MAYO CLINIC

REVIEW

The International Society for the Study of Women's Sexual Health Process of Care for Management of Hypoactive Sexual Desire Disorder in Women

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Abstract

The International Society for the Study of Women's Sexual Health process of care (POC) for management of hypoactive sexual desire disorder (HSDD) algorithm was developed to provide evidence-based guidelines for diagnosis and treatment of HSDD in women by health care professionals. Affecting 10% of adult females, HSDD is associated with negative emotional and psychological states and medical conditions including depression. The algorithm was developed using a modified Delphi method to reach consensus among the 17 international panelists representing multiple disciplines. The POC starts with the health care professional asking about sexual concerns, focusing on issues related to low sexual desire/interest. Diagnosis includes distinguishing between generalized acquired HSDD and other forms of low sexual interest. Biopsychosocial assessment of potentially modifiable factors facilitates initiation of treatment with education, modification of potentially modifiable factors, and, if needed, additional therapeutic intervention: sex therapy, central nervous system agents, and hormonal therapy, guided in part by menopausal status. Sex therapy includes behavior therapy, cognitive behavior therapy, and mindfulness. The only central nervous system agent currently approved by the US Food and Drug Administration (FDA) for HSDD is flibanserin in premenopausal women; use of flibanserin in postmenopausal women with HSDD is supported by data but is not FDA approved. Hormonal therapy includes off-label use of testosterone in postmenopausal women with HSDD, which is supported by data but not FDA approved. The POC incorporates monitoring the progress of therapy. In conclusion, the International Society for the Study of Women's Sexual Health POC for the management of women with HSDD provides a rational, evidence-based guideline for health care professionals to manage patients with appropriate assessments and individualized treatments.

 ■ Mayo Clin Proc. 2018;93(4):467-487

The International Society for the Study of Women's Sexual Health (ISSWSH) process of care (POC) for hypoactive sexual desire disorder (HSDD) in women provides a consensus management guideline for the diagnosis and treatment of HSDD, the most common sexual dysfunction in women (Figure 1). Given recent research and increasing public awareness about HSDD, greater numbers of women are anticipated to seek treatment for HSDD from a health care professional (HCP). This POC model consists of an evidence-based approach to identification, diagnosis, and treatment, emphasizing biopsychosocial assessment and education. It highlights opportunities to address modifiable factors, includes patient needs and preferences in the decision-making process, and defines

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ARTICLE HIGHLIGHTS

- Hypoactive sexual desire disorder (HSDD), the most common sexual dysfunction in women, has been associated with negative emotional and psychological states, as well as medical conditions including depression; therefore, a guideline for management of HSDD has been developed for health care professionals by the International Society for the Study of Women's Sexual Health.
- This guideline starts with questions to ask regarding sexual health concerns and moves on to diagnosis of generalized acquired HSDD. Treatment begins with education, modification of potentially modifiable factors, and, if needed, additional therapeutic interventions.
- The choice of therapeutic intervention is most often dependent on patient (and partner) preferences and goals.

situations for specialized referral. The model incorporates the following essential principles: (1) identification of subtypes of HSDD, (eg, generalized vs situational and acquired vs lifelong), with emphasis on associated concomitant medical and psychological factors, (2) importance of patient and partner education during all phases of management, (3) goal-oriented focus with patient and partner needs and preferences guiding recommendations for treatment, and (4) clear guidance for follow-up and consideration for referral.

METHODS

This HSDD POC was developed under the auspices of the ISSWSH with input from an international multidisciplinary panel. After a planning conference call, panelists were asked to individually conduct an evidence-based literature review. The panel of 17 researchers and clinicians, ISSWSH members and nonmembers, convened for 2 days to review and discuss management strategies for HSDD using a modified Delphi method.[1-3] This iterative process involved presentations summarizing the current literature, debate and discussion of divergent opinions concerning HSDD assessment and management, and consensus development of a clinical guideline for the HCP. There was no industry participation in any part of the process.

BACKGROUND

Definition of HSDD

Women who are persistently and recurrently not interested in sexual activity who report the absence of sexual fantasies and who are bothered by their lack of sexual interest are said to be experiencing distressing low sexual desire.[4] Because there is substantial experimental and clinical evidence for this classification,[4-8] we will adopt the widely utilized diagnostic label of HSDD to describe women who are distressed by their clinically low levels of sexual desire and utilize the definition developed by the ISSWSH nomenclature committee.[9] This definition states:

HSDD manifests as *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.

Hypoactive sexual desire disorder may be lifelong or acquired and generalized or situational. This definition should be understood in a biopsychosocial context and therefore can be applied to both somatic and psychiatric diagnostic schema.[9]

Clinical Significance and Epidemiology

Hypoactive sexual desire disorder is associated with negative emotional and psychological states, as well as medical conditions including depression.[10-12] Women with HSDD may experience decreased quality of life including impaired body image, self-confidence, and self-worth and feel less connected to their partners.[10] Women with HSDD also have increased health care costs and health burden.[13,14]

Mayo Clin Proc. ■ April 2018;93(4):467-487 ■ https://doi.org/10.1016/j.mayocp.2017.11.002
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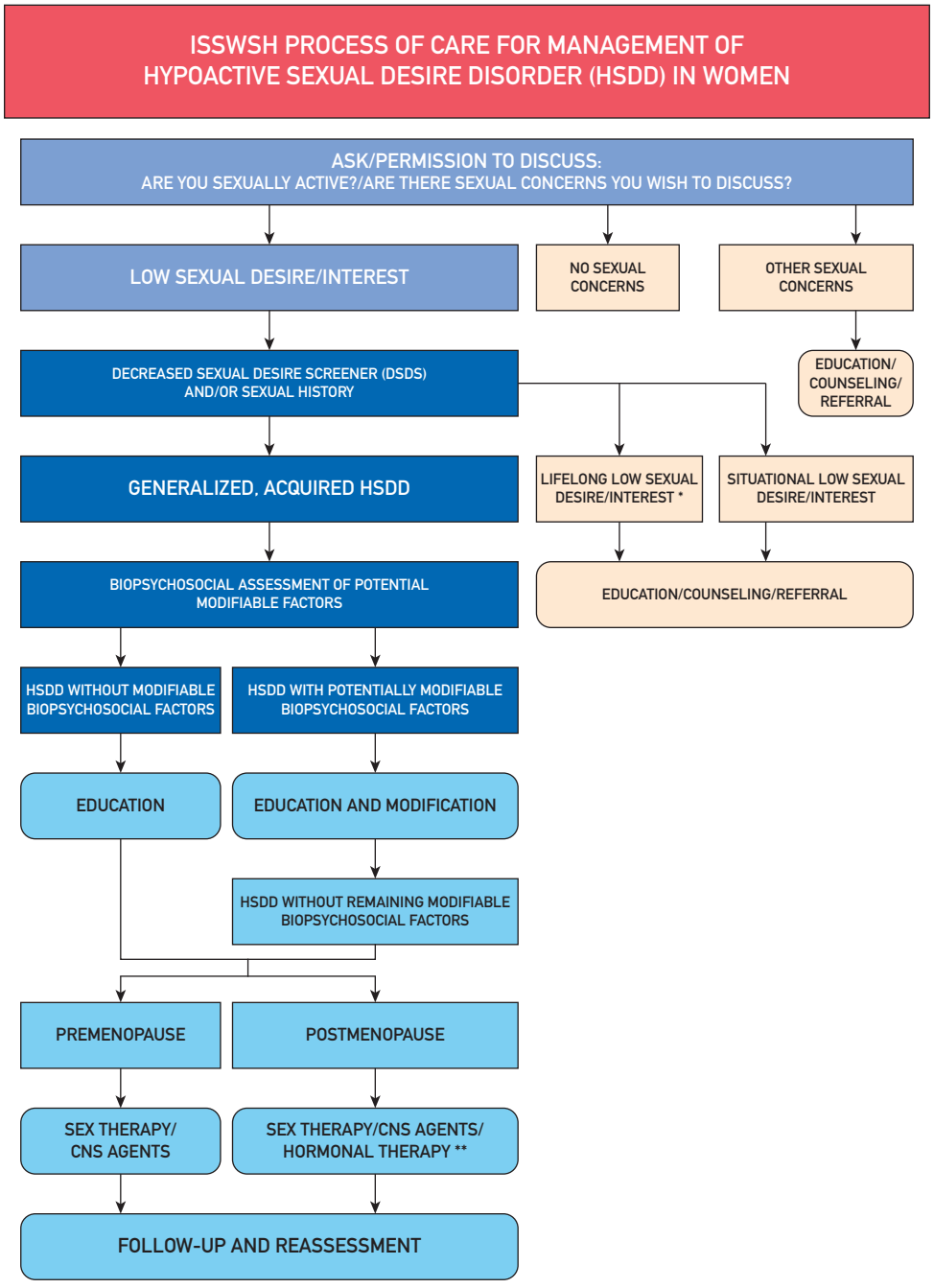

