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INVITED REVIEW

Hypoactive sexual desire in women

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Abstract

Objective: This review aims to describe low sexual desire (1) as a construct within theoretical models of female sexual response, (2) as a sexual disorder with evolving or competing nosology between the DSM-IV-TR and the DSM 5, and (3) as a clinical condition that healthcare providers need to manage, and the current status of treatment options.

Methods: We conducted a literature review of the epidemiology, diagnosis, and treatment of low sexual desire/hypoactive sexual desire disorder (HSDD).

Results: The prevalence rate of low sexual desire is high, reaching 43%, whereas that of HSDD comes close to 10%. The DSM 5 categories of female sexual disorders include female sexual interest/arousal disorder, which is a combination of the DSM-IV-TR disorders HSDD and female sexual arousal disorder.

Treatment paradigms vary and are individualized based on the biopsychosocial components of desire that are compromised in a woman. The two primary approaches to treating HSDD are psychotherapy/sex therapy (individual or couples) and pharmacotherapy. To date, there are no Food and Drug Administration–approved pharmacologic treatments. However, four investigational drugs are in mid- to late-stage clinical trial development.

Conclusions: Low sexual desire is the most prevalent sexual problem in women and should be assessed and treated by healthcare professionals. Currently, there are only modest evidence-based nonpharmacologic treatment options and no approved pharmacologic options. Despite these treatment limitations, healthcare providers can address many of the sexual health concerns of women.

Key Words: Hypoactive sexual desire – Sexual dysfunction – Low libido.

Female sexual function as research focus has largely been neglected until the last decade. Explanations for this dearth of research include societal beliefs that women should not be sexual beings unless sex is tied to procreation and the complexity of female sexual function, which has in turn challenged the development of appropriate research paradigms. In contrast to the historical neglect of female sexuality, some data support the notion that functional sexual health is a compelling part of a woman's sense of self, well being, and quality of life, whereas sexual dysfunction is a disruptive force. Sexual dysfunction has been shown to be associated with a statistically significant decrease in emotional health, energy, and social function, and is associated with relationship conflict and undiagnosed medical conditions.[1] Women with hypoactive sexual desire disorder (HSDD) are more likely than women with normal desire to agree with statements expressing negative emotional or psychological states, such as feelings of frustration, hopelessness, anger, loss of femininity, and decreased self-esteem.[2]

The World Health Organization[3] considers maintenance of sexual health as the responsibility of medical providers. In 2001, the US Surgeon General, David Satcher, in his call to action to promote sexual health as one of the goals of Healthy People 2010, described the role of healthcare professionals and the need for better education and preparation in the field of sexual health.[4] Healthcare professionals must first understand what constitutes functional sexuality before they can address sexual health in the clinical setting. Unfortunately, as is true for research, sexual medicine as a whole has not been given high priority in medical education.[5] This leaves many healthcare providers (HCPs) unprepared and even uncomfortable; this discomfort is, ultimately, an obstacle to competency and fitness. Also contributing to the underdiagnosis and undertreatment of female sexual dysfunction is the unfortunate fact that many women are hesitant to initiate a discussion of these problems with their HCPs.[6]

DESIRE: A KEY COMPONENT OF SEXUAL RESPONSE

To understand the concept of low or hypoactive desire, we need to understand desire and how it fits within an overall healthy

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sexual response. A number of models have been proposed to describe normal sexual response. Masters and Johnson[7] were the first to offer a theoretical "human sexual response cycle" that was based on their direct observations of the anatomic and physiologic changes experienced by men and women in a laboratory setting. This was a four-stage linear cycle that they labeled as "excitement," "plateau," "orgasm," and "resolution"[7] (Fig. 1). The cycle was independently modified by Kaplan[8] and Leif[9] to a triphasic model that emphasized desire—in contrast to physiologic genital arousal—as the first stage of sexual response.

In 2001, Basson[10] first published her intimacy-based circular model to help explain the multifactorial character of female sexual response. This model includes the interplay of emotional intimacy, sexual stimuli, psychological factors, and relationship satisfaction. This model also introduces the concept of receptive/responsive desire, which is the idea that arousal often precedes desire and that women often begin a sexual encounter from a position of sexual neutrality[10] (Fig. 2). It encompasses the impact of biologic and nonbiologic factors on a woman's sexual response, including motivation, interpersonal issues, cultural and religious beliefs, partner's health status, relationship quality, past sexual abuse, and distractions. Basson's model, which emphasizes that desire and arousal are difficult to separate and includes a responsive component to normal desire, serves as the basis for the DSM 5,[11] which combines the DSM-IV-TR[12] diagnoses of HSDD and female sexual arousal disorder (FSAD) into female sexual interest/arousal disorder (FSIAD).

Desire is a deceptively intricate concept that is best understood by differentiating within a biopsychosocial context and by differentiating its components: sexual drive, sexual beliefs, and sexual motivation. This biopsychosocial model of desire[12a,12b] (Fig. 3) outlined by Levine[13] suggests that desire is composed of three individual but interrelated components.

The biologic component, drive, is a spontaneous and variable sexual interest made up of cravings for sexual activity, sexual dreams, unprompted sexual thoughts, and genital sensations. It is influenced by neuroendocrine mechanisms. The second component is a sociocultural/expectation component that reflects a woman's beliefs and values about sex. The third component, motivation, reflects the emotional or interpersonal aspect of desire that is characterized by a woman's willingness to engage in sexual activity with a given partner (or alone). Motivation often carries the most weight among the components and is impacted by psychological function, relationship quality, and concerns about health, occupation, or family. The

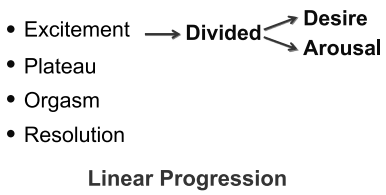

FIG. 1. Human sexual response: classic models.[7,8,9]

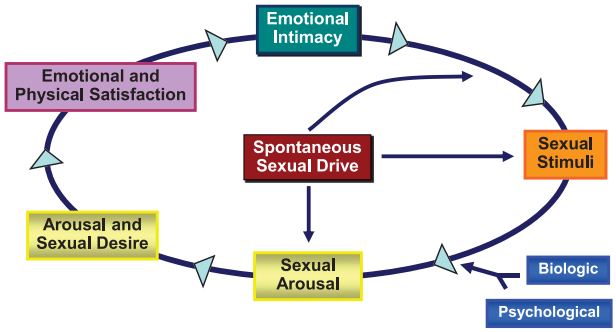

FIG. 2. Female sexual response cycle.[10]

interplay and input of all these realms yield one's sexual interest; therefore, the clinician's differential diagnosis and/or assessment of etiology must be broad, and treatment should often incorporate a biopsychosocial/integrative approach. Sexual desire is complex, and the etiologic factors contributing to problems with desire may be unique to each woman.

In reality, these theoretical models of sexual response may reflect the variation in sexuality that women experience.

One additional theory of sexual response that also keeps a biopsychosocial perspective is the dual control model of Bancroft et al.[14] This model proposes that sexual response occurs as an interaction between sexual excitatory processes and sexual inhibitory processes. The model further suggests that individuals vary in their propensity for both sexual excitation and sexual inhibition.

