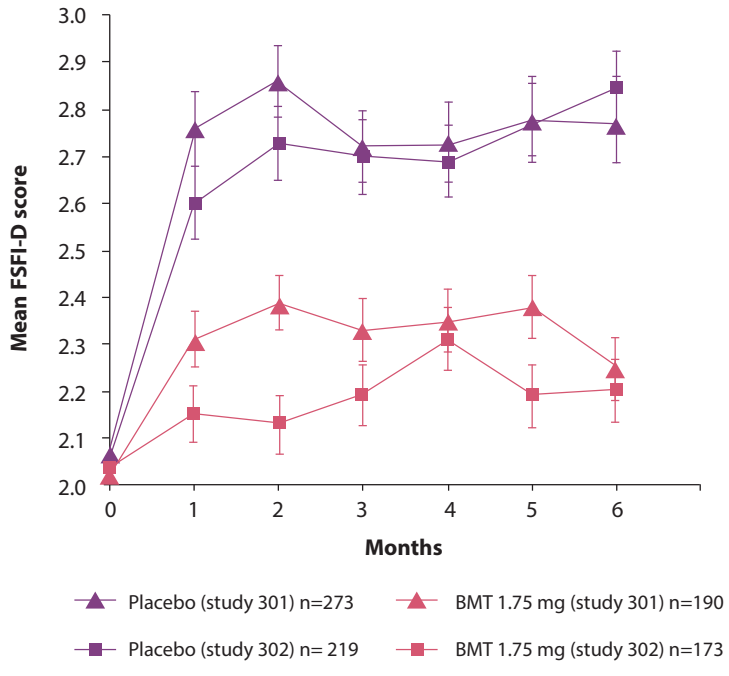
An early phase 2B clinical trial of bremelanotide, at doses of 1.25 mg and 1.75 mg, demonstrated significantly increased sexual arousal, sexual desire, and decreased associated distress in premenopausal women with FSD. Efficacy was seen in both women with HSDD and combined HSDD/female sexual arousal disorder (FSAD).[3]

The 2 "Reconnect" phase 3 clinical trials were randomized, double-blinded, placebo-controlled studies that compared the efficacy and safety of bremelanotide versus placebo in premenopausal women diagnosed with HSDD. The 2 trials enrolled nearly 1300 women with HSDD. The primary efficacy analysis population encompassed approximately 1200 women with HSDD. Bremelanotide, at a dose of 1.75 mg, or placebo, was self-administered by patients via autoinjector as needed in anticipation of sexual activity. The efficacy trial period of each study consisted of a 24-week treatment evaluation period.

The co-primary endpoints for the phase 3 clinical trials were (1) the Female Sexual Function Index: Desire Domain (FSFI-D) and (2) Female Sexual Distress Scale-Desire/Arousal/Orgasm (FSDS-DAO) Item 13. The diagnostic criteria for HSDD requires the presence of personal distress associated with the low sexual desire and does not include frequency of sexual activity or satisfaction as part of the definition, so the primary endpoints in these studies is very congruent with the disorder under study. Satisfying sexual events were relegated to a secondary endpoint. As noted in the article in this supplement by Dr. Parish, the FSFI-D is a validated patient reported outcome measurement tool of sexual desire in the context of overall sexual function. Item 13 of the FSDS-DAO is a validated patient reported outcome measurement tool of distress related to sexual dysfunction.