FIGURE 1. The International Society for the Study of Women's Sexual Health (ISSWSH) process of care for hypoactive sexual desire disorder (HSDD) algorithm begins with asking or having permission to discuss sexual concerns and focuses specifically on women who have concerns with their low sexual desire/interest. Initiation of diagnosis starts with the Decreased Sexual Desire Screener or a sexual history. Women with other sexual dysfunctions or those with lifelong or situational low sexual desire/interest are not specifically addressed in this algorithm. Women with generalized acquired HSDD then undergo a focused medical assessment to identify potentially modifiable biopsychosocial factors. Therapeutic intervention begins with education/modification of recognized modifiable factors. Women whose HSDD persists are categorized by menopausal status, and appropriate therapeutic interventions are then followed/reassessed. CNS = central nervous system. *Women with lifelong low sexual desire/interest without distress/bother may characterize themselves as asexual and should not be considered for treatment. **Women in the late reproductive years.

Epidemiologic studies assessing the prevalence of HSDD in women vary according to the (1) definition (low desire/interest; HSDD), (2) group of participants (general population, medical presentation, sex therapy clinics, age group, menopausal status, nationality), and (3) methodology (eg, self-report, interview, questionnaire; face-to-face or online; single-question response, completion of validated scale; inclusion of distress in the definition). These differences in study design have produced prevalence estimates ranging from 17% to over 50%.[15-20]

In the Prevalence of Female Sexual Problems Associated with Distress and Determinants of Treatment Seeking (PRESIDE) study, a widely cited, large population-based survey of 50,001 US women (completers, 31,531; 63% response rate; aged 18-102 years), low desire was the most common sexual problem, reported in 37.7% of participants; low desire with distress (HSDD) was present in approximately 10% of women and was more common than distressing arousal or orgasm difficulties.[21]

Physiology

Sexual desire is regulated by key regions in the brain through the action of various neurotransmitters.[22-24] Dopamine, melanocortin, oxytocin, vasopressin, and norepinephrine mediate sexual excitation, whereas opioid, serotonin, endocannabinoid, and prolactin systems mediate sexual inhibition.[22,23] Although the underlying biological causes of HSDD remain unknown, generalized HSDD likely involves either a predisposition toward inhibitory processes or neuroadaptations that result in decreased excitation, increased inhibition, or a mixture of the two.[6,25,26] Alterations in brain function and structure may be additionally modulated or reinforced by experience and behavior (experience-based neuroplasticity), further propagating the condition. This perspective is consistent with differential brain activity patterns and structural differences between women with and without HSDD.[27-30]

SCREENING FOR SEXUAL PROBLEMS

The optimal strategy for detecting sexual problems (desire, arousal, orgasm, pain) is "simply to ask" (Figure 1) during the patient visit. The sexual health interview should be conducted when it feels most natural in the encounter. Begin by asking, "Are you sexually active?" Whether the patient answers "yes" or "no," continue by asking a direct screening question such as, "Are there sexual concerns you wish to discuss?"[5] Explain that sexual problems are common and facilitate screening by assuring the patient that you, the physician, are comfortable discussing sexual issues. To normalize and legitimize sexual concerns, you may introduce a direct screening question with a "ubiquity statement" such as, "Many women having [the characteristics of the patient] have concerns about sexual functioning; what about you?"[31]

The start of ubiquity statements may include medical, social, and life-cycle issues such as, "Many women with diabetes…" or "Many women going through menopause…" You may follow the ubiquity statement with an open-ended invitation such as, "Tell me about it." If a woman reports low desire, it is important to assess the presence of distress related to low desire, which is integral to the definition of HSDD.[9] If HSDD is present, this POC should be followed. If her sexual problem is arousal, orgasm, or pain, other clinical evaluations and interventions such as education, counseling, or referral should be considered.

DIAGNOSIS

Recommended diagnostic strategies include use of the Decreased Sexual Desire Screener (DSDS) and/or a sexual history to determine the type of HSDD.

Decreased Sexual Desire Screener

The DSDS is a validated instrument for confirming the diagnosis of generalized acquired HSDD in women [*level of evidence* (*LoE*) 2].[32,33] The DSDS is brief, effective, user-friendly, and self-completed and requires no special training to administer/interpret (Figure 2).[34,35] The DSDS serves to grant permission and encourage dialogue for screening for HSDD and identification of etiologic factors, obviating potential patient and physician embarrassment.

The screener includes 5 simple "yes/no" questions. The first 4 incorporate the prerequisites for a diagnosis of generalized acquired

Mayo Clin Proc. ■ April 2018;93(4):467-487 ■ https://doi.org/10.1016/j.mayocp.2017.11.002
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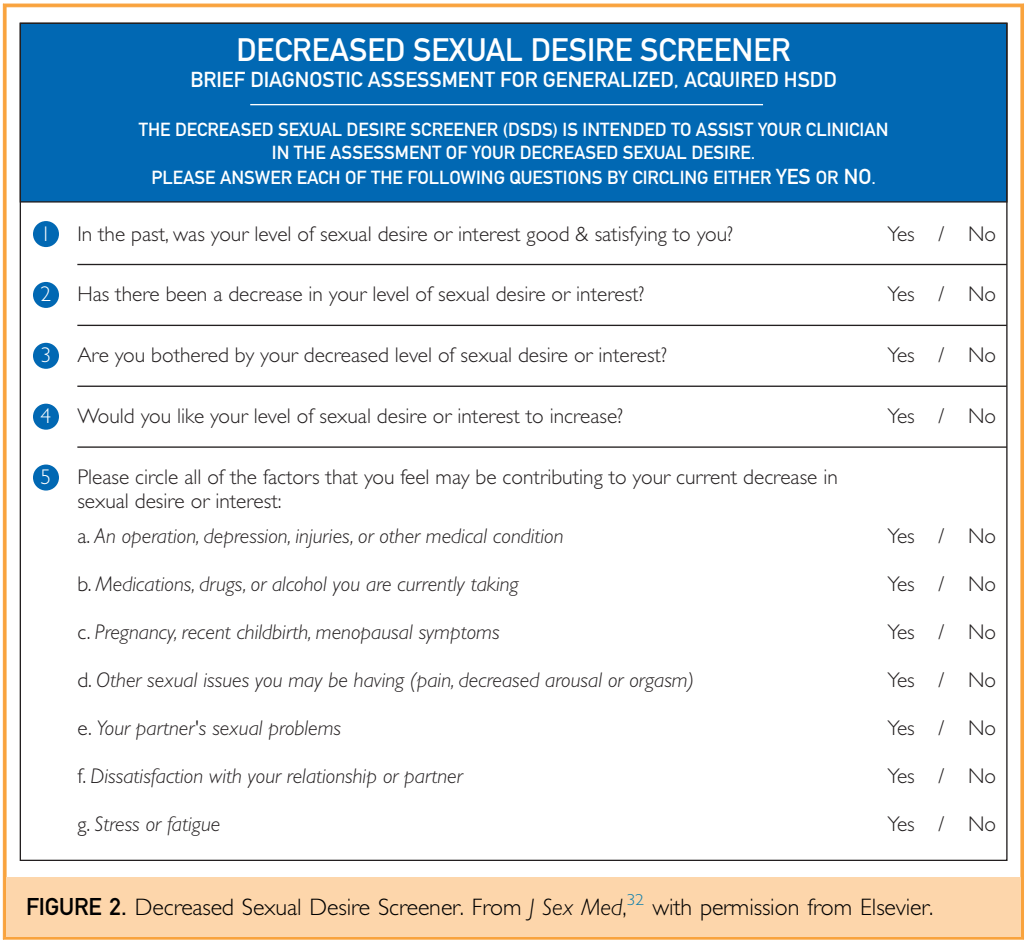