ANATOMY OF SEXUAL RESPONSE

The physiologic pathway of desire and arousal in women is an intricate neurobiologic process that we do not yet understand fully.[15] The female genital sexual anatomy includes the mons pubis; the vulva, including the labia majora, labia minora, interlabial space, and clitoris; and the inner genitalia, including the vestibule, periurethral glans and vagina, uterus, fallopian tubes, and ovaries.[16] The process of physiologic arousal is initiated by genital vasocongestion. The vulva swells, exposing the introitus; the vagina lengthens and dilates; the outer third of the vagina tightens; the clitoris increases in length and diameter; and the uterus rises above the levator plate.[17] Stimulation of the pelvic nerves induces smooth muscle relaxation and decreases resistance within arteries, leading to increased blood flow to the clitoris. This blood flow results from the active neurogenic dilation of sinusoidal blood spaces, which causes the corpora cavernosa of the clitoris to become engorged and the clitoris to become progressively more prominent. Vulvar structures become engorged but do not become erect because the thinner tunica in women does not trap venous blood but instead pools with persistent inflow and outflow.[18]

In addition, vaginal lubrication occurs because of increased pressure in the capillaries of the genital vasculature and transudation of fluid through the subepithelium of the vaginal walls.

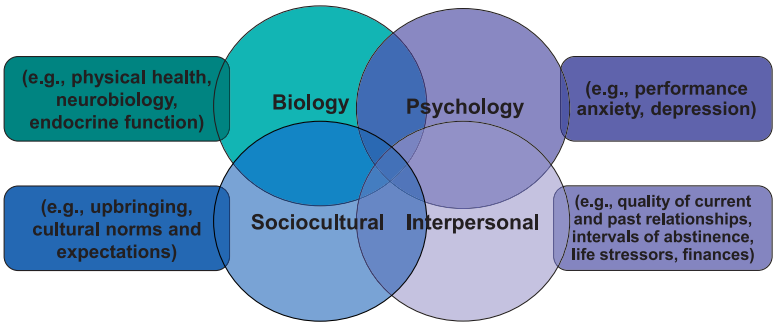

FIG. 3. Biopsychosocial model of female sexual response.[12a,12b]

PHYSIOLOGY OF DESIRE

Neuroendocrine mechanisms

Desire has been shown to be affected by the interactions of sex steroids and neurotransmitters.[15] Although the exact central neuroendocrine mechanisms remain undiscovered, several areas of the brain—including the brainstem, hypothalamus, and forebrain containing the amygdala—seem to be involved.[19] It is an active process that balances both excitatory and inhibitory factors. Excitatory factors include estrogen, testosterone, melanocortin, and oxytocin, as well as the neurotransmitters dopamine and norepinehrine.[20] Inhibitory factors include serotonin, prolactin, and endogenous opioids. The interaction between excitatory and inhibitory factors reflects the dual control model of Bancroft et al,[14] and the result of this interaction has also been referenced as the "sexual tipping point."[20]

Nitric oxide, vasoactive peptide, and acetylcholine probably play significant roles in sexual arousal.[21] Much of what we understand about their roles in female sexual excitement and response is a result of studies of penile erection and sexual biology in animal models. Sexual stimulation releases nitric oxide from the vascular endothelium, which stimulates the release of guanylate cyclase, which then converts guanosine triphosphate into cyclic guanosine monophosphate.[17] This stimulates smooth muscle relaxation in the penile arteries and corpora cavernosum, causing blood flow to the penis. Vasoactive peptide and acetylcholine have also been shown to relax smooth muscle and to increase blood flow in the penis and in animal models.

It is hypothesized that desire (more specifically drive) is triggered in areas of the hypothalamus and by the activation of the dopamine system. This system is activated early and—along with norepinephrine—increases sexual excitation and the desire to continue sexual activity.[20] The increasing state of excitement, as evidenced by increasing heart rate and blood pressure, suggests that the noradrenergic system is also involved in the sexual response. The actual neurobiology of orgasm is unknown, although it seems to include the mesolimbic dopamine pathway and the pudendal, pelvic, and hypogastric nerves. Orgasm occurs with the release of contraction-producing agents such as serotonin and oxytocin, which lead to rhythmic contractions of the levator plate, uterus, and vagina; multiple orgasms may occur if stimulation continues. The time of resolution varies among women.

Hormonal mechanisms

In premenopausal women, estradiol is primarily made in the granulosa cells of the ovaries and is the most potent and plentiful estrogen. Estrone and estriol are present but in much lower numbers and with much less affinity for the receptor.[22] After menopause, estrogen is produced from the precursors dehydroepiandrosterone (DHEA), dehydroepiandrosterone sulfate (DHEAS), and androstenedione mostly by the adrenal glands, but also by the postmenopausal ovary. Estradiol has been shown to maintain vaginal lubrication and genital sensitivity, as well as clitoral, vaginal, and urethral blood flow.[23] Both natural and surgical menopause will result in the permanent decline of ovarian estrogen production and, ultimately, an estrogen-deficient state.

The androgens DHEAS, DHEA, and androstenedione are prohormones and are converted into testosterone and dihydrotestosterone; thus, they are the more abundant androgens in circulation. Via theca cells, the ovary produces 25% of testosterone, 50% of androstenedione, and 20% of DHEA in the circulation, whereas the adrenal gland produces 25% of testosterone, 50% of androstenedione, 50% of DHEA, and 100% of DHEAS. The remaining 30% of circulating DHEA is made via the peripheral conversion of DHEAS.[24] Testosterone is also produced in the central nervous system, starting from cholesterol. Testosterone and dihydrotestosterone are the most potent androgens and are almost entirely bound to either sex hormone–binding globulin (SHBG) or albumin proteins. The remaining 1% to 2% is considered freely circulating and available to androgen- and estrogen-responsive tissues at multiple sites throughout the body, including the brain and skin.[25] SHBG is synthesized in the liver and serves as the carrier protein for estrogen and testosterone. It regulates the amount of free hormones circulating in the blood. Estrogen stimulates SHBG production, whereas increased levels of testosterone decrease SHBG synthesis. SHBG can be affected by medications through the hepatic first-pass metabolism.

Androgen levels are at their highest when a woman is in her 20s and then gradually decline over time such that when a

woman is in her 40s, she has about half the level of circulating testosterone.[26] There seems to be no further significant decrease after natural menopause, as ovarian production of androgen precursors remains relatively constant. This is supported by the fact that bilateral oophorectomy results in a 40% to 50% decrease in circulating total and free testosterone levels when compared with age-matched controls with ovaries and natural menopause.[27]

EPIDEMIOLOGY

The prevalence of HSDD is difficult to determine because it varies depending on the population surveyed. In the National Health and Social Life Survey, loss of interest in sex was the most prevalent sexual problem among women participating in this study, occurring in 33% of 1,749 women aged 18 to 59 years.[28] Segraves and Woodard[29] suggested that if the studied population were restricted to those reporting frequent problems with desire, then the prevalence of HSDD would be between 5.4% and 13.6%. The Prevalence of Female Sexual Problems Associated with Distress and Determinants of Treatment Seeking (PRESIDE) survey[30] of 31,581 US women aged 18 years or older included a validated questionnaire (to evaluate sexual function) and a validated measure of distress. In this study, 8.9% of women aged 18 to 44 years, 12.3% of women aged 45 to 64 years, and 7.4% of women older than 65 years had low desire and distress. The results from the PRESIDE survey also indicated that decreased sexual desire is associated with such negative effects as poor self-image, mood instability, depression, and strained relationship with the partner.[30] Intuitively and in keeping with a biopsychosocial perspective, one may consider these negative effects as both potential causes and effects of decreased sexual desire.

