SEXUAL MEDICINE REVIEWS

Hypoactive Sexual Desire Disorder: A Review of Epidemiology, Biopsychology, Diagnosis, and Treatment

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ABSTRACT

Introduction: Hypoactive Sexual Desire Disorder (HSDD) is defined in the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Revised* (DSM-IV-TR) as persistent deficient sexual fantasies and desire for sexual activity that causes marked distress or interpersonal difficulty. In the *Diagnostic and Statistical Manual of Mental Disorders*, *Fifth Edition* (DSM-5), HSDD has been subsumed by Female Sexual Interest/Arousal Disorder. However, decades of research based on DSM-IV-TR HSDD criteria form the foundation of our understanding of the essential symptom of distressing low sexual desire, its epidemiology, clinical management, and treatment.

Aim: This publication reviews the state of knowledge about HSDD.

Methods: A literature search was performed using terms HSDD and female sexual dysfunction (FSD).

Main Outcome Measures: Physicians acknowledge that FSD is common and distressing; however, they infrequently address it, citing low confidence, time constraints, and lack of treatment as barriers.

Results: HSDD is present in 8.9% of women ages 18 to 44, 12.3% ages 45 to 64, and 7.4% over 65. Although low sexual desire increases with age, distress decreases; so prevalence of HSDD remains relatively constant across age. HSDD is associated with lower health-related quality of life; lower general happiness and satisfaction with partners; and more frequent negative emotional states. HSDD is underdetected and undertreated. Less than half of patients with sexual problems seek help from or initiate discussions with physicians. Patients are inhibited by fear of embarrassing physicians and believe that physicians should initiate discussions. The Decreased Sexual Desire Screener, a tool for detecting and diagnosing HSDD, is validated for use in general practice.

Conclusion: Women can benefit from intervention in primary care, behavioral health and sexual medicine settings. Psychotherapeutic and pharmacological interventions aim to enhance sexual excitatory process and decrease inhibitory processes. Flibanserin, the first centrally acting daily medication for HSDD, was recently approved in the US for premenopausal women.

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Key Words: Hypoactive Sexual Desire Disorder; Female Sexual Dysfunction; Distressing Low Desire; Female Sexual Interest/Arousal Disorder; Flibanserin

INTRODUCTION

Low or decreased sexual desire that causes personal distress, the core symptom of Hypoactive Sexual Desire Disorder (HSDD) as defined in the *Diagnostic and Statistical Manual, Fourth Edition, Revised* (DSM-IV-TR),[1] is a relatively common but commonly undiagnosed problem that significantly affects the lives of approximately 8.9% of U.S. women between the ages of 18 and 44, 12.3% ages 45 to 64, and 7.4% over 65.[2] Women can benefit from behavioral and pharmacological interventions. The first barrier to providing this benefit is detection and diagnosis of the disorder. However, the private and personal nature of sexual activity and the potential for feelings of shame, inadequacy, and embarrassment create unique challenges to effective communication about sexual health for both patient and physician. These barriers, combined with lack of awareness of the prevalence and opportunity to treat HSDD on the part of both patient and clinician, are among those responsible for current underdetection and undertreatment. The goal of this paper

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report is to describe the epidemiology and impact of HSDD in the context of female sexual dysfunction in general, discuss etiological factors, strategies for screening and diagnosing, and comment on existing and emerging treatments.

In the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5), HSDD has been subsumed by Female Sexual Interest/Arousal Disorder (FSIAD).[3] This revision in the nomenclature remains controversial,[4–6] Regardless of the merits of the change in diagnostic criteria, several decades of research based on the DSM-IV-TR criteria for HSDD form the foundation of our understanding of the essential symptom of distressing low sexual desire, its epidemiology, clinical management, and treatment. In fact, assertions about the epidemiology of FSIAD have been based on extrapolation of studies using HSDD rather than FSIAD criteria.[5] The purpose of this publication is to review the state of knowledge about HSDD that is based on the DSM-IV-TR criteria.

DEFINING HYPOACTIVE SEXUAL DESIRE DISORDER

HSDD was defined in the DSM-IV-TR as persistent or recurrent deficient (or absent) sexual fantasies and desire for sexual activity that causes marked distress or interpersonal difficulty and is not better accounted for by another psychiatric disorder (except another sexual dysfunction), problems in the relationship, or due exclusively to the direct effect of a substance, medication, or general medical condition.[1] The American Urological Association (AUA) added to this definition an absence of sexual thoughts and a lack of desire in response to sexual stimulation. A further modification of the DSM definition is the specification that the decrease in interest in sex must exceed that normally observed with increasing age and with the duration of sexual relationships.[7–9,10]

HSDD may be subtyped as "due to psychological factors" when these play the major role and medications, substances, and medical conditions play no role; or "due to combined factors" when, in addition to psychological factors, substances or medical conditions contribute to but are not the exclusive cause of hypoactive desire. HSDD that is due *exclusively* to a general medical condition or medication is considered to be "sexual dysfunction due to a medical condition" or "substance-induced sexual dysfunction." HSDD is usually not diagnosed when the sexual dysfunction is due exclusively to another psychiatric disorder (other than another sexual dysfunction) such as major depressive disorder, unless the decreased desire predated the depression or is "a focus of independent clinical attention."[1]

HSDD may be lifelong (no prior history of normal functioning) or acquired (previous normal functioning) and may occur only in limited circumstances (situational) or affect all aspects of sexual experience (generalized). This discussion focuses on generalized acquired HSDD (i.e. occurring after previously normal levels of desire and in all situations).

The main difference between the DSM-IV-TR and DSM-5 is the merger of desire and arousal into the single FSIAD.[3,11] In DSM-5 severity is graded as mild, moderate, and severe; and symptoms must be present for at least 6 months during more than 75% of encounters. Both DSM-IV-TR and -5 classify their respective disorders as lifelong or acquired and generalized (all partners, activities, forms of sexual expression) or situational (certain partners, practices).

As previously mentioned, this reclassification remains controversial. Proponents offer a number of reasons for combining the two. These include difficulty in clearly defining desire, the observation that women often have sexual activity in the absence of desire, the relatively low frequency of fantasy in women, the complexity of understanding spontaneous vs responsive desire, and the common co-occurrence of decreased desire and low arousal.[12] Advocates of the DSM-5 FSIAD diagnosis assert that a circular model in which arousal may precede desire, discussed below, rather than a linear model in which desire precedes arousal, better describes female sexual response and supports the diagnostic merging of desire and arousal.[6] Those opposed to the reclassification, citing evidence from nontreatment studies of HSDD[13] and randomized trials of flibanserin,[14] describe significantly different symptom syndromes in women who met DSM-IV-TR criteria for HSDD and FSIAD. They argue that the diagnosis of FSIAD is based on clinical judgment and expert opinion rather than empirical evidence.[5,11,15] They conclude that merging these 2 distinct clinical syndromes will lead to unreliable diagnoses, obscure understanding of response to treatment, and result in excessive variability in the natural history and course of illness.[15] Critics also point out the lack of empirical evidence justifying the rejection of diagnoses based on the linear model of sexual response and replacing it with one based exclusively on a circular sexual response.[5]

HSDD and Other Female Sexual Dysfunction

HSDD is a category of Female Sexual Dysfunction (FSD), which has been classified in terms of the affected stage of the "sexual response cycle" as it is classically conceived: desire, arousal, and orgasm. DSM-IV-TR Female Sexual Arousal Disorder (FSAD) is characterized by a personally distressing absence or inadequacy of the emotional and physical manifestations of sexual excitement, including genital lubrication and swelling. Orgasm phase disorders are characterized by delayed, infrequent, or absent orgasm or markedly reduced intensity of orgasmic sensation on almost all or all occasions. A fourth category of FSD includes the DSM-IV-TR Sexual Pain Disorders, Dyspareunia, and Vaginismus, which are combined in DSM-V into Genitopelvic Pain/Penetration Disorder (GPPPD). Not included in DSM, noncoital pain, characterized by genital pain with noncoital sexual activity, also is described.[16] A central tenet of all these disorders is that they are characterized by personal distress, which may be mild, moderate, or severe (DSM-5).

Desire Disorders and the Sexual Response Cycle

Female sexual dysfunction has been classified in DSM on the basis of the traditional human sexual response cycle, which when first described by Masters and Johnson[17] consisted of 4 phases: excitement, plateau, orgasm, and resolution. Kaplan[18] as well as Lief[19] modified this model by adding a desire phase and eliminating the plateau and resolution phases, resulting in the current linear 3-phase model: desire, arousal, and orgasm.[20] The description of female sexual function and the classification of dysfunction based on the 3 phases of the sexual response cycle[1] have been augmented by other concepts that identify greater variability and additional complexity in female sexual functioning.[10,21] Basson and others argue that the linear model may not describe female sexual experience as well as it characterizes male sexual response. According to incentive motivation model,[22] the 3 phases may occur in different sequences and are more circular than linear. Women may experience arousal, orgasm, and satisfying sexual experiences without initially, or ever, having desire for sex as a distinct subjective experience. Women may be motivated to engage in sexual activity for many reasons besides desire for sexual activity per se, including intimacy or bonding, desire, wanting to feel attractive or desired, or to communicate affection for a partner.[1,23–25] Accordingly, sexually stimulating physical intimacy, initiated in response to one of these motives, may lead to arousal and only subsequently to what has been called "responsive desire." An absence of responsive desire is therefore included in the AUA Foundation definition of hypoactive sexual desire disorder.[1,7,10,23,26–28]

Advocates offer the circular model as normative for female sexual experience, especially for those in long-term relationships. However, others including Sand and Giraldi argue that women with distressing low desire are more likely to endorse the circular-Basson model as accurately representing their experience compared with women who report a more linear sexual response.[29] Sand and Fisher found that in a community sample of nurses the Masters and Johnson, Kaplan, and Basson models were endorsed by equal proportions of women. Women who endorsed the circular model were more likely to have scores indicative of sexual dysfunction (Female Sexual Function Index $<$ 26.55).[29–31] Giraldi et al's study of 573 Danish women also found that equal numbers of women endorsed each of the 3 models and 12.5% favored none of the models; women who endorsed the circular model or none of the models were more likely to have sexual dysfunction and distress.[32]

Levine offers yet another perspective on female sexual responsiveness.[33] He describes "three components of desire." Drive, the first component, consists of biological mechanisms that drive spontaneous sexual interest. The second, "cognitive" component, is determined by the individual's expectations, beliefs, and values about sex. The third component, "motivation," reflects the emotional and interpersonal factors that influence the individual's willingness to engage in sexual activity. Motivation is affected by the quality of the individual's relationship, psychological functioning, concerns about children, and other psychological factors.