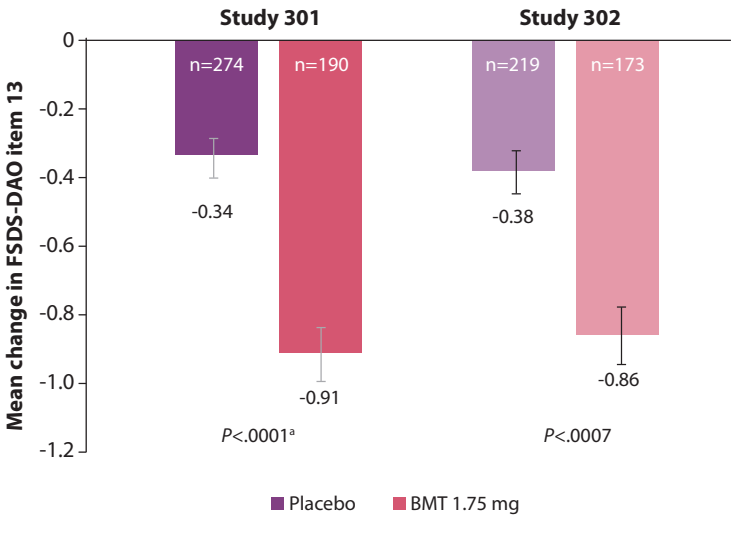
The results of the Reconnect studies demonstrated that bremelanotide achieved the pre-specified co-primary efficacy endpoints of (1) improvement in desire

FIGURE 1 Mean FSFI-D scores for placebo and BMT over the core (double-blind) phase



Abbreviations: BMT, bremelanotide; FSFI-D, Female Sexual Function Index: Desire Domain.

FIGURE 2 Change in FSDS-DAO item 13 score



aP values determined by unadjusted Wilcoxon rank-sum test. Error bars are standard error of the mean.
Abbreviations: BMT, bremelanotide; FSDS-DAO, Female Sexual Distress Scale-Desire/Arousal/Orgasm.

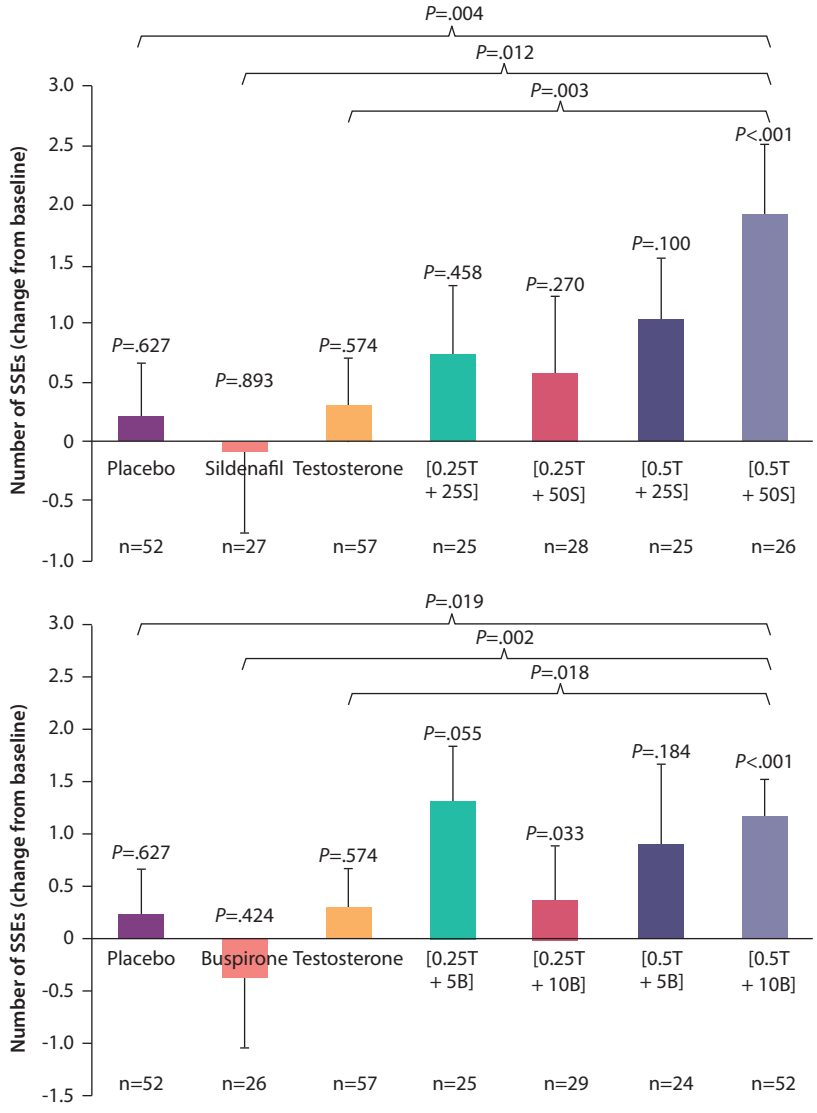
(**FIGURE 1**) and (2) decrease in distress associated with low sexual desire (**FIGURE 2**). The results also demonstrated a significant increase for bremelanotide regarding improvement in desire compared with placebo in both trials—with *P*=.0002 and *P*<.0001. As for reduction in distress, bremelanotide demonstrated a statistically significant reduction in both trials versus placebo, *P*<.0001 and *P*=.0057.[4–6]