The Women's International Study of Health and Sexuality (WISHeS)[2] included women aged 20 to 70 years from the United States and Europe. It demonstrated that, on average, women with low desire engaged in sexual activity less frequently and experienced less enjoyment. It also indicated that the prevalence of low desire with distress in a US population was 14% in premenopausal women, 9% in naturally postmenopausal women, 26% in surgically postmenopausal women aged 20 to 49 years, and 14% in surgically postmenopausal women aged 50 to 70 years.

Furthermore, as noted previously, the Women's International Study of Health and Sexuality[2] demonstrated that women with HSDD experienced decreased self-esteem and agreed with statements expressing negative emotional or psychological states.

The second National Survey of Sexual Attitudes and Lifestyles,[31] a computer-assisted self-interview, which included 6,942 British women aged 16 to 44 years, found that 10.7% of the women reported lacking interest in sex for 6 months or longer. In addition, 27.9% sought help for this decreased desire.

Owing to the fact that very little is known about the natural course of HSDD and its consequences, the HSDD Registry for Women[32] was designed to characterize a large (1,500 women) cross-section of women with HSDD and to prospectively investigate several biopsychosocial factors associated with HSDD. The registry was also designed to evaluate treatment use, rates of symptom remission or progression, and treatment outcomes. Results indicate that HSDD is associated with a number of factors, including poor self-image, stress, and fatigue. The registry has also provided information on the treatment-seeking patterns of registry participants and information differentiating the characteristics of postmenopausal participants from premenopausal participants.[32-35]

TYPOLOGY

Sexual disorders are classified within the DSM. Since the publication of the DSM-III[36] in 1980, HSDD has been classified as a sexual disorder under the name "inhibited sexual desire disorder"; the name was changed to HSDD in the DSM-III-R[37] in 1987. HSDD, as stated in the DSM-IV-TR[12] version, is defined as "persistently or recurrently deficient (or absent) sexual fantasies and desire for sexual activity. It causes marked personal distress and/or personal difficulties and cannot be better accounted for by another primary disorder, drug/medication or general medical condition. The judgment of deficiency by the clinician is subjective and must take into account the normal fluctuation seen with relationships over time, age, personal health and life circumstances."

On May 27, 2013, the DSM 5[11] was released, revising many of the previous DSM-IV-TR classifications of psychiatric disorders, including female sexual disorders. The entire DSM 5 revision across all psychiatric conditions has been the source of tremendous controversy and debate, which have not resolved with its publication. The revision of the classifications and nosology of female sexual disorders has been one of the most contested. More specifically, the DSM 5 has essentially combined HSDD and FSAD, and this disorder is now classified as FSIAD (Tables 1 and 2).

There are several concerns with this new classification.

1. The term "desire" has now been eliminated and replaced with the term "interest." Desire has been the term and construct that has been the basis of almost all research in the area of "HSDD," and replacing it with a term that does not have 30 years of data behind it may be problematic both in clinical practice and in clinical research. Brotto[38] explained that a number of epidemiologic studies over the years have used the term "lack of interest" instead of "desire." She argued that desire connotes the more biologic component of drive. However, Levine's[13] delineation of desire as encompassing the biopsychosocial concepts of drive, sociocultural impact, and interpersonal/intrapersonal motivation has been accepted for 25 years. Furthermore, she acknowledged that "interest" may not be an ideal term because it is devoid of any sexual meaning.
2. Clayton et al[39,40] provided evidence that the DSM 5[11] would raise the bar so high for diagnosis that many of the women who would otherwise have met the DSM-IV-TR[12] criteria for FSAD or HSDD would no longer meet the criteria for the DSM 5[11] FSIAD and thus would be

TABLE 1. *DSM 5: female sexual disorders*

Female orgasmic disorder	Presence of either of the following on all or almost all (75%-100%) occasions of sexual activity: 1. Marked delay in, marked infrequency of, or absence of orgasm 2. Markedly reduced intensity of orgasmic sensations
Female sexual interest/ arousal disorder	Lack of or significantly reduced sexual interest/arousal as manifested by three of the following: 1. Absent/reduced interest in sexual activity 2. Absent/reduced sexual/erotic thoughts or fantasies 3. No/reduced initiation of sexual activity and unreceptive to partner's attempts to initiate 4. Absent/reduced sexual excitement/ pleasure during sexual activity in almost all or all (75%-100%) sexual encounters 5. Absent/reduced sexual interest/arousal in response to any internal or external sexual/erotic cues (written, verbal, or visual) 6. Absent/reduced genital or nongenital sensations during sexual activity in almost all or all (75%-100%) sexual encounters
Genitopelvic pain/ penetration disorder	Persistent or recurrent difficulties with one or more of the following: 1. Vaginal penetration during intercourse 2. Marked vulvovaginal or pelvic pain during intercourse or penetration attempts 3. Marked fear or anxiety about vulvovaginal or pelvic pain in anticipation of, during, or because of vaginal penetration 4. Marked tensing or tightening of pelvic floor muscles during attempted vaginal penetration
	Symptoms persisted for a minimum of 6 mo, were not better explained by a nonsexual mental disorder or a consequence of severe relationship distress or other significant stressors, and were not attributed to the effects of a substance/medication or other medical conditions

From the American Psychiatric Association.[11]

undiagnosed and untreated. They compared 231 women diagnosed as having HSDD (using the DSM-IV-TR[12] criteria) with 250 women with no desire problems.

3. Clinical trial development may be similarly impacted. Therefore, many phase 2 and phase 3 trials for "HSDD" treatments are now designed with inclusion criteria that meet both the DSM-IV-TR[12] criteria for HSDD and the DSM 5[11] criteria for "FSIAD." Each disorder is further subtyped into lifelong versus acquired, and generalized versus situational. Because sexual problems tend to overlap with one another, the best approach for clinical practice is to identify the most problematic or primary issue and to focus initial treatment there.

FACTORS ASSOCIATED WITH HSDD

It is easy to see why a clinically adequate definition of hypoactive sexual desire remains elusive—women do not seem to follow one universal sexual response and often present clinically with concerns that are often interdependent.

This is exacerbated, in part, by the common overlap of the biopsychosocial components of desire that have been compromised. Evaluating the potential contributing factors to reports of low desire and the original presentation and duration of such complaints is essential. Desire is such a complex concept that diagnosis, identification of the etiology of the problem, and development of a treatment plan can oftentimes be confusing for both a woman and her clinician.