DECREASED SEXUAL DESIRE SCREENER

BRIEF DIAGNOSTIC ASSESSMENT FOR GENERALIZED, ACQUIRED HSDD

THE DECREASED SEXUAL DESIRE SCREENER (DSDS) IS INTENDED TO ASSIST YOUR CLINICIAN IN THE ASSESSMENT OF YOUR DECREASED SEXUAL DESIRE.
PLEASE ANSWER EACH OF THE FOLLOWING QUESTIONS BY CIRCLING EITHER YES OR NO.

1	In the past, was your level of sexual desire or interest good & satisfying to you?	Yes / No
2	Has there been a decrease in your level of sexual desire or interest?	Yes / No
3	Are you bothered by your decreased level of sexual desire or interest?	Yes / No
4	Would you like your level of sexual desire or interest to increase?	Yes / No
5	Please circle all of 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 condition*	Yes / No
	b. *Medications, drugs, or alcohol you are currently taking*	Yes / No
	c. *Pregnancy, recent childbirth, menopausal symptoms*	Yes / No
	d. *Other sexual issues you may be having (pain, decreased arousal or orgasm)*	Yes / No
	e. *Your partner's sexual problems*	Yes / No
	f. *Dissatisfaction with your relationship or partner*	Yes / No
	g. *Stress or fatigue*	Yes / No

FIGURE 2. Decreased Sexual Desire Screener. From *J Sex Med*,[32] with permission from Elsevier.

HSDD: (1) previous satisfaction with her desire/interest in sex, (2) a decrease from prior satisfaction, (3) bother by the decline in sexual desire, and (4) wish for improvement in her sexual desire.[26,32] Responses of no previous satisfaction with her desire/interest in sex, and therefore no decrease from prior satisfaction, would be consistent with lifelong low sexual desire/interest. In the fifth query, the patient is asked to identify with "yes/no" responses which, if any, of the 7 listed groups of factors might apply to her situation, potentially having an adverse effect on her sexual desire/interest (Figure 2).[32] Low sexual desire and the associated distress and behavioral adaptations may impact the partner relationship, or problems in the partner relationship may contribute to low desire.

If a woman responds "no" to at least 1 of the first 4 questions, she does not meet criteria for generalized acquired HSDD but could meet criteria for either situational or lifelong low sexual desire/interest. If the patient answers "yes" to questions 1 through 4 and "no" to all the factors in question 5, she has generalized acquired HSDD. If any of the factors in question 5 are present, the HCP must evaluate and consider differential diagnoses including biological etiologies of low desire, as well as decide whether the responses to question 5 indicate generalized acquired HSDD or situational low sexual desire/interest. Situational loss of desire may occur in response to a temporary stressful life situation. Individuals with no/low sexual interest over their lifetime and who are not distressed may be asexual and as such do not meet criteria for HSDD, and no intervention is indicated.[36] Comorbid conditions such as arousal and orgasmic disorder do not rule out a concurrent diagnosis of HSDD.

If the DSDS suggests the diagnosis of low sexual interest without distress, distressing lifelong sexual desire, or situational low sexual desire, the HCP should consider strategies that

TABLE 1. Physical Examination to Evaluate Other Factors Contributing to Decreased Desire

Condition	Assessment
Clitoral adhesions/phimosis or clitoral atrophy	Visual examination under magnification
Urethral meatal prolapse, telescoping of urethral meatus	Visual examination under magnification
Vulvodynia	Assess sensitivity to pressure with cotton swab around vestibule from 1-o'clock to 11-o'clock positions
High-tone pelvic floor dysfunction	Manual examination
Labial resorption; vulvar, vestibular, or vaginal atrophy	Visual examination under magnification, vaginal smear (wet mount)
Vulvar dystrophies and dermatoses	Visual examination under magnification, biopsy if needed
Pudendal nerve disorder	Assess tenderness at ischial spine, assess tenderness of pelvic floor muscles
Lumbar-sacral spinal pathology	Quantitative sensory testing, bulbocavernosus reflex latency testing, magnetic resonance imaging of lumbar and sacral spine

engage education and/or counseling or referral to a specialist. In those with generalized acquired HSDD, the HCP may elicit a sexual history or proceed with the POC. In summary, the DSDS offers the HCP a quick, nonthreatening way to screen for and diagnose HSDD in the clinical setting and begin to identify modifiable factors/etiologies.[32]

Sexual History

In addition to the DSDS, the HCP may also conduct a sexual history. This may include past and present characteristics of the patient's sexual desire/interest and other aspects of sexual function such as arousal, orgasmic function, and/or any pain/discomfort during sexual activity. Sexual function may be assessed with regard to either partnered or unpartnered sexual activity and may include a history of her past and present partner relationships and sexual experiences. If a sexual desire discrepancy exists between the patient and her partner, it may only be considered HSDD if the desire discrepancy causes her distress.[9] The evaluation may also include a brief psychosocial assessment because sexual dysfunction may affect the patient's self-esteem and coping ability, as well as her social and occupational role performance.

When a woman endorses distressing low sexual desire, the interview should proceed with questions related to the diagnosis of HSDD including: low motivation for participation in sexual activity, loss of spontaneous sexual desire (including sexual thoughts and fantasies), lack of desire in response to erotic cues and stimulation, low initiation and avoidance of situations that could lead to sexual activity, and participation in sexual activity due to obligation or fear of losing her partner.[26]

BIOPSYCHOSOCIAL ASSESSMENT OF POTENTIAL MODIFIABLE FACTORS

For women with a diagnosis of generalized acquired HSDD, HCPs should next obtain a history, perform a physical examination as considered appropriate, and order blood testing when indicated to clarify any modifiable factors.

Physical Examination

A general physical examination of patients who experience HSDD has a low diagnostic yield and does not identify the specific cause of the HSDD in most cases. However, a focused examination, including a pelvic examination with assessment of the vulvar and vaginal tissue, may be appropriate if indicated (Table 1). A physical examination may also reveal signs of hormone insufficiency states.[26] The physical examination also provides an excellent opportunity for patient education and reassurance regarding normal genital anatomy. The findings on this examination may be used to identify referral needs.