The preliminary review of the overall safety population (1247 patients) indicated bremelanotide was well tolerated. The most frequent adverse event was nausea, which was generally mild in nature. In contrast to the initial findings with flibanserin, a phase 1 study conducted in both men and women demonstrated no clinically significant pharmacokinetic interactions between alcohol and bremelanotide—either overall or by sex.[7] Additionally, no significant drug-related hypotensive or orthostatic hypotensive effects were seen. Finally, there was no increased frequency of treatment-emergent adverse events, and no participants discontinued the study because of adverse events.

Combination Testosterone Agents

Two other emerging agents involve on-demand oral (sublingual) testosterone treatments for women with female sexual interest and arousal disorder (FSIAD). As discussed earlier in this supplement (Parish article), FSIAD reflects an inbalance between inhibition and excitation—described as the "sexual tipping point."[8] These combination agents are derived from the perspective that HSDD/FSIAD develops from 2 different causal mechanisms—a "relative insensitive brain system for sexual stimuli" and an "overactive sexual inhibition system in the brain."[9] Prior research involving 8 sexually functional women determined a time lag in the effect of testosterone that was administered sublingually, describing an immediate sharp increase in plasma testosterone (within 15 minutes), followed by a decline to baseline values within

FIGURE 3 Number of sexually satisfying events



Abbreviations: B=buspirone; FSFI-D, Female Sexual Function Index: Desire Domain; SSE, sexually satisfying events; S=sildenafil; T=testosterone.

Results for primary endpoint in all T + S and T + B treatment arms. The top and bottom panels show mean change in the number of SSEs between baseline and each of the treatment arms (error bars = standard error of the mean) for the T + S and T + B studies, respectively. The levels of significance of these changes are indicated above the associated bars. *P* values above the lines between 2 bars represent statistically significant interaction effects in the changes in the number of SSEs at the highest-dose combination compared with the placebo and monotherapies. Variances between the groups being compared were equal. Bars and error bars represent raw (non-imputed) data. *P* values and numbers shown are based on the multiply imputed data.