A biopsychosocial approach to sexual desire makes each woman's individual presentation of HSDD easier to comprehend and disentangle, keeping in mind the components of drive, social/cultural expectations, and motivation.[41]

Psychological and psychosocial factors associated with HSDD

Research has also demonstrated that there are almost countless psychological reasons why women will choose to engage in sexual activity. Some of the more frequently endorsed reasons include the wish to be close to one's partner, to feel feminine or wanted, to satisfy a partner, or to maintain a relationship.[42]

Relationship factors

Women initiate sexual activity for any number of reasons or incentives, and the feeling of sexual desire is not in and of itself usually a trigger that provokes sexual activity.[43] Some women may have sexual drive but experience distressing desire problems caused by a relationship conflict with the partner. Others may experience a satisfying sexual life with a partner without having the outright desire for sexual activity.[44] Still other women may be distressed by the lack of an available partner, whereas many may enjoy a satisfying sexual life without any partner or multiple partners. We also know that sexual satisfaction is not merely measured by the frequency of sexual activity.[45] Some studies showed that a partner's sexual dysfunction (eg, erectile dysfunction and premature ejaculation in a male partner) have a negative impact on the female partner's sexual desire.[46] Although evidence-based research demonstrating an impact of relationship factors on desire problems is minimal, clinical experience and correlational studies show that relationship and sexual satisfaction are closely linked.[44]

Psychological factors

It is also understandable that psychological factors are frequently associated with desire problems. Brotto et al[44] listed the psychological domains under which evidence has demonstrated a negative impact on desire. These include the following: sexual abuse and trauma in childhood and puberty; perceived stress; distraction; self-focused attention/anxiety; depression; personality variables (eg, Axis II personality disorders); and body image/self-consciousness. For example, a history of sexual or emotional abuse as a child or adult could, not surprisingly, alter one's expectations about and experiences with sexuality.

TABLE 2. *Comparison of the DSM-IV-TR and DSM 5 disorders related to hypoactive sexual desire*

Hypoactive sexual desire disorder	DSM-IV-TR	Persistently or recurrently deficient (or absent) sexual fantasies and desire for sexual activity. The disturbance causes marked distress or interpersonal difficulty.
Female sexual arousal disorder	DSM-IV-TR	Persistent or recurrent inability to attain, or maintain until completion of sexual activity, an adequate lubrication-swelling response of sexual excitement. The disturbance causes marked distress or interpersonal difficulty. The sexual dysfunction is not better accounted for by another disorder and is not attributed to the direct physiologic effects of a substance/medication or general medical conditions.
Female sexual interest/arousal disorder	DSM 5	Lack of, or significantly reduced, sexual interest/arousal as manifested by three of the following: 1. Absent/reduced interest in sexual activity 2. Absent/reduced sexual/erotic thoughts or fantasies 3. No/reduced initiation of sexual activity and unreceptive to partner's attempts to initiate 4. Absent/reduced sexual excitement/pleasure during sexual activity in almost all or all (75%-100%) sexual encounters 5. Absent/reduced sexual interest/arousal in response to any internal or external sexual/erotic cues (written, verbal, or visual) 6. Absent/reduced genital or nongenital sensations during sexual activity in almost all or all (75%-100%) sexual encounters Symptoms persisted for a minimum of 6 months, were not better explained by a nonsexual mental disorder or a consequence of severe relationship distress or other significant stressors, and were not attributed to the effects of a substance/medication or other medical conditions.

From the American Psychiatric Association.[11,12]

Cultural/religious factors

Cultural, social, and religious values and mores may negatively impact women's sexual desire. A review of specific cultures and religions is beyond the scope of this review on HSDD; however, problems with sexual desire are more probable among women who were raised in highly restrictive or patriarchal cultures/religions. Furthermore, some reproductive health policies and customs, and population histories of oppression and marginalization may contribute to diminished sexual desire in women.[47] Ethnic and religious differences in the prevalence rates of HSDD emphasize the impact of these factors on women's sexuality.[47] In addition, there is a paucity of studies regarding the prevalence of low sexual desire among women in same-sex relationships. What has been carried out is equivocal: Some studies suggested no greater prevalence of low sexual desire, whereas others identified internalized homophobia as a risk factor that is unique to lesbians and bisexual women.[47]

Aging factors

Although loss of desire can occur at any age, Sarrel[48] reported that about 40% of women experience decreased libido during menopause. In addition, the PRESIDE survey[30] indicated that women aged 45 to 64 years had the highest prevalence of decreased desire with distress (12.3%; vs 8.9% in women younger than 45 y and 7.4% in women 65 y or older). Sexuality remains important to older women, and it has been shown that a sexually satisfying life is important to their overall quality of life.[49] Sexual responsiveness is thought to decrease with age, and the level and amount of sexual activity and reported libido also reportedly decrease after menopause.[50] This is particularly true for women who experience a sudden loss of hormones accompanying surgical or chemical menopause. However, longitudinal studies suggest that relationship factors and other nonbiologic changes may have a stronger impact on overall sexual desire in the older population than menopause alone.[51] The Massachusetts Women's Health Survey II found that menopause status was associated with lower sexual desire. However, depression, anxiety, and other factors (such as relationship status and conflict, partner's health status, and sexual function) may have affected sexual function more.[52]

The cause of low desire as it relates to aging versus menopause has been made even harder to distinguish because of increased vulvovaginal atrophy in the aftermath of the early publication of the Women's Health Initiative and the resulting public fear of estrogen therapy. Menopause has long been assumed to result in decreased desire due to the decline in ovarian testosterone production and estrogen loss. Postmenopausal estrogen loss typically leads to vulvovaginal atrophy and dryness, as well as changes in genital function via reduced clitoral blood flow and decreased sensory perception. It is easy to see how the discomfort of vaginal dryness and genital insensitivity would interfere with a woman's responsiveness to cues and her sexual expression and have a downstream effect on desire. Estrogen therapies are effective for treating vaginal dryness and dyspareunia due to vulvovaginal atrophy, but they have not been shown to have great effect when specifically used for decreased libido, unless the decreased desire is specifically the consequence of pain or loss of genital pleasure/sensation.[53] Instead, it has been theorized that fluctuations in testosterone levels lead to decreased libido,[54] and there are data to suggest that testosterone therapy may improve HSDD in some women.

Age and length of relationship are frequently incorrectly assumed to be positively correlated. Although aging and the inevitable health problems that occur may impact sexual function, age is not a reliable predictor of a woman's relationship stage.

Postmenopausal women may be involved in a new relationship, a longstanding intimate relationship, a longstanding nonintimate/distant relationship, or no relationship at all.[55] The distinction between the age of the people in a relationship

versus the "age" (length) of the relationship is critical to understanding decreased desire. The early stages of most relationships are often the periods when a woman will experience the most sexual desire, irrespective of her age. New sexual relationships have some compelling advantages that are only experienced within the context of a new relationship. The excitement of new love/lust, the chase, the discovery, and the novelty are often the ingredients that make sex during this stage of a relationship incredibly passionate and exciting. These new exciting relationships are not exclusive to younger women. A new relationship carries these sexual advantages at any age.[55] In contrast, long-term relationships are often associated with decreased sexual desire.[56] Holding age constant, Hawton et al[57] found an inverse relationship between women's enjoyment of sexual activities and the length of the relationship.

Medical factors associated with HSDD

Much research has shown that medical conditions and treatments may negatively impact sexual desire. Table 3 lists examples of diseases with possible sexual consequences. Diseases and medical interventions can alter the physiology of sexual response both centrally and peripherally. In addition, the existence of other sexual disorders, including pain or loss of sensitivity, can evoke such a negative response that women who suffer from these can lose interest in any sexual expression.