Laboratory Testing

Laboratory and imaging investigations are dictated by the woman's medical history and physical examination findings. Because there

Mayo Clin Proc. ■ April 2018;93(4):467-487 ■ https://doi.org/10.1016/j.mayocp.2017.11.002
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TABLE 2. Recommended Blood Tests for Further Investigation if HSDD Is Concurrent With Oligomenorrhea or Amenorrhea and/or Galactorrhea

Hormone	Possible conditions	Level of evidence
Prolactin	Hyperprolactinemia causing ovarian suppression and low sex steroid production[37,38]	3
Thyroid function panel	Hypothyroidism[39] or hyperthyroidism[40]	2-3
Estradiol, progesterone, luteinizing hormone, testosterone, sex hormone—binding globulin	Oligomenorrhea or amenorrhea[5,37,41]	2-3

are no biomarkers that confirm or exclude HSDD, laboratory testing—specifically, measurement of testosterone—should not be used to make the diagnosis. Other hormone assays may be considered if there is concern about comorbid conditions contributing to low desire, although this testing is not clinically indicated on a routine basis (Table 2).[5,37-41] These tests are primarily performed to identify specific etiologies or to assess the role of concomitant medical conditions. Referral to a specialist in sexual medicine may be considered if a more specialized physical examination, testing, or treatment is needed. Reasons for referral may include primary/lifelong and/or situational low desire, relationship problems, physical or psychological trauma, endocrinopathy, complex medical problems, or treatment failures.[42]

When a woman presents with HSDD without any potentially causative comorbidity or relationship conflict, the diagnosis of HSDD without a modifiable cause can be established. In this case, menopausal status should be assessed according to the STRAW + 10 (Stages of Reproductive Aging Workshop) classification system in order to guide therapeutic decision making.[43]

MODIFIABLE FACTORS

The evaluation for HSDD should include screening for other sexual problems related to arousal, orgasm, and pain[9] in order to determine the primary vs secondary problem(s) by assessing the temporal relationship of the onset of these complaints relative to the onset of low desire. It is also necessary to determine if HSDD is lifelong or acquired and generalized (occurs in all settings with all partners) or situational. Other key areas of inquiry should include prior sexual functioning and relationship/interpersonal issues.[44-47] It is important to note that a woman can experience HSDD and not be in a stable relationship (ie, has no partner or multiple serial partners).[19]

The HCP should ask specifically about other sexual problems that might exacerbate low desire and influence the management and eventual success of treatment. In the Hypoactive Sexual Desire Disorder Registry for Women study, a large observational study of US women with clinically diagnosed generalized acquired HSDD, arousal disorders, lubrication problems, or both were reported by 50.2%, 42.5%, and 39% of women with HSDD, respectively.[48,49] A list of some potentially useful screeners and questionnaires is provided in the Supplemental Table (available online at http://www.mayoclinicproceedings.org).

In patients with generalized acquired HSDD, elicitation of the medical history should include questions about psychiatric conditions, medical problems, and menopausal status (Table 3)[50-53] and relevant medications and misuse/abuse of substances (Table 4).[54]

The assessment should include a medical, psychological, and social history to identify any factors that may be potentially reversible. Obtaining a detailed gynecologic history is important with particular attention to menstrual cycles in premenopausal women; symptoms of the genitourinary syndrome of menopause;[55] pelvic floor disorders such as urinary incontinence, fecal incontinence, prolapse, and high-tone pelvic floor dysfunction; and menopausal vasomotor symptoms, because each of these factors has been associated with lowered sexual desire.[15,19,56,57]

Bilateral salpingo-oophorectomy before natural menopause is associated with an increased likelihood of HSDD.[12] Bilateral salpingo-oophorectomy at any age is associated

TABLE 3. Medical Conditions Potentially Impacting Sexual Function[a,b]

Medical Condition	Desire	Arousal	Orgasm	Pain	Comments
Coronary artery disease	−	+	−	−	None
Hypertension	+	−	−	−	Impact of hypertension or treatment is unclear; one study found an association with low desire
Diabetes	+	−	−	−	Low desire may relate to depression and relationship status
Metabolic syndrome	+	+	+	−	None
Hypothyroidism	−	+	+	−	Increased problems with lubrication and orgasm
Pituitary tumor/hyperprolactinemia	+	−	−	−	None
Urinary incontinence	+	+	−	+	None
Renal failure	−	−	−	−	Dialysis associated with sexual dysfunction
Spinal cord injury/multiple sclerosis/ neuromuscular disorders	+	+	+	+	Direct impact on sexual response; indirect effect on desire may be mediated by arousal disorders/pain
Parkinson disease/dementia/head injury	+	−	−	−	Desire may be increased or decreased
Arthritis	−	−	−	+	Decreased mobility and chronic pain may impair sexual function
Dermatological conditions (vulvar lichen sclerosus, vulvar eczema, psoriasis, Paget disease)	−	−	−	+	None
Gynecologic conditions (genitourinary syndrome of menopause, sexually transmitted infections, endometriosis, chronic pelvic pain, childbirth, pelvic organ prolapse)	−	−	−	+	None
Malignancy and treatment (breast, anal, bladder, colorectal, and gynecologic cancers)	+	+	+	+	Sexual function may be directly or indirectly impacted by cancer diagnosis and treatment. Factors include cancer diagnosis, disease itself, treatment (surgery, radiation, chemotherapy), and body image
Major depression	+	+	+	−	None

[a]+ = affected; − = not affected.
[b]Data from references 50-52.
Adapted from *Am Fam Physician*,[53] with permission.

with lower total and free testosterone levels.[58-62] Women should be asked about other pelvic operations, trauma, or radiotherapy because these factors may be associated with pelvic pain and altered ovarian function. Other conditions associated with lower androgen levels, and potentially diminished desire, include hyperprolactinemia,[63,64] hypopituitarism, hypothalamic amenorrhea, adrenal insufficiency, primary ovarian insufficiency, and chemical ovarian suppression. Conditions that may increase sex hormone—binding globulin (SHBG) levels, and hence lower free testosterone levels, include hyperthyroidism and human immunodeficiency virus infection.[65] Overt[66-68] or subclinical[66,69] hypothyroidism and hyperthyroidism have been associated with reduced sexual desire.[68,70] Conversely, polycystic ovary syndrome is often characterized by clinical and/or biochemical signs of hyperandrogenism, with or without oligoovulation or anovulation, or polycystic ovaries. Women with polycystic ovary syndrome have psychological (feeling less attractive, less feminine, more depressed) and biological (obesity and infertility) factors that may negatively influence their sexual desire.[71]

Depressive symptoms are independently and bidirectionally associated with HSDD, with the presence of depression conferring a 50% to 70% increased risk of sexual dysfunction, and the occurrence of sexual dysfunction

Mayo Clin Proc. ■ April 2018;93(4):467-487 ■ https://doi.org/10.1016/j.mayocp.2017.11.002
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is associated with a 130% to 210% increased risk of depression.[19,72] Adding a layer of complexity, most antidepressants are associated with decreased sexual desire[73-76]; therefore, use of antidepressant medication may actually substitute one causative factor of HSDD for another. The Patient Health Questionnaire (PHQ)[77] is a validated instrument to screen for and monitor severity of depressive symptoms. In the Hypoactive Sexual Desire Disorder Registry for Women study, 34% of a clinical sample of women with acquired, generalized HSDD were found to have concurrent symptoms of depression as measured by the PHQ-9 or were being treated with antidepressant medications; however, 58% had not been diagnosed or treated for depression before entering the study.[78] In the general population PRESIDE study, 37% of women had concurrent depression as identified either by the PHQ-9, prior diagnosis of depression, or treatment with antidepressant medications.[79] Given this significant comorbidity, every patient with HSDD should be screened for depressive symptoms because major depressive disorder or treatment with an antidepressant medication may be a modifiable etiologic factor [*LoE* 2]. It is important to note that depression is also associated with significant chronic medical conditions such as diabetes.[80]

Both type 1 and type 2 diabetes mellitus almost double the risk of sexual dysfunction.[81] In the Epidemiology of Diabetes Interventions and Complications study, 57% of women with type 1 diabetes reported low sexual desire.[82] Interestingly, the prediabetic state (slightly elevated blood glucose levels) was also characterized by impairment of sexual desire and sexual satisfaction.[83] Reduced sexual desire and sexual satisfaction were strongly associated with insulin resistance (Homeostatic Model Assessment Index 1—Insulin Resistance) and therefore susceptible to changes in insulin sensitivity.[83]