Personal Distress

Personal distress or interpersonal difficulty due to decreased desire is a key feature of DSM-IV-TR criteria. "Personal" distress indicates that the patient herself is bothered by her low desire, while "interpersonal" distress may result from her feeling unhappy because her low desire for sexual activity does not satisfy and causes conflict with her partner. Conversely, if the decreased desire for sex with her partner is due primarily to interpersonal conflict or dissatisfaction with the partner, the decrease in desire can be better explained by the relational discord and not HSDD. Bancroft and others have argued that inhibition of sexual interest and response may be an adaptive response to unresolved difficulties in a relationship.[9] Likewise, women who begin sexual activity without a subjective experience of sexual desire but experience responsive desire in the course of arousal and are satisfied with their sexual experiences and not distressed by the absence of subjective desire would not meet criteria for HSDD. The criteria for FSIAD in the DSM-5 do not distinguish between personal and interpersonal distress but does classify distress as mild, moderate, or severe.

PREVALENCE OF HSDD

National Health and Social Life Survey

The first systematic assessment of the prevalence of sexual problems in the United States that employed rigorous sampling methodologies was the National Health and Social Life Survey (NHSLS).[34] This oft-cited study established the high frequency of sexual problems among United States women; but as has been equally frequently pointed out, the NHSLS study did not assess personal distress associated with sexual problems and thus could not determine the frequency of sexual disorders. Low sexual desire for a period of at least 1 month in the previous 12 months was the most common sexual problem reported and was present in 31.6% of women.[35] The prevalence of lack of interest in sex was inversely related to educational attainment; more common in Black compared with White women; and more common in women with a history of sexually transmitted disease, poor to fair health, emotion problems, stress, and falling income. Women with desire problems reported their frequency of sexual activity as no more than once monthly and thinking about sex less than once weekly. Compared with women with no sexual problems, those with desire, arousal, or pain problems were more likely to have low physical and emotional satisfaction with sexual partners and low general happiness.

Subsequent studies employing methods that are more consistent with current diagnostic criteria have used the Profile of Female Sexual Function (PFSF)[36,37] and the Personal Distress Scale (PDS)[38] to define low sexual desire and personal distress, respectively, and have shed more light on the prevalence of low

sexual desire and distress. West et al assessed 1944 nonpregnant women aged 30 to 70 in steady relationships for 3 months or longer. The prevalence of low sexual desire was 36.2%, and the prevalence of distressing low sexual desire consistent with a diagnosis of HSDD was 8.3%.[39] The prevalence of low sexual desire increased with age, and the prevalence was higher in surgically menopausal women regardless of their current age or their age at the time of surgery. The highest rate of low sexual desire with distress was observed in young, surgically menopausal women (19.8%).

Although the prevalence of low sexual desire increases with age, distress about low sexual desire decreases with age; thus, the prevalence of distressing low sexual desire stays relatively constant with increasing age. In West's study, women between 60 and 70 years of age and naturally postmenopausal women had the highest prevalence of low sexual desire but a lower prevalence of associated distress.[39] Naturally menopausal women had the lowest prevalence of distressing low sexual desire (6.6%) despite a high prevalence of low sexual desire (52.4%). Another study by Hayes et al conducted in the United States and Europe in women aged 20 to 70 also found that the proportion of women with low desire increased with age, but the increase was counterbalanced by a decrease in the proportion of women distressed about low sexual desire; as a result, the prevalence of distressing low sexual desire was relatively constant with age (6% to 13% in Europe and 12% to 19% in the United States).[40]

The PRESIDE Study

In a more recent study, the Prevalence of Female Sexual Problems Associated with Distress and Determinants of Treatment Seeking (abbreviated as PRESIDE), desire, arousal, and orgasm problems in a population-based survey of adult U.S. women were evaluated.[2] A response of never or rarely to the single question, "How often do you desire to engage in sexual activity?" was used to define a problem with desire, and the Female Sexual Distress Scale (FSDS)[41] was used to define distress (score of at least 15 out of possible 48). The combination of low desire plus an FSDS score of 15 or higher was used as the self-report survey-based indicator of decreased sexual desire with distress. This study has the virtues of using a large (n = 31,581) demographically representative sample and of including a measure of personal distress. Its principal limitations include the use of self-report data rather than clinical evaluation; recruitment of subjects from a commercial research panel whose members' willingness to participate in surveys may be associated with characteristics related to sexual beliefs or functioning; and a response rate of 63%, which, however, is comparable to other community surveys of sexual functioning.

Almost half (43.1% age-adjusted estimate) of women reported some sexual problem. Low desire, present in 37.7% (age-adjusted estimate) of subjects, was the most common sexual problem reported, followed by low arousal (25.3%) and low orgasm (21.1%). Sexually related personal distress (FSDS >15) was present in 22.2% of subjects. There was a dramatic relationship between the prevalence of sexual problems and age: about one-quarter (27.2%) of younger women (ages 18-44), close to half (44.6%) of mid-aged women (ages 45-64), and most (80.1%) of older women (≥65 years old) had at least 1 problem. However, only 12.6% of older women had sexually related personal distress, compared with 25.5% of mid-aged and 24.4% of younger women.

A sexual problem with associated personal distress was present in 12.0% of women, and most common in mid-aged women (14.8%), followed by younger women (10.8%) and lowest in older women (8.9%). Decreased sexual desire with distress was reported in 8.9% of women ages 18 to 44, 12.3% ages 45 to 64, and 7.4% over 65.The prevalence of desire and arousal phase problems accompanied by personal distress followed the same age-related pattern, but distressing orgasm problems occurred with similar frequency in mid-aged and older women.

Co-occurrence of Other Sexual Problems

Among all women in the PRESIDE study population, distressing low sexual desire occurred along with a second distressing sexual problem in fewer than 5%, and 2.3% of all women had all 3 distressing problems.[2] However, among women with distressing low sexual desire, half (52.5%) reported a second or third distressing sexual problem.[42] Consistent with this, the correlation of low sexual desire with arousal and orgasm problems and diminished sexual pleasure (without regard to personal distress), as reported in a study of European women, was very strong (0.63, 0.53, and 0.75, respectively).[26]

The HSDD Registry for Women was a multicenter, longitudinal study of women with HSDD that enrolled 1500 women between 2008 and 2010.[43] Among the 426 premenopausal women who reported recent sexual activity and who therefore could be assessed, 50.2% also had arousal problems, 42.5% lubrication problems, and 39.0% both problems. Among the 174 sexually active postmenopausal women, 58.0% had arousal problems; 56.9%, lubrication; and 49.4%, both problems.[44]

LOW DESIRE AND QUALITY OF LIFE

Women with sexual problems and distressing low sexual desire in particular have lower health-related quality of life. This association was demonstrated in the NHSLS in which women with desire, arousal, and sexual pain problems had lower physical and emotional satisfaction with their partners and lower general happiness than women without sexual problems.[35] In a study of postmenopausal United States women, distressing low sexual desire was associated with lower health-related quality of life in 7 of 8 domains of functioning including physical function, physical role functioning, general health, vitality, social functioning, emotional role functioning, and mental health.[45] Women with low desire were more likely to be dissatisfied with their sex life, their partner, or marriage and experience more negative

emotional states including frustrations, hopelessness, anger, poor self-esteem, and loss of femininity.

All studies of these associations have been cross-sectional, and thus no conclusions can be drawn about the causal relationships between sexual dysfunction and poor quality of life. Poor quality of life may be the cause of sexual problems, its consequence, or the result of some other problem that is also causing sexual issues.

ETIOLOGY OF LOW SEXUAL DESIRE AND DISTRESS

Multivariate analysis of subjects' characteristics in the PRESIDE study revealed a number of important variables associated with distressing low sexual desire.[42]

Partners and Life Situation

Life situation and social status had a significant relationship with the prevalence of distressing low sexual desire.[42] Working women and mid-aged (compared with younger or older women) were more likely to have distressing low sexual desire. Women with a sexual partner, whether or not they were married or living with someone, were more likely to have distressing low sexual desire.[42] However, marital status also had an independent relationship with distressing low sexual desire; married women or those living with a spouse or partner were more likely to have distressing low sexual desire than single women.[42] When marital status and availability of a sexual partner were considered together, single women with a sexual partner were at lowest risk.

Culture, Race, and Ethnicity

Culture and race appear to have a significant association with the prevalence of distressing low sexual desire. In the PRESIDE study, Caucasian women were more likely than Black women to have distressing low sexual desire. In the WISHES study, comparing the prevalence of female sexual problems in 4 European countries, prevalence varied significantly. The lowest prevalence of low sexual desire occurred among women in France (21%), with significantly increasing prevalence in Italy, the United Kingdom, and Germany (28%, 34%, and 36%).[46] These differences were most notable in pre- and naturally postmenopausal women and less so after surgical menopause. The authors of this study speculate that the observed differences are likely to be due to a combination of cultural and other regional factors and mention differences in the use of postmenopausal hormone treatment and religious attitudes toward sexual activity as examples.

Menopause, General Health, and Psychiatric Disorders

In the PRESIDE study, postmenopausal women, especially young women with surgical menopause,[26,45] were more likely to have distressing low sexual desire. No significant association was observed with the current use of hormones in postmenopausal women. Each decrement of the 5-point self-assessed health scale was associated with a greater probability of distressing low sexual desire, as were comorbid thyroid disease or urinary incontinence. There was a dramatic positive association between depression (defined as a positive response to either of the 2 screening questions employed in the PHQ-2 assessment of depression, i.e. depressed mood or anhedonia during the previous 2 weeks, or the current use of antidepressant medication), as well as anxiety and the probability of distressing low sexual desire. In the HSDD Registry for Women Study, one third of the 1088 premenopausal women presented with symptoms or a diagnosis of depression, and they reported poorer relationships and sexual function.[47]

Psychophysiological Models of HSDD

In an effort to integrate the complex interaction of psychosocial and physiological potential causes of HSDD, Bancroft and others have offered the following concepts.

- Dual control of sexual interest and response: Sexual response is the result of an interaction between sexual excitatory and inhibitory forces that may act independently. Low desire may be the result of insufficient excitatory processes or increased inhibition of sexual interest or response. Inhibition of sexual interest or response may be a healthy adaptive response to a distressing relationship or life circumstances that serves to help avoid risky, distressing, or threatening sexual situations and behavior.[9,48–50]
- Three domains of factors may influence sexual excitation and inhibition[9]:
  - Relationship and life situation, e.g. marital problems, life stress, fatigue.
  - Personal sexual behaviors and history, e.g. a tendency to react to sexual difficulties with inhibition of sexual interest as a result of learned behaviors, cultural influences, past trauma.
  - Physical, medical and medication factors such as menopausal status, use of exogenous hormones and other medications, medical illnesses.

This model provides a framework for understanding the possible causes of HSDD by allowing consideration of factors that would either decrease sexually excitatory processes or increase inhibitory processes.

