MAYO CLINIC

Hypoactive Sexual Desire Disorder: International Society for the Study of Women's Sexual Health (ISSWSH) Expert Consensus Panel Review

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Abstract

The objective of the International Society for the Study of Women's Sexual Health expert consensus panel was to develop a concise, clinically relevant, evidence-based review of the epidemiology, physiology, pathogenesis, diagnosis, and treatment of hypoactive sexual desire disorder (HSDD), a sexual dysfunction affecting approximately 10% of adult women. Etiologic factors include conditions or drugs that decrease brain dopamine, melanocortin, oxytocin, and norepinephrine levels and augment brain serotonin, endocannabinoid, prolactin, and opioid levels. Symptoms include lack or loss of motivation to participate in sexual activity due to absent or decreased spontaneous desire, sexual desire in response to erotic cues or stimulation, or ability to maintain desire or interest through sexual activity for at least 6 months, with accompanying distress. Treatment follows a biopsychosocial model and is guided by history and assessment of symptoms. Sex therapy has been the standard treatment, although there is a paucity of studies assessing efficacy, except for mindfulness-based cognitive behavior therapy. Bupropion and buspirone may be considered off-label treatments for HSDD, despite limited safety and efficacy data. Menopausal women with HSDD may benefit from off-label testosterone treatment, as evidenced by multiple clinical trials reporting some efficacy and short-term safety. Currently, flibanserin is the only Food and Drug Administration–approved medication to treat premenopausal women with generalized acquired HSDD. Based on existing data, we hypothesize that all these therapies alter central inhibitory and excitatory pathways. In conclusion, HSDD significantly affects quality of life in women and can effectively be managed by health care providers with appropriate assessments and individualized treatments.

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Hypoactive sexual desire disorder (HSDD), the most prevalent female sexual health problem,[1] was considered the persistent or recurrent deficiency or absence of sexual fantasies and desire for sexual activity with marked distress or interpersonal difficulty not otherwise accounted for by a general medical or psychiatric condition. An HSDD may be primary or secondary, lifelong or acquired, or generalized or situational. The broadened definition of HSDD may include any of the following: (1) lack of motivation for sexual activity as manifested by either reduced or absent spontaneous desire (sexual thoughts or fantasies) or reduced or absent responsive desire to erotic cues and stimulation or inability to maintain desire or interest through sexual activity or (2) 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, incompetence, loss, sadness, sorrow, or worry.[2]

Women with HSDD have been found to have impaired body image, self-confidence,

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and self-worth and to feel less connected to their partners.[3] Total health care expenditures compared with a control patient cohort were higher for women with HSDD, including outpatient office visits, prescription medication use, and other medical services, including radiology, laboratory, and outpatient procedures.[4] Comorbidities include depression and fatigue, similar to chronic conditions such as diabetes and back pain.[4,5] Research on the neuroendocrine central mechanisms of sexual desire has led to an improved understanding of the underlying pathogenesis of this biopsychosocial condition. Misunderstandings about HSDD exist, leaving few clinicians feeling competent to inquire about or treat this condition.

Despite the existence of numerous publications on HSDD, what has been lacking is a concise resource that assists the clinician (internists/primary care physicians, gynecologists, urologists, and advanced practice providers) in competently screening the female patient for HSDD and providing appropriate therapeutic options in a biopsychosocial paradigm. To this end, the International Society for the Study of Women's Sexual Health (ISSWSH) commissioned a panel of experts to write a concise review of the state-of-the-art understanding of the neural circuitry that regulates sexual desire, including a plausible explanation for persistent states of both normal and hypoactive sexual desire; a description of current on- and off-label treatment strategies, including their benefits and pitfalls; and a discussion of the rationale for using various therapies.

METHODS

In January 2016, the ISSWSH executive committee chose co-chairs for this project to identify potential panelists based on individuals' publications and research. After a planning conference call with the chosen experts, panelists were asked to individually perform an evidence-based literature review in their respective topics, identifying high-quality publications that they judged to be important and pertinent to the topic. Literature selection criteria were not systematically defined but were based on the expertise and experience of each panelist. The panel of 13 researchers and clinicians convened in Dallas, Texas, to present and discuss the current state of knowledge of HSDD. Participants declared potential conflicts of interest and were ISSWSH members and nonmembers. Panelists deliberated on the history, pathogenesis, diagnostic process, and treatment of HSDD and were assigned to writing groups for the development of this article.

The ISSWSH is a not-for-profit multidisciplinary academic and scientific organization dedicated to supporting the highest standards of ethics and professionalism in the research, education, and clinical practice of women's sexual health. The ISSWSH received an unrestricted grant from industry for the development of this document. No industry representatives were present in the closed committee meetings; there was no industry participation in the evidence selection, discussion, or creation of this document; and there was no attempt by industry to influence its content.

