 REVIEW ARTICLE

The pathophysiology of hypoactive sexual desire disorder in women

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Abstract

Hypoactive sexual desire disorder (HSDD) is defined as a deficiency or absence of sexual fantasies and desire for sexual activity that causes marked distress or interpersonal difficulty. The dysfunction cannot be better accounted for by another psychiatric disorder (except another sexual dysfunction) and must not be due exclusively to the physiological effects of a substance or a general medical condition. HSDD occurs in approximately 1 in 10 adult women in the USA and its prevalence appears to be similar in Europe. A number of potential causative and contributory factors to low sexual desire have been identified, reflecting the interplay among hormonal, neurobiological, and psychosocial factors. One theory is that sexual desire is controlled in the brain by a balance between inhibitory and excitatory factors. In general, dopamine, estrogen, progesterone, and testosterone play an excitatory role in sexual desire, whereas serotonin, prolactin, and opioids play an inhibitory role. It is hypothesized that decreased sexual desire may be due to a reduced level of excitatory activity, an increased level of inhibitory activity, or both. A greater understanding of the complex pathophysiology of HSDD would improve the identification and management of women for whom low sexual desire is a concern.

1. Introduction

Hypoactive sexual desire disorder (HSDD) is a common sexual complaint affecting approximately 1 in 10 adult women in the USA [1,2] and its prevalence appears to be similar in Europe (7%-16%) [3] and Australia (16%) [4]. HSDD is usually defined as persistently or recurrently deficient (or absent) sexual fantasies and desire for sexual activity [5]. The judgment of deficiency is made by the clinician, taking into account factors that may affect sexual functioning, such as age and the context of the person's life. The disturbance must cause marked distress or interpersonal difficulty and cannot be better accounted for by another primary psychiatric disorder (except another sexual dysfunction) or due exclusively to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition. Subtypes of HSDD are specified depending on whether the disorder is lifelong or acquired, generalized or situational, and due to psychological factors or combined psychological/medical factors [5].

The age at onset for individuals with lifelong forms of HSDD is puberty [5]. More frequently, however, the disorder develops in adulthood, after a period of adequate sexual interest, and the loss of sexual desire may be continuous or episodic [5].

HSDD occurs in both premenopausal and postmenopausal women [1–3]. It is associated with significant levels of emotional and psychological distress, as well as lower sexual and relationship satisfaction [2,3]. HSDD is also associated with reduced general health, including aspects of mental and physical health [2,3]. Although the impact of HSDD on patients can be considerable, women are reluctant to seek medical attention for their condition [6]. This is compounded because clinicians frequently do not inquire about the sexual health of their patients [7].

Because female sexual disorders have been studied, in general, less than male disorders, our understanding of the pathophysiology of low or decreased sexual desire and female sexual dysfunction in general is limited. The aim of this review is to examine our current understanding of the pathophysiology of HSDD, including hormonal, neurobiological, and psychosocial factors.

2. Female sexual response

In the 1960s, Masters and Johnson introduced what is now considered the classic linear model of female sexual response based on a physiologic foundation [8]. They proposed a linear model of sexual response for both men and women composed of 4 stages, beginning with excitement/arousal and proceeding to plateau, orgasm, and resolution. In 1979, Kaplan added the concept of desire to the model and condensed the response into 3 phases: desire, arousal, and orgasm [9]. More recently, Basson suggested a model of the female sexual response that incorporates motivations other than sexual desire such as sexual intimacy, sexual stimuli, and relationship...
satisfaction (Fig. 1) [10], which may be affected by numerous psychosocial issues (e.g., satisfaction with the relationship, self-image, and previous sexual experiences). In fact, some women initiate sexual activity, some are receptive to partner approach, and some may participate in sexual activity without desire or for emotional motivations; however, no model of female sexual response is consistently endorsed by all women [11]. In a recent survey, a community sample of women were equally likely to endorse each of the 3 different models [11]. Further, the Basson model appears to be more reflective of women experiencing sexual dysfunction as measured by the Female Sexual Function Index (FSFI) [11,12].

3. Pathophysiology

The basis of desire in women involves interactions among multiple neurotransmitters, sex hormones, and a variety of psychosocial factors. Human sexual desire is associated with both the limbic system and higher cortical brain areas.