Central Nervous System and HSDD

There is a growing understanding of the role of specific neurotransmitters and brain pathways associated with sexually excitatory processes (dopaminergic pathways in the limbic system and hypothalamus) and inhibitory processes (opioid, endocannabinoid, and serotonergic systems).[51] Recent studies using functional brain scanning have demonstrated distinguishable patterns of brain activity during erotic compared with nonerotic experiences. Different patterns of activation when viewing erotic

compared with nonerotic films[52] have been reported in women, and these patterns also differ between pre- and postmenopausal women.[53] Specific differences in encoding arousing stimuli and/or retrieval of past erotic experiences have been reported between women with HSDD, who appeared to allocate more attention to monitoring and/or evaluating their own responses, compared with women without sexual dysfunction. No relationship was observed between peripheral sexual response, as measured by vaginal photoplethysmography, and brain activation patterns in either group, a finding consistent with research on the weak relationship between measures of genital and subjective arousal in women.[54] Further studies will be needed to deepen understanding of the female sexual response and its relationship to brain activation patterns and the processing of erotic stimuli by women with and without HSDD.

Hormonal Influences

Although the effect of hysterectomy and oophorectomy on young women may not be due entirely to sex hormone changes, the high prevalence of HSDD in young surgically menopausal women compared with premenopausal women and naturally postmenopausal women is strong evidence for the effect of significant rapid changes in hormonal levels on desire.[2,25,26,45] The age-related decline in androgens parallels the age-related increase in HSDD in midlife women; naturally postmenopausal women also have higher rates of low desire compared with premenopausal women, supporting the role of hormonal effects on desire.[55,56]

Estrogen deficiency has been clearly linked to vulvovaginal mucosal changes and dyspareunia, which may contribute to decreased desire in affected women.[57]

Testosterone levels have shown variable association with desire disorders.[25,58] One study demonstrated lower levels of androgens in healthy premenopausal women with sexual problems compared with women without sexual problems[59]; in another study, 15 premenopausal women with lifelong absence of sexual desire had lower free testosterone levels than women with "intact" sexual drive.[60] A study of postmenopausal women revealed a positive correlation between free testosterone levels and self-reported desire in sexagenarians.[61] By contrast other studies, including 2 large population studies, have failed to show significant correlation between sexual function and testosterone levels.[62–64] In a recent cross-sectional study of 560 pre- and postmenopausal women, free testosterone and androstenedione correlated with sexual desire; however, in the subset of women aged 45 to 65 only androstenedione levels were associated with sexual desire.[65] Several explanations have been offered for these variable findings, including genetic differences in the response to androgens and the multiplicity of effects that changes in any 1 hormone have on the entire system.[58] In addition, the measurement of testosterone levels presents several challenges. Assays for testosterone have not been designed for low levels in women; levels may vary during menstrual cycles; and current methods do not measure testosterone produced in target cells.[66]

The effect of oral contraceptives (COCs) on sexual functioning is controversial. Some studies show an association between the use of OCs and sexual problems, including decreased interest in sexual activity and sexual arousal.[67–71] This may be due to the effect of decreased testosterone production and increased sex hormone binding globulin which further decreases free testosterone.[72] These effects may persist to some extent for years after oral contraceptives have been stopped. The use of OCs has also been associated with vestibulodynia or vulvovestibulitis, an inflammation of the vulvar vestibule in the region of the labial hymen junction, and an increase in sexual pain.[72–77] Overall, studies of the relationship of OCs on sexual functioning are mixed with studies showing increased, decreased and no change in sexual desire.[78,79] The use of oral contraception may improve sexual health indirectly by decreasing the fear of unwanted pregnancy, improving personal appearance (eg, acne) and diminishing menstrual irregularity and pain. For patients in whom OC use may be a contributing factor to sexual dysfunction, alternative forms of contraception and their risks and benefits should be discussed.

DIAGNOSIS AND EVALUATION OF HSDD

The clinical diagnosis of generalized acquired HSDD requires establishing a history of low or absent sexual fantasies, thoughts about sex, or desire for sexual activity that is associated with personal distress and/or interpersonal difficulties and not limited to a specific situation or relationship, and not better explained by a medical or nonsexual psychiatric disorder or the use of medications or substances. The diagnosis of acquired vs. lifelong HSDD requires establishing that the low desire was preceded by a period of normal sexual desire.

Barriers to Detection and Diagnosis of HSDD

Substantial barriers stand in the way of effective detection and diagnosis of HSDD. Sexual health is acknowledged to be a potentially embarrassing subject of discussion, and one that may create discomfort within the clinician–patient relationship. Both parties may have attitudes, beliefs, and behaviors that interfere with effective communication and thwart detection and diagnosis of sexual concerns and disorders.

Healthcare Professionals' Attitudes and Behavior

Research demonstrates that healthcare professionals know that sexual dysfunction is common and distressing, but infrequently initiate discussion or evaluation of sexual functioning with their female patients. In a fax/e-mail study of a random sample of practicing physicians that used a case vignette–based survey and obtained an 8.8% response rate, 21% of obstetricians/gynecologists and 38% of primary care physicians (PCPs) stated they were not at all confident about treating HSDD.[80] In multivariate analysis low confidence was associated with perceived time constraints, perceived lack of effective therapy, fewer years in

practice, and fewer patients who reported distressing sexual problems per week. Of note, female PCPs were less confident than males in their ability to treat HSDD, an association that was not observed in obstetricians/gynecologists. Time constraints and lack of therapeutic options also were cited by respondents as barriers to initiating discussion of sexual health. Respondents believed that medical and residency education provided inadequate preparation for sexual history taking; however, participation in continuing medical education and practice experience were associated with greater confidence in the multivariate analysis.

A nonsystematic survey of physicians who visited a pharmaceutical company booth at obstetrician/gynecologist, endocrine, menopause, and reproductive medicine professional meetings revealed that, even among these physicians, the majority (58%) initiated conversations about sexual functioning with fewer than 25% of their patients and a similar proportion (60%) reported that fewer than 25% of their patients initiated such conversations.[81] Physicians cited time, embarrassment of either party, and lack of treatment and training as the most common causes of not evaluating sexual functioning; findings that were echoed in an Israeli study.[82] Most of the physicians surveyed at professional meetings (61%) rated their knowledge of FSD as only fair to poor, and their level of comfort paralleled their self-assessed knowledge. Nevertheless, these physicians did not commonly refer patients to sexual medicine specialists; 68% made referrals for fewer than 25% of women whom they determined to have FSD. Most physicians felt that treatments for FSD had only fair (45%) or poor (41%) effectiveness. In a more systematic survey of an academic primary care clinic in which half of potential subjects responded, 90% of clinicians reported little confidence in making the diagnosis of HSDD, and 90% of physicians had not screened a patient for HSDD. Faculty were more confident than residents.[83] A review of the literature on sexual medicine education confirms that the many significant barriers to providing effective care for women's sexual health are poorly and variably addressed by existing curricula.[84]

Patients' Attitudes and Experience

Patients' attitudes and expectations contribute to the underdetection of sexual problems. In a survey of 500 male and female adults, 71% of participants expressed concern that physicians would not take them seriously and 68% thought their physicians would be embarrassed discussing a sexual concern, despite their willingness to discuss sexual problems themselves.[85] A web-based survey about seeking help for sexual problems involving 3807 women, 77% of whom had low desire, revealed that 40% of women with sexual problems did not seek help from physicians; and half (54%) would like to but did not because they would be embarrassed (22%), did not think they could get help (17%), or it didn't occur to them to seek help from a doctor (12%). Half of participants who consulted physicians felt that the doctor listened (52%) without reluctance (49%) or avoidance (48%), but only 39% felt that the physician appreciated the significance of their problem to them; and fewer (24%) felt that the doctor helped them with their nervousness in talking about sex.[86] An international study of 27,500 men and women revealed that half of all sexually active participants had at least 1 sexual problem, but only 19% had sought medical care; and only 9% reported being asked about sexual health in the previous 3 years.[87] In a preliminary analysis of the first 724 women enrolled in the HSDD Registry for Women Study, 53% had not sought formal healthcare. Women seeking care were more likely to be married/cohabiting, postmenopausal, insured, using more than 5 medications, depressed, have longstanding sexual desire problems, or feel that their relationship or sense of femininity/sexual self was threatened by HSDD.[88]

Strategies to Improve Detection and Diagnosis of HSDD

The simplest and most obvious strategy for detecting all sexual concerns and problems is simply to ask. In an early study, only 3% of almost 900 women in an obstetrics/gynecology practice spontaneously mentioned sexual problems, and an additional 16% revealed problems when asked.[89] Detecting decreased desire and assessing the features of HSDD despite attitudinal and behavioral barriers may be improved by using effective patient-centered communication and screening tools.

Screening With a "Ubiquity Statement" Closed-ended Question and Open-ended Follow-up

The simplest approach to detection is to ask a direct screening question such as, "Do you have any problems or concerns related to sex?" where it feels the most natural. Screening may be facilitated by setting the stage for this direct question by preemptively assuring the patient that you, the clinician, will not be embarrassed about discussing sexual issues and also by stating your understanding that having sexual problems is common and not abnormal or deviant. Both of these tasks can be accomplished with a 3-step strategy based on the work of Sadovsky, who described the first 2 steps of the process: (1) a "ubiquity statement," (ie, a statement taking the form of, "Many women having [the characteristics of the patient] have concerns about sexual functioning,") followed by (2) a closed-ended question; "How about you?"[90] The stem for ubiquity statements include medical, social and life-cycle issues such as:

- Many women with diabetes…
- Many women going through menopause…
- Many women with young children…
- Many women whose husbands have had heart disease…
- Many women who are working and raising children at the same time…

The ubiquity statement and closed-ended question demonstrate that the clinician is not embarrassed and thinks that discussing sexual health is important and simultaneously

"normalizes" and "universalizes" sexual concerns for women in the patient's situation.[91–94] (3) The third step of the ubiquity statement screen for sexual problems is an open-ended follow-up to any acknowledgement of sexual concern such as, "Tell me about it."

Screening Tools: The DSDS

The Decreased Sexual Desire Screener (DSDS) is a self-report questionnaire that has been validated as a tool that can assist clinicians in making an accurate diagnosis of HSDD[95] (Table 1). The first 4 yes/no questions establish the presence of an acquired, distressing, decrease in sexual desire that the patient would like to increase. The fifth question presents a number of potential causes or exacerbating factors for loss of desire. Patients who do not endorse all of the first 4 questions are unlikely to have HSDD. Those who do endorse all 4 need a clinical assessment to confirm their responses and determine what role any of the items endorsed on question 5 may be playing in the decreased desire. Clinical assessment also is required to determine whether decreased desire is "generalized" or only in the context of a specific relationship or situation.

Table 1. Decreased Sexual Desire Screener (DSDS)

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

The patient qualifies for the diagnosis of generalized, acquired HSDD if

- She answers "YES" to all of questions 1–4, and your review confirms "NO" to all of the factors in question 5.

The patient MAY qualify for the diagnosis of generalized, acquired HSDD if

- She answers "YES" to all of questions 1–4 and "YES" to any of the factors in question 5; clinical judgment is required to determine if 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.