History of HSDD and Nosology

Historically, the diagnoses of female sexual dysfunctions have been made principally by clinical presentation and patient history rather than by nosology based on etiology, pathogenesis, and clinical phenomenology. Development of the diagnostic concept of HSDD is closely tied to the evolution of the *Diagnostic and Statistical Manual of Mental Disorders (DSM)* system, the diagnostic classification system of the American Psychiatric Association.[6] The diagnostic category of HSDD has existed for approximately 30 years, with its antecedents labeled differently but defined in a similar manner.[7-11] The definition has evolved with the text-revised versions of the *DSM-IV* and the *DSM-5*.[10,11] In the *DSM-5,* HSDD has been eliminated as a distinct nosologic entity and has been replaced with an amalgamation of the *DSM-IV* HSDD and female sexual arousal disorder diagnoses, termed female sexual interest/arousal disorder. This revised classification has been controversial among experts in the area of sexual medicine because there is little empirical support or validation of the new diagnostic category/criteria in contemporary clinical research.[12,13]

Concern over what some consider to be the inappropriate elimination of the diagnostic

category of HSDD in *DSM-5* has resulted in the development of an autonomous nosology for female sexual dysfunctions by two international panels of experts in sexual medicine (the ISSWSH Nomenclature Committee and the International Consultation in Sexual Medicine).[2,14] Importantly, the ISSWSH nosology retains HSDD as a distinct diagnostic entity, consistent with what many believe to be empirically based clinical experience. This classification system is also consistent with the *International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10)* nomenclature system,[15] which is used throughout the world and applies to both the somatic and psychiatric diagnostic systems. In the *ICD-10*, HSDD (*ICD-10* code F 52.0) is represented as an independent diagnostic category, as it had been in the *DSM* system before *DSM-5*.

Epidemiology

Hypoactive sexual desire disorder is a common but frequently undiagnosed condition. Initially, epidemiologic studies examining the prevalence of low desire in women did not take into account the associated bother and distress, a cardinal symptom of HSDD. However, they did associate lower quality-of-life measures (eg, physical and emotional satisfaction with sexual partners and general happiness) in women with low desire compared with women with no sexual problems.[16] In later studies that examined low sexual desire with distress in large cohorts of premenopausal and postmenopausal women in the general population, the overall prevalence of HSDD ranged from approximately 8% to 19%.[1,17-19] These studies also found associations between distressing low sexual desire and lower health-related quality of life, as well as psychosocial factors such as dissatisfaction with sex life, partner, or marriage and negative emotional states, including frustration, hopelessness, anger, poor self-esteem, and loss of femininity.

When subgroups were further characterized, women with a current spouse or partner were more likely to experience concomitant distress with low sexual desire than nonpartnered women.[20] In addition, self-assessed poor health, thyroid disease, and urinary incontinence were associated with increased probability of distressing low sexual desire. There was also a marked association between depression and anxiety and distressing low sexual desire.[21] Interestingly, although the prevalence of low sexual desire increased with age and was higher in naturally menopausal women, the prevalence of associated distress declined with increasing age.[17] Similarly, in a study of US and European women aged 20 to 70 years, the occurrence of low desire increased with age and distress about low desire decreased, resulting in relatively constant prevalence rates of distressing low sexual desire with age (12%-19% in the United States and 6%-13% in Europe).[18]

One potential limitation of population-based surveys is that the data are self-reported, with no independent verification. Thus, it is important that a multicenter, longitudinal, observational study of women with clinically diagnosed HSDD was initiated in 2008 and completed enrollment of 1592 participants into an HSDD registry.[22] Among the baseline findings, one-third of the 1088 premenopausal women had symptoms or a clinical diagnosis of depression.[23] In a subgroup of 426 premenopausal women and 174 postmenopausal women with HSDD, a significant proportion (54% premenopausal; 66% postmenopausal) had concomitant arousal or lubrication problems.[24] These data illustrate the importance of accurately and completely assessing patients presenting with HSDD to detect any possible concomitant conditions and optimize treatment.

Physiologic Mechanisms Modulating Sexual Desire

Sexual desire has been studied in both the clinical and laboratory settings. Validated patient-reported instruments (eg, the Female Sexual Function Index) enable clinically sensitive assessment of changes in sexual desire. In animal studies, sexual desire can be reliably inferred from behaviors that anticipate or solicit sexual interaction or otherwise indicate sexual interest. These behaviors and underlying cognitive, emotional, and regulatory processes are controlled by brain systems involved in sexual excitation and inhibition.[25-30]