Metabolic syndrome (MetS) is a group of cardiovascular risk factors: high blood pressure, elevated blood glucose level, abnormal cholesterol levels, and abdominal obesity. Data for a relationship between MetS and HSDD are conflicting. In a study of 376 postmenopausal community-dwelling women, those with MetS had significantly lower sexual desire compared with other women.[84] Three smaller case-control studies did not find any significant association between MetS and sexual desire.[85-87] Whereas in population-based studies sexual desire is inversely associated with body mass index,[88-90] 3 clinical studies of women seeking or undergoing weight loss treatment did not find an increase in sexual desire.[91-93] However, observational studies have consistently indicated a trend toward improvement in sexual desire after weight loss,[94,95] potentially due to improved body image. Both obesity and MetS have been

TABLE 4. Medications Associated With Female Sexual Dysfunction

Medication	Desire disorder	Arousal disorders	Orgasm disorders
Anticholinergics	−	+	−
Antihistamines	−	+	−
Amphetamines and related anorexic drugs	−	−	+
Cardiovascular and antihypertensive medications			
Antilipid medications	+	−	−
β-Blockers	+	−	−
Clonidine	+	+	−
Digoxin	+	−	+
Spironolactone	+	−	−
Methyldopa	+	−	−
Hormonal preparations			
Danazol	+	−	−
GnRH agonists	+	−	−
Hormonal contraceptives	+	+	−
Antiandrogens	+	+	+
Tamoxifen	+	+	−
GnRH analogues	+	+	−
Ultralight contraceptive pills	+	+	−
Narcotics	+	−	+
Psychotropics			
Antipsychotics	+	+	+
Barbiturates	+	+	+
Benzodiazepines	+	+	−
Lithium	+	+	+
SSRIs	+	+	+
TCA	+	+	+
MAO inhibitors	−	−	+
Venlafaxine	+	+	+
Other			
Histamine 2 receptor blockers and promotility agents	+	−	−
Indomethacin	+	−	−
Ketoconazole	+	−	−
Phenytoin sodium	+	−	−
Aromatase inhibitors	+	+	−
Chemotherapeutic agents	+	+	−

GnRH = gonadotropin-releasing hormone; MAO = monoamine oxidase; SSRIs = selective serotonin reuptake inhibitors; TCA = tricyclic antidepressants; + = yes; − = no.
Adapted from *Fertil Steril*,[54] with permission from Elsevier.

associated with increased baseline clitoral vascular resistance and impaired sexual arousal, suggesting that the negative impact of these metabolic phenotypes on sexual function is primarily at the genital level rather than a central effect.[96]

Various neurologic diseases have been associated with decreased sexual desire, notably multiple sclerosis[97,98] and spinal cord injury,[99] but data are limited.

Decreased sexual desire is a common issue for women after a diagnosis of breast cancer, ranging from 23% to 80% of women.[100,101] Sexual problems are independently associated with being postmenopausal (potentially provoked by chemotherapy), having vasomotor symptoms, and taking an aromatase inhibitor (AI).[101,102] Chemotherapy increases the likelihood of sexual complaints compared with surgery and/or radiation.[103] In addition, AI therapy is associated with vaginal dryness, dyspareunia, and decreased sexual desire.[102,104]

Medications that lower testosterone production include combined hormonal contraceptives (CHCs; oral, transvaginal, and transdermal),[105] chemical ovarian suppression by gonadotropin-releasing hormone analogues, and pharmacological glucocorticoid administration. Some other compounds exhibit antiandrogen activity (spironolactone, cyproterone acetate, flutamide, and finasteride). Drugs increasing SHBG levels, and hence lowering free testosterone levels, also include oral estrogens, CHCs, tamoxifen, and thyroxine.[65] A double-blind, placebo-controlled, randomized trial determined that a levonorgestrel-containing oral contraceptive lowers sexual desire in comparison with placebo.[106] Even though all CHCs suppress ovarian testosterone production, the greatest increase in SHBG level is seen with the higher ethinyl estradiol doses (30-35 μg) and with third- or fourth-generation progestins.[105] A recent study found evidence for a role of the CAG repeat length of the androgen receptor on the sexual desire of contraceptive users.[107] In addition, drugs that may elevate prolactin levels and, in part, decrease sexual desire include antipsychotics and others.[38,108] We conclude that CHCs may be associated with HSDD in some women, and thus, change of medication may improve desire [*LoE* 2].

TREATMENT

Therapeutic strategies for this POC include education and, if needed, addressing modifiable factors. Should generalized acquired HSDD persist, treatment may include sex therapy, central nervous system (CNS) agents, and hormonal agents, taking into account menopausal status.

First- and Second-Line Therapies

Education. Effective patient education requires knowledge, time, communication skills, and bibliographic resources that facilitate positive sexual behavioral changes.[43] Education may be structured in 3 parts. First, provide information on normal sexual functioning. This information may include a description of spontaneous and responsive sexual desire, the role of motivation in sexual desire, the importance of adequate sexual stimulation, the impact of pleasurable sexual experiences on desire, and the influence of age and relationship duration.[109-111] Second, educate the patient about factors that are derived from the sexual and medical history that may disrupt sexual desire (eg, mood disorders, relationship satisfaction, body image).[5] Third, HCPs may assess motivation for treatment and discuss treatment options.[5,112] If the patient has a partner, involving the partner in treatment may sometimes be helpful. Education should continue throughout the process, including patient follow-up.

Modification of Potentially Contributing Factors. The next intervention level includes modification of factors thought to be playing a role in HSDD. The following paragraphs summarize strategies for intervention for some of the more common modifiable factors associated with HSDD and are based on consensus expert opinion.

Treatment of genital arousal symptoms and pain with vaginal lubricants, vaginal moisturizers, low-dose vaginal estrogen or intravaginal dehydroepiandrosterone (DHEA),[113] or physical therapy (for hypertonic, tender pelvic floor muscles)[114,115] and menopausal vasomotor symptoms with systemic hormone therapy[116] may relieve symptoms and therefore improve desire. In particular, pain with sexual activity should be addressed before treatment of HSDD.

In women with type 2 diabetes, limited evidence suggests that lifestyle modifications that include substantial weight loss may

Mayo Clin Proc. ■ April 2018;93(4):467-487 ■ https://doi.org/10.1016/j.mayocp.2017.11.002
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TABLE 5. Psychological Factors and Treatment Strategies

Psychological factor	Recommended approach
Depression/anxiety	Pharmacotherapy/cognitive behavioral therapy
Poor self-esteem/body image	Psychotherapy
Stress/distraction	Cognitive behavioral therapy
History of abuse (physical, sexual, emotional)	Psychotherapy
Substance abuse	Psychotherapy
Self-imposed pressure for sex	Office-based counseling or refer for cognitive behavioral therapy
Religious, personal, cultural or family values, beliefs, and taboos	Office-based counseling or refer for cognitive behavioral therapy
Relationship factors	Office-based counseling or refer for individual/couples therapy
Lifestyle factors (eg, fatigue, sleep deprivation)	Office-based counseling
Sexual factors (eg, inadequate stimulation)	Office-based counseling

alleviate sexual dysfunction.[37] Treatment of gynecologic disorders and urinary or fecal incontinence may positively impact sexual desire.[50,51] Malignant disorders may adversely affect sexual function either directly, as the result of the disorder itself, or indirectly, related to the cancer diagnosis or treatment, and addressing sexual changes resulting from cancer or treatment may lead to improved sexual function.[117]

Sleep problems and insomnia in particular are common concerns among women. In the Women's Health Initiative Observational Study, higher insomnia scores and shorter durations of sleep (<7-8 hours) were associated with decreased sexual function.[118] Improving duration and quality of sleep may positively affect sexual function.