The patient does NOT qualify for the diagnosis of generalized, acquired HSDD if

- She answers "NO" to any of the questions 1–4.

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The DSDS was designed for use in general practice by internists, family physicians, and gynecologists without expertise in sexual medicine. In the validation study the DSDS used by physicians without special expertise had a sensitivity of 0.84, specificity of 0.88, and overall diagnostic accuracy of 85.2% in the study sample, which had a 54% prevalence of HSDD.[95] In trials of flibanserin, the DSDS demonstrated a sensitivity of 0.95 in 911 U.S. women and 0.96 in 630 European women when interpreted in consultation with the subjects by clinicians without specialization or training in FSD.[96] Although the DSDS was designed and validated as a patient self-report questionnaire, it also should be effective as a semi-structured clinician-administered interview guide.

Other Screening Tools

Although the DSDS is based on the DSM-IV-TR diagnostic criteria for HSDD, other screening tools for FSD have been developed that are more dimensional and less specific to HSDD.[30] The Female Sexual Function Index (FSFI) is a 19-item self-report instrument that assesses key dimensions of sexual function including desire, subjective arousal, lubrication, orgasm, satisfaction, and pain. It has been validated and reliably discriminates between sexually disordered and healthy women; it detects change with treatment and is appropriate for clinical use (www.fsfiquestionnaire.com).[31,97] The maximum score is 36, with a score <26.5 indicating sexual dysfunction. The Female Sexual Distressed Scale – Revised version (FSDS-R) is a validated questionnaire consisting of 13 items assessing distress, embarrassment, dissatisfaction, and other negative feelings associated with sexual problems, including one that specifically addresses low desire.[98]

Using Patient-Centered Dialog to Diagnose HSDD

Whether using the DSDS or the ubiquity statement screen, positive responses to closed-ended questions about decreased sexual desire should be followed by "directive open-ended questions" about the core symptoms of decreased desire and associated "bother" or distress.

Directive open-ended questions, which "direct" the patient to a particular topic but leave the format of the patient's response "open" to the patient, are an essential component of patient-centered communication.[99] Patient-centered communication is distinguished from physician-centered communication by including consideration of the patient's psychosocial context, their emotional responses to problems, and the patient's therapeutic alliance with the clinician.[100] Patient-centered communication has been shown to improve patient education, adherence to treatment, patient satisfaction, and patterns of care.[99, 101–105]

One way to conduct an interview with a patient who has confirmed that they have distressing decreased desire in response to a close-ended question would be to ask an open-ended follow-up such as, "Tell me more about the decrease in your level of sexual desire or interest and how it affects your life." It is likely that patients will respond with a brief but informative narrative about their problem with decreased desire. If their response doesn't clarify whether the decreased desire is generalized or situational, a specific question can follow. If the patient's response doesn't clarify the extent of personal distress or bother, a focused open-ended question about bother or impact on life should be asked.

Assessing Potential Causes and Exacerbating Factors

Potential causes and exacerbating factors for decreased desire need to be assessed to determine whether the decrease in desire can be better explained by another medical or nonsexual psychiatric disorder or is exclusively due to the use of a medication or substance. If other medical or psychiatric disorders, medications, or substances are playing a role, the clinician should try to determine whether the decreased desire is merely exacerbated by or principally caused by these factors. Many of the causative and contributing factors may be problems worthy of attention in their own right.

Depression

Depression is a common cause or exacerbating factor for distressing low sexual desire. Strategies for assessing depression are available for use in the ambulatory setting, including the PHQ-2/9 diagnostic tools.[106–108] As discussed above, anhedonia and decreased libido are core symptoms of depression; therefore, determining whether the loss of desire is due to depression alone may be difficult. One study has demonstrated a bidirectional association between depression and sexual dysfunction.[109] Treatment of a mood disorder may shed some light on the independence of comorbid HSDD. Most antidepressants are associated with both orgasm and desire disorders[110]; therefore, treatment of depression with medication may substitute one cause of sexual dysfunction for another. However, in the HSDD Registry for Women Study, use of antidepressant medication was associated with more severe sexual dysfunction, primarily in women with residual symptoms (ie, inadequately treated depression) but not in women whose depression was in remission.[47] Also, a placebo-controlled study of depression maintenance therapy with duloxetine suggests that treatment emergent sexual dysfunction during the maintenance phase is more associated with depression status than with the use of that medication.[111] Bupropion appears to be associated with significantly less sexual dysfunction compared with selective serotonin reuptake inhibitors (SSRIs) and selective serotonin and norepinephrine uptake inhibitors (SNRIs).[112,113] Mirtazapine and vilazodone also may have fewer adverse sexual effects than the SSRIs and SNRIs.[114,115] Use of antidepressant and other medications as well as drugs and alcohol should be included in the evaluation of all female sexual dysfunctions.

Other Sexual Problems

Screening for other sexual problems or disorders is an important element in the assessment of HSDD. When patients indicate that arousal, orgasm, or sexual pain problems may be contributing to desire problems, these need to be evaluated as well; and diagnoses of arousal and/or orgasm disorder can be made concurrently with that of HSDD. The timing of onset of arousal and orgasm problems in relationship to the onset of desire problems is important. Desire may decrease in response to frustrating or distressing experiences with arousal and orgasm, and these conditions may indeed be the underlying cause of sexual dysfunction and distress. A variety of instruments previously mentioned have been developed to help screen for the spectrum of female sexual disorders.[30,31,97]

Partner's Sexual Problems and Dissatisfaction With the Relationship

A woman's problem with sexual function may be due to or exacerbated by a partner's sexual problems.[116] Decreased desire, erectile dysfunction, and premature or delayed ejaculation in male partners may produce frustration with sexual activity that leads to a reflexive decrease in desire. Understanding the impact of a male partner's sexual problems requires some knowledge of those disorders. Sexual dysfunction in partners may equally affect lesbian relationships,[117] and clinicians must guard against assuming that the patient has a heterosexual orientation regardless of the patient's marital or maternal status. Addressing low desire associated with a partner's sexual problems should include assessment of the patient and partner's sexual practices, frequency of sexual activity, and discrepancies in desire for sex. It is also important to find out if and how the patient communicates about sexual concerns or practices with her partner.[118]

Dissatisfaction with a partner or relationship may be an important cause of sexual problems and may be due to dissatisfaction with the partner as a sexual partner or dissatisfaction about any other aspect of the relationship.[116,119–122] Women who only experience decreased desire towards their partner but have sexual fantasies or interest in sexual activity, do not have generalized HSDD; they have a desire problem that is specific to their relationship.

A common cause of stress and dissatisfaction among sexual partners is a discrepancy in the frequency of their desire for sex.[120,123] Women may assess their own level of sexual desire by the extent that it matches their partner's desire for sexual activity. There is significant variation across and within cultures and across individuals independent of culture in attitudes about accommodating the expectations of the other for sexual activity. It is most important that clinicians become aware of the variation in cultural and personal norms that affect these behaviors and

seek to clarify what they are for each patient. It is essential that clinicians not uncritically apply their own beliefs and attitudes, and to that end it may be important to reflect upon their own personal beliefs and consider how they may differ from those of the patients they care for.

Physical Examination and Laboratory Evaluation

Recommendations for the physical and laboratory evaluation of sexual dysfunction have been provided by International Consultation in Sexual Medicine.[124] Evaluation of HSDD may include a focused physical exam, including a pelvic exam, if indicated by the clinical situation. Laboratory testing may include measurements of testosterone. Total testosterone levels have been standardized for men, but may be less reliable at the lower concentrations seen in women.[125] Only unbound testosterone, 1% to 2% of total, is biologically available; two thirds is tightly bound to sex hormone-binding globulin (SHBG) and one third more loosely bound to albumin. Therefore free testosterone should be measured directly or calculated based on sex hormone-binding globulin and albumin levels (http://www.issam.ch/freetesto.htm), when levels of SHBG are altered such as in women receiving oral estrogens or women with central adiposity.[126]

Other hormone assays including estradiol, progesterone, luteinizing hormone, follicle stimulating hormone, prolactin, and thyroid-stimulating hormone should be obtained to evaluate demonstrated or potential comorbid conditions. Referral to a specialist for more specialized physical exam, testing, and treatment should be considered when there are contributing comorbid disorders beyond the clinician's expertise or in some complex circumstances such as primary lifelong sexual disorders, anatomical deformity, physical and psychological trauma, and treatment failure.[124]

TREATMENT

As the underlying cause of decreased sexual desire may be multifactorial, an appropriate treatment plan may be multifaceted. Psychosocial, behavioral, and biological causes and contributing factors are all potential targets of intervention. Any of the full range of problems that may contribute to decreased sexual desire should be the initial focus of intervention. Modalities that may be of direct benefit include sex therapy, psychotherapy,[127–129] and treatment of vulvovaginal atrophy, vaginal dryness, and dyspareunia in postmenopausal women.[130,131] The role of the primary care physician and the threshold for referral to a behavioral health clinician or sexual medicine expert will depend upon the clinician's comfort and interest in treating sexual problems, the patient's willingness to see other clinicians, and the cost and availability of sexual medicine consultation (see International Society for the Study of Women's Sexual Health "Find a Provider" for sexual medicine referral resources; http://isswsh.org/).

Psychotherapeutic, Behavioral, and Sex Therapy Interventions

Primary care physicians can begin effective discussions about sexual health and, depending on their interest and expertise, engage in basic sexual health counseling and/or refer to sexual and behavioral health experts as previously discussed (see American Association of Sexuality Educators, Counselors and Therapists for sex therapy referral resources; http://www.aasect.org/). Basic understanding of sex therapy and other behavioral treatments can provide the foundation for office-based counseling as well as effective referrals to specialists. The overall goal of sex therapy is to create or restore "mutual sexual comfort, satisfaction, and pleasure."[132] The strategic objective of therapy, as articulated by the "dual control model" of sexual excitation, is to decrease inhibitory and enhance sexually excitatory processes.[48,133]

A variety of modalities may be employed to accomplish these goals.

Knowledge and communication between partners are a critical foundation for any intervention. It is essential to assess the patient's and partner's beliefs about sex and sexual functioning, address myths and mistaken beliefs, and enhance understanding with essential and correct information about sex and sexual functioning. It is equally important to assess the patient's ability to communicate their experience, feelings, and preferences with their partners. Upon this foundation, efforts to decrease inhibitory processes can focus on, among other things, negative beliefs and feelings about sex, body image concerns, and problems with relationships, including pressure to perform, or general deficits in a loving environment in which the woman feels safe and valued.[132] Excitatory processes can be enhanced with education about sexual techniques, as well as "setting the stage" for and planning sexual activity.