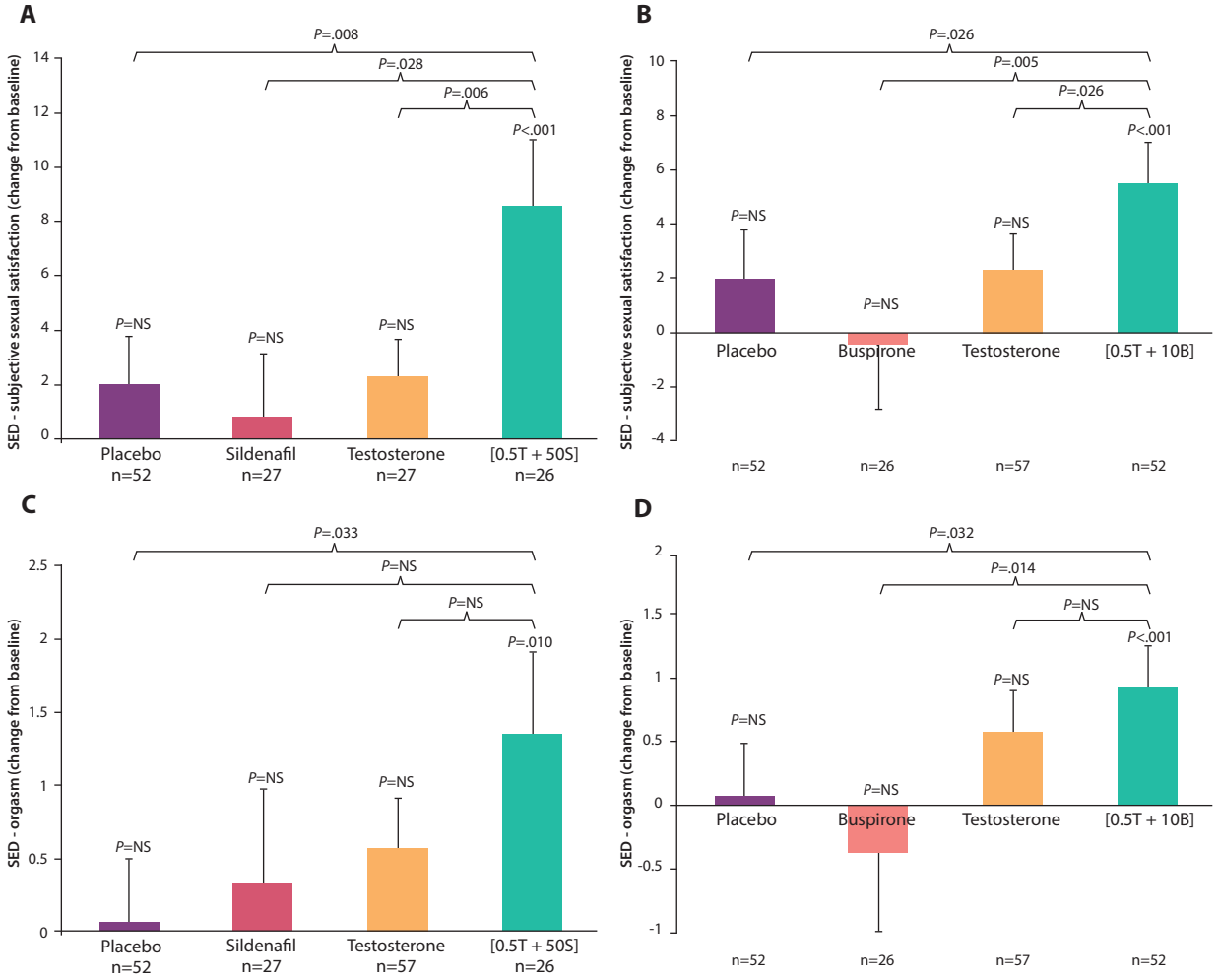
90 minutes.[10] However, within 3 to 4.5 hours after reaching peak testosterone levels, women reported a statistically significant increase in genital responsiveness, along with significant increases in genital arousal and subjective reports of "genital sensations" and "sexual lust." Administration of sublingual testosterone (0.5 mg) increases the sensitivity of the brain to sexual cues, regardless of circulating plasma levels of testosterone.[11]

In light of this information, investigators combined testosterone with 2 other agents believed to either increase the excitatory mechanisms or minimize inhibitory mechanisms in women prone to sexual inhibition.[9] Each of the agents are used "on-demand," and are recommended to be ingested about 3.5 hours prior to intended time of sexual activity.