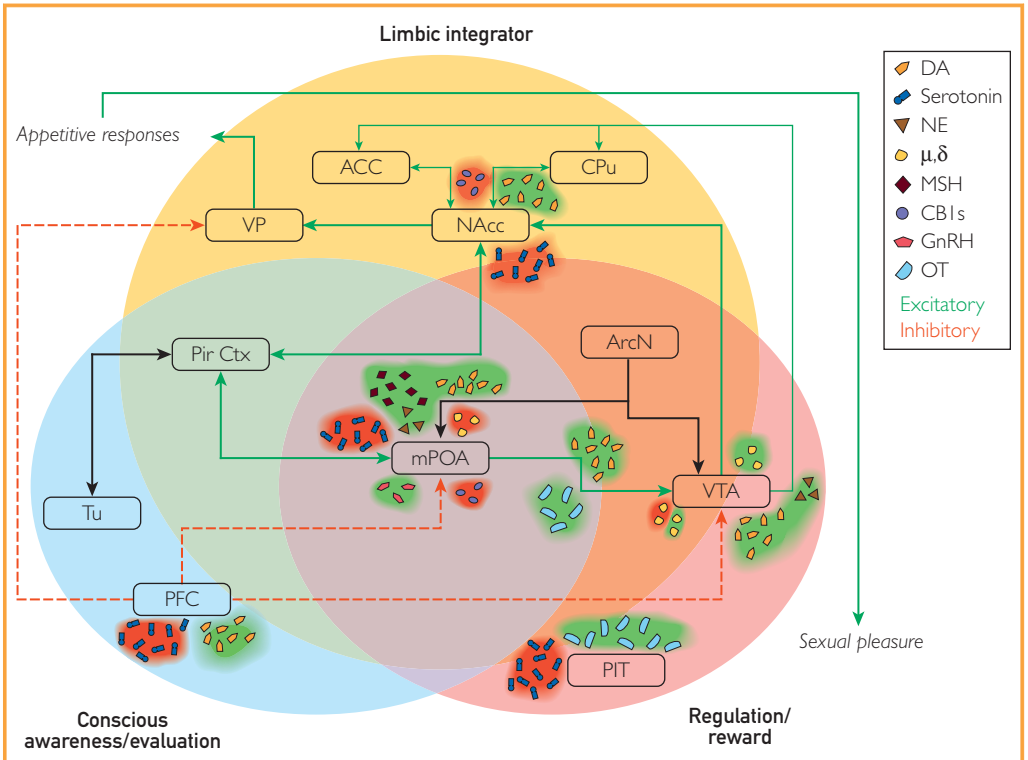

FIGURE 1. Neural pathways regulating sexual desire in the brain. The main excitatory (solid green) and inhibitory (dashed red) pathways between key brain regions are depicted. Black pathways represent known connections that can be both excitatory and inhibitory. Neurotransmitters (see icon key) and their approximate sites of action are shown. Each neurotransmitter is highlighted to denote the excitatory (green) or inhibitory (red) effect on specific pathways or at specific sites. The number of icons indicates the relative strength of influence of a given neurotransmitter. The Venn diagram overlay represents 3 interactive functional systems that process external stimuli through evaluation of sexual reward that may be integrated to facilitate or attenuate appetitive responses characteristic of sexual desire. ACC = anterior cingulate cortex; ArcN = arcuate nucleus of the hypothalamus; CB1s = cannabinoid type 1 receptor; CPu = caudate-putamen; δ = delta opioid receptors; DA = dopamine; GnRH = gonadotropin-releasing hormone; μ = mu opioid receptors; mPOA = medial preoptic area; MSH = melanocyte-stimulating hormone; NAcc = nucleus accumbens; NE = norepinephrine; OT = oxytocin; PFC = prefrontal corex; Pir Ctx = piriform cortex; PIT = pituitary; Tu = olfactory tubercle; VP = ventral pallidum; VTA = ventral tegmental area. Adapted from *Encyclopedia of Behavioral Neuroscience*.[29]

Neural Regulation. Key regions in the brain that regulate sexual desire include the prefrontal cortex, locus coeruleus, medial preoptic area, paraventricular nucleus, and reward- and attention-processing centers of the ventral tegmental area and the nucleus accumbens (Figure 1).[25-30] Sexual excitation involves the actions of brain dopamine, melanocortin, oxytocin, vasopressin, and norepinephrine. These neurotransmitters coordinate pathways in the hypothalamus, limbic system, and cortex to process and respond to sexual stimuli. Sexual inhibition involves brain opioid, serotonin, and endocannabinoid systems that are activated normally during sexual refractoriness or as a function of primary aversion or secondary avoidance. These inhibitory systems blunt the ability of excitatory systems to be activated.

A large aggregate of animal and human literature on the psychopharmacology of sexual motivation and desire[28-30] reports that sexual desire can be inhibited by drugs or conditions that (1) decrease brain dopamine levels, (2) augment the action of brain serotonin specifically through serotonin 2A

receptors, or (3) increase opioids acting at mu receptors. Conversely, sexual desire can be stimulated by drugs or conditions that (1) increase hypothalamic and mesolimbic dopamine or (2) decrease serotonin release or inhibit postsynaptic binding in the prefrontal cortex. Drugs that can selectively activate these stimulatory pathways or reduce inhibitory pathways are being actively evaluated for the treatment of HSDD, with one (flibanserin) currently approved by the Food and Drug Administration (FDA).

Hormonal Regulation. Sexual motivation and desire peaks in women and nonhuman mammalian females during the periovulatory period.[31-34] This peak is driven by ovarian hormone actions that prime excitatory sexual systems in the brain and periphery.[35] However, during much of the 20th century it was generally believed that women's sexual desire was not influenced by ovarian hormones.[36] Although earlier equivocal studies suggested that adrenal androgens were crucial to women's sexual desire,[37] evidence that ovariectomy reduced or eliminated women's sexual desire was not published until the 1980s.[38-40] Because these ovariectomized women had functioning adrenal cortices, these findings ruled out the notion that adrenal androgens were critical to women's sexual desire. Thus, the focus shifted to ovarian corticosteroids, including estradiol and testosterone, as modulators of women's sexual desire.

Although there remain problematic aspects with the accuracy of testosterone assays for women and in interpreting different experimental designs, hormone therapy studies found that testosterone increased sexual desire in surgically and naturally postmenopausal women, as well as in premenopausal women.[41,42] In these studies, total testosterone plasma levels were in the upper normal or supraphysiologic range, although this does not necessarily predict levels of bioavailable and free testosterone.[36] In contrast, in a study of naturally menopausal women, the decline in sexual desire was best predicted by declines in estradiol rather than testosterone.[43] In premenopausal women, studies of changes in sexual desire in relation to changes in ovarian hormone levels across the menstrual cycle have produced mixed results, potentially due to differences in methods, including using frequency of sexual intercourse as a proxy for sexual desire and the interval of ovarian hormone measurements.[36,44] Nevertheless, when sexual desire and ovarian hormone levels were measured daily, estradiol was positively correlated with sexual desire, progesterone was associated with decreased sexual desire, and testosterone levels did not predict any aspect of women's sexual desire.[43]

Yet, recent clinical consensus statements do not support the use of estrogen as a therapeutic intervention to treat HSDD.[45] In addition, ovarian testosterone levels show a short-term rise during ovulation. It is possible that this rise could activate excitatory sexual mechanisms directly through androgenic action or indirectly either through conversion to estrogen by aromatase. Alternatively, the secreted androgen may bind to corticosteroid hormone-binding globulins in blood, thus allowing more estradiol to get into the brain, where it stimulates excitatory sexual mechanisms. Thus, hormones are important regulators of sexual desire but are among a myriad of other factors that are integrated in the excitatory and inhibitory pathways in the brain.