Dopamine appears to be a key neurotransmitter in the modulation of sexual desire. The ventral tegmental area (VTA) is the primary source of dopamine to the mesolimbic and mesocortical pathways. The mesolimbic pathway connects the VTA to the nucleus accumbens and the mesocortical pathway connects the VTA to the frontal cortex. In rats, dopamine appears to enhance sexual desire, the subjective sense of excitement, and the desire to continue sexual activity once sexual stimulation has been initiated [13]. In rats, estradiol facilitates dopamine release and testosterone potentiates the synthesis of nitric oxide, which controls dopamine release [14,15]. Thus, steroid hormones appear to increase available dopamine, creating a neurochemical state in which sexual stimuli are more likely to induce a sexual response.

Increasing levels of serotonin (e.g., reuptake inhibition, as with the selective serotonin reuptake inhibitors, SSRIs) can diminish the effects of dopamine on sexual function [16]. Although this negative feedback may be important during resolution, excessive and/or chronic serotonergic neurotransmission decreases sexual desire. Serotonergic pathways provide direct signals from the Raphé nuclei to brain centers involved in the sexual response. In addition, there are specific indirect pathways from the prefrontal cortex through which serotonin exerts effects on the midbrain and brainstem.

Endogenous opioids, which play a role in the subjective experience of pleasure and reward, also modulate the perceived intensity of sexual desire in humans [17]. Natural rewards such as having an orgasm depend on a preceding build-up of sexual tension to fully develop their pleasurable potential. Following the experience of orgasm, desire decreases and requires a certain time span to reach its former level and intensity. In contrast to the motivational effects of dopamine in the anticipation of reward, opiates may reduce pleasure-seeking and thus orgasmic experience. Therefore, they may have an inhibitory effect on sexual desire.

Testosterone appears to be the primary sex steroid influencing desire, and may be involved in the initiation of sexual activity, while progesterone may mediate receptivity to partner approach [18]. However, attempts to relate circulating levels of testosterone to sexual desire in women have yielded inconsistent results [19]. Testosterone function may, at least in part, be modulated by the neurotransmitters dopamine and serotonin by way of the hypothalamus and associated limbic structures [13]. In addition, decreased levels of bioavailable testosterone may lead to symptoms consistent with androgen insufficiency manifested as a diminished sense of well-being or dysphoric mood, persistent fatigue, and changes in sexual function, including diminished desire, reduced sexual receptivity, and diminished sexual pleasure [20]. Down-regulation of testosterone also influences desire with the pituitary hormone, prolactin, negatively influencing sexual function, both directly and via an inverse relationship to dopamine function [16]. Thus, in general, dopamine, estrogen, progesterone, and testosterone play an excitatory role in sexual desire, while serotonin, opioids, and prolactin play an inhibitory role (Fig. 2).

The concepts of sexual excitation and inhibition in the brain are central to modulation of sexual desire and sexual behavior. The central assumption of the “Dual Control Model” described by Janssen and Bancroft [21] is that sexual desire and response depend on a balance between inhibitory and excitatory mechanisms in the brain. Individual propensities for sexual excitation and inhibition are thought to be independent of one another and vary from person to person. The model assumes that in the majority of individuals, inhibition is adaptive and helps the individual avoid sexually risky or threatening situations. However, levels of inhibitory tone that are too

![Fig. 1](image1.png) Non-linear model of female sexual response. Adapted with permission granted by Lippincott, Williams & Wilkins from: Basson R. Female sexual response: the role of drugs in the management of sexual dysfunction. Obstet Gynecol 2001; 98(2):350-3.

![Fig. 2](image2.png) Positive and negative central effects of neurotransmitters and hormones on sexual desire.
low or too high may contribute to problems ranging from high-risk sexual behaviors to sexual dysfunctions. Problems with excitation and inhibition may be additive; that is, when strong sexual inhibition is paired with low excitation, sexual response may be particularly impaired, and if low inhibition is combined with high excitation, high-risk sexual situations may be subjectively experienced as more difficult to avoid. It is hypothesized that the low sexual desire of HSDD is due to a reduced level of excitatory activity, an increased level of inhibition, or both. This imbalance may disrupt the sexual response at any point during the cycle.

4. Factors that may affect sexual desire

Our current understanding of risk factors for HSDD is incomplete, as much of the evidence concerning the etiology of HSDD comes from cross-sectional epidemiological studies that identify associations rather than cause-and-effect relationships. However, it is known that a number of psychological and sociological variables may affect sexual desire, as may the aging process, menopause, the presence of co-morbid disease, and certain medications.