Table 4 lists common medications that are associated with reduced sexual desire. Medications that provide therapeutic benefit for disease can negatively impact a woman's sexual response. Combined oral contraceptives have been well used for a variety of gynecologic conditions, in addition to pregnancy prevention. Over the years, the type, strength, and combination of estrogen and progestin components have been manipulated to provide the fewest adverse effects while still maintaining contraceptive safety and efficacy. This scientific pursuit has resulted in thousands of studies during which treatment success and adverse effects of pregnancy prevention and benign gynecologic diseases were evaluated.[96] Despite this body of literature, the reported effects on female sexuality remain controversial. Recent review articles by Burrows et al[96] and Pastor et al[97] outlined mixed results on libido; some demonstrated positive or mostly neutral effects on libido,[98,100-108] whereas others demonstrated negative effects on libido.[109-114]

In addition, there is now an appreciation for a possible association of vulvar vestibular pain with the use of combined oral contraceptives in some women.[115-118] Selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors are the most commonly prescribed antidepressants.[119,120] Unfortunately, they also cause sexual adverse effects, including decreased desire, arousal difficulties, and delayed/absent orgasm. The reported incidence varies among studies and ranges from 30% to 70%.[121-123]

TABLE 3. *Long-term diseases that negatively affect sexual function*

Mood disorders[58-60]	Major depression, bipolar disorder
Anxiety disorders[30,61]	
Psychotic disorders[62]	Schizophrenia[63]
Neurological disorders[64]	Parkinson's disease, cerebrovascular disease, multiple sclerosis,[65] head injury[66]
Endocrine disorders[67]	Diabetes, thyroid disorders, hyperprolactinemia,[68] adrenal insufficiency[69]
Urological conditions[70]	Renal failure,[71,72] urinary tract infections,[73] urinary incontinence[74]
Cardiac and vascular diseases	Hypertension,[75] coronary artery disease,[76] myocardial infarction[77]
Gynecologic disorders	Sexually transmitted diseases,[78] chronic pelvic pain/endometriosis,[79] dyspareunia/vulvar pain disorders,[80] vulvovaginal atrophy,[81] chronic vulvovaginal candidiasis,[82] postpartum period and physical changes,[83] pelvic organ prolapse[84]
Cancer treatment, surgical treatment, and chemotherapy[85]	Breast,[86] anal, bladder, colorectal, and gynecologic cancers
Dermatologic conditions[87]	Eczema, psoriasis,[88] Paget's disease, vulvar dystrophy

TABLE 4. *Examples of medications that may be associated with sexual desire problems*

Antidepressants/mood stabilizers	SSRIs and SNRIs,[59] antipsychotic drugs[66,89]
Cardiovascular/ antihypertensive agents[90]	Digoxin, lipid-lowering agents, β-blockers,[91,92] ACE inhibitors,[93] angiotensin II antagonists[94]
Hormones/antiandrogen agents[95]	Oral contraceptive pills,[96-98] GnRH agonists, spironolactone
Others[99]	Histamine receptor blockers, narcotics, amphetamines, chemotherapeutic agents, antiepileptic drugs[64]

SSRI, selective serotonin reuptake inhibitor; SNRI, serotonin-norepinephrine reuptake inhibitor; ACE, angiotensin-converting enzyme; GnRH, gonadotropin-releasing hormone.

SCREENING FOR AND EVALUATION OF LOW SEXUAL DESIRE

Sexual problem identification should be a routine part of health care. A thorough sexual history and/or physical examination should assess medical, psychosocial, sexual, reproductive, and surgical information. The review of systems can be an ideal time to elicit such concerns. Postpartum and postsurgical periods must include a discussion and an assessment. However, during a typical office visit, several barriers interfere with the communication of sexual function concerns. This lack of discussion of sexual concerns may be the result of incomplete or insufficient knowledge of the HCP, poor training in taking an effective sexual history, a perceived lack of office time, a limited number of approved and efficacious psychotherapeutic or pharmacologic options for treatment, and uneasiness of the woman and the HCP to discuss such issues.[6]

Direct questioning about specific sexual practices and activities is critical to uncovering a woman's sexual concerns and signals that the HCP is comfortable with discussing sexual health concerns. Studies have shown that women are reluctant to initiate discussions about sexual concerns but very much want their HCP to set up the environment and to open a dialogue for this to take place.[124]

When conducting the interview, the HCP should express empathy and encourage open communication. Furthermore, it

TABLE 5. *Suggested questions to assess sexual function*

How do you describe the problem?
How long has the problem been present?
Was the onset sudden or gradual?
Is the problem specific for a situation or partner, or is it present in all situations and all partners?
Were there any triggering events?
Are there nonsexual problems with your primary sexual partner or any sexual relationships?
Are there current life stressors that might be contributing to sexual problems?
Are you experiencing any feelings that interfere with your sexual function, which may include stress, guilt, depression, resentment, anger, and/or fear?
Do you have any concerns about your body image or physical appearance?
Are there any physical problems, such as fatigue, pain, or long-term illnesses, that may contribute to your sexual problems?
Are there problems in desire, arousal, or orgasm?
Is there a history of physical, emotional, or sexual abuse?
Does your partner have any sexual problems?

From Basson.[125]

is important that the HCP asks about sex and the sexual function of partners and does not assume that the woman's sexual behavior is limited to one partner or to an identified partner or spouse.

Evaluation of an identified problem

Any office visit can include a brief assessment of sexual function. First, legitimize the importance of assessing sexual function and normalize the discussion as part of routine information in history taking and physical examination. Second, include open-ended questions regarding any sexual concerns. Third, review problems within sexual response, including desire, arousal, orgasm, and pain. Table 5 provides a list of key questions to include in an initial screen for sexual problems. These questions help to identify the specific components of the sexual problem and help to address a woman's perceptions of the problem, its timeline, and its context, and other psychosocial, relationship, and health problems that might contribute to a sexual complaint. Answers to these questions not only assist in isolating the key issues and etiologies but also serve as a basis for treatment considerations.[126]

A thorough sexual history and/or physical examination must be pursued to uncover the physiologic and anatomic factors involved with the sexual complaint. No standard laboratory tests or imaging studies are required for the initial evaluation of a woman with normal examination results. Clinicians should attend to the physical features relevant to sexual function. Of course, nonbiologic factors (eg, psychological, relationship, social, and situational stresses) should be considered as the primary or coexisting sources of low desire. Each step of the examination should be explained to the woman and consented by her (particularly in women with a history of abuse or pain). This may increase her sense of control and may help establish trust with the HCP. The examination is also an opportunity to provide education about anatomy and female sexual function. As noted previously, many medical and psychiatric conditions, as well as medications (prescription and over-the-counter), may impact sexual function, and an assessment of these should be included in the evaluation (Tables 3 and 4).

A number of screening tools/questionnaires are available. However, some tools are better suited for a research setting than for clinical practice.[6] Commonly used validated scales include those presented in Table 6. When choosing a questionnaire, clinicians must consider what they are hoping to accomplish and whether they are looking for generic or condition-specific information. One validated scale that was specifically developed for use by clinicians not experienced in sexual medicine is the Decreased Sexual Desire Screener[134] (www.obgynalliance.com/files/fsd/DSDS_Pocketcard.pdf). It is a five-question self-administered survey that helps identify generalized acquired HSDD in premenopausal and postmenopausal women in a time-efficient manner. Another validated tool for office-based use is the Brief Profile of Female Sexual Function.[136] This seven-question self-administered survey measures the loss of sexual desire and function in postmenopausal women with HSDD. The Pelvic Organ Prolapse/Urinary Incontinence Sexual Questionnaire is a short-form 12-question self-administered test that measures sexual function in women with pelvic organ prolapse and/or urinary incontinence.[135] The Handbook on Female Sexual Health and Wellness[137] is a collection of resources and practical tools to aid clinicians caring for the sexual health of women.