As noted previously, depression has a bidirectional association with sexual dysfunction, and adequate treatment of depression may positively impact sexual function.[5,72] Additionally, antidepressant medications are commonly associated with treatment-emergent sexual dysfunction, a potential adverse effect that may result in discontinuation of treatment and impaired quality of life.[75,119,120] Management strategies for antidepressant-related sexual dysfunction include behavioral (eg, exercise, scheduling sexual activity, vibratory stimulation),[121,122] complementary (eg, acupuncture),[123] and pharmacological (eg, dose reduction or discontinuation, switching to a drug with fewer sexual adverse effects, and adding antidotes/adjunctive treatment) therapies.[124-127] Other commonly used medications potentially impacting sexual function include CHCs, AIs, and spironolactone.[54] Reviewing a patient's medication list and modifying medication regimens potentially impacting sexual function (Table 4) may improve sexual desire. Alcohol, smoking and illicit substance use may also contribute to sexual dysfunction.

Several psychological factors that may contribute to loss of sexual desire may be modifiable. Table 5 lists the most common psychological factors contributing to HSDD. Relationship factors frequently adversely impact sexual desire. Health care professionals may use office-based counseling or may consider referring the patient to an individual or couples therapist to modify negative communication patterns, to address partner sexual dysfunction, to modify the partner's pressure or demanding behavior for sex, and to help problem solve when lack of time and/or privacy are contributing factors.[51] Office-based counseling may also be useful to reevaluate and alter interfering beliefs and values[128] and should be continued in follow-up.

Third-Line Treatment Options

Sex Therapy. A range of psychological interventions has been developed to treat sexual dysfunctions in women, independent of menopausal status. Focused sex therapy for HSDD is unlikely to be effective if relationship problems contributing to low desire or as a result of HSDD (ie, power, control, trust) for women with a partner, sexual dysfunction in the partner, or a history of sexual, physical, or emotional abuse are not addressed.

Three frequently used psychological interventions are behavior therapy, cognitive behavior therapy (CBT), and mindfulness therapy. Behavior therapy attempts to alleviate

sexual difficulties through a combination of techniques including education, communication skills training, and sensate focus exercises.[129,130] On their own, sensate focus exercises are unlikely to be effective for HSDD in women [*LoE 5*].

Cognitive behavior therapy is designed to challenge unrealistic beliefs that may be contributing to sexual problems and to alter behaviors that maintain HSDD. For example, individuals may be making cognitive errors, personalizing, or catastrophizing.[131] With the help of the therapist, the patient learns to identify and challenge the unrealistic beliefs that trigger negative behaviors and emotions regarding sexual activity. A meta-analysis of 20 small studies using psychological interventions vs a wait-list control in multiple settings in the treatment of various types of sexual dysfunctions in men and women (4 of the 20 studies were of HSDD in women)[132] found that psychological interventions were effective in reducing symptom severity and, to a lesser degree, improving sexual satisfaction among women with low sexual desire [*LoE 1*]. A more recent, more specific review[133] found 3 studies in which CBT in women with HSDD was effective vs wait-list controls.

Mindfulness-based CBT includes exercises that aim to cultivate present-moment awareness and nonjudgmental observation of experiences.[134-136] When applied to HSDD, mindfulness exercises may help decrease cognitive distraction during sexual activity and increase awareness of pleasurable sensations.[136-139] Two wait-list controlled studies support mindfulness meditation training in women with HSDD.[133] To date, 5 studies have evaluated the incorporation of mindfulness training into a CBT intervention for women with non-HSDD female sexual problems[140-144] and found improvements in sexual desire and related distress. Mindfulness therapy has demonstrated preliminary levels of effectiveness in the treatment of this disorder among women.[144-146]

CNS Agents. Flibanserin is currently the only US Food and Drug Administration–approved medication for generalized acquired HSDD in premenopausal women. Flibanserin (100 mg dosed at bedtime) is a nonhormonal, centrally acting, daily, oral, multifunctional serotonin agonist and antagonist.[147] Efficacy was established in 3 pivotal trials in more than 3500 women, demonstrating a statistically significant and clinically meaningful improvement in the level of sexual desire and the number of sexually satisfying events and a decrease in distress compared with placebo [*LoE 1*].[148-150] Clinical trials of flibanserin in postmenopausal women have found similar efficacy, but it is not currently Food and Drug Administration–approved in this population.[151] Approximately 50% of women with HSDD respond to flibanserin, and it may take up to 8 weeks for efficacy to emerge. The most common adverse events (AEs) in premenopausal women are dizziness (9.2%), somnolence (8.3%), nausea (6.5%), and fatigue (3.7%)[147]; placebo-corrected rates are similar to other CNS-active agents. Most AEs are mild, transient, and mitigated with bedtime dosing. In the trials, discontinuation due to AEs was 13% in premenopausal women treated with flibanserin compared with 6% with placebo.

Flibanserin labeling has a boxed warning that concomitant alcohol use is contraindicated on the basis of the results of an alcohol challenge study that found an increase in sedation, syncope, and hypotension in the treatment group (23 men and 2 women).[152] However, alcohol use was not restricted and did not increase such AEs over placebo in the 3 major pivotal trials that were limited to premenopausal women.[153] A postapproval alcohol interaction study performed in 96 women (≤45 years old) revealed no effect of concomitant ethanol ingestion for somnolence, drowsiness, orthostatic blood pressure, vertigo, or hypotension with no reports of syncope, although a small increase in dizziness was reported at the highest dose of ethanol (0.6 g/kg) when taken with flibanserin (39.8%) compared with flibanserin alone (31.3%).[152] A risk evaluation and mitigation program requires certification of prescribers and pharmacies in consenting patients to avoid alcohol.

Other CNS-active agents approved for other indications have been used off-label for the treatment of HSDD despite limited efficacy and safety data. Bupropion, which acts to enhance dopamine and norepinephrine, was found in a randomized, double-blind, placebo-controlled trial (at 300-400 mg/d) to improve sexual desire vs placebo in women

Mayo Clin Proc. ■ April 2018;93(4):467-487 ■ https://doi.org/10.1016/j.mayocp.2017.11.002
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with HSDD, but enrollment was insufficient to reach statistical significance, as prespecified in the study protocol [*LoE 2*].[154] Adverse effects of bupropion used for treatment of major depression or smoking cessation include tremor (13.5%), agitation (9.7%), dry mouth (9.2%), constipation (8.2%), dizziness (6.1%), and nausea/vomiting (4%).[155] In women with antidepressant-induced sexual dysfunction, the addition of sustained-release bupropion (300 mg/day) improved sexual desire vs placebo.[125]

Buspirone, which reduces serotonin inhibition, is another off-label treatment that has been used for antidepressant-associated sexual dysfunction. One trial found improvement in sexual function (including "low libido") in depressed women with selective serotonin reuptake inhibitor–induced sexual dysfunction with buspirone (30-60 mg/d) compared with placebo (58% vs 30%) [*LoE 2*].[6,156] The most common adverse effects of buspirone in studies of generalized anxiety disorder (approved indication) are dizziness (9%), nervousness (4%), nausea (3%), and headache (3%).