The first agent combines testosterone with the phosphodiesterase type 5 inhibitor (PDE5i) sildenafil (T+S), and is specifically designed for women with FSIAD resulting from a relative insensitive brain system for sexual stimuli, or low sensitivity for sexual cues.[12] PDE5-inhibitors increase genital sexual response in the presence of sexual stimulation; as such, combining sublingual testosterone with a PDE5i might enhance sexual responsiveness. The second agent is targeted for women with FSIAD resulting from an "overactive sexual inhibition system in the brain" and combines testosterone with the serotonin1A receptor agonist buspirone (T+B).[13] As testosterone administration increases brain sensitivity to sexual cues, it might exacerbate inhibitory responses in women prone to sexual inhibition. This process likely involves 5-hydroxytryptamine (5-HT, or serotonin); as such, the addition of a 5-HT receptor agonist, such as bupropion, might negate the inhibitory response and allow for sexual response.[13]

The 2 agents were tested in nearly 500 women with FSIAD in a multicenter US-based phase 2b trial. Women were allocated to either agent using a personalized medicine approach that considered genetic, hormonal, and psychological variables believed to identify "low sensitivity to sexual cues" or "overactive sexual inhibition" subgroups.[11] The 3 random-

FIGURE 4 Subjective sexual satisfaction and orgasm



Abbreviation: B=buspirone; NS=not significant; S=sildenafil; SED, sexual event diary; T=testosterone.

Results for subjective sexual satisfaction and orgasm at the highest-dose combinations for placebo and monotherapies. Panels A and B show the comparisons between the high-dose combinations (T 0.5 + S 50 and T 0.5 + B 10, respectively) and the placebo and monotherapies (T 0.5, S 50, B 10) for change from baseline in subjective sexual satisfaction. Panels C and D show the comparisons between the high-dose combinations and the placebo and monotherapies, respectively, for change in arousal from baseline. Panels C and D also show the comparisons of high-dose combinations with placebo and monotherapies, respectively, for change in the number of orgasms from baseline. *P* values above each bar represent the level of significance of the change from baseline in the treatment arm in question. *P* values above the lines between 2 bars represent the interaction effects in changes of subjective sexual satisfaction and the changed number of orgasms at the highest-dose combination compared with placebo and monotherapies. Variances between the groups being compared were equal. The bars and error bars represent the raw (non-imputed) data. *P* values and numbers are based on multiply imputed data. Imputed data analysis did not differ substantially from the complete case analysis.

ized clinical trials compared placebo versus monotherapy with either of the agents in the combinations versus various dosages of the combinations over an 8 week active treatment period. Specifically, women with low sensitivity for sexual cues were given testosterone with sildenafil, and women with overactive inhibition were allocated to receive testosterone with buspirone. Using change in SSEs as the primary endpoint for each study, both agents demonstrated significant increases from baseline compared with placebo or monotherapy. In both groups, the combination significantly increased the number of SSEs versus placebo and monotherapies (**FIGURES 3 AND 4**). The most common adverse effects included flushing (testosterone with sildenafil, 3%; testosterone plus buspirone, 2%); headache (2% placebo; testosterone with sildenafil, 9%), dizziness (testosterone with buspirone, 3%) and nausea

(testosterone plus sildenafil, 3%; testosterone with buspirone, 3%). The investigators note that the drugs not only increase desire for sex but help make sexual activity more satisfying.

However, the effects of these combinations on distress was not investigated, nor was the persistence of benefits/improvements after treatment cessation.[11] Further, there are no data regarding long-term safety.

Conclusion

The past decade has seen important advances in the development of pharmacologic therapies for the management of HSDD/FSIAD in premenopausal women, including FDA approval of the first agent, flibanserin. However, safety considerations regarding its concomitant use with alcohol has limited its acceptance and use.

Off-label testosterone continues to be a popular treatment; the 2 new on-demand sublingual treatments that combine testosterone with another already-approved agent appear promising, but additional research is needed to determine long-term safety and tolerability and effectiveness. Bremelanotide represents a potential new therapy with a unique mechanism of action. Intermittent subcutaneous BMT has demonstrated significant benefit in improving sexual desire and reducing distress in clinical trials involving more than 1200 women, with no major safety concerns.