4.1. Psychosocial variables

Among the psychosocial variables that can affect a woman’s desire, perhaps the most important is her relationship with her sexual partner. The Women's International Study of Health and Sexuality (WISHeS) study (funded by Proctor and Gamble Pharmaceuticals) was conducted in 1999–2000 among 4517 women, aged 20–70 years, residing in France, Germany, Italy, the UK, and the USA [2,3]. The results of this survey showed that HSDD was associated with significant emotional and psychological distress, as well as lower sexual and relationship satisfaction [2,3]. Women with HSDD were 11 times more likely to feel dissatisfied with their sex lives and 2.5 times more likely to feel dissatisfied with their marriage or partner relationship than women who did not have low desire [2]. Compared with women without HSDD, less than 10% of whom experienced negative emotional or psychological states “often,” “very often” or “always,” more than 80% of women with HSDD felt concerned, unhappy, or that they were letting their partner down [2,3].

Consistent with these findings, results from the 1992 National Health and Social Life Survey conducted in the USA—involving 1749 women aged 18–59 years—showed that low sexual desire in women is commonly associated with reduced feelings of physical and emotional satisfaction and decreased feelings of happiness with their partners [22]. Reduced pleasure or satisfaction with sexual experiences may influence sexual receptivity and sexual interest, leading to further decreases in sexual or relationship satisfaction. Indeed, results from a recent study of 58 mid-life women support a bidirectional causal model in which dyadic sexual interaction and physical affection improve mood and reduce stress, with improved mood and reduced stress in turn increasing the likelihood of future sex and physical affection [23]. Bancroft et al. [24] postulated that negative emotional responses and lack of emotional well-being during sexual activity with a partner were major contributors to sexual distress, rather than changes in physical or genital aspects of sexual response.

On the basis of survey data, several psychosocial factors have been linked to women’s sexual satisfaction and desire. These include stable past and current mental health, positive emotional well-being and self-image, rewarding past sexual experiences, positive feelings for the partner, and positive expectations for the relationship [24–26].

4.2. Aging

Despite reports that a higher proportion of older women experience reduced desire, many investigations have found that the prevalence of reduced desire associated with distress or HSDD does not increase with age [22,27]. A secondary analysis of patients participating in the WISHeS study showed that the proportion of women with low desire increased significantly with age, while the proportion of women distressed about their low desire decreased with age, so the prevalence of HSDD remained essentially constant [28].

In 2006, the Prevalence and Correlates of Female Sexual Disorders and Determinants of Treatment Seeking (PRESIDE) study (funded by Boehringer Ingelheim GmbH) was undertaken by mailing surveys to over 50,000 women, aged 18–102 years, in the USA [1]. The survey population was selected to be a representative sample of women in the USA based on a variety of demographic variables, including age, race, geographical location, marital status, education, and household income. The response rate was high (63.2%) with 31,581 returns. In this study, the prevalence of low desire associated with distress was found to be higher in mid-life women (45–64 years, 12.3%) than in younger women (18–44 years, 8.9%) or older women (≥65 years, 7.4%).

4.3. Perimenopause/ menopause

Surgically postmenopausal women are at increased risk of HSDD [2,3]. In the European cohort of the WISHeS study, women who had undergone a surgical menopause were twice as likely to have HSDD than premenopausal or naturally postmenopausal women (OR 2.1; 95% CI, 1.4–3.4, P < 0.01) [2,3]. In the US cohort, surgically postmenopausal women aged 20–49 years were nearly 3 times as likely to have HSDD as their premenopausal counterparts (OR 2.7; 95% CI, 1.5–5.0, P < 0.01) [2,3].

In general, premenopausal women are hormonally replete with regard to estrogen, progesterone, and testosterone. After removal of the ovaries, a woman’s hormonal status is drastically altered, with an almost complete loss of estrogen and a 50% loss of androgens [29]. The majority of surgically postmenopausal women aged 20–49 years in the US cohort of the WISHeS study used estrogen therapy, but not androgen therapy [2,3]. The authors hypothesized that the increased odds of a young surgically postmenopausal woman having HSDD results from diminished levels of androgens, most notably testosterone. In addition, surgery itself may have a physical, as well as an emotional, impact on sexuality; removing or altering female reproductive organs may lead to discomfort during sexual encounters and leave women feeling less feminine, sexual, and desirable [30].

Declining estrogen and testosterone levels during the perimenopause may be associated with a flagging sex drive, but for women who endorse the Basson model [10], this may not be associated with a recognizable change in sexual desire or response. In other words, if desire is not the motivating force for sexual activity, then the loss of spontaneous desire may not have a great impact on a woman’s sexual life if her partner is still interested and initiates sexual activity [31,32].

4.4. Comorbidities and medications

It is important to note that the diagnostic criteria for HSDD stipulate that the sexual dysfunction cannot be better accounted for by another primary psychiatric disorder (except another sexual dysfunction) and must not be due exclusively to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition [5]. A clinician must make a judgment as to whether the loss of desire a woman is experiencing may be accounted for by a medical condition or the use of a drug or medication. Timing of onset of HSDD versus the diagnosis of a medical condition or initiation of a medication, may aid in assessment.