A mainstay of sex therapy, "sensate focus" or "nondemand" or "sensual touching," can decrease the inhibitory effects of performance anxiety with exercises that employ a graded transition from nonsexual to sexual touching. This technique simultaneously increases excitatory processes by focusing attention on the sensuality of touch.[132] A study of a 10-session cognitive behavioral therapy program that combined communication and sexual skill training, sensate focus exercises and other strategies to lower sexual and performance anxiety showed improvement in women, most of whom had more than 1 sexual disorder. However, the program had greatest impact on anorgasmia and arousal problems and less on low interest in sex.[129] There is additional evidence that cognitive behavioral therapy, psychoeducational and mindfulness techniques may be of benefit to women with sexual distress and dysfunction.[134–137]

Pharmacological Treatment

Flibanserin has recently been approved in the United States for the treatment of HSDD in premenopausal women. Flibanserin is a centrally acting postsynaptic 5-HT1A (serotonin) receptor agonist and a 5-HT2A antagonist that produces a decrease in

serotonin activity and an increase in dopamine and norepinephrine activity in brain pathways associated with sexual desire.[51,138–140] This combination of effects is thought to favorably influence the balance of neurotransmitter activity in women with HSDD by suppressing sexually inhibitory serotonergic activity and promoting excitatory dopaminergic and noradrenergic effects.[51,138,139] The efficacy of a 100 mg daily dose of flibanserin in premenopausal women with HSDD is supported by 3 randomized placebo-controlled clinical trials,[141–143] all of which demonstrated a significant increase in "satisfying sexual events," a primary endpoint used in all 3 studies. A second coprimary endpoint, self-reported desire using a daily e-diary, was used in 2 of these studies and was not significantly different in the flibanserin treated women compared with placebo.[141,143] However, the validity of this measure was seriously questioned,[144] and sexual desire measured with the Female Sexual Function Index (FSFI) desire domain score,[97] a secondary measure in the first 2 studies, was used as the second coprimary outcome in the third study.[142] The FSFI desire domain score, consisting of 1 item assessing frequency and 1 item on the level of desire,[97] was significantly different in flibanserin-treated subjects in all 3 studies.[141–143] In all 3 studies the efficacy of flibanserin was also supported by significant effects on the secondary endpoints of the Female Sexual Distress Score-Revised (FSDS-R) total score and FSDS-R item 13, which assesses distress due to low desire specifically,[98] and the FSFI total score. The efficacy of flibanserin in postmenopausal women was supported in a randomized placebo-controlled study that demonstrated significant effects on the coprimary endpoints of satisfying sexual events and FSFI desire domain score as well as FSDS-R total and distress scores and the FSFI total score.[145] However, flibanserin has not been approved for use in postmenopausal women.

Overall, flibanserin was well tolerated. The most common side effects in women taking 100 mg per day were somnolence (11.9–14.4% vs 3.1–1.3% in placebo), dizziness (10.3–12.2% vs 1.1–2.0%), nausea (7.7–11.9% vs 2.2–4.1%), and fatigue (5.7–9.6% vs 2.7–6.8%). Discontinuation rates due to adverse effects for women taking 100 mg per day were 13.4% vs 10.1% for placebo,[143] 11.4% vs 3.4%,[141] and 9.6% vs 3.7%.[142]

The rate of serious adverse events in premenopausal women on 100 mg per day ranged from 0.7% to 1%, most of which were felt to be unrelated to the use of flibanserin. However, in 24-week randomized placebo-controlled trials of flibanserin, hypotension was observed in 0.2% of patients taking flibanserin compared with 0.1% of subjects taking placebo, and syncope occurred in 0.4% on flibanserin compared with 0.2% on placebo.[146] In a dedicated alcohol interaction study of 23 men and 2 women, 17% of those administered 100 mg of flibanserin and the equivalent of 2 standard drinks of alcohol (consumed over 10 minutes in the morning) experienced hypotension or syncope requiring clinical intervention. All of the subjects experiencing these adverse effects were men. Orthostatic hypotension was observed in 25% of subjects who consumed 100 mg of flibanserin and the equivalent of 4 drinks. Concern about this adverse effect has led the FDA to require that pharmacies that dispense and practitioners who prescribe flibanserin be certified with a risk evaluation and mitigation program (REMS) that includes elements to assure safe use (ETASU), including mandatory counseling about this risk. Flibanserin, which is marketed as Addyi, will carry a boxed warning highlighting the risks of "potentially serious hypotension and syncope" in patients who drink alcohol or take medicines or supplements that interfere with the breakdown of flibanserin (moderate or strong CYP3A4 inhibitors), and in patients who have liver impairment. Addyi is contraindicated in these patients.

Other Nonhormonal and Hormonal Pharmacological Treatments

Centrally active substances affecting serotonergic, melatonergic, and dopaminergic pathways, as well as genital vasoactive substances, have been evaluated in the treatment of HSSD[27,147,148] Buproprion has been used for treatment of HSDD[149,150] and as a treatment for sexual dysfunction secondary to the use of SSRIs, and may play a role in the treatment of decreased desire in that setting.[151–153] The effectiveness of buproprion has not been established in well-designed clinical trials, and it is not approved for treatment of HSDD.

As previously discussed, vulvovaginal atrophy and associated genitourinary symptoms of menopause such as vaginal dryness and dyspareunia should be addressed in women with HSDD.[27] First-line therapies include vaginal moisturizers (2 to 3 times per week) and lubricants with sexual activity.[131] Systemic estrogen (oral, transdermal, and high-dose intravaginal rings) and local vaginal estrogen therapy (conjugated estrogen and estradiol cream, ultra-low-dose vaginal tablet, and low-dose intravaginal ring) are effective in alleviating symptoms of dyspareunia associated with vulvovaginal atrophy.[130,131,154] When estrogen therapy is used only for vaginal symptoms, local low-dose vaginal therapy is recommended.

Ospemifene is a daily, orally administered selective estrogen receptor modulator (SERM) that has estrogen agonist effects in the vagina but appears to have no clinically significant effect on the breast or endometrium. Ospemifene was approved in 2013 for the treatment of dyspareunia and vaginal dryness secondary to vulvovaginal atrophy.[155–158] Ospemifene is a treatment option for women whose genitourinary symptoms of menopause are not relieved by nonpharmacological treatments and who are not candidates for or don't want to use intravaginal treatment.

The role of androgens remains controversial.[27,66,159,160] Randomized trials over the last 15 years have demonstrated the efficacy of testosterone therapy in women with HSDD. Studies of testosterone therapy in women with low desire after surgical menopause (oophorectomy) have demonstrated increases in libido and sexual satisfaction in women on estrogen.[161–166] In naturally menopausal women with low desire on estrogen,

testosterone has been shown to increase desire, the frequency of satisfying sexual events, and to decrease personal distress.[167,168] Both naturally and surgically menopausal women not on estrogen replacement have shown similar benefits from testosterone therapy in these 3 measures of sexual function.[161,166,168,169] In studies of 6 months[168] and 1 year[169] duration, testosterone was well tolerated. Almost all observed androgenic effects were mild; the only statistically significant androgenic adverse effect was increased hair growth in women on 300 μg of testosterone in the longer study.[169]

To date, studies of parenteral testosterone treatment achieving physiological levels have not shown an increased risk of breast cancer, adverse effects on the endometrium, increased lipids, or other cardiovascular risk factors, or cardiovascular or thromboembolic events.[170,171] A report of a since terminated randomized clinical trial of topical testosterone gel that enrolled 3656 postmenopausal women, including women with cardiovascular risk factors, also demonstrated very low rates of cardiovascular events (0.58%) and breast cancer (0.24%) after more than 4000 subject-years of exposure.[172,173] Adverse events observed in an open-label extension of up to 4 years duration of 2 trials of a transdermal testosterone patch were also limited to unwanted hair growth and application site reaction.[174] Testosterone therapy is not approved by the FDA for the treatment of HSDD. A transdermal testosterone preparation was approved for treatment of hypoactive sexual desire after surgical menopause in Europe in 2006, but it was subsequently withdrawn by the manufacturer in 2012.[175] After other causes of low desire have been addressed, a trial of off-label transdermal testosterone has been recommended.[125] The 2014 Endocrine Society Guidelines on androgen therapy in women supports the short-term use of high physiological doses of testosterone in postmenopausal women with HSDD.[176] The guidelines note that endogenous testosterone levels do not predict response to this therapy; however, women should be monitored for signs of androgen excess. Monitoring testosterone levels may play a role in avoiding supra physiological doses.

Several treatments for HSDD are currently undergoing clinical trials. A novel approach based on the dual control model (inhibition vs excitation)[177] employing testosterone in combination with buspirone to reduce sexual inhibition or with sildenafil to enhance genital excitation is currently under investigation. Testosterone increases the brain's sensitivity to sexual cues which is necessary for the effect of PD5 inhibitors on genital excitation.[178] Buspirone, a 5-HT 1A receptor agonist, is thought to reduce sexual stimulation-induced, prefrontal cortex-mediated sexual inhibition.[179] The developers of the testosterone/buspirone and testosterone/sildenafil combination medications have used psychological assessments of attention to sexual cues to identify subtypes of patients with HSDD who would differentially benefit from one or the other pharmacological strategy. A bupropion and trazadone combination is also being evaluated because of the role that these 2 antidepressant medications play in regulating 5-HT and norepinephrine, both of which are involved modulating sexual inhibition and excitation.[180] Bremelanotide, a melanocortin 4 receptor agonist originally studied for sunless tanning, was noted to increase sexual arousal and desire. Early experience with intranasal administration raised concern about increased blood pressure which was less evident in subsequent trials of lower-dose subcutaneous formulations.[180]

SUMMARY AND CONCLUSION

Low desire in women is an extremely common problem (37.7%), and low desire that causes personal distress — the essential symptom of HSDD — is common (7% to 12% of women). Low desire increases with age, but distress decreases; therefore the prevalence of distressing low desire is relatively constant across age. It is highest in young surgically menopausal (oophorectomized) women and lower in naturally menopausal women. HSDD is associated with significant functional impairment, dissatisfaction with relationships, and low general happiness. HSDD may be lifelong or acquired, generalized or situational. Although HSDD is associated with a variety of factors, it should be distinguished from sexual dysfunctions that can be better explained by a general medical condition, nonsexual psychiatric disorder, or the use of a substance or medication. HSDD can be understood dynamically as an imbalance in the relationship of sexual excitatory and inhibitory processes that are independent of one another and determine sexual response. Inhibitory factors belong to 3 domains: life situation and relationship factors; personal sexual beliefs, behaviors, and history; and biological — comorbid medical and mental disorders, medications, and substance use. Communication between patient and healthcare providers and patients and their sexual partners is critical for effective clinical management of HSDD. Primary care counseling, sex therapy, and psychotherapy all can play a role in treating HSDD. Flibanserin is the first centrally-acting, daily medication available to treat premenopausal women with HSDD. Postmenopausal women with vulvovaginal atrophy and dyspareunia will benefit from low-dose local vaginal estrogen therapy or a selective estrogen receptor modulator. Surgically and naturally menopausal women may benefit from testosterone therapy. Buproprion may be of benefit in antidepressant medication-induced FSD.