Pathogenesis of HSDD. The precise biological alterations that cause HSDD remain incompletely characterized. Clinically, no identifiable hormonal differences characterize premenopausal women with HSDD. Postmenopausal women often experience lower levels of sexual desire but have lower rates of distress.[46] Although lower testosterone levels have been associated with decreased sexual desire, there is no level of testosterone that predicts HSDD.[47] Similarly, low sexual desire is also associated with decreased estradiol levels, but women with HSDD do not necessarily have low estradiol levels. Thus, although ovarian corticosteroids may modulate women's sexual desire, their exact role in HSDD remains unclear.

Irrespective of whether imbalances in hormone levels play a causative role, it is likely that primary and secondary generalized HSDD involves either a predisposition toward inhibitory pathways in the brain[48] or functional and structural neuroadaptations in these systems that result in decreased excitation, increased inhibition, or some mix of the two. Such dynamic alterations in brain function and

structure may be additionally modulated or reinforced by experience and behavior, further propagating the condition. This process of experience-based neuroplasticity is not unique to HSDD and links behavior to cellular mechanisms (neuronal circuits), synaptic mechanisms (long-term potentiation or inhibition of synaptic strength), and molecular mechanisms (ion channels, cell surface receptors, transcriptional and translational events, and epigenetic modifications).[49,50] This proposed mechanism is also consistent with differential brain activity patterns and structural differences between women with and without HSDD.[51-54]

Among the most dramatic differences, positron emission tomography studies of volunteers shown erotic videos indicate that women with HSDD have weaker activation of the cerebral cortex in the right hemisphere and significantly less deactivation in the left hemisphere compared with women who do not have HSDD (Figure 2A). It is possible that the weaker activation of the right side may represent a muted response to sexual cues, whereas the inability to deactivate higher-order analytical processing on the left side may perpetuate inhibitory neural pathways. Mechanistically, experience-based neuroplasticity may explain how multiple modalities of psychological and medical treatment can benefit a patient with HSDD by potentially modulating the underlying sexual inhibition and excitation mechanisms in the brain (Figure 2B).

Diagnosis of HSDD

The diagnosis of HSDD begins with a thorough history to determine whether the root cause is neurobiological, interpersonal, psychosocial, or some combination of these. The diagnosis of HSDD may include bothersome/distressing symptoms of reduced motivation for participation in sexual activity due to decreased spontaneous desire (sexual thoughts/cognitions or fantasies), sexual desire in response to erotic cues and stimulation, or ability to maintain desire or interest through sexual activity. Symptoms may also include distressing behavioral manifestations of amotivation, such as (1) reduced or absent initiation of sexual activity, (2) avoidance of situations that could lead to sexual activity (eg, going to bed after partner is asleep, restricting casual physical contact so as not to lead the partner to misperceive an interest in sex, etc), and (3) participation in sexual activity only out of obligation or fear of loss of partner. Relationship issues may lead to low desire but should be addressed and excluded as the primary etiology before diagnosing generalized acquired HSDD. The diagnosis of HSDD does not require complete loss of sexual desire but rather a change for at least 3 months from what it was previously. Importantly, personal distress is a prerequisite for the diagnosis of HSDD. The distress may manifest as frustration, grief, incompetence, loss, sadness, sorrow, low self-esteem, confusion, or worry, but these should not be the cause of the diminished desire.[10,14]

History/Screening. Health care providers should initiate the general discussion and assessment of sexual concerns because patients are often uncomfortable and unwilling to bring up the topic. Initial screening tools can facilitate the discussion of HSDD. The Decreased Sexual Desire Screener (Table 1), a 5-question instrument completed by the patient, was developed and validated for use by clinicians to aid in making the diagnosis of HSDD in premenopausal and postmenopausal women per the *DSM-IV-TR* and ISSWSH criteria.[2,56,57] Women indicate *yes*/*no* responses to the 5 questions (Table 1). The purpose of questions 1 through 4 is to determine whether there is HSDD. If the patient responds *yes* to all the questions, this is consistent with generalized acquired HSDD.

The purpose of question 5 is to help determine whether the etiology of HSDD is primary or secondary. In the case of secondary HSDD, it is important to treat the underlying cause. The presence of psychiatric and medical conditions, other sexual issues in the woman or her partner, use of substances/medications, or relationship problems as a cause of the diminished desire would be consistent with a diagnosis of secondary HSDD. Discrepancy of the level of desire between a woman and her partner does not qualify the person with the lower desire as having HSDD per se. Note that having regular sex with a partner does not necessarily indicate that a woman does not have HSDD given that women have