Loss of interest in sexual activity may accompany or be exacerbated by chronic medical conditions [33]. Indeed, compared with women without HSDD, women with HSDD in the WISHeS study had reduced general health, as assessed using the Short Form-36 (SF-36)
Further, lower health status was proportional to the risk of having HSDD in the PRESIDE study [1].

Sexual disorders are often co-morbid; for example, low sexual interest is frequently associated with problems of sexual arousal or with orgasm difficulties, particularly in postmenopausal women [5]. The deficiency in sexual desire may be the primary dysfunction or it may be a response to problems with arousal or orgasm.

Lower urinary tract symptoms including urinary incontinence have been associated with an increased risk of sexual dysfunction [34]. Leakage of urine with penetration (or with orgasm) often reduces sexual motivation. (This is different from the normal fluid release that occurs in some women during orgasm.) Other medical conditions associated with reduced sexual desire include neurological diseases such as multiple sclerosis, Parkinson’s disease, and head injury; coronary artery disease and myocardial infarction; renal failure; diabetes; adrenal disease; and breast cancer [33,35].

Depressive disorders are often associated with low sexual desire and the onset of depression may precede, co-occur with, or be the consequence of deficient sexual desire. In a recent study, 80% of untreated patients with mood or anxiety disorders reported reduced sexual desire [36]. However, patients with depression often do not appear to be distressed by their lack of interest in sex [37]. Certain treatments for depression, notably the SSRIs, may themselves cause sexual problems [38].

In addition to SSRIs, drug-induced sexual dysfunction may be attributed to a variety of agents used to treat hypertension, schizophrenia, and certain cancers, particularly treatments for hormone-sensitive tumors [39]. The mechanism of action behind iatrogenic sexual dysfunction varies by drug class. Antihypertensive agents are proposed to affect sexual function via central adrenergic inhibition and blockade of adrenergic receptors. Antipsychotics are dopamine blockers, have anticholinergic effects, may increase prolactin levels, and produce sedative effects. Use of exogenous opioids is associated with HSDD and orgasmic difficulties [40].

The impact of oral contraceptives on sexual functioning is controversial, although the weight of evidence suggests that negative effects may occur, but only in a minority of women [41,42]. Of course, this conclusion is limited by the nature of the studies that have been done. The wide variety of hormonal medications available limits studies addressing differences related to dose, type of hormone, or route of administration.

5. Assessment of patients with HSDD

Our understanding of the complex interrelationships among hormonal, neurobiological, and psychosocial factors that contribute to decreased sexual desire is improving. It is clear that a clinician should consider a range of factors in women presenting with sexual concerns. Any changes in sexual desire, sexual behaviors, initiation of sexual activity, receptivity to partner approach, or sexual function should be investigated. Discussions about sexuality should include open-ended questions. If a sexual concern is elicited, a focused history should include menstrual, reproductive, and sexual histories; status of current relationships and sexual activity (including the partner’s sexual function, health status, stress level and availability for sex); family and personal beliefs about sexuality; and history of sexual trauma or abuse (which may or may not be associated with sexual dysfunction [43]). Additional elements of the history include medical and surgical history (including evaluating stress response, sleeping patterns and physical activity); medication use; alcohol, and illicit drug use; family history; and birth control method. Unfortunately, clinicians are often uncomfortable with, and poorly educated about, obtaining a comprehensive sexual history [44]. There are a number of validated self-report and interview-based tools for assessing female sexual function, but to date, these have primarily been used in research settings. The Decreased Sexual Desire Screener (DSDS) is an easy-to-use, brief assessment instrument that can be used to diagnose generalized acquired HSDD in women presenting with complaints of decreased sexual desire, which may be useful in the primary care setting, and help clinicians begin a conversation about sexual health with their patients [45].

There are no approved pharmacological therapies for the treatment of HSDD in premenopausal women, although several types of treatment are currently under investigation [46].

6. Conclusions

HSDD is characterized by a deficiency or absence of sexual fantasies and desire for sexual activity, which causes the patient marked distress or interpersonal difficulty. Although HSDD is frequently encountered and has received increasing attention in recent years, it often remains unrecognized among non-specialist healthcare providers and the general public. Further research will provide additional insights into the hormonal, neurobiological, and psychosocial factors that can contribute to low sexual desire in women of all ages, with the ultimate goal of achieving more effective intervention in women who are distressed by low sexual desire.

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