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REFERENCES

1. American Psychiatric Association. Diagnostic and Statistical Manual Of Mental Disorders, Fourth Edition, Revised: DSM-IV-TR. Washington, D.C.: American Psychiatric Association; 2003.
2. Shifren JL, Monz BU, Russo PA, et al. Sexual problems and distress in United States women: prevalence and correlates. **Obstet Gynecol 2008; 112:970.**
3. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition: DSM-5. Arlington, VA: American Psychiatric Association; 2013.
4. Derogatis LR, Clayton AH, Rosen RC, et al. Should sexual desire and arousal disorders in women be merged? **Arch Sex Behav 2011; 40:217.**
5. Balon R, Clayton AH. Female sexual interest/arousal disorder: a diagnosis out of thin air. **Arch Sex Behav 2014; 43:1227.**
6. Tiefer L, Laan E, Basson R. Missed opportunities in the patient-focused drug development public meeting and scientific workshop on female sexual dysfunction held at the FDA, October 2014. **J Sex Res 2015; 52:601.**
7. Basson R, Leiblum S, Brotto L, et al. Definitions of women's sexual dysfunction reconsidered: advocating expansion and revision. **J Psychosom Obstet Gynaecol 2003; 24:221.**
8. Klusmann D. Sexual motivation and the duration of partnership. **Arch Sex Behav 2002; 31:275.**
9. Bancroft J, Loftus J, Long JS. Distress about sex: a national survey of women in heterosexual relationships. **Arch Sex Behav 2003; 32:193.**
10. Segraves R, Balon R, Clayton A. Proposal for changes in diagnostic criteria for sexual dysfunctions. **J Sex Med 2007; 4:567.**
11. Sungur MZ, Gunduz A. A comparison of DSM-IV-TR and DSM-5 definitions for sexual dysfunctions: critiques and challenges. **J Sex Med 2014; 11:364.**
12. Brotto LA. The DSM diagnostic criteria for hypoactive sexual desire disorder in women. **Arch Sex Behav 2010; 39:221.**
13. Derogatis LR, Clayton AH, Rosen R, et al. Do multiple convergent measures of female sexual dysfunction (fsd) support sexual desire and arousal disorders as distinct diagnoses? **J Sex Med 2010; 7:S142.**
14. Clayton AH, Derogatis LR, Rosen R, et al. Do clinical research data support sexual desire and arousal disorders as distinct diagnoses? **J Sex Med 2011; 7:S143.**
15. Derogatis LR, Laan E, Brauer M, et al. Responses to the proposed DSM-V changes. **J Sex Med 2010; 7:1998.**
16. Basson R, Berman J, Burnett A, et al. Report of the international consensus development conference on female sexual dysfunction: definitions and classifications. **J Urol 2000; 163:888.**
17. Master WH, Johnson VE. Human Sexual Response. Boston, MA: Little Brown, Co.; 1966.
18. Kaplan HS. Hypoactive sexual desire. **J Sex Marital Ther 1977; 3:3.**
19. Leif HI. Inhibited sexual desire. **Med Aspects Hum Sex 1977; 7:94.**
20. Kingsberg SA, Janata JW. Female sexual disorders: assessment, diagnosis, and treatment. **Urol Clin North Am 2007; 34:497, v—vi.**
21. Basson R. Women's sexual function and dysfunction: current uncertainties, future directions. **Int J Impot Res 2008; 20:466.**
22. Basson R. Female sexual response: the role of drugs in the management of sexual dysfunction. **Obstet Gynecol 2001; 98:350.**
23. McCall K, Meston C. Cues resulting in desire for sexual activity in women. **J Sex Med 2006; 3:838.**
24. Meston CM, Buss DM. Why humans have sex. **Arch Sex Behav 2007; 36:477.**
25. Meston CM, Bradford A. Sexual dysfunctions in women. **Annu Rev Clin Psychol 2007; 3:233.**
26. Dennerstein L, Koochaki P, Barton I, et al. Hypoactive sexual desire disorder in menopausal women: a survey of Western European women. **J Sex Med 2006; 3:212.**
27. Basson R. Clinical practice. Sexual desire and arousal disorders in women. **N Engl J Med 2006; 354:1497.**
28. Brotto LA, Bitzer J, Laan E, et al. Women's sexual desire and arousal disorders. **J Sex Med 2010; 7:586.**
29. Sand M, Fisher WA. Women's endorsement of models of female sexual response: the nurses' sexuality study. **J Sex Med 2007; 4:708.**
30. Meston CM, Derogatis LR. Validated instruments for assessing female sexual function. **J Sex Marital Ther 2002; 28:S155.**
31. Wiegel M, Meston C, Rosen R. The female sexual function index (FSFI): cross-validation and development of clinical cutoff scores. **J Sex Marital Ther 2005; 31:1.**
32. Giraldi A, Kristensen E, Sand M. Endorsement of models describing sexual response of men and women with a sexual partner: an online survey in a population sample of Danish adults ages 20-65 years. **J Sex Med 2015; 12:116.**

33. Levine S. Sexual life. New York: Plenum Press; 1992.
34. Laumann EO, Gagnon JH, MIchael RT, et al. The Social Organization of Sexuality: Sexual Practices in the United States. Chicago, Ill: University of Chicago Press; 1994.
35. Laumann EO, Paik A, Rosen RC. Sexual dysfunction in the United States: prevalence and predictors. **J Am Med Assoc 1999; 281:537.**
36. Derogatis L, Rust J, Golombok S, et al. Validation of the profile of female sexual function (PFSF) in surgically and naturally menopausal women. **J Sex Marital Ther 2004; 30:25.**
37. Rust J, Derogatis L, Rodenberg C, et al. Development and validation of a new screening tool for hypoactive sexual desire disorder: The Brief Profile of Female Sexual Function (B-PFSF). **Gynecol Endocrinol 2007; 23:638.**
38. Derogatis LR, Rust J, Golombok S, et al. A patient-generated multinational inventory to measure distress associated with low desire (PDS©); 2004, Atlanta, Georgia.
39. West SL, D'Aloisio AA, Agans RP, et al. Prevalence of low sexual desire and hypoactive sexual desire disorder in a nationally representative sample of US women. **Arch Intern Med 2008; 168:1441.**
40. Hayes RD, Dennerstein L, Bennett CM, et al. Relationship between hypoactive sexual desire disorder and aging. **Fertil Steril 2007; 87:107.**
41. Derogatis LR, Rosen R, Leiblum S, et al. The Female Sexual Distress Scale (FSDS): initial validation of a standardized scale for assessment of sexually related personal distress in women. **J Sex Marital Ther 2002; 28:317.**
42. Rosen RC, Shifren JL, Monz BU, et al. Correlates of sexually related personal distress in women with low sexual desire. **J Sex Med 2009; 6:1549.**
43. Rosen RC, Connor MK, Maserejian NN. The HSDD registry for women: a novel patient registry for women with generalized acquired hypoactive sexual desire disorder. **J Sex Med 2010; 7:1747.**
44. Maserejian NN, Shifren J, Parish SJ, et al. Sexual arousal and lubrication problems in women with clinically diagnosed hypoactive sexual desire disorder: preliminary findings from the hypoactive sexual desire disorder registry for women. **J Sex Marital Ther 2012; 38:41.**
45. Leiblum SR, Koochaki PE, Rodenberg CA, et al. Hypoactive sexual desire disorder in postmenopausal women: US results from the Women's International Study of Health and Sexuality (WISHeS). **Menopause 2006; 13:46.**
46. Graziottin A. Prevalence and evaluation of sexual health problems — HSDD in Europe. **J Sex Med 2007; 4:S211.**
47. Clayton AH, Maserejian NN, Connor MK, et al. Depression in premenopausal women with hsdd: baseline findings from the HSDD Registry for Women. **Psychosom Med 2012; 74:305.**
48. Bancroft J, Graham CA, Janssen E, et al. The dual control model: current status and future directions. **J Sex Res 2009; 46:121.**
49. Carpenter D, Janssen E, Graham C, et al. Women's scores on the sexual inhibition/sexual excitation scales (SIS/SES): gender similarities and differences. **J Sex Res 2008; 45:36.**
50. Janssen E, Vorst H, Finn P, et al. The Sexual Inhibition (SIS) and Sexual Excitation (SES) Scales: II. Predicting psychophysiological response pattens. **J Sex Res 2002; 39:127.**
51. Pfaus JG. Pathways of sexual desire. **J Sex Med 2009; 6:1506.**
52. Park K, Kang HK, Seo JJ, et al. Blood-oxygenation-level-dependent functional magnetic resonance imaging for evaluating cerebral regions of female sexual arousal response. **Urology 2001; 57:1189.**
53. Jeong GW, Park K, Youn G, et al. Assessment of cerebrocortical regions associated with sexual arousal in premenopausal and menopausal women by using BOLD-based functional MRI. **J Sex Med 2005; 2:645.**
54. Arnow BA, Millheiser L, Garrett A, et al. Women with hypoactive sexual desire disorder compared to normal females: a functional magnetic resonance imaging study. **Neuroscience 2009; 158:484.**
55. Davis SR. Androgen use for low sexual desire in midlife women. **Menopause 2013; 20:795.**
56. Davison SL, Bell R, Donath S, et al. Androgen levels in adult females: changes with age, menopause, and oophorectomy. **J Clin Endocrinol Metab 2005; 90:3847.**
57. Ibe C, Simon JA. Vulvovaginal atrophy: current and future therapies (CME). **J Sex Med 2010; 7:1042.**
58. Bancroft J. Sexual effects of androgens in women: some theoretical considerations. **Fertil Steril 2002; 77:S55.**
59. Guay A, Jacobson J, Munarriz R, et al. Serum androgen levels in healthy premenopausal women with and without sexual dysfunction: Part B: Reduced serum androgen levels in healthy premenopausal women with complaints of sexual dysfunction. **Int J Impot Res 2004; 16:121.**
60. Riley A, Riley E. Controlled studies on women presenting with sexual drive disorder: I. Endocrine status. **J Sex Marital Ther 2000; 26:269.**
61. Bachmann GA, Leiblum SR. Sexuality in sexagenarian women. **Maturitas 1991; 13:43.**
62. Gerber JR, Johnson JV, Bunn JY, et al. A longitudinal study of the effects of free testosterone and other psychosocial variables on sexual function during the natural traverse of menopause. **Fertil Steril 2005; 83:643.**
63. Santoro N, Torrens J, Crawford S, et al. Correlates of circulating androgens in mid-life women: the study of women's health across the nation. **J Clin Endocrinol Metab 2005; 90:4836.**
64. Davis SR, Davison SL, Donath S, et al. Circulating androgen levels and self-reported sexual function in women. **J Am Med Assoc 2005; 294:91.**
65. Wahlin-Jacobsen S, Pedersen AT, Kristensen E, et al. Is there a correlation between androgens and sexual desire in women? **J Sex Med 2015; 12:358.**
66. Wierman ME, Basson R, Davis SR, et al. Androgen therapy in women: an Endocrine Society clinical practice guideline. **J Clin Endocrinol Metab 2006; 91:3697.**