Drug development research for HSDD has been directed toward finding CNS agents that specifically activate stimulatory pathways or reduce inhibitory pathways regulating sexual desire.[157] Therapies in clinical trial development include bremelanotide[158-164] and combination therapies: testosterone with sildenafil and testosterone with buspirone[165-167] and bupropion with trazodone.[168]

Hormonal Therapy. Testosterone therapy was initially approved in Europe for the treatment of HSDD in surgically menopausal women and is currently approved in Australia for women with testosterone deficiency and associated symptoms such as low sexual desire. However, testosterone therapy in women remains an off-label treatment in other countries. Oral testosterone therapy is not recommended because there are substantial intraindividual and interindividual variations in absorption such that levels achieved are often supraphysiologic and may result in lipid/cardiac effects and hepatotoxicity.[169] Studies using transdermal testosterone have consistently revealed efficacy for the treatment of HSDD in both naturally and surgically postmenopausal women, either alone or in combination with menopausal estrogen therapy [*LoE 1*].[26,65,170] Four published 24-week phase 3 clinical trials in naturally and surgically postmenopausal women with HSDD found that a 300-μg/d testosterone patch significantly improved the primary efficacy measures of sexual desire and frequency of satisfying sexual events (measured by proprietary instruments) vs placebo.[171-174] Levels of sexually related distress also decreased significantly compared with placebo in 3 of the 4 studies.

The most common AEs in descending order were application site reactions, acne, breast pain, headache, and hirsutism. Laboratory findings (liver function and hematologic tests, lipid profiles, clotting measures, and carbohydrate metabolism) remained essentially unchanged from baseline and did not differ among treatment groups.[171-176] In postmenopausal women, when serum free testosterone is maintained within the normal range for premenopausal women, short-term safety data are reassuring [*LoE 1*].[170,177,178] However, the long-term safety of testosterone use in postmenopausal women is limited to observational studies.[179] Likewise, long-term (beyond 2 years) safety data with regard to breast cancer and cardiovascular events are limited to observational trials and are inconclusive.[171,176,179,180] Studies involving reproductive-aged women are lacking.

If testosterone therapy is being considered (at the discretion of the patient and the HCP), baseline and follow-up testosterone values may be assessed [*LoE 2-3*].[26] Normal testosterone ranges have been reported for women of different age groups, but there is no minimal value for any androgen that can be used to identify women with HSDD.[65,181] Most circulating testosterone is bound to proteins (ie, SHBG, albumin), and only 1% to 2% of the total testosterone is unbound or free and biologically active.[65] Sex hormone–binding globulin levels vary considerably among individuals[58] and may be increased by oral estrogens, hormonal contraception, and thyroid hormone replacement and lowered by central adiposity and oral androgen therapy.[181,182] Most radioimmunoassays lack the precision to accurately measure total testosterone levels in women[183] such that, when possible, testosterone should be measured by liquid

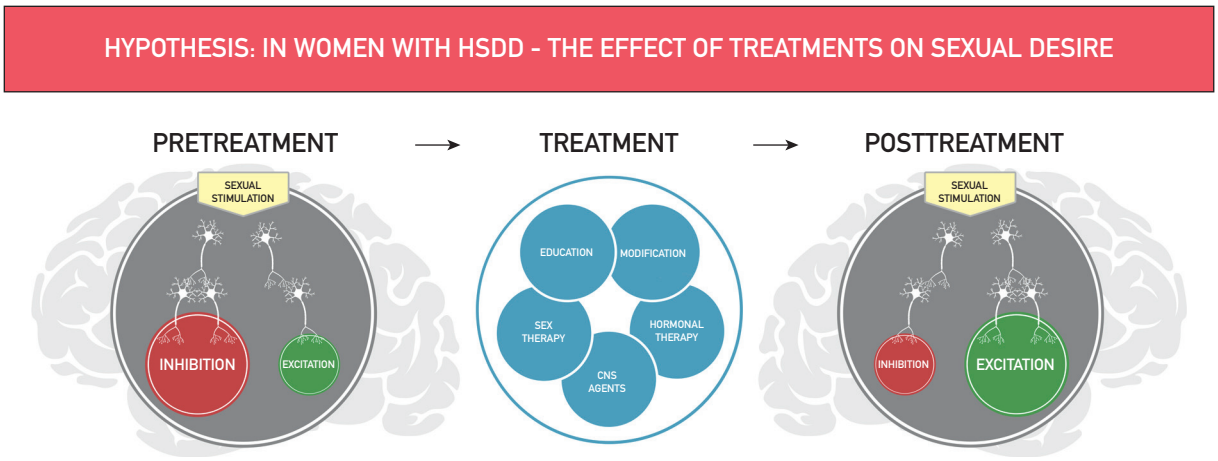

FIGURE 3. Hypothetical impact of treatments for hypoactive sexual desire disorder (HSDD). Although the precise etiology of HSDD remains unknown, the activities of inhibitory brain neurotransmitters (opioids, serotonin, and endocannabinoids) are thought to be greater than the activities of excitatory brain neurotransmitters (dopamine, melanocortin, oxytocin, vasopressin, and norepinephrine) in the presence of sexual cues and stimuli. Although the initial molecular mechanisms may vary, sex therapy, central nervous system agents, or hormonal agents used in treating HSDD may ultimately cause similar underlying changes in brain function and structure within neural circuits that regulate sexual desire such that excitation systems can be activated to a greater extent than inhibitory systems in the presence of cues and stimuli.

chromatography—mass spectrometry, which is increasingly becoming available to clinicians.[184] Free testosterone levels can be calculated from measured total testosterone and SHBG levels using an online calculator.[185] Women using testosterone should have regular follow-up blood testosterone measurements to ensure that supraphysiologic therapy is avoided.[170]

Testosterone formulations for women are not globally available, so clinicians are commonly limited to prescribing compounded formulations or testosterone formulations for men modified to much lower administered doses (usually one-tenth of the male dose) because supraphysiologic concentrations can cause virilization [*LoE Expert opinion/clinical principle*].[65,170] When a trial of testosterone therapy is initiated, treatment should be discontinued if the patient experiences no improvement in symptoms after 6 months.[170]

The synthetic orally active steroid tibolone is weakly androgenic and lowers SHBG, resulting in an increase in endogenous free testosterone.[186] Although a small randomized clinical trial of women with sexual dysfunction found tibolone to be marginally more effective for low desire than transdermal hormone therapy,[187] a recent meta-analysis failed to confirm tibolone's benefit on sexual desire in postmenopausal women [LoE 2-3].[116]

Concerning oral DHEA, systematic reviews and meta-analyses have found no statistically significant benefit of systemic DHEA on female sexual dysfunction [LoE 1].[188]

Follow-up and Reassessment

Reassessment and follow-up should be conducted at regular intervals at the discretion of the HCP. This step facilitates patient communication including discussion regarding other problems, patient concerns regarding treatment (eg, adverse drug reactions), and other sexual dysfunctions such as pain, partner issues, or lifestyle factors such as emotional distress. Patients may change medication regimens for other conditions that may impact treatment of HSDD. The need for dosage titration or substitution of one therapy for another may be considered at each follow-up visit. Patients may change treatment preferences, seek new information, or wish to reevaluate their current treatment regimen. Lastly, general medical and psychosocial reassessment should occur at regular intervals, depending on the health and

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psychosocial needs of the patient. Follow-up is intended to monitor the progress of therapy and the medical status of the patient (and partner) and provides an opportunity for further patient education.

DISCUSSION

The management steps within this POC are dependent on first asking about sexual health concerns, then distinguishing among the sexual dysfunctions to identify women with HSDD, and finally making the appropriate selection of treatment options. Treatments may include education, addressing potentially modifiable factors, psychological therapy, CNS agents, or hormone therapy. Management principles include taking into account risk to benefit ratio, degree of invasiveness, and cost in order to provide individualized care. The final decision with regard to treatment is most often dependent on patient (and partner) preferences and goals. This factor is clinically relevant considering the lack of comparison data to prioritize these therapies for HSDD.