When conducting a brief screen or assessment of sexual problems, clinicians will often notice comorbidity among sexual problems. Women with HSDD commonly present with concomitant symptoms of decreased lubrication, decreased genital sensation, and difficulty reaching orgasm. In contrast, women with chronic vulvar pain or difficulties in arousal may develop HSDD. For example, if a postmenopausal woman with severe vulvovaginal atrophy has pain with every sexual encounter, it would not be surprising that she would lose her desire for sexual activity. However, in this case, the primary diagnosis would be genitourinary pain/penetration disorder

TABLE 6. *Validated tools that can be used to measure female sexual dysfunction*

Tool	Assessed area
Female Sexual Function Index[127]	Desire, arousal, orgasm, and pain
Female Sexual Function Index 6 Item[128]	Desire, arousal, orgasm and pain
Brief Sexual Symptoms Checklist[129]	
Female Sexual Distress Scale—Revised[130]	Distress
Intimate Relationship Scale[131]	Changes in sexual relationship
Sexual Quality of Life—Female[132]	Quality of life in women with female sexual arousal disorder
Golombok-Rust Inventory of Sexual Satisfaction[133]	Quality of sexual relationship
Decreased Sexual Desire Screener[134]	Brief diagnostic tool for hypoactive sexual desire disorder
Pelvic Organ Prolapse/Urinary Incontinence Sexual Questionnaire[135]	Sexual function in women with prolapse and/or urinary incontinence

with secondary HSDD. Similarly, women with loss of genital sensations or anorgasmia may subsequently develop symptoms of decreased sexual desire. The key to appropriate evaluation is to determine the primary sexual problem to develop the most effective treatment plan.

The PLISSIT model[138] can be a helpful tool for discussing health concerns with women and guides basic office-based counseling. It is a classic office-based approach to sex therapy that was designed to assist HCPs who wish to incorporate some behavioral and psychological sex therapy techniques into their general practice:

- Permission (P): Women are given permission to discuss their problems and emotions and to explore new solutions.
- Limited information (LI): The HCP provides some basic education specific for sexual function or sexual physiology or provides educational resources such as literature, videos, and erotica.
- Specific suggestions (SS): The HCP provides specific directives or advice to address the presenting problem.
- Intensive therapy (IT): The HCP provides referral for individual or couples therapy to address HSDD that requires more intensive treatment than the office-based suggestions of the steps above.

Figure 4 provides an example of applying the PLISSIT model in a clinical setting.

TREATMENT

The first step in the successful treatment of female sexual dysfunction is to ensure that an integrated (biopsychosocial) approach is taken. The treatment of HSDD is guided by targeting the components of desire that are impaired.

Psychotherapy treatments of hypoactive sexual desire

Although there are very few outcome studies on the psychotherapeutic treatments of HSDD, psychotherapy has been clinically used for decades. Psychotherapy is typically favored when the HSDD DSM specifiers are acquired/situational and treatment will focus on modifying precipitating or contributing circumstances or behaviors.[49] However, when the low desire is determined to be secondary to psychological factors such as relationship problems, personality traits, depression, anxiety, poor body image, or sexual abuse/assault, psychotherapy should address these problems either in conjunction or before treating the symptom of hypoactive sexual desire.[44] Sex therapy and cognitive-behavioral therapy (individual and/or couples) are the major treatment approaches represented in the empirical literature. Traditional sex therapy is a behavioral treatment used to improve a person's erotic experiences and to reduce anxiety and self-consciousness about sexual performance.

Sensate focus, originally developed by Masters and Johnson,[139] is the best example of behavioral sex therapy and consists of a progressive series of "homework" between partners designed to enhance partners' awareness of pleasurable experiences and their own preferences for sexual touch while reducing anxiety through graded exposure. Sex therapy is only modestly effective in treating women with low sexual desire.[47,139]

Cognitive-behavioral sex therapy includes traditional behavioral sex therapy components but puts a greater emphasis on modifying thought patterns or beliefs that interfere with intimacy and sexual pleasure.[47]

Example of Using the PLISSIT Model

- (P) Permission: The HCP explicitly encourages a woman to discuss any sexual concerns or questions she may have and validates her right to satisfying sexual function.
- (LI) Limited Information: the practitioner may educate the patient about sexual physiology or suggest educational resources such as literature, videos, and erotica.
- (SS) Specific Suggestions: The HCP provides tailored approaches designed to improve sexual and emotional communication such as sensate focus exercises, masturbation, Kegel exercises, technical advice regarding sexual positions, and the use of lubricants or dilators.
- (IT) intensive therapy: may involve referral for individual or couples therapy to deal with longstanding conflict that is contributing to a woman's HSD.

FIG. 4. The PLISSIT model. HCP, healthcare provider; HSD, hypoactive sexual desire.

Mindfulness-based cognitive-behavioral treatments have also shown excellent promise for sexual desire problems. Brotto et al,[140] in one of the few empirically tested outcome studies of psychotherapy, demonstrated that a brief mindfulness-based cognitive-behavioral intervention was successful in improving sexual desire and arousal problems in gynecologic cancer survivors.[140]

Office-based counseling

Although psychotherapy/sex therapy is recommended for most women who present to their HCPs with HSDD, it may also be helpful for the HCPs to consider using the previously described PLISSIT model to offer some office-based counseling as well. For some, basic office counseling may be sufficient. For others, it may be partially helpful until they take the step of following through on a referral for psychotherapy. It is often useful to remind women in long-term relationships that committed couples are at risk for desire problems caused by boredom and complacency. Counseling suggestions may include ideas for rekindling energy and interest, such as planning romantic interludes/dates, changing sexual scripts/patterns, and incorporating erotic literature or films.

Testosterone treatment and desire

The evidence that low testosterone levels are not directly associated with loss of sexual desire may create confusion because, at first pass, it seems inconsistent with the evidence from multiple treatment trials indicating that exogenous testosterone improves sexual desire. The confusion arises from the fact that serum levels of testosterone do not necessarily correlate with women's sexual function[141] and have not been independently associated with well-being in postmenopausal women.[142] This may be explained by the known imprecision of testosterone assays at the lower end of the female range and the fact that measuring circulating testosterone levels may not reflect true tissue concentrations.[25] Compelling evidence suggests that testosterone plays a role in female sexual desire in some premenopausal and postmenopausal women. Premenopausal women with androgen insufficiency or low levels of androgens due to hypopituitarism, premature ovarian failure, adrenal insufficiency, or oophorectomy experience a diminished sense of well-being, fatigue, and decreased sexual desire.[25] Numerous studies involving postmenopausal women also showed that low testosterone levels were associated with loss of sexual desire and sexual pleasure, decreased physical well-being, and persistent fatigue.[25] Furthermore, current research is examining a genetic component for androgen receptors that may help explain this variation in women's sensitivity and response to testosterone treatment.[143]

The relationship between androgens and sexual desire was established nearly 75 years ago and was further validated by clinical research on postmenopausal women in the 1980s and 1990s (for review, see Traish et al[144] and Segraves and Woodard[29]). It was during this time that the benefit of testosterone with estrogen was identified, and this combined therapy reportedly resulted in improved sexual activity, satisfaction, pleasure, and orgasm.[145-147] Routes of administration during that time included oral administration, intramuscular injection, and subcutaneous implants.