67. Graham CA, Ramos R, Bancroft J, et al. The effects of steroidal contraceptives on the well-being and sexuality of women: a double-blind, placebo-controlled, two-centre study of combined and progestogen-only methods. **Contraception 1995; 52:363.**
68. Adams DB, Gold AR, Burt AD. Rise in female-initiated sexual activity at ovulation and its suppression by oral contraceptives. **N Engl J Med 1978; 299:1145.**
69. Sanders SA, Graham CA, Bass JL, et al. A prospective study of the effects of oral contraceptives on sexuality and well-being and their relationship to discontinuation. **Contraception 2001; 64:51.**
70. Caruso S, Agnello C, Intelisano G, et al. Sexual behavior of women taking low-dose oral contraceptive containing 15 microg ethinylestradiol/60 microg gestodene. **Contraception 2004; 69:237.**
71. Graham CA, Bancroft J, Doll HA, et al. Does oral contraceptive-induced reduction in free testosterone adversely affect the sexuality or mood of women? **Psychoneuroendocrinology 2007; 32:246.**
72. Panzer C, Wise S, Fantini G, et al. Impact of oral contraceptives on sex hormone-binding globulin and androgen levels: a retrospective study in women with sexual dysfunction. **J Sex Med 2006; 3:104.**
73. Bazin S, Bouchard C, Brisson J, et al. Vulvar vestibulitis syndrome: an exploratory case-control study. **Obstet Gynecol 1994; 83:47.**
74. Berglund AL, Nigaard L, Rylander E. Vulvar pain, sexual behavior and genital infections in a young population: a pilot study. **Acta Obstet Gynecol Scand 2002; 81:738.**
75. Bohm-Starke N, Johannesson U, Hilliges M, et al. Decreased mechanical pain threshold in the vestibular mucosa of women using oral contraceptives: a contributing factor in vulvar vestibulitis? **J Reprod Med 2004; 49:888.**
76. Bouchard C, Brisson J, Fortier M, et al. Use of oral contraceptive pills and vulvar vestibulitis: a case-control study. **Am J Epidemiol 2002; 156:254.**
77. Sjoberg I, Nylander Lundqvist EN. Vulvar vestibulitis in the north of Sweden. An epidemiologic case-control study. **J Reprod Med 1997; 42:166.**
78. Davis AR, Castano PM. Oral contraceptives and libido in women. **Annu Rev Sex Res 2004; 15:297.**
79. Stuckey BG. Female sexual function and dysfunction in the reproductive years: the influence of endogenous and exogenous sex hormones. **J Sex Med 2008; 5:2282.**
80. Abdolrasulnia M, Shewchuk RM, Roepke N, et al. Management of female sexual problems: perceived barriers, practice patterns, and confidence among primary care physicians and gynecologists. **J Sex Med 2010; 7:2499.**
81. Bachmann G. Female sexuality and sexual dysfunction: are we stuck on the learning curve? **J Sex Med 2006; 3:639.**
82. Press Y, Menahem S, Shvartzman P. [Sexual dysfunction — what is the primary physicians role?]. **Harefuah 2003; 142:662, 719.**
83. Harsh V, McGarvey EL, Clayton AH. Physician attitudes regarding hypoactive sexual desire disorder in a primary care clinic: a pilot study. **J Sex Med 2008; 5:640.**
84. Parish SJ, Clayton AH. Sexual medicine education: review and commentary. **J Sex Med 2007; 4:259.**
85. Marwick C. Survey says patients expect little physician help on sex. **J Am Med Assoc 1999; 281:2173.**
86. Berman L, Berman J, Felder S, et al. Seeking help for sexual function complaints: what gynecologists need to know about the female patient's experience. **Fertil Steril 2003; 79:572.**
87. Moreira ED Jr, Brock G, Glasser DB, et al. Help-seeking behaviour for sexual problems: the global study of sexual attitudes and behaviors. **Int J Clin Pract 2005; 59:6.**
88. Maserejian NN, Parish S, Shifren JL, et al. Healthcare utilization in women diagnosed with hypoactive sexual desire disorder: interim baseline results from the HSDD Registry for Women. **J Womens Health (Larchmt) 2010; 19:2001.**
89. Bachmann GA, Leiblum SR, Grill J. Brief sexual inquiry in gynecologic practice. **Obstet Gynecol 1989; 73:425.**
90. Sadovsky R, Alam W, Enecilla M, et al. Sexual problems among a specific population of minority women aged 40-80 years attending a primary care practice. **J Sex Med 2006; 3:795.**
91. Roberts S. Motivating Change: Behavior Change Counseling using the Brief Negotiation method. The Permanente Medical Group, 2005.
92. Stephenson BJ, Rowe BH, Haynes RB, et al. The rational clinical examination. Is this patient taking the treatment as prescribed? **J Am Med Assoc 1993; 269:2779.**
93. Hahn SR. Patient-centered communication to assess and enhance patient adherence to glaucoma medication. **Ophthalmology 2009; 116:S37.**
94. Hahn SR, Friedman DS, Quigley HA, et al. Effect of patient-centered communication training on discussion and detection of nonadherence in glaucoma. **Ophthalmology 2010; 117:1339.**
95. Clayton AH, Goldfischer ER, Goldstein I, et al. Validation of the Decreased Sexual Desire Screener (DSDS): A brief diagnostic instrument for generalized acquired female Hypoactive Sexual Desire Disorder (HSDD). **J Sex Med 2009; 6:730.**
96. Clayton AH, Goldfischer E, Goldstein I, et al. Validity of the decreased sexual desire screener for diagnosing hypoactive sexual desire disorder. **J Sex Marital Ther 2013; 39:132.**
97. Rosen R, Brown C, Heiman J, et al. The Female Sexual Function Index (FSFI): a multidimensional self-report instrument for the assessment of female sexual function. **J Sex Marital Ther 2000; 26:191.**
98. Derogatis L, Clayton A, Lewis-D'Agostino D, et al. Validation of the female sexual distress scale-revised for assessing distress in women with hypoactive sexual desire disorder. **J Sex Med 2008; 5:357.**

99. Roter DL, Hall JA. Doctors talking with patients/patients talking with doctors: Improving communication in medical visits. Second edition. Westport, Connecticut: Praeger; 2006.

100. Mead N, Bower P. Measuring patient-centredness: a comparison of three observation-based instruments. **Patient Educ Couns 2000; 39:71.**

101. Mead N, Bower P, Hann M. The impact of general practitioners' patient-centredness on patients' post-consultation satisfaction and enablement. **Soc Sci Med 2002; 55:283.**

102. Roter DL, Hall JA. Physician's interviewing styles and medical information obtained from patients. **J Gen Intern Med 1987; 2:325.**

103. Roter DL, Hall JA, Kern DE, et al. Improving physicians' interviewing skills and reducing patients' emotional distress. A randomized clinical trial. **Arch Intern Med 1995; 155:1877.**

104. Roter DL, Hall JA. Consequences of talk: The relationship between talk and outcomes. Doctors talking with patients/patients talking with doctors: Improving communication in medical visits. Second edition. Westport, Connecticut: Praeger; 2006. p. 143.

105. Roter DL, Hall JA. Improving talk through interventions. Doctors talking with patients/patients talking with doctors: Improving communication in medical visits. Second edition. Westport, Connecticut: Praeger; 2006. p. 163.

106. Kroenke K, Spitzer RL, Williams JB. The Patient Health Questionnaire-2: validity of a two-item depression screener. **Med Care 2003; 41:1284.**

107. Spitzer RL, Kroenke K, Williams JB. Validation and utility of a self-report version of PRIME-MD: the PHQ primary care study. Primary Care Evaluation of Mental Disorders. Patient Health Questionnaire. **J Am Med Assoc 1999; 282:1737.**

108. Spitzer RL, Kroenke K, Williams JB, et al. A brief measure for assessing generalized anxiety disorder: the GAD-7. **Arch Intern Med 2006; 166:1092.**

109. Atlantis E, Sullivan T. Bidirectional association between depression and sexual dysfunction: a systematic review and meta-analysis. **J Sex Med 2012; 9:1497.**

110. Clayton AH. Female sexual dysfunction related to depression and antidepressant medications. **Curr Womens Health Rep 2002; 2:182.**

111. Montejo AL, Perahia DG, Spann ME, et al. Sexual function during long-term duloxetine treatment in patients with recurrent major depressive disorder. **J Sex Med 2011; 8:773.**

112. Gartlehner G, Hansen RA, Morgan LC, et al. Comparative benefits and harms of second-generation antidepressants for treating major depressive disorder: an updated meta-analysis. **Ann Intern Med 2011; 155:772.**

113. Clayton AH, Balon R. The impact of mental illness and psychotropic medications on sexual functioning: the evidence and management. **J Sex Med 2009; 6:1200.**

114. Clayton AH, Kennedy SH, Edwards JB, et al. The effect of vilazodone on sexual function during the treatment of major depressive disorder. **J Sex Med 2013; 10:2465.**

115. Clayton AH, Croft HA, Handiwala L. Antidepressants and sexual dysfunction: mechanisms and clinical implications. **Postgrad Med 2014; 126:91.**

116. Dunn KM, Croft PR, Hackett GI. Satisfaction in the sex life of a general population sample. **J Sex Marital Ther 2000; 26:141.**

117. Tracy JK, Junginger J. Correlates of lesbian sexual functioning. **J Womens Health (Larchmt) 2007; 16:499.**

118. Litzinger S, Gordon KC. Exploring relationships among communication, sexual satisfaction, and marital satisfaction. **J Sex Marital Ther 2005; 31:409.**

119. Witting K, Santtila P, Alanko K, et al. Female sexual function and its associations with number of children, pregnancy, and relationship satisfaction. **J Sex Marital Ther 2008; 34:89.**

120. Witting K, Santtila P, Varjonen M, et al. Female sexual dysfunction, sexual distress, and compatibility with partner. **J Sex Med 2008; 5:2587.**

121. Dunn KM, Croft PR, Hackett GI. Association of sexual problems with social, psychological, and physical problems in men and women: a cross sectional population survey. **J Epidemiol Community Health 1999; 53:144.**

122. Metz ME, Epstein N. Assessing the role of relationship conflict in sexual dysfunction. **J Sex Marital Ther 2002; 28:139.**

123. Bodenmann G, Ledermann T, Bradbury TN. Stress, sex, and satisfaction in marriage. **Personal Relationships 2007; 14:551.**

124. Hatzichristou D, Rosen RC, Derogatis LR, et al. Recommendations for the clinical evaluation of men and women with sexual dysfunction. **J Sex Med 2010; 7:337.**

125. Khera M. Testosterone therapy for female sexual dysfunction. **Sex Med Rev 2015; 3:137.**

126. Fiers T, Kaufman J. Free and bioavailable testosterone calculator, Available at: http://www.issam.ch/freetesto.htm 2015., Accessed October 18, 2015.