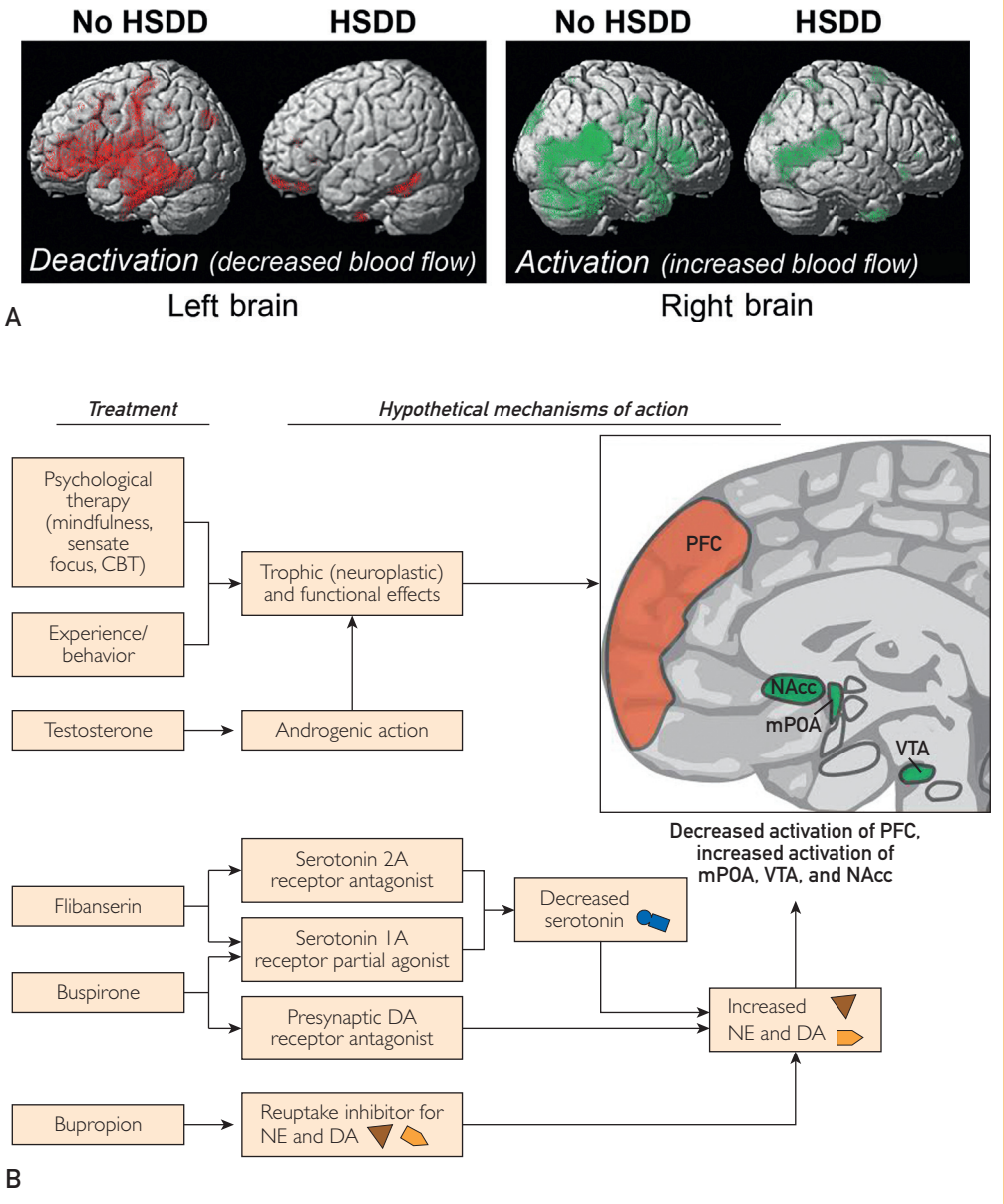

FIGURE 2. A, Changes in neural activity in response to viewing an erotic video in women with or without hypoactive sexual desire disorder (HSDD) assessed by positron emission tomography. Decreased activation, observed primarily in the left hemisphere, is shown in red, and increased activation, observed primarily in the right hemisphere, is shown in green. Minimal deactivation was observed in the right hemisphere and minimal activation was observed in the left hemisphere. Adapted with permission from *Sex Med Rev*.[55] B, Current treatments for HSDD and their hypothetical mechanisms of action. All treatment modalities are hypothesized to modify the functional neural pathways summarized in Figure 1 through experiential stimuli, corticosteroid hormone action, and/or modulation of neurotransmitter levels. CBT = cognitive behavior therapy; DA = dopamine agonist; mPOA = medial preoptic area; NAcc = nucleus accumbens; NE = norepinephrine; PFC = prefrontal cortex; VTA = ventral tegmental area.

TABLE 1. Decreased Sexual Desire Screener

1. In the past, was your level of sexual desire or interest good and satisfying to you?	O Yes	O No
2. Has there been a decrease in your level of sexual desire or interest?	O Yes	O No
3. Are you bothered by your decreased level of sexual desire or interest?	O Yes	O No
4. Would you like your level of sexual desire or interest to increase?	O Yes	O No
5. Please check all the factors that you feel may be contributing to your current decrease in sexual desire or interest:		
a. An operation, depression, injuries, or other medical conditions	O Yes	O No
b. Medications, drugs, or alcohol you are currently taking	O Yes	O No
c. Pregnancy, recent childbirth, menopausal symptoms	O Yes	O No
d. Other sexual issues you may be having (pain, decreased arousal, or orgasms)	O Yes	O No
e. Your partner's sexual problems	O Yes	O No
f. Dissatisfaction with your relationship or partner	O Yes	O No
g. Stress or fatigue	O Yes	O No

- If the patient answers *no* to any of the questions 1-4, then she does not qualify for the diagnosis of generalized acquired hypoactive sexual desire disorder (HSDD).
- If the patient answers *yes* to all of the questions 1-4, and your review confirms *no* answers to all of the factors in question 5, then she does qualify for the diagnosis of generalized acquired HSDD.
- If the patient answers "*yes*" to all of the questions 1-4 and "*yes*" to any of the factors in question 5, then decide whether the answers to question 5 indicate a primary diagnosis other than generalized acquired HSDD. Comorbid conditions such as arousal or orgasmic disorder do not rule out a concurrent diagnosis of HSDD.