Many of the key randomized clinical trials that studied the effects of exogenous testosterone on postmenopausal women with HSDD are presented in Table 7. These studies demonstrated efficacy as established by significant changes in satisfying sexual events (SSEs) and desire compared with placebo (in surgically and naturally postmenopausal women with and without exogenous estrogen).[148-150,152-156]

Although the absolute change in SSEs from baseline to the end of treatment may seem modest (eg, Buster et al[150]; the baseline SSE per month was 3, and the mean increase was 2.1 SSEs/month in the testosterone group vs 0.98 SSEs/month in the placebo group), the change was statistically significant, and, more importantly, the women reported clinically meaningful benefit.[157]

More recently, results from two large randomized, placebo-controlled, phase 3 trials of transdermal testosterone gel did not demonstrate the efficacy of testosterone compared with placebo among surgically and naturally postmenopausal women with and without estrogen.[158,159] These surprising results may actually represent an overly robust placebo response more than an actual lack of efficacy.

Although testosterone plays a role in drive, motivation, and sexual sensation, it is important to understand that, because there is little correlation between HSDD and serum androgen levels, they should not be used as a diagnostic measure of sexual dysfunction.[141] When hormone assays are used, it is important to include the measurement of SHBG and to calculate the free androgen index (total testosterone/SHBG), which is a more accurate reflection of the hormonal milieu than total testosterone or bioavailable/free testosterone alone. An example of a free and bioavailable testosterone calculator can be found at

TABLE 7. *Randomized, placebo-controlled, clinical trials demonstrating the efficacy of transdermal testosterone patch in postmenopausal women*

	Testosterone dose (μg/d)	Participants	n	Concomitant estrogen
Shifren et al[148]	150/300	Surgically postmenopausal	75	Yes
Braunstein et al[149]	150/300/450	Surgically postmenopausal	447	Yes
Buster et al[150]	300	Surgically postmenopausal	533	Yes
Simon et al[151]	300	Surgically postmenopausal	562	Yes
Davis et al[152]	300	Surgically postmenopausal	61	Yes (patch)
Davis et al[153]	300	Surgically postmenopausal	76	Aromatase inhibitor
Shifren et al[154]	300	Naturally postmenopausal	486	Yes
Davis et al[155]	150/300	Naturally postmenopausal/surgically postmenopausal	814	No
Panay et al[156]	300	Naturally postmenopausal	272	(Predominantly no)

http://www.issam.ch/freetesto.htm.[159a] Evidence for the efficacy of TTP use in premenopausal women with HSDD exists but is less vigorous, and conclusions for use in this population remain undecided.[160] In addition, the potential risk of fetal exposure to androgen therapy among women of reproductive age remains a concern.

Adverse effects and safety data on testosterone use

Only limited long-term safety data on testosterone use for the treatment of HSDD are available. This was the reason that the Food and Drug Administration (FDA) Advisory Committee failed to approve in December 2004 the use of a testosterone product for women.[161] After reviewing the data from the clinical trials of TTP in postmenopausal women, the committee accepted the efficacy of TTP but deemed the safety data inadequate.[162]

As result of this decision, the new drug application was withdrawn in the United States. It was subsequently submitted to and approved in the European Union but has recently been discontinued by the company that markets it. The major concerns regarding safety included the potential effects of long-term androgen exposure on the cardiovascular system, breast, endometrium, liver, and psychological well-being. The minor concerns included the known adverse effects of increased hair growth and acne. Postmenopausal women already have a high testosterone-to-estrogen ratio, and the effects of promoting this profile for the long term is unknown.

The short-term adverse effects and safety data for TTP were well documented in the randomized patch studies, but these data do not go beyond 2 years. Nachtigall et al[163] demonstrated a 4-year open-label extension safety summary of data from more than 900 surgically postmenopausal women receiving estrogens who participated in a study of 300 μg of TTP. In this study, again no increase in the rate of major adverse effects was found. The most common adverse events were application site reactions and unwanted hair growth.

In 2012, Davis and Braunstein[25] addressed some of these safety concerns in their review of the current literature. The most common adverse effects of testosterone in clinical studies were acne and increased body and facial hair with increased depilation rates, but the finding of virilization had not been observed. With respect to cardiovascular disease, they cited both observational and prospective studies in postmenopausal women that have examined the association between testosterone levels, atherosclerosis, cardiac events, and death, and have not demonstrated a causal role.[164,165]

For exogenous doses of testosterone at treatment levels consistent with those described for HSDD, there seems to be no adverse effects on the cardiovascular system, and any lipid alteration is dependent on the route of administration.[25] By avoiding the first-pass liver effects, TTPs, sprays, and other nonoral approaches do not alter the lipid profile and do not increase viscosity, as determined by plasma concentrations of fibrinogen and triglycerides. In transdermal patch studies, basal insulin and glucose levels remained unchanged, suggesting that physiologic levels of testosterone do not lead to insulin resistance.[25] Davis and Braunstein[25] even cited data from a study of 293 female-to-male transsexuals who received male doses of testosterone for 2 months to 41 years and had no increased cardiovascular mortality.

Testosterone can potentially exert an effect on the endometrium via local aromatization to estrogen; however, because aromatase activity has not been detected here, there should be no adverse uterine effects. Endometrial biopsies of postmenopausal women given oral testosterone alone for 3 months did not show any growth or proliferative changes.[166] In the APHRODITE study,[155] 12 months or two doses of TTP did not yield any adverse endometrial effects.

Although the hyperandrogenism seen in women with polycystic ovarian syndrome has not been associated with an increased risk of breast cancer, the breast does contain the aromatase enzyme complex and androgen receptors.[167] This leads to concern over exogenous testosterone therapy, especially in light of the results of combined estrogen-progestin therapy in the postmenopausal population of the Women's Health Initiative study[168]; however, similar increases in breast cancer risk were not seen in the estrogen-only treatment group, which is more relevant to the current context.[169] Davis and Braunstein[25] stated that, collectively, the data on breast cancer risk with exogenous testosterone therapy suggest a neutral or possibly protective effect. In fact, although the available safety data are not conclusive, they are reassuring with respect to cardiovascular, breast, and endometrial outcomes.[25] This has also been maintained by Bitzer et al,[170] who essentially stated in a review in 2008 that the available literature does not allow for conclusions to be drawn about the safety of testosterone therapy. However, long-term published data from large clinical trials of testosterone use are not available. In the APHRODITE trial[155] of 814 postmenopausal women not receiving estrogen, four cases of breast cancer were detected in the testosterone group, whereas there was none in the placebo group. The authors of the APHRODITE study suggested that the excess of cases in the testosterone group may have been attributable to chance. Yet, they acknowledged the possibility of a causal relationship.[154]

To address the long-term safety issues raised by the FDA, BioSante conducted a large phase 3 long-term safety study focusing on cardiovascular and breast cancer risks using a testosterone transdermal gel.[171] This safety trial was a randomized, placebo-controlled, multicenter, cardiovascular events–driven adaptive design comparison of a testosterone gel 300 μg/day (LibiGel) versus a placebo gel for the treatment of HSDD in naturally and surgically postmenopausal women with known cardiovascular risk. Enrollment at the end of approximately 4 years reached 3,656 randomized postmenopausal women with HSDD and cardiovascular risk, with accumulated exposure of more than 5,000 women-years.[171] Although the efficacy studies for LibiGel did not show any improved outcome over placebo, the data from their large safety trial helped to support the safety of using exogenous testosterone in postmenopausal women—even in women at risk for cardiovascular disease.[25,171]