127. O'Donohue W, Dopke CA, Swingen DN. Psychotherapy for female sexual dysfunction: a review. **Clin Psychol Rev 1997; 17:537.**

128. Heiman JR. Psychologic treatments for female sexual dysfunction: are they effective and do we need them? **Arch Sex Behav 2002; 31:445.**

129. McCabe MP. Evaluation of a cognitive behavior therapy program for people with sexual dysfunction. **J Sex Marital Ther 2001; 27:259.**

130. Suckling J, Lethaby A, Kennedy R. Local oestrogen for vaginal atrophy in postmenopausal women. **Cochrane Database Syst Rev 2006; 4:CD001500.**

131. Tan O, Bradshaw K, Carr BR. Management of vulvovaginal atrophy-related sexual dysfunction in postmenopausal women: an up-to-date review. **Menopause 2012; 19:109.**

132. Leiblum SR, Wiegel M. Psychotherapeutic interventions for treating female sexual dysfunction. **World J Urol 2002; 20:127.**

133. Bancroft J, Janssen E. The dual control model of male sexual response: a theoretical approach to centrally mediated erectile dysfunction. **Neurosci Biobehav Rev 2000; 24:571.**

134. Brotto LA, Krychman M, Jacobson P. Eastern approaches for enhancing women's sexuality: mindfulness, acupuncture, and yoga (CME). **J Sex Med 2008; 5:2741.**

135. Brotto LA, Basson R, Luria M. A mindfulness-based group psychoeducational intervention targeting sexual arousal disorder in women. **J Sex Med 2008; 5:1646.**

136. Brotto LA, Mehak L, Kit C. Yoga and sexual functioning: a review. **J Sex Marital Ther 2009; 35:378.**

137. Brotto LA, Seal BN, Rellini A. Pilot study of a brief cognitive behavioral versus mindfulness-based intervention for women with sexual distress and a history of childhood sexual abuse. **J Sex Marital Ther 2012; 38:1.**

138. Borsini F, Evans K, Jason K, et al. Pharmacology of flibanserin. **CNS Drug Rev 2002; 8:117.**

139. Thorp J Jr, Palacios S, Symons J, et al. Improving prospects for treating hypoactive sexual desire disorder HSDD): development status of flibanserin. **BJOG 2014; 121:1328. http://dx.doi.org/10.1111/1471-0528.12878, Epub 2014 June 9.**

140. Stahl SM, Sommer B, Allers KA. Multifunctional pharmacology of flibanserin: possible mechanism of therapeutic action in hypoactive sexual desire disorder. **J Sex Med 2011; 8:15.**

141. Derogatis LR, Komer L, Katz M, et al. Treatment of hypoactive sexual desire disorder in premenopausal women: efficacy of flibanserin in the VIOLET Study. **J Sex Med 2012; 9:1047.**

142. Katz M, Derogatis LR, Ackerman R, et al. Efficacy of flibanserin in women with hypoactive sexual desire disorder: results from the BEGONIA trial. **J Sex Med 2013; 10:1807.**

143. Thorp J, Simon J, Dattani D, et al. Treatment of hypoactive sexual desire disorder in premenopausal women: efficacy of flibanserin in the DAISY Study. **J Sex Med 2012; 9:793.**

144. Kingsberg SA, Althof SE. Satisfying sexual events as outcome measures in clinical trial of female sexual dysfunction. **J Sex Med 2011; 8:3262.**

145. Simon JA, Kingsberg SA, Shumel B, et al. Efficacy and safety of flibanserin in postmenopausal women with hypoactive sexual desire disorder: results of the SNOWDROP trial. **Menopause 2014; 21:633.**

146. FDA Briefing Document. Joint Meeting of the Bone, Reproductive and Urologic Drugs Advisory Committee BRUDAC) and the Drug Safety and Risk Management (DSaRM) Advisory Committee: NDA 022526 Flibanserin. Federal Drug Administration; 2015 Jun 4.

147. Segraves R, Woodard T. Female hypoactive sexual desire disorder: History and current status. **J Sex Med 2006; 3:408.**

148. Segraves RT. Management of hypoactive sexual desire disorder. **Adv Psychosom Med 2008; 29:23.**

149. Segraves RT, Croft H, Kavoussi R, et al. Bupropion sustained release (SR) for the treatment of hypoactive sexual desire disorder (HSDD) in nondepressed women. **J Sex Marital Ther 2001; 27:303-316.**

150. Segraves RT, Clayton A, Croft H, et al. Bupropion sustained release for the treatment of hypoactive sexual desire disorder in premenopausal women. **J Clin Psychopharmacol 2004; 24:339.**

151. Rudkin L, Taylor MJ, Hawton K. Strategies for managing sexual dysfunction induced by antidepressant medication. **Cochrane Database Syst Rev 2004; 4:CD003382.**

152. Taylor MJ, Rudkin L, Hawton K. Strategies for managing antidepressant-induced sexual dysfunction: systematic review of randomised controlled trials. **J Affect Disord 2005; 88:241.**

153. Taylor MJ. Strategies for managing antidepressant-induced sexual dysfunction: a review. **Curr Psychiatry Rep 2006; 8:431.**

154. The 2012 Hormone Therapy Position Statement of The North American Menopause Society. **Menopause 2012; 19:257.**

155. Bachmann GA, Komi JO. Ospemifene effectively treats vulvovaginal atrophy in postmenopausal women: results from a pivotal phase 3 study. **Menopause 2010; 17:480.**

156. Simon JA, Lin VH, Radovich C, et al. One-year long-term safety extension study of ospemifene for the treatment of vulvar and vaginal atrophy in postmenopausal women with a uterus. **Menopause 2013; 20:418.**

157. Portman DJ, Bachmann GA, Simon JA. Ospemifene, a novel selective estrogen receptor modulator for treating dyspareunia associated with postmenopausal vulvar and vaginal atrophy. **Menopause 2013; 20:623.**

158. Goldstein SR, Bachmann GA, Koninckx PR, et al. Ospemifene 12-month safety and efficacy in postmenopausal women with vulvar and vaginal atrophy. **Climacteric 2014; 17:173.**

159. Braunstein GD. The Endocrine Society Clinical Practice Guideline and The North American Menopause Society position statement on androgen therapy in women: another one of Yogi's forks. **J Clin Endocrinol Metab 2007; 92:4091.**

160. Panzer C, Guay A. Testosterone replacement therapy in naturally and surgically menopausal women. **J Sex Med 2009; 6:8.**

161. Shifren JL, Braunstein GD, Simon JA, et al. Transdermal testosterone treatment in women with impaired sexual function after oophorectomy. **N Engl J Med 2000; 343:682.**

162. Braunstein GD, Sundwall DA, Katz M, et al. Safety and efficacy of a testosterone patch for the treatment of hypoactive sexual desire disorder in surgically menopausal women: a randomized, placebo-controlled trial. **Arch Intern Med 2005; 165:1582.**

163. Buster JE, Kingsberg SA, Aguirre O, et al. Testosterone patch for low sexual desire in surgically menopausal women: a randomized trial. **Obstet Gynecol 2005; 105:944.**

164. Davis SR, Goldstat R, Papalia MA, et al. Effects of aromatase inhibition on sexual function and well-being in postmenopausal women treated with testosterone: a randomized, placebo-controlled trial. **Menopause 2006; 13:37.**

165. Davis SR, van der Mooren MJ, van Lunsen RH, et al. Efficacy and safety of a testosterone patch for the treatment of hypoactive sexual desire disorder in surgically menopausal women: a randomized, placebo-controlled trial. **Menopause 2006; 13:387.**

166. Davis SR, Braunstein GD. Efficacy and safety of testosterone in the management of hypoactive sexual desire disorder in postmenopausal women. **J Sex Med 2012; 9:1134.**

167. Shifren JL, Davis SR, Moreau M, et al. Testosterone patch for the treatment of hypoactive sexual desire disorder in naturally menopausal women: results from the INTIMATE NM1 Study. **Menopause 2006; 13:770.**

168. Panay N, Al-Azzawi F, Bouchard C, et al. Testosterone treatment of HSDD in naturally menopausal women: the ADORE study. **Climacteric 2010; 13:121.**

169. Davis SR, Moreau M, Kroll R, et al. Testosterone for low libido in postmenopausal women not taking estrogen. **N Engl J Med 2008; 359:2005.**

170. Davis SR. Cardiovascular and cancer safety of testosterone in women. **Curr Opin Endocrinol Diabetes Obes 2011; 18:198.**

171. Somboonporn W, Davis S, Seif MW, et al. Testosterone for peri- and postmenopausal women. **Cochrane Database Syst Rev 2005; 4:CD004509.**

172. Snabes MC. 22nd Annual Meeting of The North American Menopause Society September 21-September 24, 2011, Washington, DC: P79: LibiGel (testosterone gel) safety study completes enrollment and continues with a low cv event rate. **Menopause 2011; 18:1370.**

173. White WB, Grady D, Giudice LC, et al. A cardiovascular safety study of LibiGel (testosterone gel) in postmenopausal women with elevated cardiovascular risk and hypoactive sexual desire disorder. **Am Heart J 2012; 163:27.**

174. Nachtigall L, Casson P, Lucas J, et al. Safety and tolerability of testosterone patch therapy for up to 4 years in surgically menopausal women receiving oral or transdermal oestrogen. **Gynecol Endocrinol 2011; 27:39.**

175. European Medicines Agency. Intrinsa (testosterone) Withdrawal of the marketing authorisation in the European Union 2012 July 11. European Medical Agency, 2012 July 11, Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Public_statement/2012/06/WC500128837.pdf., Accessed August 19, 14 A.D.

176. Wierman ME, Arlt W, Basson R, et al. Androgen therapy in women: a reappraisal: an Endocrine Society clinical practice guideline. **J Clin Endocrinol Metab 2014; 99:3489.**

177. Bloemers J, van Rooij K, Poels S, et al. Toward personalized sexual medicine (part 1): integrating the "dual control model" into differential drug treatments for hypoactive sexual desire disorder and female sexual arousal disorder. **J Sex Med 2013; 10:791.**

178. Poels S, Bloemers J, van Rooij K, et al. Toward personalized sexual medicine (part 2): testosterone combined with a PDE5 inhibitor increases sexual satisfaction in women with HSDD and FSAD, and a low sensitive system for sexual cues. **J Sex Med 2013; 10:810.**

179. van Rooij K, Poels S, Bloemers J, et al. Toward personalized sexual medicine (part 3): testosterone combined with a Serotonin1A receptor agonist increases sexual satisfaction in women with HSDD and FSAD, and dysfunctional activation of sexual inhibitory mechanisms. **J Sex Med 2013; 10:824.**

180. Belkin ZR, Krapf JM, Goldstein AT. Drugs in early clinical development for the treatment of female sexual dysfunction. **Expert Opin Investig Drugs 2015; 24:159.**