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sex for many reasons unrelated to sexual desire (eg, sexual coercion or out of fear or duty).[58]

Obtaining a detailed description of the woman's problem, including the onset, duration, and severity of her low sexual desire symptoms and her level of distress and bother, may further establish the diagnosis and guide treatment. Overlap of female sexual disorders is common, such as HSDD impairing arousal that impairs orgasm or may lead to pain (eg, attempting penetration without adequate lubrication because she is not interested or aroused). A full sexual history can help delineate the primary problem, establish diagnoses, and assist in developing an approach to individualize treatment.

Additional Evaluation/Testing. Although a physical examination is not required to make the diagnosis of HSDD, it may be appropriate, based on history, to rule out other factors that may be contributing to the low sexual interest condition, such as concerns of pain with sexual activity or findings consistent with hormone insufficiency states.

Although laboratory testing is not used to make a diagnosis of HSDD, thyroid hormone and prolactin levels should be measured where clinically indicated to exclude an endocrine

TABLE 2. Example of Using the PLISSIT Model

- **(P) Permission:** the provider explicitly encourages a woman to discuss any sexual concerns or questions she may have and validates her right to satisfying sexual function.

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- **(LI) Limited Information:** the practitioner may educate the patient about sexual physiology or suggest educational resources such as literature, videos, and erotica.

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- **(SS) Specific Suggestions:** the clinician provides tailored approaches designed to improve sexual and emotional communication, such as sensate focus exercises, masturbation, Kegel exercises, technical advice regarding sexual positions, and the use of lubricants or dilators.

↓

- **(IT) Intensive Therapy:** may involve referral for individual or couples therapy to deal with long-standing conflict that is contributing to a woman's hypoactive sexual desire.

problem that may be causing or contributing to low desire. Testosterone and sex hormone-binding globulin levels are also not required for the diagnosis of HSDD but are recommended if considering testosterone therapy.

Referral for assessment by a psychotherapist is indicated if psychological or interpersonal/relationship problems seem to be etiologically related to the low desire or as a component of a multimodal treatment approach regardless of etiology. Referral for psychotherapy assessment should not limit or postpone further medical evaluation of HSDD if indicated.

Treatment of HSDD

The treatment of HSDD may engage both psychosocial and biological strategies because psychosocial/interpersonal and biological factors impact each other.[59] However, it is reasonable to sequence treatment that focuses on the suspected primary contributing component(s), emphasizing treatment of the factors that are most distressing to that individual woman. Brief office-based counseling may be helpful using the PLISSIT model (Permission, Limited Information, Specific Suggestions, and Intensive Therapy), a stepped approach specifically for general health care providers caring for women with sexual concerns (Table 2).[60] If psychotherapy is indicated, the patient should be referred to a sex therapist for management, including determination of the appropriate form of therapy for that patient or couple.

Cognitive and Motivational Aspects. Psychotherapy is a recognized treatment strategy for HSDD, typically focused on modifying thoughts, beliefs, behaviors, emotions, and relationship communication/behaviors that interfere with desire. Cognitions typically addressed include negative thoughts, beliefs, expectations, cultural and religious standards, and attributions about sex, sexual activity, and altering/correcting other thoughts that inhibit sexual desire/lack of desire. Reactive sexual behaviors (or avoidance) maintain negative cognitions/emotional reactions, contributing to loss of desire. With modification of these behaviors to elicit positive emotional reactions and with positive reinforcement, the behaviors are more likely to be repeated and continued. Emotions refer to negative and positive feelings, such as confidence, body image, and resentments. Relationship dimensions are (1) identification of aspects such as couple expectations, autonomy, cohesion, and commitment; (2) cooperation, including interactions, conflict handling, and pressure from partner; (3) emotional intimacy, such as relationship feelings, empathy, and pressure; and (4) determination regarding whether the relationship conflict is the source of loss of desire or whether loss of desire led to relationship conflict.[59] A woman with a desire discrepancy (less desire than her partner) may feel pressured and consequently perceive sex as a chore or, worse, aversive. The treatment focuses on the dynamic interplay between the woman and her partner in their sexual relationship. Questions during the assessment may focus on how the woman/couple function cognitively, their sexual behavior and skills, communication of sexual needs, and sufficiency of sexual stimulation.

Sensate focus. Sensate focus therapy involves a graded series of nondemand sensual touching exercises.[61] Typically used with couples, the objectives of sensate focus therapy are to reduce anxiety and avoidance of sensual touching or sexual activity, improve sexual communication between partners, and improve intimacy by reintroducing sexual activity in a gradual way. Exercises begin with nongenital touching and with successful achievement of each progressive series of exercises move to genital touching and, ultimately, penetrative sexual activity/intercourse or other genital sexual activity. Sensate focus may be more helpful in a subgroup of women with HSDD secondary to penetration-related anxiety and associated behavioral avoidance.