INVESTIGATIONAL TREATMENTS ON THE HORIZON

On September 24, 2012, the FDA announced, as part of the Prescription Drug User Fee Act (PDUFA V), that female sexual dysfunction is one of 20 disease areas to be focused on regarding its impact on women's daily lives, the types of treatment benefit that matter most to women, and women's perspectives on the adequacy of available therapies.[172]

Centrally acting agents

Flibanserin is another nonhormone agent undergoing investigation with three completed phase 3 pivotal trials.[173-175]

As described by the dual control model of Bancroft et al,[14] HSDD has been hypothesized to be caused by an imbalance in excitatory and inhibitory activities that regulate sexual response within the central nervous system.[14] The prefrontal cortex is involved in the inhibitory control of motivational behavior, including sexual behavior. Dopamine and norepinephrine have been shown to be excitatory factors, whereas serotonin has been shown to be inhibitory. Flibanserin acts as a postsynaptic serotonin receptor 1A (5-HT_{1A}) agonist/serotonin receptor 2A antagonist (5-HT_{2A}). Stimulating the 5-HT_{1A} seems to have prosexual effects, and inhibiting serotonin receptor 2A (5-HT_{2A}) may also have prosexual effects. Three pivotal randomized controlled trials have been conducted—all comparing flibanserin 100 mg with placebo in premenopausal women. The first two trials used SSEs and an e-diary (an electronic diary that prompts women to assess their desire daily) as co–primary endpoints. Although there was a statistically different improvement in SSEs from baseline in the flibanserin group versus the placebo group, the e-diary did not show a statistical difference. The third pivotal trial used SSEs and the Female Sexual Function Index desire domain as co–primary endpoints. In this trial, the mean (SE) change in SSEs from baseline to the end of study (24 wk) for the treatment group was 2.5 (SE 4.6) versus 1.4 (SE 4.5) for the placebo group ($P < 0.001$). The mean (SE) Female Sexual Function Index desire domain score change from baseline was 1.0 (0.1) for the treatment group, versus 0.7 (0.1) for placebo ($P < 0.001$).[172,173,175]

Flibanserin has been studied in more than 11,000 women and has been resubmitted to the FDA for consideration.

Bremelanotide, a melanocortin receptor 4 agonist, is a synthetic peptide analog of the naturally occurring hormone α-melanocyte-stimulating hormone. Bremelanotide has shown benefit in improving sexual desire and arousal in postmenopausal women. It was initially formulated as a nasal spray, but development was stopped because of adverse blood pressure effects.[176]

It has been reformulated as a subcutaneous injection. In a recently completed phase 2B clinical trial, bremelanotide in 1.25- and 1.75-mg doses significantly increased sexual arousal, sexual desire, and the number of sexually satisfying events, and decreased associated distress in premenopausal women with HSDD. In the phase 2B trial that has yet to be published,[177] bremelanotide showed a statistically significant increase in the number of SSEs versus placebo (mean [SE] increase in SSEs, 0.8 [2.9] for 1.75 mg ($P = 0.0215$) and 0.7 [2.4] for 1.25/1.75 mg pooled ($P = 0.0180$) vs 0.2 [2.3] for placebo) and a statistically significant decrease in distress as measured by the Female Sexual Distress Scale-Desire, Arousal, Orgasm (FSDS-DAO) compared with placebo.

Lybrido and Lybridos are combination sublingual drugs that are under development for the treatment of HSDD.[178-180]

Lybrido[179] is designed for women whose HSDD is caused by overactivation of sexual inhibitory mechanisms and combines testosterone with a phosphodiesterase inhibitor (PDE5). PDE5 inhibitors cause an increase in physiologic genital response. Although clinical trials of sildenafil versus placebo conducted in women with sexual arousal disorder (FSAD) showed no significant differences (perhaps due in part to FSAD being the primary diagnosis in not quite 50% of women),[181] the combination therapy is theorized to work differently and in a different population of women. The testosterone-induced increase in sexual motivation facilitates a peripheral response via PDE5 inhibition. The increased peripheral response provides, in turn, a potent sexual cue to the more sexually sensitive brain, creating a positive feedback loop that further increases sexual motivation, desire, and sexual responsiveness.

Lybridos[180] combines testosterone with buspirone and is designed for women with HSDD who also have sexual inhibition. Short-term treatment with a 5-HT_{1A} agonist might decrease serotonergic inhibitory control in the prefrontal cortex and therefore might inhibit the inhibition of sexual responses in certain women with HSDD. In Lybridos, the pharmacologic effects of the 5-HT_{1A} agonist coincide with the sexual motivational window induced by testosterone administration.

Investigational treatments of depression and/or antidepressant-induced sexual dysfunction

Extended-release gepirone is an investigational drug for the treatment of depression and sexual dysfunction. Similar to flibanserin, it has a 5-HT_{1A} mechanism of action (but does not affect other serotonin receptors), has been shown in phase 2 clinical trials to have a prosexual effect at daily dosing of 40 to 80 mg, and has improved HSDD in women diagnosed with depression.[182]

Although not an investigational drug or a drug that is indicated for the treatment of sexual dysfunction, sustained-released bupropion is an antidepressant that has been shown to have a moderate prosexual effect and is often used to treat the sexual adverse effects of SSRIs. It blocks the uptake of dopamine and norepinephrine and has been found to significantly improve sexual arousal and orgasm, but not sexual desire alone, in nondepressed women.[29]

As described earlier, clinical trials have not shown sildenafil to be more effective than placebo in treating women with a spectrum of sexual disorders.[181] However, a small randomized controlled trial demonstrated that sildenafil (adjustable dose, 50 or 100 mg) was significantly more effective than placebo in reducing SSRI/serotonin-norepinephrine reuptake inhibitor–induced sexual dysfunction.[183]

Other hormone treatments

DHEA is a prohormone of testosterone that is available as an over-the-counter supplement in tablets of 25 to 50 mg. Clinical trials using DHEA in a transdermal vaginal approach for the treatment of HSDD and vaginal atrophy and for the prevention of osteoporosis are now being conducted.[184]

CONCLUSIONS

Hypoactive sexual desire, categorized either as HSDD (as per the DSM-IV-TR)[12] or as FSIAD (as per the DSM 5),[11] is a highly prevalent medical condition that negatively impacts women's sexual lives and overall quality of life. Yet, the condition remains underdiagnosed by clinicians and has few treatment options. However, several factors are converging to create a palpable shift toward greater attention and awareness. The inclusion of hypoactive sexual desire as a topic for a *Menopause* invited review is evidence of this swing. Greater societal acceptance of women's entitlement to healthy sexual function has helped this shift, although many postmenopausal women continue to hold the belief that society disapproves of their sexuality.[185]

The continued pursuit of pharmacologic agents to treat the physiologic component of hypoactive desire is certainly one of the stronger forces influencing greater attention by researchers and clinicians. Even the FDA has weighed in on this shift by including female sexual dysfunction as a disease area deserving focus. Furthermore, several pharmacologic agents targeting hypoactive sexual desire are in phase 2 or phase 3 development. Despite this positive momentum, if clinicians do not address the sexual concerns of women, then those women with hypoactive sexual desire who would otherwise want to be evaluated and treated will remain invisible and untreated. Some of the major barriers to HCPs addressing the sexual concerns of women are their lack of knowledge of the condition, their discomfort in addressing the topic, and their confusion over treatment within a biopsychosocial model. The value of this review will be determined by its effectiveness in removing those barriers.

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