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Counseling Your Patients About Hypoactive Sexual Desire Disorder and Advances in its Diagnosis and Treatment

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1. **Which of the following symptoms would you identify as being associated with Hypoactive Sexual Desire Disorder (HSDD)? (Select 2)**
   a) Lack of motivation for sexual activity
   b) Decreased or absent spontaneous sexual thoughts or fantasies
   c) Problems achieving genital arousal
   d) Decreased or absent response of desire to erotic cue or stimulation
   e) Inability to maintain interest through sexual activity
   f) Experiencing painful intercourse
   g) Loss of desire to initiate or participate in sexual activity

2. **Which of the following disorders is the most distressful to women?**
   a) Orgasmic disorder
   b) Sexual arousal disorder
   c) Sexual desire disorder
   d) Not sure

3. **The first agent approved by the FDA for the treatment of HSDD in premenopausal women was:**
   a) Testosterone
   b) Flibanserin
   c) Bupropion
   d) Buspirone

4. **A 52-week study of Bremelanotide vs placebo in premenopausal women with HSDD showed:**
   a) Improvement in desire
   b) Decrease in distress associated with low sexual desire
   c) Both A + B

5. **How would you rate your ability to apply what you've learned to improve the following areas of your practice:**

	Significantly improved	Sufficient improvement	About the same	Slightly improved	Not improved
a) Describing the components of a comprehensive sexual history	○	○	○	○	○
b) Beginning a dialogue with patients regarding sexual health concerns	○	○	○	○	○
c) Accurately diagnosing hypoactive sexual desire disorder	○	○	○	○	○
d) Providing treatment options that include pharmacologic therapy	○	○	○	○	○
e) Incorporating the Decreased Sexual Desire Screener (DSDS) tool to screen for HSDD	○	○	○	○	○

6. How often will you now:

	Much more often than before	More often than before	About the same	Slightly less often than before	Much less often than before
a) Ask your female patients about their sexual health	○	○	○	○	○
b) Use a screening tool to screen for HSDD	○	○	○	○	○
c) Include a pharmacologic option when discussing treatment options	○	○	○	○	○

7. How does the FDA-mandated Risk Evaluation and Mitigation Strategy (REMS) program required of flibanserin impact your current practice?
a) I am certified in prescribing flibanserin
b) I am still uncertain about the risks with flibanserin and may apply for the certification in the future
c) I do not intend to apply for the certification/I will evaluate other management options

8. How many patients presenting with sexual problem reports (pain, etc.) or low sex drive do you see every month?
a) 0
b) <10
c) 11 – 25
d) 26 – 35
e) >36

9. What percentage of your patients with HSDD will benefit from the changes you will make in their care as a result of participating in this activity?
a) 0%
b) ~25%
c) ~50%
d) ~75%
e) ~100%

10. Which of the following are the most important barriers that prevent you from optimally managing/ counseling your patients about HSDD? Select all that apply.
a) Insurance reimbursement or state regulations
b) Patients' personal out-of-pocket costs
c) Patients' reluctance to discuss symptoms
d) Low awareness of treatment options
e My discomfort discussing symptoms
f) Low interprofessional collaboration/communication
g) I do not have any barriers
h) Other. Please specify: _____

11. Which of the following changes are you planning on making as a result of participating in this activity? Select all that apply.
a) Enquire about sexual health more proactively
b) Discuss/offer management options with patients
c) Educate staff/patients about existing and emerging options for HSDD
d) Obtain more information about HSDD and its management
e) Research insurance/payers and my state requirements and regulations
f) Communicate/collaborate with the members of the interdisciplinary team
g) Other. Please specify: _____

12. After this activity, I am able to better communicate and collaborate with the members of the interprofessional team and improve the care of patients with HSDD.
a) Agree
b) Disagree
c) Neutral

13. The presentation was fair, balanced, and free of commercial bias.
a) Agree
c) Disagree