Cognitive Behavior Therapy. Cognitive behavior therapy (CBT) focuses on altering thoughts and behaviors that distract or result in inhibiting (or nonexciting) sexual thoughts in a sexual situation with specific focus on automatic thoughts and beliefs that may inhibit sexual desire (cognitive component).[62] The behavioral component of therapy serves to change sexual behavior by focusing on pleasure and not on sexual form and planned sexual activity and self-exploration instead of avoidance of sexual activity. An important part of the CBT approach is education that may help the

woman and her partner understand the physiology and psychology of sexual desire and change the perception of what is desire and sex.

McCabe[63] found a CBT program to be effective in 44.4% of women with sexual health concerns. Cognitive behavior therapy was most likely to be effective in women with anorgasmia and sexual arousal disorder and least likely to be effective in women who experienced a lack of sexual interest. A total of 54% of women who underwent CBT still reported a lack of sexual interest after CBT. Trudel et al[64] found that 74% of women with HSDD were considered to be improved by the end of a CBT group intervention. A total of 64% remained improved at 1-year follow-up after CBT. Neither study had an adequate control group paradigm.[65]

Mindfulness. The goal of mindfulness-based cognitive therapy is to encourage participants to connect and engage with their sexuality by learning and practicing a variety of mindfulness exercises that attempt to improve awareness of the here and now and acceptance and self-compassion.[66] Therapy also includes an educational component regarding female sexuality and sexual function. Session content may include helping women discover the ways in which sexual interest and motivation are influenced by thoughts, feelings, behaviors, and relationships. Another goal is to improve awareness and, thus, alter the effect of sexual function on mood and self-esteem.

The paucity of clinical trials and lack of adequate controls in the published studies that evaluate the efficacy of psychotherapeutic treatments of HSDD makes it difficult to draw any useful conclusions at this time.[63-66]

Neuroendocrine/Neurochemical Aspects

Flibanserin. Flibanserin, dosed at 100 mg at bedtime, is a nonhormonal, centrally acting, postsynaptic serotonin 1A receptor agonist and a serotonin 2A receptor antagonist (a multifunctional serotonin agonist and antagonist) that results in a decrease in serotonin activity and an increase in dopamine and norepinephrine activity.[67] Flibanserin is currently the only FDA-approved treatment for generalized acquired HSDD in premenopausal women in the United States. A risk evaluation and mitigation program requires certification of prescribing health care providers and pharmacists. Efficacy may not emerge for several weeks, and treatment should be discontinued after 8 weeks if no benefit is realized.[68] Given the limited clinical experience with flibanserin due to its recent approval, additional information is provided herein.

Statistically significant efficacy was established in 3 North American pivotal clinical trials in premenopausal women with HSDD, with daily dosing of flibanserin 100 mg at bedtime demonstrating increased sexual desire, decreased sexually related distress, and increased satisfying sexual events.[68,69] The clinically meaningful benefit of this therapy was established based on the patient global impression of improvement, which demonstrated self-reported responder rates for sexual desire (minimally, much, or very much improved) of 54% to 58% in premenopausal women for flibanserin vs 40% to 48% for placebo treatment. Similar efficacy and safety results were seen in studies of flibanserin in postmenopausal women,[70] but flibanserin is not yet approved in this population.

Safety was also established in clinical trials where the most common adverse events (AEs) in terms of placebo-corrected rates of occurrence in premenopausal women were dizziness (9.2%), somnolence (8.3%), nausea (6.5%), and fatigue (3.7%). Note that these types of AEs are not uncommon with central nervous system–active medications that influence serotonin. Most AEs were transient or episodic, were mild to moderate in severity, and were mitigated by bedtime dosing. The discontinuation rate due to AEs was 13% in patients treated with flibanserin 100 mg and 6% in patients treated with placebo.[68-71] A dedicated driving study found that flibanserin use did not have a negative effect on next-day cognitive function or driving performance.[68] These results are reassuring regarding the sedating effects of flibanserin.

An alcohol interaction study, in which excessive exposure to alcohol was observed to add to the adverse effects of flibanserin when given in the morning, found increased frequency and severity of sedation, hypotension, and syncope, which resolved in all cases with lying down/Trendelenburg position.[71] As a result of this study, flibanserin has a boxed warning highlighting the increased risks of "serious hypotension and syncope" with concomitant use of alcohol.

In the clinical trials leading to approval, alcohol intake was not restricted, and 58% of women (n = 898) treated with flibanserin 100 mg reported "social drinking" at study entry. Although alcohol consumption was not monitored during the trials, rates of syncope and presyncope (including hypotension) remained low in the flibanserin group (0.8% in drinkers and 0.2% in nondrinkers) vs the placebo group (0.3% in drinkers and 0.2% in nondrinkers).[71] In comparison, hypotension and syncope are reported to have an annual incidence of 6% in the general population and to account for 1% to 3% of emergency department visits and hospitalizations.[72]

Testosterone. Testosterone therapy is an evidence-based off-label treatment for perimenopausal and postmenopausal women with HSDD.[73-79] Transdermal testosterone therapy using the 300-μg/d patch has been consistently reported in multiple studies to be effective for the treatment of HSDD. In double-blind, placebo-controlled clinical trials in naturally and surgically menopausal women, testosterone therapy resulted in statistically significant improvements in the number of satisfying sexual events, sexual desire, and sexual distress that were 2-fold greater than placebo.[44,79] The short-term safety of testosterone has been reported across studies, and the most common AEs include hirsutism and acne, which occur at placebo-corrected rates of 3% to 8% in treated women, although some studies in surgically menopausal women have reported essentially no difference between testosterone and placebo treatment groups regarding AEs.[79] Long-term safety of testosterone therapy regarding breast cancer and cardiovascular outcomes are limited to observational studies.[80-82] Women prescribed off-label testosterone for HSDD should be carefully monitored. Efficacy may not emerge for several weeks, and treatment should not be continued beyond 6 months if no benefit is realized.[83] Ideally, formulations should be developed specifically for women.