Although the precise mechanisms for any given treatment may vary, we hypothesize that all effective treatments for HSDD result in functional changes in the neural pathways regulating sexual desire in order to enable excitation to overcome inhibition in the appropriate context of spontaneous sexual thoughts and/or visual/aural/physical stimulation (Figure 3). This hypothesis is consistent with studies demonstrating neuroplastic alterations regulating neurogenesis, synaptic plasticity, and synaptic activity associated with all of the recommended interventions: mindfulness and cognitive behavioral therapy,[189-192] steroid hormones,[193,194] and CNS-active drugs that modulate the neurotransmitter systems mediating HSDD.[195-197]

Given the unmet need of women with HSDD, developmental efforts are continuing for new safe and effective treatments. However, cost of development and regulatory requirements remain substantial obstacles. It should be emphasized that the impact of any drug therapy is not to circumvent the inhibitory influence on sexual desire that normally predominates. Rather, modulation of neuroendocrine systems may facilitate the activation of sexual desire pathways when both physiologic stimulation and social context are sufficient and appropriate.

This ISSWSH POC is an international consensus guideline to help HCPs in the management of women with HSDD. Health care professionals are encouraged to initiate a conversation with their patients about sexual activity and sexual satisfaction. Asking about these issues using the techniques noted in this POC can demonstrate a deeper interest on the part of the HCP in aspects of life that may be extremely important to patients. The depth of the inquiry can depend on the interests and depth of experience of the HCP. Self-recognition of an HCP's clinical and practice limitations can result in appropriate referral of a woman for a distressing problem, both empowering the patient and leading to successful outcome.

CONCLUSION

The ISSWSH POC provides guidelines for clinicians caring for women to diagnose HSDD and provide management, taking into account all the contributing biopsychosocial aspects: physical, medical, and medication factors; relationship and life situations; and personal sexual behaviors and history in order to provide education, modification of existing factors, and treatment based on shared decision making between the patient and her HCP. The ultimate goal of all treatment programs is improved function via a working partnership between the patient and her HCP.

ACKNOWLEDGMENTS

We thank Sue W. Goldstein, ISSWSH global development chair, for her tireless assistance in completing this project and Tessa Benitez, General Manager of ISSWSH.

SUPPLEMENTAL ONLINE MATERIAL

Supplemental material can be found online at: http://www.mayoclinicproceedings.org. Supplemental material attached to journal articles has not been edited, and the authors take responsibility for the accuracy of all data.

Abbreviations and Acronyms: **AE** = adverse event; **AI** = aromatase inhibitor; **CBT** = cognitive behavior therapy; **CHC** = combined hormonal contraceptive; **CNS** = central nervous system; **DHEA** = dehydroepiandrosterone; **DSDS** = Decreased Sexual Desire Screener; **HCP** = health care professional; **HSDD** = hypoactive sexual desire disorder; **ISSWSH** = International Society for the Study of Women's Sexual Health; **LoE** = level of evidence; **MetS** = metabolic syndrome; **PHQ** = Patient Health Questionnaire; **POC** = process of care; **SHBG** = sex hormone–binding globulin

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Grant Support: Funding for this project was provided by the International Society for the Study of Women's Sexual Health from unrestricted educational grants from Valeant Pharmaceuticals International, Inc, AMAG Pharmaceuticals, Emotional Brain BV, and Palatin Technologies, Inc.

Potential Competing Interests: Dr Clayton has received grants from Auspex Pharmaceuticals, Inc, Forest Laboratories, Inc/Allergan, Genomind, Inc, Janssen Pharmaceuticals, Inc, Palatin Technologies, Inc, Sage Therapeutics, and Takeda Pharmaceutical Company Limited: has received personal fees for consulting services from Forest Laboratories, Inc/Allergan, Palatin Technologies, Inc, S1 Biopharma, Inc, Valeant Pharmaceuticals International, Inc, and Takeda Pharmaceutical Company Limited; and has shares/restricted stock units from Euthymics Bioscience, Inc, and S1 Biopharma, Inc.

Dr Goldstein is a consultant for AMG Pharmaceuticals, Atyu BioScience, Inc, Ipsen Biopharmaceuticals, Inc, Shionogi Inc, Strategic Science & Technologies, LLC, and Valeant Pharmaceuticals International, Inc: has received grants from Valeant Pharmaceuticals International, Inc, and Shionogi Inc; has received speaker's fees from AMAG Pharmaceuticals, ASCEND Therapeutics US, LLC, Cynosure, Inc, Nuelle, Inc, S1 Biopharma, Inc, Shionogi Inc, and Valeant Pharmaceuticals International, Inc; is on the advisory boards of Emotional Brain BV, Nuelle, Inc, The Female Health Company, and Valeant Pharmaceuticals International, Inc; and has participated in clinical trials supported by JoyLux, Inc, Palatin Technologies, Inc, and TherapeuticsMD, Inc.

Dr Kim is a consultant for Valeant Pharmaceuticals International, Inc and Sprout Pharmaceuticals, Inc, and has received research grants from Valeant Pharmaceuticals International, Inc, and Astellas Pharma US, Inc.

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Dr Parish is a consultant for The Female Health Company; is on the advisory boards of Emotional Brain BV, Palatin Technologies, Inc, Pfizer, Inc, and Valeant Pharmaceuticals International, Inc; has received consulting fees/honoraria from Allergan, AMAG Pharmaceuticals, and Valeant Pharmaceuticals International, Inc; has received speaker's fees from Pfizer, Inc, and Valeant Pharmaceuticals International, Inc; and has received writing support from Pfizer, Inc.

Dr Simon is on the advisory boards of and is a consultant for AbbVie Inc, Allergan, AMAG Pharmaceuticals, Amgen Inc, Apotex Inc, ASCEND Therapeutics US, LLC, Azure Biotech, Inc, JDS Therapeutics, LLC, Merck & Co, Inc, Millendo Therapeutics, Inc, Noven Pharmaceuticals, Inc, Novo Nordisk A/S, Nuelle, Inc, Perrigo Company plc, Radius Health, Inc, Regeneron Pharmaceuticals, Roivant Sciences LTD, Sanofi, Sebela Pharmaceuticals Inc, Sermonix Pharmaceuticals, Shionogi Inc, Sprout Pharmaceuticals, inc, Symbiotec Pharmalab Pvt Ltd, TherapeuticsMD, Inc, Valeant Pharmaceuticals; is a speaker for Amgen, Eisai, Merck, Noven Pharmaceuticals, Novo Nordisk, Shionogi, and Valeant Pharmaceuticals International, Inc; has received research grants as principal investigator for AbbVie Inc, Actavis Pharma, Inc, Agile Therapeutics, Bayer Healthcare Pharmaceuticals LLC, GlaxoSmithKline plc, New England Research Institutes, Novo Nordisk A/S, Palatin Technologies, Inc, Symbio Research, TherapeuticsMD, Inc; and has stock (direct purchase) in Sermonix Pharmaceuticals.

Dr Davis is a consultant for and has received research grants from Lawley Pharmaceuticals Pty Ltd; has received speaker's fees from Pfizer, Inc, Abbott, and Besins Healthcare; and has received fees for development of educational presentations from Pfizer, Inc.

Dr Freeman is a consultant for Procter & Gamble and has received consulting fees from AMAG Pharmaceuticals; has received grants from Proctor & Gamble; and has received speaker's fees from Omnia-Prova Education Collaborative.

Dr Kingsberg is a consultant for SST Corporation, AMAG Pharmaceuticals, Emotional Brain BV, Endoceutics, Inc, Materna Medical, Valeant Pharmaceuticals International, Inc, Duchesnay USA, Shionogi Inc, TherapeuticsMD, Inc, Pfizer, Inc, Simbionix USA Corporation, and IVIX, Ltd; has received speaker's fees from Valeant Pharmaceuticals International, Inc, and AMAG Pharmaceuticals; has received fees for development of educational presentations from AMAG Pharmaceuticals, Endoceutics, Inc,

Valeant Pharmaceuticals International, Inc, and Pfizer, Inc; has received speaking and consulting fees from Nuelle, Inc; and has stock options in Viveve, Inc.

Dr Kirana has received personal fees from The Menarini Group and Recordati SpA.

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