Bupropion. Bupropion, a norepinephrine-dopamine reuptake inhibitor, is approved as an antidepressant and a treatment for smoking cessation, but it is used as an off-label treatment for HSDD.[84-86] Bupropion sustained-release 150- to 400-mg daily dosing has been investigated in several clinical trials for the treatment of HSDD, improving sexual function as measured by the Changes in Sexual Functioning Questionnaire and the Brief Index of Sexual Functioning for Women.[85,86]

Although safety data for bupropion is not specifically available in women diagnosed as having HSDD, the most common AEs in terms of placebo-corrected rates of occurrence in placebo-controlled clinical trials for depression were tremor (13.5%), agitation (9.7%), dry mouth (9.2%), constipation (8.7%), excessive sweating (7.7%), dizziness (6.1%), and nausea/vomiting (4%). The AEs caused discontinuation of treatment in approximately 10% of 2400 patients and volunteers in clinical trials.[87]

Buspirone. Buspirone, a serotonin 1A partial agonist, is approved as an anxiolytic for the management of generalized anxiety disorder or the short-term relief of symptoms of anxiety, and it is used as an off-label treatment for HSDD.[88-90] When buspirone was coadministered with selective serotonin reuptake inhibitors for the treatment of depression, a reduction in selective serotonin reuptake inhibitor—induced sexual dysfunction was noted. Fifty-eight percent of individuals treated with buspirone reported an improvement in sexual function compared with 30% treated with placebo.[89] Studies of treatment of HSDD have not been published.

Similar to bupropion, safety data for buspirone is not specifically available in women diagnosed as having HSDD. The most common AEs in terms of placebo-corrected rates of occurrence in placebo-controlled clinical trials were dizziness (9%), nervousness (4%), nausea (3%), and headache (3%). Approximately 10% of 2200 anxious patients in trials discontinued treatment due to an AE.

Future

This ISSWSH expert consensus panel reviewed current evidence related to multiple facets of the most common female sexual dysfunction, HSDD, including epidemiology, physiology, pathophysiology, diagnosis, and treatment. The aim was to review the state-of-the-art, clinically relevant information that would be used by the health care provider to

facilitate a broader understanding of the condition of HSDD in affected women who present during routine office visits. In the future, ISSWSH plans to develop a focused consensus document exclusively concerning a first-ever step care, diagnostic, and treatment paradigm for the management of women with HSDD by the primary care physician. Also note that other medical therapies for HSDD are in development. Among these, bremelanotide, a centrally acting synthetic melanocortin peptide, has demonstrated clinical efficacy in phase 2 studies.[90]

CONCLUSION

Hypoactive sexual desire disorder in women is an important female sexual dysfunction that has been well-characterized for more than 3 decades. Based on contemporary research, the pathogenesis of HSDD is attributed to an imbalance in central sexual excitatory (dopamine, norepinephrine, melanocortin, and oxytocin) and sexual inhibitory (serotonin, opioid, endocannabinoid, and prolactin) pathways. Epidemiologic studies have identified multiple contributing factors, such as psychological conditions, relationship concerns, medical conditions, medications, and menopause.

The health care provider should be aware that diagnostic assessment of a woman with HSDD engages a biopsychosocial perspective and is primarily based on history. The Decreased Sexual Desire Screener is a validated instrument that aids in HSDD diagnosis. The treatment of HSDD may also engage both psychosocial and biological strategies. Treatment should focus on the factors that are most distressing to the individual. Brief office-based counseling or referral for sex therapy may be helpful. Bupropion or buspirone may be used as off-label treatments for HSDD. Menopausal women with HSDD may benefit from off-label testosterone therapy. Flibanserin is currently the only FDA-approved medication for the treatment of premenopausal women with HSDD, having been found to have clinically meaningful benefit in multiple randomized, double-blind, placebo-controlled trials involving thousands of participants. In conclusion, HSDD is a highly prevalent but often undiagnosed condition that can effectively be managed by the nonspecialist with appropriate assessment and individualized treatment.

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Abbreviations and Acronyms: **ACC** = anterior cingulate cortex; **AE** = adverse event; **ArcN** = arcuate nucleus of the hypothalamus; **CB1s** = cannabinoid type 1 receptor; **CBT** = cognitive behavior therapy; **CPu** = caudate-putamen; **δ** = delta opioid receptors; **DA** = dopamine; **DSM** = Diagnostic and Statistical Manual of Mental Disorders; **FDA** = Food and Drug Administration; **GnRH** = gonadotropin-releasing hormone; **HSDD** = hypoactive sexual desire disorder; **ICD-10** = International Statistical Classification of Diseases and Related Health Problems, 10th Revision; **ISSWSH** = International Society for the Study of Women's Sexual Health; **μ** = mu opioid receptors; **mPOA** = medial preoptic area; **MSH** = melanocyte-stimulating hormone; **NAcc** = nucleus accumbens; **NE** = norepinephrine; **OT** = oxytocin; **PFC** = prefrontal corex; **Pir Ctx** = piriform cortex; **PIT** = pituitary; **Tu** = olfactory tubercle; **VP** = ventral pallidum; **VTA** = ventral tegmental area

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